The Epidemiology and Patient Perspectives of Glucocorticoid Use in Rheumatoid Arthritis and Other Inflammatory Diseases

Rachel Black
MBBS (The University of Adelaide)

Adelaide Medical School,
Faculty of Health and Medical Sciences
The University of Adelaide

May, 2019

Table of Contents

List of Tables and Figures

Included Publications

R.J. Black, R.M. Joseph, B. Brown, M. Movahedi, M. Lunt, W.G. Dixon, Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study, Arthritis research & therapy 2015;17:375. https://doi.org/10.1186/s13075-015-0895-8.

R.J. Black, S. Lester, R. Buchbinder, C. Barrett, M. Lassere, L. March, S. Whittle, C.L. Hill, Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry, Arthritis research & therapy 2017;19:253. https://doi.org/10.1186/s13075-017-1461-3.

R.J. Black, S.M. Goodman, C. Ruediger, S. Lester, S.L. Mackie, C.L. Hill, A Survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases: The Patient Perspective, J Clin Rheumatol 2017;23:416-20. https://doi.org/10.1097/RHU.0000000000000585.

R.J. Black, C.L. Hill, S. Lester, W.G. Dixon, The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis, PloS one 2016;11:e0166468. https://doi.org/10.1371/journal.pone.0166468.

R.J.Black, S.Lester, C.L.Hill, W.G. Dixon, Oral glucocorticoid use and the development of cataracts and glaucoma in patients with incident rheumatoid arthritis. (To be submitted)

Appendices

R.J. Black, J.C. Robson, S.M. Goodman, E. Hoon, L.Y. Lai, L.S. Simon, E. Harrison, L. Neill, P. Richards, L.M. Nelsen, J.M. Nebesky, S.L. Mackie, C.L. Hill, A Patient-reported Outcome Measure for Effect of Glucocorticoid Therapy in Adults with Inflammatory Diseases Is Needed: Report from the OMERACT 2016 Special Interest Group, The Journal of rheumatology 2017. https://doi.org/10.3899/jrheum.161083.

J.T.L. Cheah, R.J. Black, J.C. Robson, I.Y. Navarro-Millan, S.R. Young, P. Richards, S. Beard, L.S. Simon, S.M. Goodman, S.L. Mackie, C.L. Hill, Toward a Core Domain Set for Glucocorticoid Impact in Inflammatory Rheumatic Diseases: The OMERACT 2018 Glucocorticoid Impact Working Group, The Journal of rheumatology 2019. https://doi.org/10.3899/jrheum.181082.

Abstract

The overarching theme is to improve understanding of oral glucocorticoid (GC) use, including the benefits and harms of GC treatment in inflammatory rheumatic diseases, with an emphasis on rheumatoid arthritis (RA). The introduction summarises inflammation as a normal physiological process, and its contribution to chronic inflammatory diseases, commonly treated with GCs. It further describes GCs in detail, identifying three key areas where the literature is lacking and/or conflicting that are addressed as the thesis aims.

The first section of the thesis explores how GCs are used in RA and the influence of patient and prescriber factors in two large databases in the United Kingdom (UK) and Australia. In Chapter 2, primary care data from clinical practice research datalink (CPRD) demonstrated that half of patients with incident RA received GCs in primary care, with an average GC use of 7.5 mg (prednisolone equivalent daily dose, PEQ) for 25% of the time. GCs were prescribed more commonly in certain high-risk populations. In Chapter 3, data from Australian Rheumatology Association Database (ARAD), found the probability of GC use has decreased over time. In contrast to CPRD, GC use in ARAD RA patients was less likely with increasing age, with older patients being less likely to commence GCs, but also less likely to cease GCs.

The second section of the thesis explores the patient perspective of the benefits and harms of GC use, and the need for a patient reported outcome measure (PRO). A cross-sectional survey administered to GC users with rheumatic diseases in Australia and United States (US) demonstrated that most patients with rheumatic diseases feel that GCs are effective treatments and that the benefits of GC use, outweigh the harms. Many adverse effects important to patients, cannot be easily measured, such as skin thinning/easy bruising, sleep disturbance, mood disturbance, and change in facial shape. This chapter also discusses the role of Outcome Measures in Rheumatology (OMERACT) in developing a PRO for GC use, describing additional work by the author contributing to both this thesis and the OMERACT GC working group.

The final section of the thesis focuses on cataract and glaucoma, as two important potential harms of GC use. Chapter 5 presents a published manuscript reporting the results of a systematic literature review and meta-analysis, concluding that although the current literature suggests a possible association between GC use and the development of cataract, this risk cannot be accurately quantified in RA from the available evidence.

In addition, there was insufficient evidence to determine the risk of GC use and the development of glaucoma.

To address this gap in the literature, analyses of different models of GC exposure in CPRD were performed to quantify the risk of developing cataracts and glaucoma in RA patients. The results demonstrated that current GC exposure is associated with a two-fold increased risk of developing cataracts and 60% increased risk of developing glaucoma in patients with RA. For cataracts, cumulative doses greater than 1000mg PEQ are associated with increased risk, more so at doses above 4000mg PEQ, whereas for glaucoma, the risk is seen only with higher cumulative doses greater than 4000mg. The results of these three sections of work expand current knowledge about GC use, with opportunities for the findings to be directly translated and improve clinical care.

Thesis Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

I acknowledge the support I have received for my research through the provision of:

- Australian Government Research Training Program Scholarship
- Arthritis South Australia and Australian Rheumatology Association (South Australia) postgraduate grant (2014)
- Ken Muirden Overseas Training Fellowship, an educational research grant jointly funded by Arthritis Australia and Roche Products Pty Ltd. (2013)

Rachel Black

22nd May 2019

Acknowledgements

Firstly, I would like to acknowledge the financial support I received from an Australian Government Research Training Program Scholarship, an Arthritis South Australia and Australian Rheumatology Association (South Australia) Postgraduate Grant (2014), and the Ken Muirden Overseas Training Fellowship, an educational research grant jointly funded by Arthritis Australia and Roche Products Pty Ltd. (2013).

I would also like to acknowledge and thank Professor Catherine Hill, who has encouraged and mentored my research career since I began my rheumatology training in 2010. Her encouragement and assistance in applying for an overseas training fellowship set me on the path to commencing this PhD in 2013, and as my supervisor, her guidance and unconditional support have kept me driven and focussed through the challenges and successes of my candidature. She has been truly generous with the opportunities she has made available to me and I will always be grateful for her guidance, support and friendship.

I would also like to thank Professor Will Dixon, who has also been pivotal in helping to shape my research career. I am immensely grateful to have had the opportunity to work under his mentorship at the Arthritis Research UK centre for Epidemiology, University of Manchester for the first year of my candidature. As my supervisor during my time in Manchester and ongoing since my return to Adelaide, his enthusiasm for research and generosity with his time and knowledge has been truly appreciated.

Thanks to my primary supervisor, Professor Les Cleland, who oversaw my candidature with genuine interest, willingly contributing his research experience and expertise.

In addition to my supervisors, I would also like to thank Sue Lester, who has provided immeasurable support throughout my candidature. She has not only provided statistical support, but has been a mentor, sounding board and friend. She has guided me with patience and kindness, helping me to understand complicated statistical concepts and become a better researcher.

I thank my colleagues in Manchester, Meghna, Sarah, John, Jenny, James, Audrey, Madhura and Rebecca for the warm welcome, stimulating discussions, experiences shared, and friendships that will last a lifetime. Thanks also to my co-authors for their valuable advice and expertise.

Thank you to my father-in-law for his belief in me as a researcher and for reading the final draft with his experienced eye.

As always, I am grateful to my parents and siblings for their love, support and encouragement in everything I do.

To my children Isabelle and Mae, who were both born during my candidature and who bring joy and happiness to my life every day, I can't wait to give you more 'mummy-time' very soon and look forward to watching you become strong, inquisitive women. Last but not least, love and thanks to my husband who has supported my career from medical school, to internship, through nightshifts and fellowship exams, who uprooted his life for a year to join me on an adventure in the UK and has now seen me through to the completion of this PhD and thesis. I love you and could not have achieved this without you.

List of Abbreviations

ACPA	antibodies to citrullinated peptides
ACR	American College of Rheumatology
ACTH	adrenocorticotrophic hormone
AEs	adverse effects
AP-1	activator protein-1
ARAD	Australian Rheumatology Association Database
AS	ankylosing spondylitis
BDES	Beaver Dam Eye Study
bDMARDs	biologic disease modifying anti-rheumatic drugs
BISED	Barbados Incidence study of Eye Diseases
BMES	Blue Mountains Eye Study
BMPs	bone morphogenetic proteins
BNF	British National Formulary
boDMARDs	bio-original disease modifying anti-rheumatic drugs
bsDMARDs	biosimilar disease modifying anti-rheumatic drugs
CI	confidence interval
COBRA	COmbinatietherapie Bij Reumatoide Artritis (Dutch acronym)
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase-2
CPRD	clinical practice research datalink
CRH	corticotrophin releasing hormone
csDMARDs	conventional synthetic disease modifying anti-rheumatic drugs
DAMPs	damage-associated molecular patterns
EGF	epidermal growth factor
EULAR	European League against Rheumatism
FGF-2	fibroblast growth factor-2
GC	glucocorticoid
GCA	giant cell arteritis
GILZ	glucocorticoid induced lucine zipper
GM-CSF	granulocyte macrophage colony stimulating factor
GP	general practitioner
GPRD	General Practice Research Database
GREs	glucocorticoid response elements
GRs	glucocorticoid receptors
GTI	glucocorticoid toxicity index
HAQ	Health Assessment Questionnaire

HR	hazard ratio
IGF-1	insulin-like growth facto -1
IgG	immunoglobulin-G
IL-1b	interleukin-1b
IL-6	Interleukin-6
IOP	intra-ocular pressure
ISAC	Independent Scientific Advisory Committee
JAK	Janis kinase
JIA	juvenile idiopathic arthritis
LEDGF	lens epithelium derived growth factor
MAP kinase	mitogen-activated protein kinase
MBS	Medicare Benefits Schedule
mGR	membrane-bound GR
MHRA	Medicines and Healthcare Products Regulatory Agency
MKP-1	mitogen-activated kinase phosphatase-1
Na/K	sodium-potassium
ndd	numeric daily dose
NF-kb	nuclear factor kappa-beta
nGREs	negative glucocorticoid response elements
NHS	National Health Service
OAG	open angle glaucoma
OMERACT	Outcome Measures in Rheumatology
OR	odds ratio
PAI-1	plasminogen activator inhibitor-1
PAMPs	pathogen-associated molecular patterns
PBS	Pharmaceutical Benefits Scheme
PDGF	platelet derived growth factor
PEQ	prednisolone equivalent daily dose
PI-3 kinase	phosphoinositide-3 kinase
PMR	polymyalgia rheumatica
POAG	primary open angle glaucoma
PRO	patient reported outcome measure
PRRs	pattern recognition receptors
PsA	psoriatic arthritis
PSCs	posterior subcapsular cataracts
qty	quantity
RA	rheumatoid arthritis
RANK	receptor activator of nuclear factor κB

RANKL	receptor activator of nuclear factor κB ligand
RES	Rotterdam Eye Study
RF	rheumatoid factor
SGK	serum glucocorticoid kinase
SIGs	special interest groups
SLE	systemic lupus erythematosus
SLPI	secretory leukocyte peptidase inhibitor
TGF-b	transforming growth factor-beta
TNF	tumour necrosis factor
TNFα	tumour necrosis factor alpha
UK	United Kingdom
US	United States
UTS	'up-to-standard'
VAMP	Value Added Information Medical Products
VAS	visual analogue scale
VIP	Visual Impairment Project

1 Introduction

1.1 Inflammation

Inflammation is an essential protective response to infection and tissue damage (1). There are five classical signs of inflammation, including redness (rubor), heat (calor), pain (dolor), swelling (tumor) and loss of function (2). These occur as a result of the cellular and vascular changes that make up the inflammatory process. Inflammation is initiated by immune cells already resident within the affected tissue, such as macrophages, dendritic cells and mast cells. These cells possess pattern recognition receptors (PRRs), which bind two subclasses of molecules: pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (3). When PAMPs or DAMPs bind to PRRs in response to infection or tissue damage, inflammation is initiated and signalling pathways lead to the release of inflammatory mediators, including cytokines and chemokines (3). These, in turn, trigger the vascular components of inflammation, including arteriolar dilatation leading to increased blood flow to the affected region, presenting as heat and redness, and increased capillary permeability leading to protein leakage and oedema, which presents as swelling. The final stage of acute inflammation is control and resolution of the process and repair of damaged tissue. If this stage fails to occur, acute inflammation can become chronic, leading to chronic inflammatory diseases including Rheumatoid Arthritis (RA) (4).

1.2 Glucocorticoids

Glucocorticoids (GCs) are a class of medications commonly used in the treatment of chronic inflammatory disorders, targeting multiple stages of the inflammatory process. GCs, along with mineralocorticoids, are the two main subtypes of corticosteroid hormones produced in the adrenal cortex. Naturally occurring GCs include cortisol (hydrocortisone), corticosterone and cortisone, while aldosterone is a naturally occurring mineralocorticoid. Like many physiological processes, synthetic versions of these hormones have been developed for their therapeutic effects. Synthetic GCs were first shown to be effective anti-inflammatory medications in 1948, when Hench and Kendall reported the almost ‘miraculous’ effects of synthetic cortisone (known as Compound E) administered to a patient with RA (5). In 1950, along with Reichstein, they were awarded the only Nobel Prize for Rheumatology for this work (6). There was rapid progression in this area, and by 1958 there were six synthetic glucocorticoid agents

available for the treatment of inflammatory conditions. However, as these agents were rapidly adopted for their therapeutic effects, the multitude of adverse effects (AEs) also became apparent.

Physiological Effects

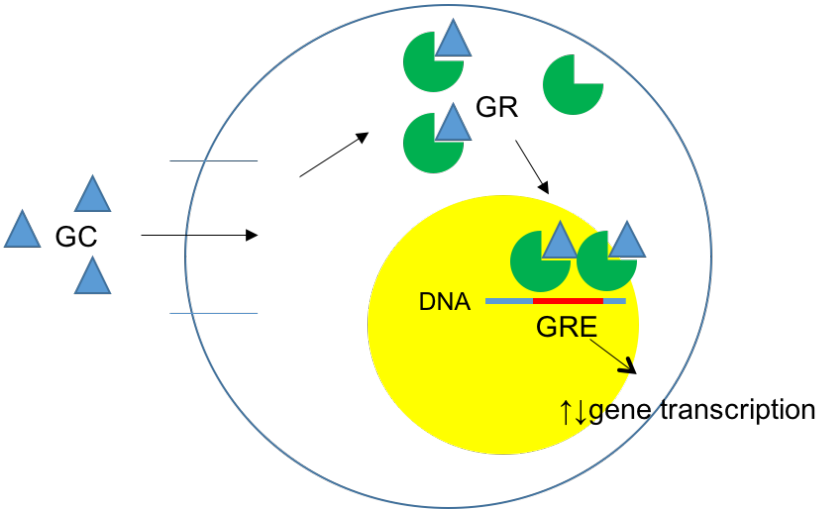
Physiological GC (cortisol) secretion, which is regulated by adrenocorticotrophic hormone (ACTH), is produced in the anterior pituitary and released in bursts. ACTH production is in turn driven by corticotrophin releasing hormone (CRH) from the hypothalamus. Pulses of ACTH occur every 30-120 minutes. The varying amplitude of ACTH pulses leads to the normal diurnal rhythm of cortisol production. Plasma cortisol is highest in the early morning, low in the afternoon and evening, and lowest one to two hours after sleep begins. Cortisol has a negative feedback on ACTH and CRH production, therefore when GC production is impaired, as in Addison disease, ACTH is elevated. Similarly, excess GC (either endogenous or exogenous) suppresses ACTH (7). The effects of GCs are often broadly divided into metabolic and immune. However, GC receptors can be found in almost all cell types and the effects of GCs are widespread, affecting all major body systems (8).

The metabolic effects of GCs include: 1. The stimulation of hepatic gluconeogenesis, with conversion of protein to carbohydrate and the storage of carbohydrate as glycogen (9), 2. Mobilisation of amino acids from extrahepatic tissues, making them available as substrates for gluconeogenesis (10), 3. Inhibition of glucose uptake in peripheral tissues such as muscle and adipose tissue in order to conserve glucose for glycogen production in the liver (9), and 4. Contradictory adipogenic and lipolytic effects on lipid metabolism, which occur through a number of different mechanisms (11). GCs increase the hydrolysis of circulating triglycerides by lipoprotein lipase activity, increasing the amount of fatty acids in the circulation, which are then available for ectopic fat distribution (liver, muscle, and central adipocytes) (12). They also increase lipid production in hepatocytes through increased expression of fatty acid synthase (13). The dual action of GCs on adipocytes appears to be dependent on the cell type, with adipogenic effects of GCs promoting pre-adipocyte conversion to mature adipocytes resulting in hyperplasia of the adipose tissue, and lipolytic effects primarily affecting mature adipocytes (14). The immune effects of GCs include anti-inflammatory and immunosuppressive effects, which occur via a number of complex mechanisms as described below. GCs help to protect cells from damage caused by the inflammatory response.

Mechanisms of action

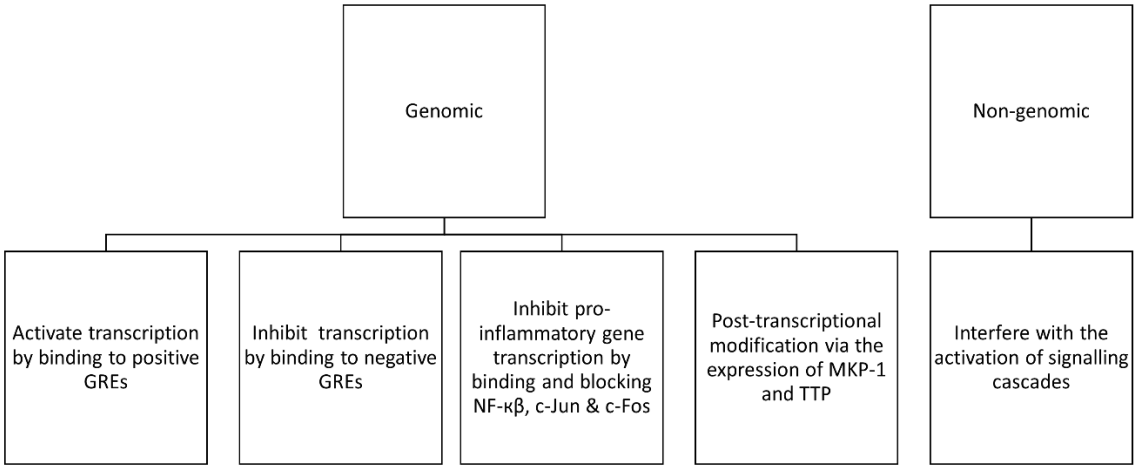
When GC molecules enter a cell, they bind to inactive, protein-bound glucocorticoid receptors (GRs) in the cytoplasm. After GC binding, the GR detaches from its proteins and the GC/GR complex can then enter the nucleus where it binds to glucocorticoid response elements (GREs) on target genes. The binding of the GC/GR complex to the GRE leads to gene transcription, the production of messenger RNA and the synthesis of proteins (Figure 1.1).

Figure 1.1. GC Receptor Activation



Three types of GREs have been described: 1. Simple GREs occur in the promoter regions of target genes and typically bind homo-dimeric GC/GR complex, 2. Composite GREs also occur in the promoter region but bind other transcription factors together with the GC/GR complex, and 3. Tethering GREs are sites on DNA that bind other transcription factors (NF-κβ, Stat3) which in turn bind the GC/GR complex (15, 16). GC mechanisms of action can be divided into genomic and non-genomic effects (17) as summarised in Figure 1.2.

Figure 1.2. Glucocorticoid Genomic and Non-Genomic Mechanisms of Action



Transcriptional mechanisms

The GC/GR interaction with the GRE complex can lead to transcriptional activation (trans-activation) of genes encoding anti-inflammatory proteins such as annexin 1, mitogen-activated kinase phosphatase-1 (MKP-1), glucocorticoid induced lucine zipper (GILZ) and secretory leukocyte peptidase inhibitor (SLPI). The GC/GR complex can also regulate gene transcription via negative GREs (nGREs) which occur on genes encoding interleukin-1β (IL-1β), as well as those relevant to GC AEs such as osteocalcin (bone metabolism), corticotropin releasing hormone (hypothalamic-pituitary axis) and keratins (skin structure) (18). The GC/GR complex also causes transcription repression (trans-repression) of genes encoding pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, IL-8, tumour necrosis factor (TNF) and granulocyte macrophage colony stimulating factor (GM-CSF) as well as other inflammatory mediators such as cyclooxygenase-2 (COX-2) (19). This occurs when the GC/GR complex binds to and blocks other pro-inflammatory transcription factors such as nuclear factor kappa-beta (NF-κβ) and activator protein-1 (AP-1, comprised of c-Jun and c-Fos).

Post-transcriptional mechanisms

In non-inflammatory states, after transcription has occurred, the mRNA encoding pro-inflammatory genes (such as IL-1β, IL-6, IL-8 and TNF) is unstable and rapidly degraded by RNases (20, 21). However, in states of active inflammation, inflammatory cytokines activate the p38 MAP kinase pathway, which stabilises mRNA and promotes the translation of more inflammatory cytokines (22). GC activation of MKP-1 leads to reduced p38 MAP-kinase activity (23), reducing mRNA stability and inflammatory

cytokine production (24). GCs can also reduce mRNA stability by increasing the expression of proteins such as tristetraprolin (20, 25).

Non-genomic mechanisms

Four non-genomic mechanisms by which GCs might affect inflammation, have been described. These include: 1. Signalling pathway via a membrane-bound GR (mGR), 2. Direct membrane effects, 3. Interaction of the GR with other proteins in the cytoplasm and 4. GR translocation on mitochondria (16). mGR was first described in 1999, when GC binding to the cell membrane was observed in mouse and human lymphoid cell lines (26). The amount of mGR in monocytes is correlated with clinical status in systemic lupus erythematosus (SLE) (27), RA (28) and ankylosing spondylitis (AS) (29), suggesting a role in inflammatory diseases, however further work is needed to define this apparent functionality (16). Direct membrane effects of GCs have been described, including: increased membrane lipid mobility in lymphocytes and some cancer cells (30).This suggests GCs are able to directly modulate of the physiochemical properties of the cell membrane in order to regulate cell functions such as Na and Ca ion channels, cell fluid shift response and tight junction formation. The binding of GCs to GRs in the cytoplasm leads to rapid (within minutes) intracellular signalling events separate from transcriptional interactions with the GREs (31). Translocation of the GC/GR complex to mitochondria influences sensitivity to GC-induced apoptosis (32).

Therapeutic Use of GCs

Due to their widespread anti-inflammatory actions, synthetic GCs are frequently used to treat many chronic inflammatory disorders, including those affecting the musculoskeletal, respiratory, gastrointestinal, neurological and renal systems, as well as the skin. In addition, they are also used to treat hormone deficient endocrine conditions and malignancies and to prevent rejection in transplant medicine. Approximately 0.5-1% of the adult population are long-term GC-users (33-35). Asthma is the most common indication for GC use, followed by polymyalgia rheumatic (PMR) and giant cell arteritis (GCA), chronic obstructive pulmonary disease (COPD) and RA (34). Indications for GC therapy are listed in Table 1.1.

Table 1.1. Indications for Glucocorticoid Therapy by Specialty

Respiratory	Asthma	**Gastroenterology**	Ulcerative colitis
	COPD		Crohn's disease
	Hypersensitivity pneumonitis		Autoimmune hepatitis
	Sarcoidosis	**Haematology**	Lymphoma
	Eosinophilic pneumonia		Leukaemia
	Non-specific interstitial pneumonia		Haemolytic anaemia
			ITP
Rheumatology	Rheumatoid arthritis		Multiple myeloma
	Psoriatic arthritis	**Ophthalmology**	Uveitis
	Systemic lupus erythematosus		Keratoconjunctivitis
	Sjögren's syndrome	**Neurology**	Multiple sclerosis
	Polymyalgia rheumatica		Myasthenia gravis
	Giant cell arteritis		Cerebral oedema
	Inflammatory myositis	**Renal**	Glomerulonephritis
	Polyarteritis nodosa		Nephrotic syndrome
	ANCA associated vasculitis		Acute interstitial nephritis
	Behçet's Disease	**Other**	Neoplasms
	IgG4 related disease		Transplantation
Allergy	Urticaria	**Endocrinology**	Addison's disease
	Allergic rhinitis	(usually at	Adrenal insufficiency
	Angioedema	physiologic	Congenital adrenal
	Anaphylaxis	doses)	Hyperplasia
	Food allergies		
	Drug allergies		
	Nasal polyps		
Dermatology	Atopic dermatitis/eczema		
	Cutaneous vasculitis		
	Cutaneous lupus		
	Contact dermatitis		
	Psoriasis		
	Pemphigus vulgaris		

ITP=Idiopathic thrombocytopenic purpura

There are many different routes by which GCs can be administered, including systemic (oral, intramuscular, intravenous), rectal, intra/peri-articular injections, epidural injections, inhaled preparations, intranasal preparations, intradermal injections, topical dermatologic preparations (creams or ointments), topical ocular preparations applied to the eyes or eyelids (eye drops or eye ointments), preparations for periocular delivery (subconjunctival, subtenon's or retrobulbar injections) and intravitreal preparations

(injections or implants). The evidence for the use of GCs administered via various routes to treat different inflammatory conditions is vast and beyond the scope of this thesis.

Glucocorticoid Adverse Effects

Soon after GCs were introduced into clinical practice for their anti-inflammatory effects, their many AEs were also recognised and described. AEs associated with GC use are listed below, in Table 1.2 (36).

Table 1.2. Glucocorticoid Adverse Effects

Dermatological	**Musculoskeletal**	**Endocrine and metabolic**
Thin/fragile skin	Osteoporosis	Weight gain
Easy bruising	Fragility fractures	Moon-like facies
Acne	Avascular necrosis	Truncal obesity
Striae	Proximal myopathy	Buffalo hump
Hirsutism	Tendon rupture	Diabetes
Alopecia	**Psychological**	Insulin resistance
Impaired wound healing	Sleep disturbance	Hyperglycaemia
Gastrointestinal	Agitation	Anovulation, irregular periods
Gastro-oesophageal reflux	Anxiety	**Infectious**
Peptic ulcer	Depression	Viral infections
Bloating	Irritability	Bacterial infections
Nausea/vomiting	Euphoria	Increased frequency
Colitis	Poor concentration	Increased severity
Pancreatitis	Hyperactivity	Atypical infections
Increased appetite	Reduced libido	Skin infections
Cardiovascular	Psychosis	Thrush- oral, vaginal
Hypertension	**Ophthalmological**	**Other**
Dyslipidaemia	Cataract	Altered taste
Atherosclerosis	Glaucoma	Voice hoarseness
Cardiovascular disease	**Neurological**	
Palpitations	Tremor	
Fluid retention	Headache	
Peripheral oedema	Vertigo	
	Dizziness	
	Tinnitus	

Modified from Hoes et al, Ann Rheum Dis 2009

In the general population, GCs account for 2.5% of all adverse drug reactions leading to hospital admission (37). GCs use is also known to be associated with increased mortality (38-40). In rheumatology, clinical guidelines advocate for short-term use of low dose GCs (41-43), an acknowledgment that longer duration of therapy and higher dosages are associated with increased risk of developing certain AEs such as infection (44). Indeed, the concept of a 'steroid-sparing agent' reflects a recognised need to limit exposure to GC adverse effects.

The first recommendation from the European League against Rheumatism (EULAR) guidelines for the use of systemic GCs in rheumatic diseases is that the potential harms of GCs be discussed with patients prior to therapy (45). However, while GC AEs are well described in the literature, the evidence quantifying these harms is often lacking. The impact of dose, duration of therapy and how recently GCs were used is largely unknown for many GC AEs. Recent work looking at infection and diabetes has used novel statistical methods to better define GC exposure and address some of these unanswered questions (44, 46).

Balancing the benefits and harms of glucocorticoid treatment

The balance between the benefits and harms of treatment, underpins all medical management. Four key aspects of any benefit and harm have been described, including: 1. Its nature, described by its quality, intensity, and time course (onset, duration, and reversibility), 2. The probability that it will occur, 3. Its importance to the person experiencing it, and 4. How the benefit can be maximised, or the harm prevented or minimised (47). To ensure shared decision making, clinicians must be able to communicate to patients the potential benefits and harms of a given treatment so that informed therapeutic decisions can be made. This is dependent not only on the four elements of the risks and benefits of a given therapy being known, but also on the clinician's ability to understand and communicate risk and the patient's ability to understand this information (48).

Like all medications, the decision to treat with GCs is based on an assessment of the benefits of treatment, weighed against the potential harms of GC AEs (47). In some circumstances, this decision is clear-cut because the condition being treated is either life or organ-threatening and GCs are the only viable treatment option. An example is GCA, a form of vasculitis that primarily affects the elderly. Patients with this condition are at risk of blindness if not treated with high doses of GCs, making the decision to treat with GCs relatively straightforward. In other conditions, such as RA, the use of GCs is more controversial.

1.3 Glucocorticoid Use in Rheumatoid Arthritis

Rheumatoid Arthritis

RA is a chronic inflammatory arthritis that affects approximately 0.5-1% of the population worldwide (49, 50). It classically presents as a symmetrical polyarthritis which often begins in the small joints of the hands and feet, however it can affect all peripheral joints as well as the cervical spine. In Australia, the prevalence of RA is 2% (1.7% in females, 1.4% in males), based on self-reported data from the Australian Bureau of Statistics 2014-2015 National Health Survey (51). Inflammation of the joint synovium leads to the acute symptoms of joint pain, swelling and stiffness, while the long-term consequences of untreated persistent inflammation include joint damage and deformity. RA was the first condition in which GCs were shown to be effective as anti-inflammatory agents over 60 years ago and are still commonly used as therapeutic options today. However, the treatment of RA has evolved dramatically since Hench and Kendall first discovered the effectiveness of GCs. The recognition of the need for early diagnosis and treatment within a 'window of opportunity' has altered the course of the disease significantly, and disease deformity is now less common. Treatment options for RA have grown exponentially, and include conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs) and new targeted synthetic DMARDs (tsDMARDs)(52). With the recent development of biosimilar bDMARDs, these can now be divided into bio-original (boDMARDs) and biosimilar (bsDMARDs). The different DMARD categories, medications and mechanisms of action are shown below in Table 1.3.

Table 1.3: Disease Modifying Anti-Rheumatic Drugs, Categories and Mechanisms

DMARD Category	Medications	Mechanism of Action
csDMARDs	*Still commonly used in RA*	
	Methotrexate	Purine metabolism inhibitor
	Sulfasalazine	Suppression of IL-1 & TNF-alpha, induces apoptosis of inflammatory cells and increases chemotactic factors
	Hydroxychloroquine	Suppression of TNF-alpha, induces apoptosis of inflammatory cells and decreases chemotaxis
	Leflunomide	Pyrimidine synthesis inhibitor
	No longer commonly used in RA	
	IM Gold injections	Unknown, inhibits antigen processing by macrophages
	Penicillamine	Reduces numbers of T-lymphocytes
	Chloroquine	Suppression of IL-1, induces apoptosis of inflammatory cells and decreases chemotaxis
	Cyclosporine A	Calcineurin inhibitor
	Azathioprine	Purine synthesis inhibitor
bDMARDs	Abatacept	T-cell costimulatory signal inhibitor
	Anakinra	IL-1 receptor antagonist
	Adalimumab	TNF inhibitor
	Etanercept	TNF inhibitor
	Golimumab	TNF inhibitor
	Infliximab	TNF inhibitor
	Rituximab	Anti-CD20 (B-cell) monoclonal antibody
	Tocilizumab	IL-6 receptor antagonist
tsDMARDs	Tofacitinib	Janis kinase (JAK) inhibitor
	Baracitinib	JAK inhibitor

Inflammation in Rheumatoid Arthritis (RA)

RA is thought to develop as a result of an underlying genetic predisposition, such as the HLA-DRB1 shared epitope, combined with a number of environmental triggers which may include smoking, periodontitis and alterations to the gut microbiome(53). RA is an autoimmune disorder in which joint inflammation(synovitis) is often (but not always) triggered by autoantibodies including rheumatoid factor (RF) and antibodies to citrullinated peptides (ACPA) (53). These autoantibodies have been shown to precede clinical RA by an average of 3-5 years (54). Synovitis occurs when leukocytes accumulate in the synovial compartment due to cell migration. The cellular composition of synovitis in RA includes both innate immune cells (monocytes, dendritic cells, mast cells and innate lymphoid cells) and adaptive immune cells (T-helper-1 and T-helper-17 cells, B cells, plasmablasts and plasma cells) (55). This mix of inflammatory cells in the synovial compartment is regulated by a complex network of cytokines and chemokines, including pro-inflammatory mediators, like tumour necrosis factor alpha (TNFα) and interleukin 6 (IL-6) (56). Activated fibroblasts, together with the accumulated immune cells, trigger osteoclast generation via the interaction between receptor activator of nuclear factor κB ligand (RANKL) and its receptor RANK (57). This results in bony erosions, which form at the junction between cartilage, periosteal synovial membrane insertion and bone.

GC anti-inflammatory effects in RA

GC treatment has multiple cell-specific anti-inflammatory effects in RA (58). T-cells play a central role in the pathogenesis of RA, as evidenced by the high levels of T cells in inflamed synovium(59). GCs are thought to reduce T-cell induced inflammation via a number of mechanisms, including inhibition of T-cell cytokine production and a reduction in the number of activated T-helper cells (TH1 and TH17) (58). B-cells have an important role in the pathogenesis of RA, producing autoantibodies against citrullinated proteins, forming aggregates at sites of inflammation in bone, synovium and cartilage and they are also the predominant antigen presenting cell in the late stages of the disease (60). The actions of GCs on B-cells are not well understood, with conflicting studies on their ability to suppress B-cell production of immunoglobulin-G (IgG). In the early phase of RA, antigens are presented by dendritic cells. Glucocorticoids induce apoptosis of immature dendritic cells and also inhibit dendritic cell migration, differentiation, maturation and antigen presentation (58). Macrophages also play an important role in the aetiology of RA, with the number of macrophages markedly increased in patients with RA compared to healthy individuals (53). In RA, GC therapy is associated with a substantial decrease in the number of macrophages in synovial tissues. GCs also induce an anti- inflammatory macrophage phenotype, characterised by increased phagocytosis, decreased adhesiveness and reduced expression of classical

pro-inflammatory cytokines such as TNF, IL-1β and IL-6 (58). GCs also increase osteoclast maturation, but inhibit osteoblast proliferation and can induce apoptosis or autophagy of these cells (58).

GC use in RA

GCs are used in approximately 60% of patients with RA worldwide (61). They have been shown to have disease modifying properties (62, 63), however there was significant heterogeneity in the dosage protocols used in these efficacy studies, with starting doses as high as 60mg used in some studies, compared to low doses of 5mg daily used in other studies (64), Table 1.4. Furthermore, there are concerns about the long-term use of GCs in RA, due to their significant AE profile (65, 66), and the availability of many effective, alternative therapies. For this reason, international guidelines recommend that the lowest possible dose and duration of GC therapy be used, usually in the setting of newly diagnosed active disease or disease flares (67, 68). However, many still advocate for the long-term use of low dose oral GCs in RA, arguing that the disease modifying benefits outweigh the potential harms, which can often be medically managed (63). With manuscript titles such as 'Resolved: low dose prednisolone is indicated as a standard treatment in patients with rheumatoid arthritis' (69) and 'Resolved: low-dose glucocorticoids are neither safe nor effective for the long-term treatment of rheumatoid arthritis' (70) appearing alongside each other in the same issue of the same journal, it is clear that the question surrounding the role of GC use in RA is not resolved.

Table 1.4 GC Protocols in RCTs of GC Efficacy in RA

Study name and details	Protocol in GC-treatment group
ARC Kirwan et al. (1995)(71) 2 year study, *n*= 128 (glucocorticoid, 61; control, 67)	7.5 mg predniso(lo)ne, with any DMARD
COBRA Boers et al. (1997) (72) 80 week study, *n* = 155 (glucocorticoid, 76; control, 79)	60 mg predniso(lo)ne tapered to 0 mg over 28 weeks, with methotrexate, sulfasalazine
BeSt Goekoop-Ruiterman et al. (2007) (73) 2 year study, *n*= 508 (glucocorticoid, 133; control, 375)	60 mg predniso(lo)ne tapered to 0 mg over 28 weeks, with methotrexate, sulfasalazine
Hansen et al. (1999) (74) 1 year study, *n*= 102 (glucocorticoid, 51; control, 51)	Median 6 mg predniso(lo)ne, with any DMARD
FIN-RaCo Mottonen et al. (1999) (75) 2 year study, *n*= 195 (glucocorticoid, 97; control, 98)	Median 5 mg predniso(lo)ne for ≥9 months, with sulfasalazine, methotrexate, hydroxychloroquine
van Everdingen et al. (2002) (76) 2 year study, *n*= 81 (glucocorticoid, 41 control, 40)	10 mg predniso(lo)ne, no DMARD (sulfasalazine rescue after 6 months)
TICORA Grigor et al. (2004) (77) 1.5 year study, *n* = 110 (glucocorticoid, 55; control, 55)	Intra-articular GCs were administered to each swollen joint as therapy with each new DMARD begun, oral GCs as part of step-up protocol, with sulfasalazine, methotrexate, hydroxychloroquine, cyclosporine
WOSERACT Capell et al. (2004) (78) 2 year study, *n*= 128 (glucocorticoid, 61; control, 67)	7 mg predniso(lo)ne, with sulfasalazine
LDPT Wassenberg et al. (2005) (79) 2 year study, *n*= 76 (glucocorticoid, 34; control, 42)	5 mg predniso(lo)ne, with intramuscular gold or methotrexate
BARFOT Svensson et al. (2005) (80) 2 year study, *n*= 258 (glucocorticoid, 119; control, 139)	7.5 mg predniso(lo)ne, with any DMARD
CARDERA Choy et al. (2008) (81) 2 year study, *n*= 376 (glucocorticoid, 131; control, 236)	60 mg predniso(lo)ne tapered to 0 mg over 34 weeks, with methotrexate or methotrexate and ciclosporin

Modified from Hoes et al. Nature Reviews Rheumatology, 2010 (64)

Given the multitude of treatment options and poorly defined role of GCs in the management of RA, the question arises as to how GCs are actually used to treat RA in 'real-life' clinical practice and what factors influence this? Concern about GC AEs is well-described in the literature, and it is likely that certain patient characteristics such as age, comorbidities and concurrent therapies might affect GC prescribing and use to differing extents. The divided opinions about GC use in RA, also highlighted in the literature, suggest that different prescribers may have vastly different values surrounding GC use and therefore the patient characteristics that influence one prescriber might differ from those that influence another. To expand these questions further, it also worth considering factors that influence whether GCs are commenced or ceased.

Rheumatologists are generally divided as to whether GCs should be used regularly as disease modifying agents, or more sparingly to treat disease flares (82). These differing clinician attitudes are well documented in the rheumatology literature and are in part driven by evidence gaps, particularly the quantification of risks associated with GC use and how these risks vary with differing levels of exposure, including dose, duration and timing of GC treatment (82). Patients and clinicians also place their own value judgements on GCs (82). For clinicians, their value judgements may be based on past experience with GCs, and for patients this may be influenced by the opinions of their doctors, family, friends and the media (83). As well as having different value judgements to their doctors, patients are likely to vary in how they weight the benefits and harms of treatment depending on their attitudes to risk, with some patients more benefit driven and others more risk-averse (84). Patient preferences are therefore an important consideration in the assessment of the benefits and harms of glucocorticoid treatment. How patients' preferences can be usefully captured in research and clinical settings remains challenging, particularly as eliciting preferences for GC safety is time consuming, taking over two hours per subject in a research study (85).

1.4 Glucocorticoids and Patient Reported Outcomes

In addition to discussing benefits and potential harms prior to commencing treatment, it is also important to assess and measure these benefits and harms in both clinical care and research settings. In particular, it is important to capture these outcomes from the patient perspective. Patient reported outcomes are now recognised as important indicators of quality research and clinical care, and as a consequence, the need for well-designed and validated PROs has arisen (86, 87). Numerous organisations now exist, with the purpose of bringing appropriate patient, clinician, research and industry

representatives together to develop PROs. In the field of rheumatology, OMERACT fulfils this role, with the aim to improve and standardise outcome measures in rheumatology. A key principle of OMERACT is patient involvement and there is integration of patient stakeholders in every stage of the OMERACT process (88). A current project within OMERACT is the development of a PRO for GCs, which will allow the benefits and harms of treatment to be measured from the patient perspective.

OMERACT- Outcome Measures in Rheumatology

OMERACT is an international organisation made up of an executive committee, steering committee and individual working groups which include a chair, co-chair, fellow, patients, clinicians, researchers, industry representatives and policy makers. The work of OMERACT is facilitated by the working group participants who provide input on the development of the OMERACT research agendas. The research agendas focus initially on developing a core domain set, and later on selecting measurement instruments. OMERACT have developed a number of tools to ensure these processes are consistent and evidence based. These tools include the 'OMERACT onion' for domain selection, 'the OMERACT way' for instrument selection and the OMERACT Filter 2.0 (89).

OMERACT emphasises the measurement issues to consider when selecting an instrument include truth, discrimination and feasibility. Truth refers to whether the measurement instrument actually measures what it intends to, covering issues of face, content, construct and criterion validity. Discrimination refers to whether the instrument can distinguish between situations of interest, capturing the instrument's reliability and sensitivity to change. Feasibility is about whether the measurement instrument can be applied easily, given constraints of time, money, and interpretability. This criterion addresses the pragmatic reality of using the measurement instrument (90).

OMERACT have run biennial consensus conferences since 1992. At each meeting there are educational sessions, special interest groups (SIGs) and workshops, as well as specialised programs for patients, fellows and returning-fellows. SIGs allow the international members of a working group to come together and discuss the research that has been carried out to date as well as the ongoing research agenda. Workshops bring the whole OMERACT community together to vote on the different stages of defining core outcomes and developing measurement instruments, with the aim of achieving consensus.

The spirit of OMERACT is described by the 8 C's (90):

1. Consensus-commitment
2. Communication- respectful across 5Ps stakeholders, especially patients
3. Collaboration- truly participatory across all disciplines/sectors, international representation
4. Critical- evidence driven
5. Careful/conscientious- apply critical thinking, systematic
6. Concrete outcomes- e.g. OMERACT Filter; Core Sets
7. Continuous Learning- updated methods and core sets
8. Continuity- Planned succession through Fellowship Program

Need for a patient reported outcome measure for GC use

A EULAR taskforce on GC therapy has published two systematic reviews concluding that there is a need to systematically capture GC-AEs in a standardised manner (45, 91). In addition, EULAR recommendations for GC monitoring suggest new tools are required (92), supporting the need for the development of instruments to measure the outcomes of GC therapy across a wide range of indications.

This has led to the recent development of the glucocorticoid toxicity index (GTI), which measures the physiological AEs of systemic glucocorticoid use, and includes items such as BMI, glucose tolerance, blood pressure, lipids and bone density, among others (93). However, discordance between rheumatologists and patients regarding GC AEs suggests that the physiological AEs important to clinicians may not be of highest importance to patients (85, 94). Therefore, development of a PRO that specifically measures the impact of GC use on patients' quality of life and experience, would be complementary to the GTI (95).

At OMERACT 2014, members of the PMR working group noted that many of the issues that were important to patients with PMR, were in fact related to their treatment with GCs. It was also recognised that many of these treatment outcomes cannot currently be measured. This led to the formation of the GC working group, which met for the first time at OMERACT 2016 and again at OMERACT 2018. The group has undertaken a body of qualitative and quantitative work to better understand the benefits and harms of GC therapy from the patient perspective, that will ultimately lead to the development of a GC PRO. Some of the first unanswered questions to address in this process were: how frequently do patients report having experienced different GC AEs, which of these AEs do patients experience as the worst AEs, do patients feel GCs help their disease and do they feel that the benefits of treatment outweigh the harms?

1.5 Glucocorticoid Related Eye Disease

Another aspect of GC use that is important to patients, that has had relatively little attention is eye disease. Cataracts and glaucoma are frequently listed as GC related AEs and while the literature surrounding their development in the setting of ophthalmic GC use is fairly comprehensive, they appear far less frequently in the oral GC literature, particularly in comparison to other GC AEs such as infection, diabetes, osteoporosis and fractures. Cataracts and glaucoma are the leading cause of blindness worldwide (96) and account for significant disability and healthcare related costs (97, 98). The incidence of cataracts and glaucoma increases with age (99-101) but the impact of GC use on the background incidence has not been well described, making it difficult to properly inform patients of the potential eye-related harms of GC therapy. For patients to be properly informed, a more detailed understanding of how GC use impacts the development of cataracts and glaucoma is required, including the influence of dose, duration of treatment and the timing of treatment (44).

1.5.1 Cataracts

A cataract is an opacity of the lens of the eye, which prevents light from passing through the lens and reaching the retina. Cataracts are the leading cause of blindness worldwide (51%) (102) and the second most common cause of vision impairment in Australia (97). They are associated with significant disability and cost to the healthcare system, with estimates approximating Aus$1 billion per year (97). The Australian-based Blue Mountains Eye Study (BMES) found the 10-year cumulative incidence of cataracts to be 54%, compared to 38% in the Beaver Dam Eye Study (BDES) based in Wisconsin, USA. However, age and gender-matched cumulative incidence rates were very similar with a 10-year cumulative incidence of 77% (BMES) and 75% (BDES) in those aged 65-74 years and 87% (BMES) and 88% (BDES) in those aged over 74 years. In both studies there was a statistically significant increase in cumulative incidence with increasing age ($P<0.0001$) (99, 100).

Globally, cataracts are the leading cause of blindness in those aged 50 years and older. Cataracts accounted for 35% of blindness and 25% of vision impairment in adults aged 50 years and older in 2015. However, there are large differences in the causes of blindness by region in this age group. In 2015, the proportion of blindness in those aged 50 years and older attributable to cataract ranged from <22% in high- income subregions to more than 44% in southeast Asia and Oceania (96).

Classification of cataracts

Cataracts can be defined according to their age of onset, with congenital cataracts present from birth, infantile cataracts developing in childhood and age-related/senile cataracts developing in adulthood, usually after the age of 40. There are three main subtypes of age-related cataract, including nuclear cataracts, cortical cataracts and posterior subcapsular cataracts (PSCs).

Nuclear sclerosis involves the diffuse yellowing and hardening of the entire central nucleus of the lens and tends to worsen gradually over time. Cortical cataracts involve the fibres at the periphery of the lens, with the opacification occurring in a spoke-like manner. They tend to be relatively asymptomatic until advanced, when the opacification spokes extend to the nucleus and interfere with light passing through the centre of the lens. Posterior subcapsular cataracts are caused by a granular layer of cells between the lens and its capsule. They are often the most debilitating form of cataract due to unbearable glare and often occur at a younger age compared to nuclear and cortical cataracts. Other causes of cataract include traumatic cataracts (due to blunt or penetrating eye injuries, electrocution, chemical burns or radiation exposure) and metabolic cataracts (occur secondary to diabetes, galactosaemia, Wilson disease or myotonic dystrophy).

Cataract Symptoms and Risk Factors

The symptoms of cataracts are described below in Table 1.5.

Table 1.5. Cataract Symptoms

Symptoms	Details
Blurred vision	Blurred or cloudy vision
Glare	Halos or streaks around lights
	Difficulty seeing in the presence of bright lights
Difficulty seeing in low light	Including poor night vision
Loss of ability to discern colours	Fading or yellowing of colours
Increasing myopia	Including a “second sight” phenomenon where vision improves in those with pre-existing hyperopia
Monocular diplopia	Uncommon, can occur with nuclear sclerotic cataracts

Risk Factors for developing cataracts include (103, 104):

- Increasing age
- Diabetes or hyperglycaemia
- Glucocorticoid use
- Ultraviolet exposure
- Smoking
- Excessive alcohol intake
- Obesity
- Ocular diseases: Retinitis Pigmentosa, Uveitis
- Ocular Trauma
- Prior ocular surgery
- Genetic predisposition

Treatment of cataracts- cataract surgery

The progression of age-related cataracts is variable and unpredictable. Untreated, most people with a cataract will develop severe visual impairment (105). There is no set level of visual acuity for which surgery is indicated, instead referral for cataract surgery is considered when there is visual impairment caused by the cataract, and the person's lifestyle is affected (eg. driving, reading), and the person wants to undergo surgery (105). Poor eyesight affects the ability of people to live independently and places them at risk of falls and preventable injuries (106). Benefits of surgery include improved visual acuity, improved clarity of vision and improved colour vision. Cataract surgery is the most common elective surgical procedure in Australia (107). It involves replacing the lens with a clear, permanent, artificial lens. In Australia, 90% of cataract operations are performed in people aged 60 years and over, with only 1% performed in those under 40 years of age (108). In 2014–15, the Australian cataract surgical rate was 2,138 hospitalisations per 100,000 people aged 40 years and over (108). The prevalence of PSCs is reported to be 5-15% of all cataracts (100, 109, 110), however the PSC subtype accounts for up to 40% of cataracts requiring surgery (111).

GC induced cataracts

Glucocorticoid- induced cataracts were first described by Black *et al* in 1960, and were recognised specifically as PSCs (112). In this study, 17 out of 47 patients treated with systemic GCs for RA developed bilateral PSCs, with PSCs appearing after approximately one year of GC treatment. No PSCs were found in the 19 patients who did not receive GCs. There appeared to be a dose-related response, with PSCs found in 29% of those on moderate doses of GCs (12.5-25mg/day prednisolone) compared to 75% of those receiving high doses (>25mg/day prednisolone). However, this was the first of a number

of early cross-sectional studies limited by their design in their inability to capture the effect of dose and duration of treatment over time. Systemic GCs (112), inhaled GCs (113-115) and GCs administered to the eye topically (116, 117) or via injection (118-121) have been shown to be associated with the development of PSCs. However, the results of these studies are often conflicting, for example in the Blue Mountain Eye Study (BMES) there was an association between current GC use and PSCs (OR 4.11, 95%CI 1.67–10.08) and nuclear cataracts (OR 3.45, 95% CI 1.26–9.43) but not cortical cataracts (OR 1.08, 95%CI 0.44–2.64)(122). In comparison, the Beaver Dam Eye Study (BDES) found GC use was associated with an increased incidence of cortical cataracts (OR 2.59, 95%CI 1.45–4.62) but not PSCs (OR 1.27, 95%CI 0.42–3.86) or nuclear cataracts (OR 1.41, 95%CI 0.77–2.56) (123). Very few studies have looked at the effect of dose, duration and/or the timing of GC use on the development of cataracts (124-127), and there has been no systematic review or meta-analysis to summarise and quantify these effects. It is well recognised that observational research is an ideal platform to explore long-term safety outcomes. A well-designed observational study that captures 'real-life' GC use over time, would be the ideal setting in which to address these unanswered questions relating to the development of cataracts. In addition, careful selection of analyses and modelling of time-varying GC exposure including dose, duration and timing of therapy is needed in order to capture some of the complexities of GC use.

Potential mechanisms of GC induced cataracts

A number of potential mechanistic pathways involved in the development of GC-induced PSCs have been investigated, including: 1. The role of the GC receptor in lens cells, 2. Lens epithelial cell migration, 3. Growth factors, 4. GC modifications to signal transduction and 5. Oxidation and lens hydration. The lens contains GC receptors (128, 129) that are functional and able to induce or repress gene transcription(128, 130). DNA microarray studies in cultured lens epithelial cells exposed to GCs have indicated that a broad range of transcripts are up- or down-regulated compared to unexposed cells, however only two transcripts were altered at all time points looked at in these studies (4h, 16h, 24h and 48h) (129, 130). These transcripts were for GILZ and plasminogen activator inhibitor-1 (PAI-1). These proteins have been shown to have diverse roles in different cell types, however their role in GC treated lens epithelial cells is not yet known.

Lens epithelial cells can be found underlying the lens capsule anterior to but not posterior to the lens equator. This narrow band of epithelial cells at the lens equator, proliferate and differentiate into fibre cells, enabling the lens to grow slowly throughout life as these new lens fibres are added to the cortex. This process is ordered and

carefully regulated (131). In PSC, the proliferation and differentiation of lens epithelial cells appears to be disrupted, with histologic studies of GC-induced PSC describing the migration of these cells at the posterior lens pole (132). It is not yet known if GCs have a direct effect on lens epithelial cells or whether this is an indirect effect due to changes in intra-ocular growth factors (133).

Jobling and Augusteyn (134) were the first to propose that changes in intraocular growth factor may play a role in the development of GC-induced PSCs. A number of growth factors are known to play a role in the regulation of epithelial cell differentiation into lens fibre cells, including fibroblast growth factor-2 (FGF-2), insulin-like growth facto -1 (IGF-1), epidermal growth factor (EGF), transforming growth factor-beta (TGF-β), lens epithelium derived growth factor (LEDGF), platelet derived growth factor (PDGF) and bone morphogenetic proteins (BMPs).The effects of GCs on ocular levels of growth factors is unknown but it has been hypothesised that because GCs can modify the production of growth factors in other cell types, they may also disrupt the balance of growth factors within the ocular compartments.

Glucocorticoid modifications to signal transduction in lens epithelial cells has also been proposed as a potential mechanism, based on studies that show GCs modify signal transduction in other cell types (135-137) and limited DNA array data with lens epithelial cells (128). Growth factor activity is primarily mediated through cell surface receptors that signal via mitogen-activated protein kinase (MAP kinase) and phosphoinositide-3 kinase (PI-3 kinase) signal transduction pathways. Growth factors activated by these pathways include serum glucocorticoid kinase (SGK), which is upregulated in lens epithelial cells by GC treatment (128). SGK can also promote cell survival by protecting cells against apoptosis (138). Cells obtained from human PSCs, exhibit a reduced propensity to undergo apoptosis when stimulated by staurosporine (139). These observations suggest that GC treatment may cause an anti-apoptotic response in lens epithelial cells, suppressing the differentiation of lens epithelial cells at the equator and promoting their proliferation (133).

Finally, two general mechanisms thought to play a role in the formation of cataracts are oxidation of lens proteins and disruption of the level of lens hydration (133). Some studies have suggested that GC molecules form covalent adducts with lysine residues of lens particles leading to oxidation of lens proteins and opacities (140, 141). However, other studies do not support this hypothesis (142, 143). Altered lens hydration may contribute to age-related and diabetic cataracts (144), and some have hypothesised that steroids inhibit the sodium-potassium pump (Na/K pump) in the lens epithelium,

leading to the accumulation of water within the lens fibres and agglutination of lens proteins (145). In support of this, systemic GC treatment has been shown to directly affect the expression of NA/K-ATPase pumps and intracellular fluid balance in other cell types (146, 147), and levels of NA/K-ATPase transcript were increased at 48 hours in GC treated lens epithelial cells (130).

1.5.2 Glaucoma

Along with cataracts, glaucoma is also recognised as a GC-associated eye disease. Glaucoma is a form of optic neuropathy, which occurs when the trabecular meshwork becomes blocked and aqueous humour is unable to drain. The subsequent increase in intra-ocular pressure (IOP) leads to pressure on the optic nerve and small nerve fibres of the retina causing visual impairment and visual field defects. Glaucoma accounts for 8% of blindness worldwide and is the second leading cause, after cataract (102). The prevalence of glaucoma cited in two Australian population-based studies is 3% (148, 149). Glaucoma accounts for 1.49% and 0.55% of vision impairment in non-Indigenous and Indigenous Australians, respectively (150).

Classification of glaucoma

Glaucoma can be classified into two broad categories, angle-closure glaucoma and open angle glaucoma (OAG), both of which can be primary or due to secondary causes (151). Primary angle closure glaucoma may be acute, chronic or intermittent (151). Primary open angle glaucoma (POAG) may be either high pressure or normal pressure (151). The term ‘glaucoma suspect’ describes an individual with an ocular finding that puts them at risk of developing POAG. It can be defined as an adult who has one of the following findings in at least one eye (152):

1. An optic nerve or nerve fibre layer defect suggestive of glaucoma (enlarged cup–disc ratio, asymmetric cup–disc ratio, notching or narrowing of the neuro-retinal rim, a disc haemorrhage, or suspicious alteration in the nerve fibre layer)
2. A visual field abnormality consistent with glaucoma
3. An elevated IOP greater than 21 mmHg

If two or more of these findings are present, the diagnosis of POAG is supported. Diagnosis of a ‘glaucoma suspect’ is also dependent on a normal open angle on gonioscopy (152). This involves the use of a gonio-lens in conjunction with a slit lamp to view the irido-corneal angle, the anatomical angle formed between the eye's cornea and iris (153). Ocular hypertension is defined by the following features (151):

- IOP > 21 mm Hg without treatment
- Visual field: normal
- Optic disc and retinal nerve fibre layer: normal
- Gonioscopy: open anterior chamber angle

Causes of secondary OAG include ocular diseases such as uveitis and neovascular (secondary to diabetic retinopathy), ocular trauma, and iatrogenic causes such as GCs, surgery and laser therapy (151).

Risk factors for open angle glaucoma

There are three large longitudinal studies which have investigated risk factors for OAG: the Barbados Incidence study of Eye Diseases (BISED) (154), the Melbourne Visual Impairment Project (VIP) and the Rotterdam Eye Study (RES) (155). The BISED studied the 9-year incidence of OAG in a sample of the African descent population in Barbados. The VIP studied the 5-year incidence (of 'probable OAG') in a sample of white patients in Melbourne, Australia and the RES studied the 6.5-year incidence in a sample of white patients in Rotterdam, Netherlands. The most important risk factors for OAG, seen consistently across all 3 studies were older age and baseline IOP ≥1mmHg higher than the average population(156), with the relative risk increasing by 4%-6% for each one year increase in baseline age and a 10-14% increased risk associated with higher baseline IOP. Family history of OAG was investigated in the BISED and VIP studies, however the results were conflicting, with a 2.6 fold increased risk seen in the BISED study but no significant increase in risk seen in the VIP study. In regards to comorbidities, systolic blood pressure was only reported in the BISED study and found to be associated with a 10% reduced risk of OAG per 10mmHg. Self-reported diabetes was included in all three studies and was not significant in any. Interestingly, GC use was not included in any of these 3 main studies.

GC-induced ocular hypertension and glaucoma

Steroid-induced ocular hypertension was first reported in 1950 when McLean (157) described an increase in IOP associated with the systemic administration of ACTH. Four years later, Francois was the first to report increased IOP caused by the local administration of cortisone to the eye (158). Increased IOP can occur as a consequence of oral, intravenous, inhaled, topical, periocular, or intravitreal GC therapy (121, 159-168). The mode of GC administration effects how rapidly IOP can rise, with the rise usually occurring over a period of weeks if GCs are used topically (169-171), compared to years, if used systemically (172). If the ocular hypertension is of significant magnitude, and not recognised and treated, subsequent GC-induced glaucoma can develop, a form

of secondary OAG. It is reported that IOP remains chronically elevated, converting to glaucoma in only a small subset of patients. In one series, 2.8% of eyes with GC induced ocular hypertension converted to glaucoma, and all affected patients had a family history of glaucoma (173).

Most studies describing GC induced ocular hypertension have quantified the increase in intraocular pressure associated with GC use, rather than addressing the question of risk, which is important when considering the benefits and harms of GC use. In the few studies that do address this question, the results have been conflicting. In a cross-sectional study of RA patients from 1969, only one case of glaucoma was seen among 148 oral GC users, with one case also seen among 159 non-users (174). Similarly, in a retrospective medical record review, one of 112 RA patients who received low dose GCs for >1 year developed glaucoma as did one of 112 matched RA patients not treated with GCs (175). In a German cohort of RA patients, no significant association was seen between prednisolone equivalent (PEQ) daily dose (categorised as PEQ <5mg, 5-7.5mg and >7.5mg) and the development of glaucoma (176). A case-control study using data from the Quebec universal health insurance program for the elderly, looked at the risk of developing ocular hypertension or OAG associated with oral GC use in patients aged 65 years or older (160). It found that GC current use (in the past 14 days) was associated with an increased risk of developing glaucoma (OR 1.41, 95%CI 1.22-1.63), but former use in the past 15-45 days (OR 1.18, 95% CI 0·87–1·62) or 46-365 days (OR 0·92, 95%CI 0·78–1·08) was not. It also showed that the risk increased with average daily dose (PEQ daily dose 0.4- <10mg OR 1.26, 10- <20mg OR 1.40, ≥20mg 1.88) and duration of continuous GC therapy of 3 months or more (3-5 months OR 1.63, 6-11 months OR 1.87, ≥12 months OR 1.52).

Risk factors for GC-induced ocular hypertension and glaucoma

Most of the studies looking at risk factors for GC-induced hypertension and glaucoma, focus on topical administration of GCs. This may in part be explained by the rapid increase in IOP with topical GCs compared to systemic treatment. Topical administration also allows for the other eye to act as the control. The concept of steroid responsiveness arose in the early studies of Becker (168) and Armaly (177-179), which looked at the IOP response to topical GC administration and classified responders as low, intermediate or high responders according to either their final IOP or change in IOP. Since then risk factors for steroid responsiveness have been investigated and extrapolated as risk factors for GC-induced glaucoma, but have not been confirmed in longitudinal studies. These risk factors are summarised below:

- Pre-existing POAG

  90% developed increased IOP >6mmHg after a 4-week course of topical dexamethasone 0.1% (180) and highly significant increases in IOP and decreased outflow facility were seen during a 2-4 week treatment course with topical betamethasone 0.1% (169)
- Glaucoma Suspect

  1/3 developed increased IOP >6mmHg after a 4-week course of topical dexamethasone 0.1% (180) and highly significant increases in IOP and decreased outflow facility were seen during a 2-4 week treatment course with topical betamethasone 0.1% (169)
- A first-degree relative with POAG

  Siblings (181) and offspring (182, 183) of those with POAG are more likely to be steroid responders compared to the general population
- Increasing age in adulthood (170)
- Exposure during childhood (particularly under age 6)(184)
- Autoimmune connective tissue diseases (M>F)

  34 patients with connective tissue diseases used dexamethasone drops 0.1% in one eye for six weeks. There was a higher incidence of positive steroid response than would be expected in a normal population. Most of the male patients were responders (185)
- Type 1 Diabetes Mellitus (186)
- High Myopia (187)
- Endogenous hypercorticolism (188)

Clinical features of GC-induced glaucoma

The clinical presentation of GC-induced glaucoma is indistinguishable from POAG, with the majority diagnosed when asymptomatic. The diagnosis is usually made during a routine eye test or as an incidental finding when presenting with another ophthalmic condition (e.g. diabetic retinopathy). Typically, patients only become symptomatic in late disease, when they may develop constricted visual fields or blurred vision. Occasionally, awareness of earlier visual field defects occurs when performing monocular tasks (such as using the viewfinder of a camera).

Potential mechanisms of GC-induced ocular hypertension and glaucoma

In this form of glaucoma, IOP is elevated primarily due to outflow resistance (189). Several theories have been proposed to explain how GCs impair aqueous outflow including:

1. GCs alter trabecular meshwork cell morphology by increasing nuclear transport of glucocorticoid receptors (GRs) (190).
2. GCs increase expression of extracellular matrix protein fibronectin, polymerised glycosaminoglycans, and elastin, leading to their accumulation in the trabecular meshwork, obstructing the outflow pathway (191-193).
3. The endothelial cells of the trabecular meshwork are phagocytic and can thus remove and destroy debris entering the meshwork from the anterior chamber. GCs are known to suppress this phagocytic activity, which may allow debris in the aqueous humor to accumulate and act as a barrier to outflow (194, 195).
4. GCs cause physical obstruction of the trabecular meshwork with pigmented, crystalline steroid particles (196).

Treatment of GC-induced ocular hypertension and glaucoma

Management options for GC induced hypertension and glaucoma include (197, 198):

- Cessation of GC treatment or dose reduction. In the majority of cases, an acute rise in IOP will normalise within days of discontinuing GC therapy, while more chronic forms take 1-4 weeks.
- Consideration of steroid sparing agents may be needed.
- In rare cases, IOP remains elevated after GCs are ceased and antiglaucoma medical therapy or surgery may become necessary. The duration of GC therapy may also influence the reversibility of the IOP elevation (199).
- Medical therapy may include topical beta blockers, prostaglandin analogues (latanoprost), alpha agonists (brimonidine) and carbonic anhydrase inhibitors (oral or topical).
- Surgery such as trabeculotomy or trabeculectomy are reserved for medically uncontrolled, intractable glaucoma.

1.6 Summary of the evidence gaps

In reviewing the literature, three main areas where the evidence for GC use was lacking or conflicting were identified:

1. The literature regarding oral GC use in RA is conflicting, with polarising views regarding dosing and long-term use. International guidelines advocate for the lowest possible dose to be given for the shortest duration of time, with other experts suggesting long-term use of low dose GCs, while many of the RCTs demonstrating that GCs have disease modifying effects in RA use protocols that include high dose GCs. With such variation in the literature, it is unclear how GCs are used in real-life clinical practice, how use is influenced by patient characteristics and whether this varies according to prescriber.

2. Another aspect of GC use that has received relatively little attention in the literature is the patient perception of the benefits and harms of GC use. The benefits and harms of GC therapy that are most important to patients often differ from those most important to doctors. In addition, the value judgements patients and doctors place on these benefits and harms can also vary. Patient reported outcomes are important quality indicators in research and clinical practice and play an important role in any assessment of the benefits and harms of treatment. It is therefore important to develop a PRO that will provide a standardised and validated means of measuring the benefits and harms of GC use, from the patient perspective. In order to develop such a PRO, it is necessary to first gather data on how patients treated with GCs perceive the benefits and harms of their treatment.

3. GC related eye disease, including cataracts and glaucoma, is another area under-represented in the GC literature. Cataracts and glaucoma were recognised as AEs of GC use soon after GCs were introduced as therapeutic agents over 60 years ago, however the risks have not been well quantified with conflicting results seen in the existing literature. In addition, the impact of dose, timing of dose and cumulative dose has not been clearly defined. GCs are commonly used in the treatment of RA, but there are a multitude of other treatment options available, making this an ideal condition in which to explore these unresolved questions.

1.7 Research Aims

The aims of this PhD were therefore as follows:

1. To describe the use of oral glucocorticoids and explore patient and prescriber factors that influence their use in rheumatoid arthritis in the UK (Chapter 3) and Australia (Chapter 4)
2. To better understand the benefits and harms of glucocorticoid use from the patient perspective (Chapter 5)
3. To determine whether the risk of cataract and glaucoma associated with glucocorticoid use in patients with rheumatoid arthritis can be quantified in a systematic review of the current literature (Chapter 6)
4. To quantify the risk of GC exposure and the development of cataract and glaucoma in RA and to explore the risk associated with different patterns of GC exposure, including dose, timing of dose and cumulative dose (Chapter 6)

2 Dataset Description and Methodological Challenges

The two datasets used to address research Aims 1 and 4 are described in detail below. Clinical Practice Research Datalink (CPRD) is a UK research database derived from anonymised primary care electronic medical records. CPRD was used for the work presented in Chapters 3 and 6. Australian Rheumatology Association Database (ARAD) is an Australian biologics registry. ARAD data was used for the work presented in Chapter 4.

2.1 CPRD- Clinical Practice Research Datalink

CPRD is an e-health research service that provides anonymised UK Primary Care health records for public health research. It was initially developed in London by a general practitioner, to facilitate the day-to-day management of his own general practice, in collaboration with IT staff at a shoe factory near to his practice. In 1987 Value Added Information Medical Products (VAMP) was established as a company to recruit other practices and form an information database. This initially small database grew and was donated to the Department of Health in 1993, at which time it became General Practice Research Database (GPRD). In 2012 it was expanded to allow for data linkage and re-launched as CPRD. Established linkages include Hospital Episode Statistics (hospitalisation data), Office for National Statistics6 (mortality data including causes of death), Index of Multiple Deprivation and Townsend scores (deprivation data) and disease registries including the National Cancer Intelligence Network, and the Myocardial Ischaemia National Audit Project (200).

The database benefits from the unique nature of the National Health Service (NHS) as essentially the single provider of health care in the UK. Over 98% of the UK population are registered with a primary care general practitioner (GP) and under the NHS, GP visits are free of charge (200). Each patient in the NHS has a unique patient identifier (NHS number), which can be used by a trusted third party for data linkage. This number is never released to researchers to ensure patient anonymity is always maintained. The NHS utilises a primary care gatekeeper approach to care, where patients require a referral from their general practitioner in order to access specialist care, hospital care and diagnostic tests (201, 202). As of March 2017, CPRD held data on >24 million patients from >800 GP practices. Studies have shown CPRD data to be representative of the UK population in terms of age and gender structure (203, 204), and validation

studies have demonstrated good completeness and accuracy of the data particularly for chronic diseases (205, 206).

Until recently CPRD collected data only from practices using Vision® practice management software, one of the most popular clinical systems used within primary care in the UK. This CPRD database is known as CPRD GOLD. In October 2017, CPRD launched a second database which collects data from practices using EMIS® Web, the most common software in UK primary care, used in 56% of English practices (207). This second dataset is known as CPRD Aurum, and as of September 2018, included 7 million patients who were alive and registered at contributing practices, representing around 13% of the population of England (208). A comparison of CPRD GOLD and CPRD Aurum is shown in Table 2.1.

Table 2.1. Comparison of CPRD GOLD and CPRD Aurum

	CPRD GOLD	**CPRD Aurum**
UK Countries participating	Consenting practices in England, Wales, Scotland and Northern Ireland	Consenting practices in England and Northern Ireland
Who is included?	>24 million patients from >800 GP practices using Vision® software	19 million patients from 738 GP practices using EMIS® Web software
What is recorded?	Demographics, diagnoses, symptoms, signs, prescriptions, referrals, immunisations, lifestyle factors, tests and results	Demographics, diagnoses, symptoms, signs, prescriptions, referrals, immunisations, lifestyle factors, tests and results
Period of data collection	From 1987 to present	From 1995 to present

Data Quality

CPRD has developed data quality markers over many years to account for variability between GPs and over time. They are designed to ensure logical consistency of patient registration data, complete longitudinal records and complete, continuous, plausible practice level data. There are two data quality markers used in CPRD: 1. The 'acceptability flag', which is an indicator of data quality at the individual patient level and 2. The 'up-to-standard' (UTS) date, which is an indicator of data quality at the practice level (209). Patient data are checked for a series of indicators that raise suspicion of poor data recording or identify non-continuous follow up. A patient is

flagged as unacceptable if any of these indicators are found. Criteria for acceptable patients are shown in Table 2.2.

Table 2.2: CPRD Criteria for Acceptable Patients

Criteria	Details
Gender	Must be valid (1=male, 2=female, 3=indeterminate)
Birth year	Must be present, no events prior to birth year
Age	Must be ≤ 115 at last collection date/transferred out date
First registration date	Must be on or after birth
Current registration date	Must be valid, on or after birth, on or after first registration date, permanent registration (not temporary)
Transferred out date	Must exist if there is a transferred out reason, must have a transferred out reason recorded, must be on or after the first registration date and the current registration date
Event dates	Must be 1 or more valid event dates (unacceptable if all event dates are invalid or missing)

The practice UTS date is the date from which practice data is deemed to be of research quality. It is based on two core criteria including: 1. Practice mortality rates must be within an expected range and 2. There is continuity in data recording within a practice. The first ensures that data is provided for patients who have died (patients haven't been deleted from the system), that deaths are being recorded and is a marker of irregularities in practice.

ISAC (Independent Scientific Advisory Committee) for MHRA (Medicines & Healthcare products Regulatory Agency)Database Research

ISAC is a non-statutory expert advisory body established in 2006 to provide scientific advice on research related requests to access data provided by CPRD. Members were appointed by the Department of Health Appointments Commission until 2015, and the MHRA now appoints members directly. The role of the committee is to review the scientific merit of proposals for research using CPRD data and safeguard patient confidentiality. ISAC approval was obtained for both CPRD projects included in this thesis, as detailed in the manuscripts.

Coding in CPRD GOLD

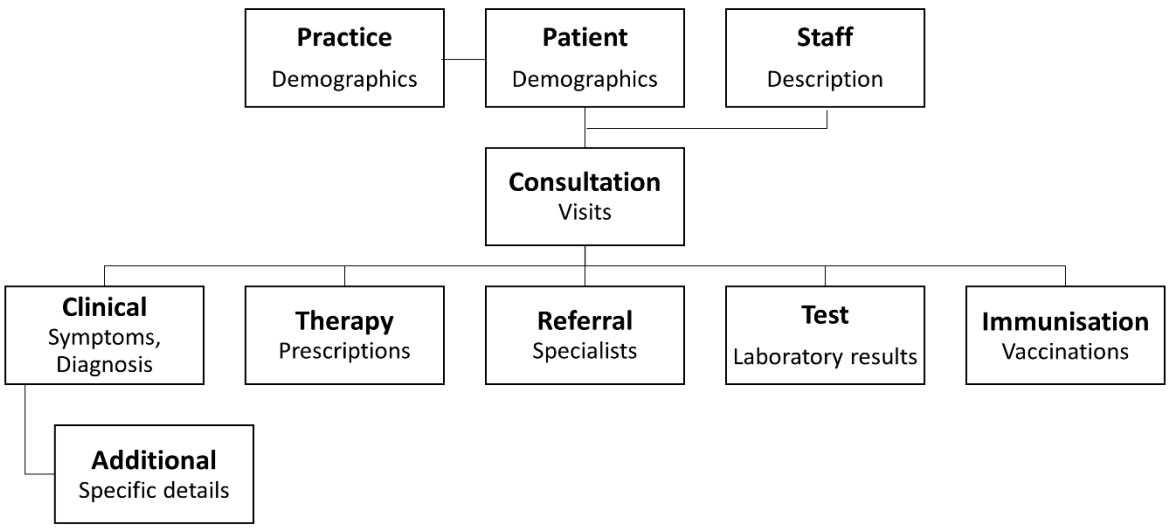
VISION and CPRD use Read codes (version 2), a hierarchical clinical classification system containing over 96, 000 codes. During a consultation, a GP, nurse, practice manager or administrator may enter a number of Read codes to describe a patient's symptoms,

diagnoses, lifestyle factors (such as smoking status), tests performed and therapy recommended. Prescriptions issued by the GP are automatically recorded with a product name, product code and British National Formulary (BNF) code, alongside the dosage instructions and quantity. Medical and Product Browsers available to generate Read and product code lists. The Medical Browser can search on Medical code, Read code or Read term. The Product Browser can search on Product code, Gemscript code, product name, drug substance name, BNF code and BNF header.

Database Structure and Files Provided

CPRD data is provided as a number of different files under the headings: clinical, additional clinical details, therapy, referral, test and immunisation. In addition, there are consultation, patient, staff and practice files containing demographic and visit details. Figure 2.1 depicts how the files fit within the database structure as described by Forbes *et al* (200). Due to the size of some of these files, some are provided in numbered sub-files that can then be merged. Relevant aspects of the main files can also be merged based on a single common variable. For example, the patient identification variable 'patid' can be used to merge the patient file with the clinical file and the Product code variable 'prodcode' can be used to merge the therapy file with the product file.

Figure 2.1 CPRD Database Structure (200)



2.2 ARAD- Australian Rheumatology Association Database

The Australian Rheumatology Association Database (ARAD) is an Australian biologic registry established in 2001. It collects patient-reported long-term safety, and other outcome data from patients with inflammatory arthritis, including RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS) and juvenile idiopathic arthritis (JIA) (210). It includes participants commenced on bDMARDS as well as controls on conventional treatments (enrolment of controls since Feb 2007), with recruitment occurring at any time after diagnosis. Participation is voluntary and rheumatologists refer patients to the registry with minimum baseline information required including diagnosis, RF and ACPA-status (ACPA collected since Nov 2010). In order to reflect real-life clinical practice, the diagnosis of participants included in the registry is based on expert clinical opinion (rheumatologist) rather than classification criteria. All participants, including controls, may commence, switch or cease bDMARDs at any point during their follow-up, as per their routine care.

Following written informed consent, participants complete a baseline ARAD questionnaire, with a follow-up questionnaire completed every 6 months for 2 years, then at 12-monthly intervals. The initial questionnaire is defined as the 'baseline' questionnaire and there are no exclusions for disease duration, prior therapies or associated comorbidities. The questionnaire was initially available only in paper-form, but an electronic version has been available since August 2009. Patients have the option to opt out of ARAD at any time or alternatively they may also convert to 'tracking only' status where they no longer complete questionnaires but agree to ongoing data linkage. The initial and follow up questionnaires collect an array of patient-reported data including:

- Demographic Data- level of education, employment status, marital status
- Smoking and alcohol consumption
- Medical Illnesses- checklist
- Cancer History-checklist and diagnosis dates
- Medical History- symptoms checklist
- Infection History- checklist, including mild, moderate or severe status
- Hospitalisations
- Weight

- Medications and other treatments for arthritis- bDMARDS, csDMARDS, oral prednisone/prednisolone, NSAIDS, analgesics, herbal or complementary medicines, joint surgery, cortisone injections (IV, IM, IA or tendon)
- Quality of life measures- HAQ, SF-36, AQOL, EURQOL
- Global evaluation of disease activity visual analogue scale (VAS) measures- amount of pain in the past week, overall arthritis activity in the past week

Oral GC data is collected on a checklist, along with other csDMARDs. Participants are asked to indicate if they have 'never taken', are 'currently taking', 'stopped taking' or 'don't know' prednisone/prednisolone. They are also asked to fill in the year the medication was commenced, any side effects (from a list of codes) and reason for stopping (also from a list of codes). ARAD does not collect information on dose and duration of therapy can only be inferred by looking at whether the patient is on prednisone/prednisolone from one questionnaire to the next. ARAD was initially established to track safety outcomes, in particular, infections and malignancies, but also other safety outcomes including death. These outcomes are captured in the questionnaire and can also be validated with data linkage to other registries including the PBS, cancer registry and death registry.

Access to bDMARDs in Australia

In Australia, there is universal access to medications via funding though the Pharmaceutical Benefits Scheme (PBS). bDMARDs have been available on the PBS since August 2004, and prior to this, were accessed through clinical trials. PBS prescribing of bDMARDs for RA, PsA, AS and JIA is restricted to rheumatologists. There are set criteria for each diagnosis, that must be met in order for a bDMARD prescription to qualify for PBS subsidisation. For RA, the criteria are as follows: 1. The patient has severe, active RA, 2. They have failed a 6-month intensive csDMARD trial with a minimum of two agents (including methotrexate) for a minimum of three months each, 3. The patient can demonstrate failure to achieve an adequate response to six months of intensive prior treatment by an elevated ESR >25mm/hr and/or an elevated CRP > 15mg/L and the patient has an active joint count of at least 20 active (swollen and tender) joints or at least 4 major active joints (elbow, wrist, knee, ankle, shoulder and/or hip). Similar prescribing criteria exist for PsA, AS and JIA.

2.3 Methodological Challenges

The specific methods for each study in this thesis, including a description of the population, exposures and outcomes are described in the manuscripts presented in

Chapters 3-6. This section of the thesis, describes in more detail some of the methodological challenges associated with the use of prescription data derived from electronic medical records (EMRs) such as CPRD.

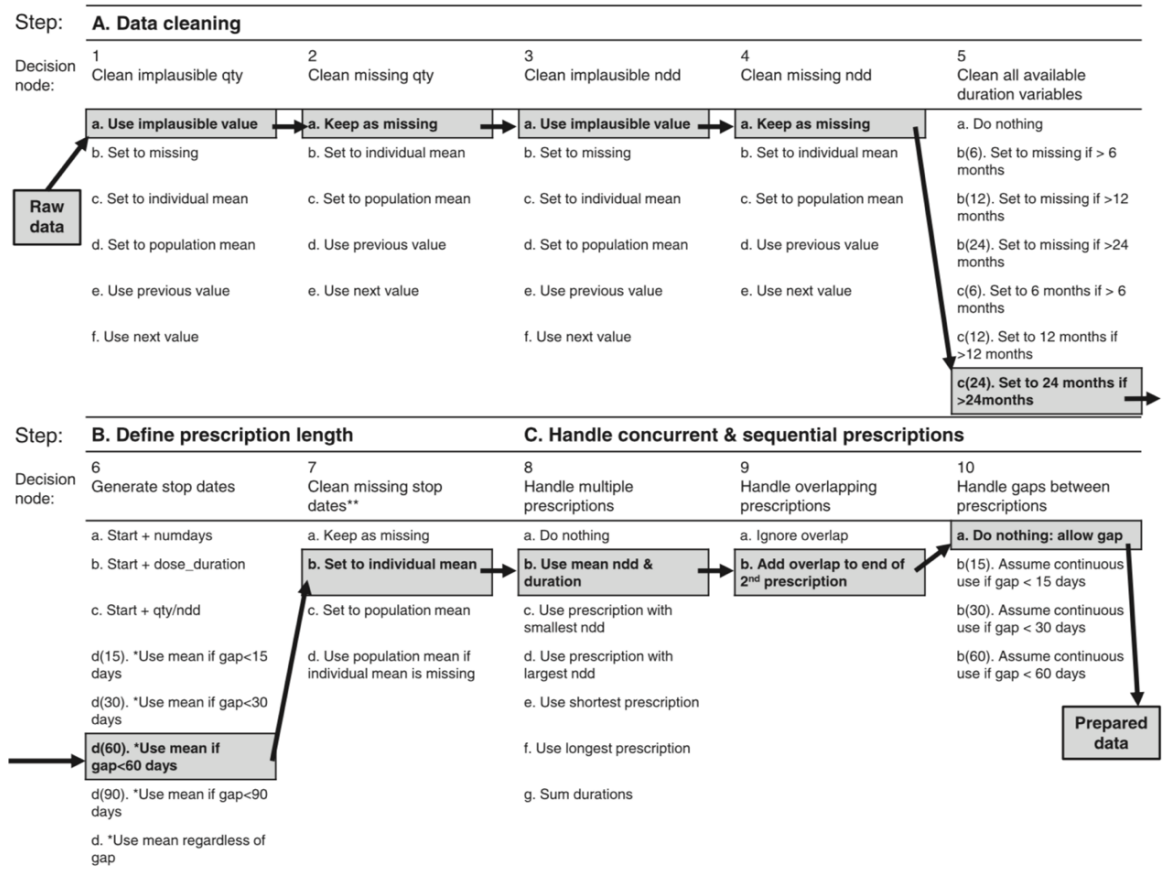
Glucocorticoid Prescription Data in CPRD

In Chapters 3 and 6, GC exposure was defined using prescription data from CPRD. Prescription information in CPRD is currently available in the 'therapy' and 'product' files, with a third 'textID' file previously available. Prescription data from the 'therapy' file includes the prescription date, numeric daily dose (ndd, number of tablets/units to be taken per day), the quantity (qty, total number of tablets prescribed) and the duration of therapy. Prescription data from the 'product file' includes the product code identifying the product used, the medication strength, formulation and route of administration. The 'text ID' file contained anonymised free text instructions e.g. "take two three times a day for 5 days". All prescriptions of GCs (prednisolone, cortisone, hydrocortisone, triamcinolone, methylprednisolone, dexamethasone, bethamethasone, budesonide and deflazacort) were identified using the product code identifying the medication prescribed. Those administered orally were then selected.

Challenges of working with an EMR derived dataset and prescription data

Datasets derived from EMRs, such as CPRD, are an invaluable resource for exploring long-term medication safety outcomes as they provide real-life data from large populations over long periods of time. However, the primary purpose of an EMR is clinical care, and this is the focus at the point of data entry, rather than research-quality data. In addition, typographical errors are not uncommon in this setting, and there are often missing, implausible and conflicting data to deal with. Recent work in the field of pharmacoepidemiology has shown that decisions made when preparing prescription data can effect outcomes to varying but sometimes significant extents (211). The authors of this work highlight that prescription data preparation is usually unreported, and they have developed a statistical algorithm and framework for capturing these important steps that can affect study reproducibility as shown below in Figure 2.2. This work highlights the importance of a systematic data cleaning process when working with prescription data derived from EMRs.

Figure 2.2 Statistical algorithm and framework for capturing the steps in prescription data preparation



Reproduced from Pye et al, Pharmacoepidemiol Drug Saf, 2018 (211)
License: https://creativecommons.org/licenses/by/4.0/ No changes were made.

Glucocorticoid Prescription Data Preparation

GC prescription data is particularly challenging to work with because of the many different GC types, formulations, routes of administration, strengths and non-standardised dosing regimens. To prepare the GC prescription data in CPRD for analysis, a data preparation script that includes a series of decisions was adapted and modified using Stata statistical software. These decisions were informed by an in-depth review of their downstream impact in a small subset of patients. Clinical experience was essential in making these decisions, in order to ensure the final dataset was clinically plausible. Although this script was prepared prior to the creation of the prescription data preparation framework described above, it can be broadly divided into the same three sections including: A. Data cleaning, B. Define Prescription Length and C. Handle concurrent and sequential prescriptions. However, to avoid unwanted downstream effects, data cleaning was required before (A1) and after (A2) defining the prescription

length. The decisions made, and their order, in the data cleaning script are detailed below:

A1. Data Cleaning: Initial data cleaning dealt with contradictory and implausible data.

Corrections for when numeric entries conflict with free text

- When free text was available and numeric entries did not match free text, the numeric entries were updated to match with the free text (numeric daily dose and duration of therapy variables were affected)

Dealing with implausible values

- If duration of therapy, numeric daily dose and quantity of tablets was entered as '0', this was deemed implausible and changed to missing
- If duration of therapy for a single script was greater than 365 days, this was deemed implausible and changed to missing

B. Define Prescription Length (duration of therapy)

- There were three possible ways to define duration of therapy which was available from the therapy file, text ID file or could be derived from the therapy file by dividing the total quantity of tablets by the numeric daily dose (qty/ndd).
- For each prescription there were three duration variables, with 0-3 durations recorded depending on the extent of missing data.
- Three different stop date variables were created using the start date and the three duration variables. These were missing if the corresponding duration of therapy variable was missing
- If only one stop date was available for a given script, this was assumed to be correct and taken as the 'real stop date'
- If two stop dates were available and the same, this stop date was assumed to be correct and taken as the real stop date
- If two stop dates were available but different, then the stop date calculated from a duration directly entered was used in preference to one derived from the calculation qty/ndd. This rule was decided on as it led to the generation of the least number if implausible daily doses (>100mg/d)

- If three stop dates were available but different, the real stop date was taken to be that based on the duration from the therapy file (again, because this produced the least number of implausible doses >100mg/d)
- The 'real duration' was taken to be that which corresponded to the 'real stop date'
- At this stage of the data cleaning, real duration and real stop were still missing for those with missing data for all three duration variables

A.2 Data cleaning: further data cleaning to deal with missing values and any implausible doses once converted to a prednisolone equivalent daily dose

Dealing with missing numeric daily dose:

- If the numeric daily dose was a missing variable, it was calculated by dividing the quantity of tablets by the real duration (qty/realduration)
- If numeric daily dose was still missing, because either quantity or real duration were missing, then it was replaced by the median numeric daily dose for that prednisolone-equivalent strength across all prescriptions

Dealing with missing quantity:

- If quantity was a missing variable, it was replaced by the median quantity for that prednisolone-equivalent strength across all prescriptions

Dealing with missing real duration and real stop:

- If real duration was missing at this point, it was calculated by dividing quantity by the numeric daily dose, qty/ndd (this was now possible for scripts where ndd or qty had been replaced by the median)
- Missing real stop dates were then calculated based on start date plus real duration

Generating a prednisolone-equivalent dose per day:

- The prednisolone equivalent strength was calculated using a standard GC conversion calculator
- The prednisolone equivalent dose per day was then calculated by multiplying the prednisolone equivalent strength by the numeric daily dose (number tabs per day)

Dealing with implausible daily doses >100mg/d

- Where possible, this was corrected by calculating a new numeric daily dose based on an alternate duration of therapy (21 scripts remained uncorrected because scripts were for methylprednisolone 100mg which converts to prednisolone 125mg)

C. Handling concurrent and sequential prescriptions

Dealing with duplicate scripts

- Scripts were considered to be true duplicates if they were for the same patient, with the same start date, stop date, product code and strength
- These duplicates were removed so that only a single copy remained

Dealing with overlapping scripts

- For scripts written for the same patient with the same start date and stop date but different strengths- the prednisolone equivalent dose was added up and excess events were deleted
- Scripts written for the same patient, on the same day but for different durations were also combined with doses for overlapping periods added together

The data preparation script described above was used to define the GC prescription data for the work presented in Chapter 3. However, due to some minor changes to CPRD file and variable names over time, this script was updated for the work presented in Chapter 6. While the statistical code had to be carefully reviewed and updated, the assumptions essentially remained unchanged. CPRD requires considerable coding to produce an analysis-ready data set, and familiarisation with the dataset and variables, learning how to use a powerful statistical software package to create the statistical code for data preparation scripts, were major components of the work in this thesis.

3 GC Use in RA in the UK (CPRD)

This chapter addresses the first aim of the thesis:

> *To describe the use of oral glucocorticoids and explore patient and prescriber factors that influence their use in rheumatoid arthritis in the UK (Chapter 3) and Australia (Chapter 4)*

3.1 Introduction

The literature clearly describes polarised views regarding GC use in RA, with some concluding that GCs should be used at 'the lowest possible dose for the shortest time possible' and others promoting the long-term use of low-dose oral GCs as disease-modifying agents (82). This chapter includes a published manuscript describing the epidemiology of oral GC use among incident RA patients in the UK and looks at patient and prescriber characteristics that influence GC use. These analyses were carried out using CPRD, which provides an ideal setting in which to explore patterns and factors influencing GC use among RA patients seen in UK primary care. As this database contains prescription data, it was possible to explore ever-never exposure as well as dose and duration of therapy. This paper also looks at patient factors, including age, gender, comorbidities and the use of other medications, and their association with GC use. In addition, prescribers were categorised as either 'high' or 'low 'GC prescribers, based on their tendency to prescribe GCs across all indications. Analyses were carried out to explore whether factors that influenced GC use differed according to prescriber tendency.

A major component of the methodology of this work involved preparing the GC prescription data, which has been described in detail in Chapter 2. Familiarisation with the variables in such a large and complex dataset was time consuming but important. Learning the required coding skills and developing the statistical code to manipulate and tidy the data was also an important part of this work, and necessary for building the GC data cleaning script used to prepare the prescription data.

The findings identified that GC use is greater among patients with characteristics which may put them at greater risk of GC AEs, including older age and cardiovascular comorbidities. These findings have the potential for clinical translation as they identify certain sub-populations where a more careful assessment of the benefits and harms of GC treatment may be indicated. In order for this work to be carried out, customised

skills in statistical coding and data cleaning are indispensable. These skills will be invaluable for future research in the current climate of 'big data'.

3.2 Manuscript: Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study

Statement of Authorship

Title of Paper	Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Black RJ, Joseph RM, Brown B, Movahedi M, Lunt M, Dixon WG: **Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study**. *Arthritis research & therapy* 2015, **17**(1):375.

Principal Author

Name of Principal Author (Candidate)	Rachel Black		
Contribution to the Paper	Responsible for the design and conception of the work, data preparation including data cleaning, data analysis and interpretation, preparation of the manuscript and acted as corresponding author.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24/04/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Rebecca Joseph		
Contribution to the Paper	Contributed to the data preparation/cleaning and critically reviewed the manuscript, with approval of the final version to be published.		
Signature		Date	19 July 2018

Name of Co-Author	Benjamin Brown
Contribution to the Paper	Contributed to the interpretation of results and critically reviewed the manuscript, with approval of the final version to be published.

Signature		Date	20/07/2018

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Mohamed Movahedi		
Contribution to the Paper	Contributed to the data cleaning/preparation and critically reviewed the manuscript, with approval of the final version to be published.		
Signature		Date	19/07/2018

Name of Co-Author	Mark Lunt		
Contribution to the Paper	Supervised the selection of appropriate analyses, interpretation of results and critically reviewed the manuscript, with approval of the final version to be published.		
Signature		Date	20/07/2018

Name of Co-Author	William Dixon		
Contribution to the Paper	Supervised the conception and design of the work, including selection of analyses, interpretation of analyses and critically reviewd the manuscript, with approval of the final version to be published.		
Signature		Date	22 July 2018

Black et al. Arthritis Research & Therapy (2015) 17:375
DOI 10.1186/s13075-015-0895-8

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study

Rachel J. Black[1,2,5*], Rebecca M. Joseph[1,3], Benjamin Brown[4], Mohammad Movahedi[1], Mark Lunt[1] and William G. Dixon[1,3,4,6]

Abstract

Background: Patients with rheumatoid arthritis (RA) have shared care between rheumatologists and general practitioners (GPs). Rheumatologists guide immunosuppressive therapy, whilst GPs rely on analgesia and glucocorticoid (GC) therapy to manage active disease. The objective of this study was to describe patterns of GC prescribing for patients with RA in primary care and to determine the influence of patient characteristics and prescriber.

Methods: Incident RA patients were identified within the Clinical Practice Research Datalink, a United Kingdom (UK) primary care research database. Descriptive statistics identified patterns of oral GC prescribing. Prescribers were categorised by their tendency to prescribe GCs (high/low). Logistic regression was used to identify baseline characteristics associated with GC prescriptions during follow-up and to examine whether baseline characteristics influenced prescribing differently in high versus low prescribers.

Results: A total of 7777 patients (47 %) received ≥1 GC prescription during follow-up. The average daily dose was 7.5 mg (IQR 5–15.3 mg). Of those who received GCs, >50 % were prescribed >10 mg/day and 20 % >30 mg/day. The median proportion of time spent on GCs was 26.3 % (IQR 3.8–70.0 %). Age and cardiovascular disease (CVD) were associated with increased likelihood of receiving GCs. High prescribers more commonly prescribed GC therapy in older patients and patients with hypertension.

Conclusions: Half of patients with incident RA received GCs in primary care. Average GC use was 7.5 mg for 25 % of the time, perhaps higher usage than rheumatologists and GPs might expect. GCs were prescribed more commonly in certain high-risk populations, including older patients and those with CVD.

Keywords: Glucocorticoids, Rheumatoid arthritis, Drug utilisation, Primary care

Background

Glucocorticoid (GC) therapy was first introduced as a treatment for rheumatoid arthritis (RA) over 60 years ago [1]. GCs have potent anti-inflammatory properties that rapidly relieve joint pain, swelling and stiffness and also prevent structural damage [2]. However, they are associated with significant and predictable side effects (SEs) of concern to both patients and physicians [3, 4]. In the general population, GCs account for 2.5 % of all adverse drug reactions leading to hospital admission [5]. Guidelines for rheumatologists advocate short-term use of GCs [6], an acknowledgment that longer duration of therapy is associated with increased risk of developing certain SEs such as infection [7].

The management of RA, a condition where disease exacerbations are part of the natural history, involves

* Correspondence: rachelblack@mail.com
[1]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute for Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Oxford Rd, Manchester M13 9PT, UK
[2]Department of Medicine, The University of Adelaide, Adelaide, SA 5005, Australia
Full list of author information is available at the end of the article

shared care between the treating rheumatologist and the patient's general practitioner (GP). Shared care for patients with RA is recommended in many international guidelines and standards of care [8–11] and is common practice in the UK. In early RA, GPs will often commence initial therapy, which may include simple analgesia, non-steroidal anti-inflammatory drugs (NSAIDs) and GCs. The treating rheumatologist then guides ongoing management with advice about disease-modifying anti-rheumatic drugs (DMARDs) and GC use. When faced with active disease, rheumatologists can initiate changes to DMARD therapy, however GPs rarely alter DMARDs and their options for treating disease flares that occur between rheumatology appointments are usually limited to GCs and analgesia. In some instances, GPs will initiate or continue GCs based on the recommendation of the treating rheumatologist, and on other occasions they may initiate therapy based on their own clinical judgement. The extent and pattern of GC prescribing for RA in primary care has not been well quantified or described. Therefore, it is not known if doses and duration of treatment are in keeping with current guidelines. It is important to understand if certain patient groups are more likely to receive GCs in primary care, in particular those at increased risk of developing GC SEs such as older patients or those with pre-existing comorbidities. Doctors are known to have differing beliefs about GC use and its risks [12–14], therefore it is also important to understand if certain doctors prescribe more GCs.

The purpose of this study is to examine how oral GCs are prescribed for patients with RA in UK primary care. The primary objective is to describe overall drug utilisation and patterns of dose and duration. Secondary objectives are to explore the association between patient characteristics and GC use, and to examine variability in prescribing practices between prescribers.

Method

Data source

This study utilised the Clinical Practice Research Datalink (CPRD) [15], an automated database that contains pseudonymised, prospectively collected electronic medical records from registered UK general practices. In the UK, healthcare is centralised through GPs and electronic medical records are maintained and updated within general practices. The electronic medical records contain all primary care details plus information about referrals. Anonymised prescriber and practice codes are also available as part of the CPRD dataset.

Studies have found the data held by the CPRD to be representative of the UK population in terms of age and gender structure [16, 17]. Validation studies have demonstrated good completeness and accuracy of the data, particularly for chronic diseases [18, 19]. The CPRD has its own internal quality measures at the patient and practice level, including acceptability flags based on contiguity and quality of patient data, and an 'up to standard' date for practices based on continuity of data recording [20]. UK primary care electronic medical records use a unique coding system with Read codes assigned to medical diagnoses and Product codes assigned to medications [21].

Population and follow-up period

Figure 1 outlines how the cohort of incident RA was derived. All patients with an RA code recorded in CPRD between 1 January 1992 and 31 December 2009 were identified. A validated algorithm, shown to have a sensitivity of 84 % and a specificity of 86 % when compared to the American College of Rheumatology 1987 revised RA classification criteria [22], was then used to identify patients with true RA. The RA diagnosis date was defined as the date of the first RA code in patients with validated RA. Patients with incident RA were identified as those with an RA diagnosis date on or after the 1 January 1992 and at least 12 months of data recorded prior to diagnosis. Those with a GC prescription greater than a pre-defined maximum prednisolone equivalent dose of 100 mg per day and those aged less than 16 years were excluded. Follow-up began on the date of RA diagnosis and ended when the patient left the practice, died, the study period finished (31 December 2009) or on the date data was last collected from the practice, whichever occurred first.

Outcome measure: glucocorticoid prescriptions

All prescriptions of oral GCs (prednisolone, cortisone, hydrocortisone, triamcinolone, methylprednisolone, dexamethasone, bethamethasone, budesonide and deflazacort) were identified. Dosages were converted to a prednisolone-equivalent daily dose. Patients were classified as having ever or never been prescribed oral GCs according to receipt of at least one prescription during their follow-up period.

Predictors: patient characteristics and prescriber tendency

Baseline patient characteristics postulated to potentially influence prescribing were divided into demographics, other inflammatory indications for GCs, GC-associated comorbidities (e.g. osteoporosis, diabetes) and DMARD use as a surrogate for disease severity (Table 1). Characteristics and DMARDs were defined as being present at baseline if the diagnosis date or first prescription date occurred on or before RA diagnosis date.

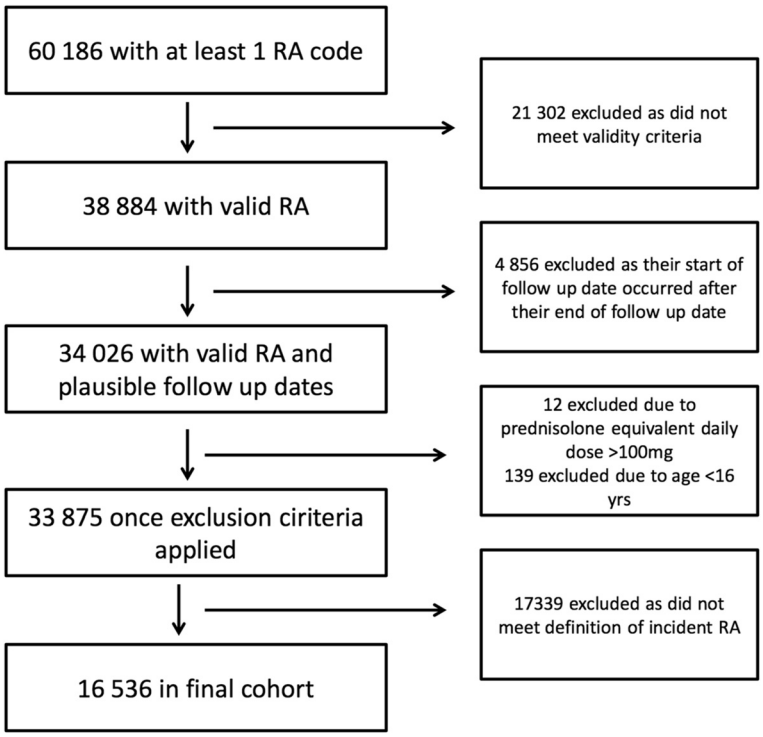


Fig. 1 Steps taken to obtain the final cohort

The primary (i.e. most frequent) prescriber of all medications was determined for each patient. For each primary prescriber, the mean proportion of time their patients spent on GCs during follow-up was calculated by dividing the length of time spent on GCs by the length of follow-up time for each patient and then determining the mean of this value amongst all patients seen by a given primary prescriber. Prescriber tendency was then assigned as 'high' or 'low' prescribers based on whether the mean proportion of time their patients spent on GCs was above or below the median value.

Statistical analysis

Descriptive analysis

Descriptive statistics were used to identify patterns of GC prescribing including: ever use (yes/no), dose,

Table 1 Patient characteristics thought to be potentially relevant to GC prescribing practices

Patient demographics	Age Gender	
GC-associated comorbidities	Musculoskeletal	Osteoporosis, avascular necrosis, myopathy
	Endocrine/metabolic	Diabetes
	Cardiovascular	Hypertension, hyperlipidaemia, cardiovascular diseases (myocardial infarction, angina, stroke)
	Gastrointestinal	Peptic ulcer disease, pancreatitis
	Psychological/behavioural	Depression, psychosis, insomnia
Inflammatory comorbidities	Respiratory	Chronic obstructive pulmonary disease, asthma, lower respiratory tract infections
	Skin diseases	Atopic eczema, cutaneous vasculitis, cutaneous lupus
	Gastrointestinal diseases	Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
DMARDs	Methotrexate	
	Sulfasalazine	
	Hydroxychloroquine	
	Leflunomide	
	Other DMARDs	Cyclosporine, azathioprine, penicillamine, chloroquine, gold

GC glucocorticoid, *DMARDs* disease-modifying anti-rheumatic drugs

duration and then dose and duration combined. Ever use was determined as a binary yes/no variable for the observation period and separately for the 12 months prior to diagnosis. For patients who received at least one GC prescription during the observation period, the average, lowest and highest prednisolone equivalent daily doses were determined for the time they were exposed. The median of these values across all treated patients was then calculated as a population summary statistic. The proportion of patients to ever receive greater than 5 mg, 10 mg, 20 mg and 30 mg per day was also determined.

The total number of patient years contributing to the follow-up period was determined, as was the number of patient years spent on and off GCs. For each patient that ever received GCs, the duration of follow-up, duration on GCs and proportion of their total follow-up time spent on GCs was determined. The median of these values was calculated as a population summary statistic.

A GC course was defined as consecutive GC prescriptions where the end date of the first prescription was not more than one calendar day different from the start date of the next prescription. The median number of courses per year and the number of patients with a single course longer than 3 months and 1 year was determined. Finally, dose and duration were combined and the proportion of patients taking more than 5 mg/day and 10 mg/day for greater than 3 months and 1 year was calculated.

The number of patients receiving a GC injection and the median number of injections per patient was also determined.

Patient characteristics

Univariate logistic regression, adjusted for age and gender, was initially carried out and then stepwise logistic regression was used to identify baseline patient characteristics associated with GC prescriptions (ever versus never) including demographics, other possible inflammatory indications, GC-associated comorbidities and DMARDs.

Prescriber tendency

Univariate logistic regression with an interaction term was used to determine the effect of prescriber tendency on the likelihood of receiving a GC prescription (ever versus never) during follow-up and to test the interaction between prescriber tendency and baseline patient characteristics, including patient demographics and GC-associated comorbidities.

All analyses were carried out using Stata version 12.1 (StataCorp LP, College Station, TX, USA). The study was approved by the CPRD Independent Scientific Advisory Committee (protocol 11_113RA2).

Results

From 1 January 1992 to 31 December 2009, 60,186 patients had at least one code for RA. Once the validated algorithm was applied to this cohort, 38,884 RA patients from 636 general practices across the UK were identified. Of these, 4856 were excluded because their RA diagnosis date occurred after their end of follow-up date, 12 were excluded due to a prednisolone-equivalent daily dose greater than a pre-defined maximum of 100 mg per day and 139 were excluded because they were aged less than 16 years. A total of 16,536 remained in the final cohort after the definition for incident RA was applied as shown in Fig. 1. The majority of the patients were female (69.3 %) and the median age was 59.8 years [interquartile range (IQR) 49.0–70.3].

Patterns of GC use

Ever use (yes/no)

There were 7777 (47 %) patients who received at least one oral GC prescription during the study period and these patients were classified as ever receiving a GC prescription. There were 3412 patients (20.6 %) who received a GC prescription in the 12 months preceding their diagnosis. Of these, 2940 (86.2 %) were prescribed further GCs during the follow-up period.

Dose

For those that ever received GCs, the population distribution was a median of 7.5 mg per day (IQR 5–15.3 mg) for the average dose, 5 mg per day (IQR 2.5–7.5 mg) for the lowest dose and 15 mg per day (IQR 7.5–30 mg) for the highest dose. Of those prescribed GCs during follow-up, 83 % ever received a prednisolone equivalent daily dose of more than 5 mg/day, 58 % more than 10 mg/day, 39 % more than 20 mg/day and 18 % more than 30 mg/day.

Duration of GC therapy

Total follow-up time was 92,641 patient years (mean 5.6 years/patient), with 14,382 (15.5 %) patient years spent on GCs and 78,259 (84.5 %) patient years spent off GCs. Of the 7777 patients who received GCs during follow-up, the median duration of follow-up time spent on GCs was 0.80 years (IQR 0.15–2.56) and the proportion of time spent on GCs was 26.3 % (IQR 3.8–70.0 %).

Of those who received GCs in the 12 months prior to diagnosis, the median proportion of time spent on GCs during that year was 22.7 % (IQR 5.4–67.2 %). Table 2 summarises GC doses and duration of use.

Of those that received GCs, the median number of GC courses throughout follow-up was 5 (IQR 2–12) and the median number of courses per year was 1.4 (IQR 0.4–3.0). The number of patients that received more than two GC courses per year was 3060 (39.3 % of those that received

Table 2 Summary statistics of GC doses and duration of use per patient during follow-up and in the 12 months prior to study entry for those patients ever prescribed GCs (n = 7777)

	Follow-up period		12 months prior to study entry	
Measure*	Median	IQR	Median	IQR
Duration of follow-up (years)	5.29	2.62–8.58	-	-
Cumulative duration of GC use (years)	0.80	0.15–2.56	0.23	0.05–0.67
Proportion of follow-up time on GCs (%)	26.3	3.8–70.0	22.7	5.4–67.2
Average dose** (mg)	7.5	5–15.3	10	5–20
Lowest dose** (mg)	5	2.5–7.5	5	3–15
Highest dose** (mg)	15	7.5–30	15	6–30

GC glucocorticoid, *IQR* interquartile range
*Summary statistics were obtained by calculating the value for each patient and then determining median values across the whole population
**All doses are prednisolone-equivalent daily doses

GCs). The median duration of each GC course was 50 days (IQR 21–111). Of those that received GCs, 57.1 % received a course longer than 3 months and 13.1 % were prescribed a GC course lasting longer than 1 year.

Dose and duration of treatment

Of those prescribed GCs, 26.6 % received continuous treatment with more than 5 mg/day for longer than 3 months and 2.4 % received continuous treatment with greater than 5 mg/day for longer than 1 year. 4.7 % received more than 10 mg/d for more than 3 consecutive months.

GC injections

There were 8373 prescriptions for GC injections (intramuscular, intra-articular and periarticular) during the study period in 2911 patients (37 % total cohort). The majority were for methylprednisolone (72 %), followed by triamcinalone (21 %), prednisolone (4 %) and hydrocortisone (3 %). The median number of injections per patient was 2 (IQR 1–3).

Patient factors associated with GC prescribing

Each 10-year increase in age was associated with a 17 % greater likelihood of being prescribed GCs [odds ratio (OR), 1.17 95 % confidence interval (CI) 1.14–1.20]. Higher GC prescribing was seen in patients with inflammatory comorbidities of the lung: asthma (OR 1.58, 95 % CI 1.42–1.76), chronic obstructive pulmonary disease (OR 1.63, 95 % CI 1.33–1.99) and lower respiratory tract infections (OR 1.22, 95 % CI 1.11–1.34). However, there was no association with inflammatory conditions of the skin or gastrointestinal tract (GI) tract (Table 3).

The association with pre-existing comorbidities known to be associated with GC therapy was less consistent. GC prescribing was higher in patients with pre-existing cardiovascular disease (CVD) (OR 1.25, 95 % CI 1.03–1.51) and in current smokers (OR 1.22, 95 % CI 1.13–1.32) but lower in patients with diabetes mellitus (DM) (OR 0.71, 95 % CI 0.62–0.82) and high cholesterol (OR 0.86, 95 % CI 0.76–0.97). There was an association with osteoporosis, depression and insomnia seen in the univariate model, but these factors were not included in the final multivariate model. There was no significant association with other GC-associated comorbidities at baseline including avascular necrosis, myopathy, hypertension (HTN), peptic ulcer disease (PUD) or pancreatitis.

A previous GC prescription prior to RA diagnosis was the strongest predictor of ever receiving a prescription post-diagnosis (OR 9.50, 95 % CI 8.51–10.60). GC prescribing was lower with baseline methotrexate and sulfasalazine use, but higher with leflunomide and 'other' DMARD use.

Prescriber tendency and GC prescribing

In total 3270 GPs were assigned as primary prescribers. The mean proportion of time their patients spent on GCs ranged from 0 to 100 % (median 11.3 %, IQR 0.11–25.9 %). GPs were thus categorised as 'high' prescribers if their patients spent a mean of ≥11.3 % of follow-up on GCs. A total of 6427 (38.9 %) patients were assigned a 'low' GC prescriber and 10,109 (61.1 %) were assigned a 'high' GC prescriber.

By definition, the likelihood of a patient receiving a GC prescription during follow-up was greater if they were seen by a 'high' GC prescriber compared to a 'low' GC prescriber (OR 3.10, 95 % CI 2.90–3.31). The probability of receiving a GC prescription increased with each decade of patient age for both 'low' (OR 1.15, 95 % CI 1.11–1.20) and 'high' (OR 1.26, 95 % CI 1.23–1.29) prescriber groups (Table 4). This effect differed significantly between the two prescriber groups (p <0.001), suggesting that although all older patients were more likely to receive GCs, the effect of age was greater in those seen by a 'high' prescriber. In other words, high prescribers were even more likely to prescribe GCs in elderly patients.

Table 3 Baseline patient characteristics associated with GC prescriptions

Variable	Ever GC use (number, %)	Never GC use (number, %)	Univariate analysis* (odds ratio, 95 % CI)	Multivariate stepwise analysis (odds ratio, 95 % CI)
Baseline demographics				
Age (decades)			1.02, 1.02–1.02**	1.17, 1.14–1.20
Gender (female)	5313, 68.32 %	6153, 70.25 %	0.94, 0.88–1.00	
Current smoking (versus never)	2147, 27.61 %	2385, 27.23 %	1.04, 1.00–1.08**	1.22, 1.13–1.32
Baseline GC-associated comorbidities				
Osteoporosis	427, 5.49 %	279, 3.19 %	1.42, 1.21–1.66**	
Avascular necrosis	7, 0.09 %	4, 0.05 %	1.68, 0.49–5.78	
Myopathy	14, 0.18 %	10, 0.11 %	1.35, 0.60–3.08	
Diabetes mellitus	603, 7.75 %	699, 7.98 %	0.85, 0.76–0.95**	0.71, 0.62–0.82
Cardiovascular disease	364, 4.68 %	264, 3.01 %	1.22, 1.04–1.44**	1.25, 1.03–1.51
Hypertension	1842, 23.69 %	1754, 20.03 %	0.98, 0.90–1.06	
Hyperlipidaemia	798, 10.26 %	830, 9.48 %	0.93, 0.84–1.04	0.86, 0.76–0.97
Peptic ulcer disease	382, 4.91 %	334, 3.81 %	1.13, 0.97–1.32	
Pancreatitis	46, 0.59 %	43, 0.49 %	1.11, 0.73–1.70	
Depression	1684, 21.65 %	1847, 21.09 %	1.11, 1.03–1.19 **	
Insomnia	985, 12.67 %	865, 9.88 %	1.21, 1.10–1.34**	
Psychosis	56, 0.72 %	52, 0.59 %	1.24, 0.84–1.81	
Baseline inflammatory comorbidities				
Chronic obstructive pulmonary disease	540, 6.94 %	189, 2.16 %	2.74, 2.31–3.25**	1.63, 1.33–1.99
Asthma	1492, 19.18 %	925, 10.56 %	2.07, 1.89–2.27**	1.58, 1.42–1.76
Lower respiratory tract infection	1717, 22.08 %	1342, 15.44 %	1.47, 1.35–1.59**	1.22, 1.11–1.34
Inflammatory bowel disease	78, 1.11 %	63, 0.72 %	1.35, 0.96–1.89	
Cutaneous lupus	13, 0.17 %	11, 0.13 %	1.30, 0.58–2.93	
Cutaneous vasculitis	6, 0.08 %	0, 0.00 %	1	
Atopic eczema	1084, 13.94 %	1127, 12.87 %	1.10, 1.00–1.20**	
Baseline DMARD use				
Methotrexate	465, 5.98 %	501, 5.72 %	1.07, 0.93–1.22	0.80, 0.66–0.97
Sulfasalazine	468, 6.02 %	581, 6.63 %	0.91, 0.80–1.03	0.69, 0.58–0.83
Hydroxychloroquine	259, 3.33 %	256, 2.92 %	1.20, 1.00–1.43**	
Leflunomide	105, 1.35 %	71, 0.81 %	1.83, 1.35–2.49**	1.75, 1.18–2.59
Other DMARDs***	277, 3.56 %	151, 1.72 %	2.06, 1.68–2.52**	1.68, 1.28–2.19

GC glucocorticoid, *DMARDs* disease-modifying anti-rheumatic drugs, *CI* confidence interval
*Adjusted for age and gender
**Significant in univariate analysis
***Other DMARDs include gold, penicillamine, cyclosporine, chloroquine and azathioprine

It was hypothesised that those with a greater tendency to prescribe GCs may be prescribing inappropriately to those with baseline GC-associated comorbidities. This was only seen for prescribers whose patients had a baseline diagnosis of HTN, who were more likely to receive a GC prescription in the 'high' prescriber group (OR 1.29 95 % CI 1.17–1.42), but not in the 'low' prescriber group (OR 1.08 95 % CI 0.95–1.24), with the effect differing significantly between groups ($p = 0.039$).

Discussion

This study set out to describe the utilisation of GC therapy for RA in primary care, patterns of GC prescribing and to examine the influence of patient factors and prescriber tendency on GC prescribing amongst GPs for patients with RA. Nearly half the cohort received a GC prescription in primary care during follow-up, consistent with the findings of the QUEST-RA study [23]. The population distribution of the mean prednisolone-equivalent daily dose was 7.5 mg, taken for around 25 %

Table 4 Effect of baseline characteristics on GC prescriptions according to prescriber tendency

Variable	Low prescriber group (OR, 95 % CI)	High prescriber group (OR, 95 % CI)	*p* value**
Demographics			
Age (decades)	1.15, 1.11–1.20*	1.26, 1.23–1.29*	<0.001
Gender (female)	0.98, 0.87–1.10	0.89, 0.82–0.97*	0.211
Current smoker (versus never)	1.09, 1.02–1.17*	1.07, 1.02–1.13*	0.744
GC-associated comorbidities			
Osteoporosis	1.49, 1.14–1.95*	1.84, 1.50–2.25*	0.225
Avascular necrosis	2.28, 0.32–16.22	1.84, 0.36–9.51	0.870
Myopathy	2.29, 0.57–9.15	1.23, 0.45–3.38	0.479
Diabetes mellitus	0.88, 0.72–1.08	1.02, 0.88–1.18	0.257
Cardiovascular disease	1.38, 1.04–1.84*	1.62, 1.31–2.00*	0.373
Hypertension	1.08, 0.95–1.24	1.29, 1.17–1.41*	0.039
Hyperlipidaemia	1.10, 0.92–1.31	1.07, 0.94–1.22	0.829
Peptic ulcer disease	1.36, 1.06–1.74*	1.33, 1.09–1.63*	0.910
Pancreatitis	1.00, 0.49–2.05	1.44, 0.81–2.54	0.442
Depression	1.09, 0.96–1.23	1.09, 0.99–1.20	0.994
Insomnia	1.27, 1.08–1.50*	1.36, 1.20–1.54*	0.548
Psychosis	1.14, 0.60–2.17	1.29, 0.78–2.14	0.767
Prior use			
GC prescription prior to follow up	6.52, 5.51–7.71*	11.76, 10.24–13.51*	<0.001

GC glucocorticoid, *OR* odds ratio, *CI* confidence interval
*Significant predictors of GC prescriptions (unadjusted)
**p value indicates significance of any differing effect between high and low prescriber groups

of follow-up time in GC users. This average dose of 7.5 mg is within the European League Against Rheumatism (EULAR) definition of low-dose therapy of ≤7.5 mg per day [24], and in keeping with studies reporting efficacy [25–28] and reduced adverse effects with low-dose therapy[4]. However, more than 50 % were prescribed doses >10 mg per day at some point and nearly 20 % were prescribed doses greater than 30 mg per day. The indication for prescriptions is not available in CPRD, therefore it is difficult to know whether high-dose steroids were prescribed for the patient's RA or for other indications. The median cumulative duration of time spent taking GCs was 0.8 years/10 months with the interquartile range spanning from 0.15 years/2 months to 2.56 years. This highlights that some patients are taking GCs for longer than recommended [29], placing them at increased risk of developing SEs [30, 31].

As expected, the presence of certain inflammatory comorbidities at diagnosis, in particular inflammatory lung conditions, influenced GC prescribing. Of concern, GC therapy was prescribed more commonly in certain higher risk populations, including older patients and those with CVD. These findings are in keeping with a recent prospective RA study that found rheumatologists were more likely to prescribe GCs and less likely to commence DMARDs in patients who develop RA at an older age, who were also more likely to have comorbidities including CVD, HTN and DM [32]. The authors postulated that this might be due to clinician concerns about the potential side effects of DMARDs in older patients, particularly those with more comorbidities. However, they also point out that DMARDs are well tolerated in older patients [33] compared to the potential difficulties of GC SEs in older patients. It has been shown that RA patients taking ≥7.5 mg prednisolone per day are at increased risk of CVD [34, 35]. Pre-existing CVD, HTN and smoking, an important risk factor for CVD, may worsen cardiovascular outcomes further. Although patients with baseline DM and hyperlipidaemia received fewer GC prescriptions, it was also concerning that other baseline conditions such as PUD had no influence on GC prescribing.

Baseline use of methotrexate and sulfasalazine was associated with less GC prescribing and is in keeping with the knowledge that early treatment of RA within the 'window of opportunity' leads to lower disease activity [36], and potentially reduced GC requirement. Several studies have suggested that GC prescribing is also influenced by biological DMARDs (bDMARDs), which have been shown to have a GC-sparing effect [37–40]. In the UK, bDMARDS can only be prescribed by rheumatologists and this data is therefore not captured by CPRD.

Therefore this study was unable to assess the influence of these agents on GC prescribing.

The strengths of this study include the large cohort size and the real-life setting in which CPRD data is captured. All oral GC prescriptions were recorded within the database, meaning there was no missing prescription data. The main limitation of this study design was the lack of access to measures of disease activity, which would be expected to be important in understanding which patients receive GC prescriptions. The information needed for standard measures of disease activity such as EULAR response and disease activity score (28-joint count) (DAS28) are not routinely collected by GPs and were therefore not available on the CPRD database. A second limitation of this study is that it was unable to assess the influence of rheumatologist prescribing practices or advice on GC prescribing in primary care as rheumatologist prescribing data is not captured in CPRD. However, it is likely that some GC prescriptions will be initiated by a rheumatologist and continued in primary care. On other occasions, GPs may initiate GCs knowing that this is the practice/recommendation of the treating rheumatologist when faced with active disease. This interaction between prescribers is of interest and warrants further investigation in the future.

Conclusions

In conclusion, this study has found that 50 % of patients with incident RA were prescribed GCs in UK primary care for 25 % of the time they were observed. Of those who received GCs, more than 50 % were prescribed doses >10 mg per day and nearly 20 % were prescribed doses greater than 30 mg per day. Many GPs and rheumatologists may be surprised by the proportion of patients, the dosages prescribed and the duration of use of GCs in primary care, highlighting the need to be aware of GC use in this setting in order to avoid excess exposure and associated side effects. Certain baseline comorbidities influenced GC prescribing, including some high-risk patient groups that were more likely to receive GC prescriptions. This information is useful for both rheumatologists and GPs involved in the care of patients with RA because it highlights the extent of GC prescribing in primary care and identifies at risk groups more likely to receive GCs. Given the variety of treatment options available for RA, it is important to consider the individual patient's specific comorbidities and risk of developing GC SEs and introduce alternative therapies where appropriate.

Abbreviations

bDMARDs: biological disease-modifying anti-rheumatic drugs; CI: confidence interval; CPRD: Clinical Practice Research Datalink; CVD: cardiovascular diseases; DAS28: disease activity score (28-joint count); DM: diabetes mellitus; DMARDs: disease-modifying anti-rheumatic drugs; EULAR: European League Against Rheumatism; GC: glucocorticoid; GP: general practitioner; HTN: hypertension; IQR: interquartile range; NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio; PUD: peptic ulcer disease; RA: rheumatoid arthritis; SE: side effect; UK: United Kingdom.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

RJB contributed to the design of the work, as well as the acquisition, analysis and interpretation of data for the work. She drafted the work and gave final approval of the version to be published. RMJ contributed to the design of the work as well as the acquisition and preparation of data for the work. She critically revised the work for important intellectual content and gave final approval of the version to be published. BB contributed to the interpretation of data for the work. He critically revised the work for important intellectual content and gave final approval of the version to be published. MM contributed to the acquisition and preparation of data for the work. He critically revised the work for important intellectual content and gave final approval of the version to be published. ML contributed to the analysis and interpretation of data for the work. He critically revised the work for important intellectual content and gave final approval of the version to be published. WGD contributed to the design of the work and interpretation of data. He critically revised the work for important intellectual content and gave final approval of the version to be published.

Acknowledgments

RJB was the recipient of the 2013 Ken Muirden Overseas Training Fellowship, an educational research grant jointly funded by Arthritis Australia and Roche Products Pty Ltd.

RMJ was funded by the NIHR Manchester Musculoskeletal Biomedical Research Unit. WGD and MM were supported by a Medical Research Council Clinician Scientist Fellowship (G0902272). We thank the Arthritis Research UK for their support: Arthritis Research UK grant number 20380. This report includes independent research supported by (or funded by) the National Institute for Health Research Biomedical Research Unit Funding Scheme. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Author details

[1]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute for Inflammation and Repair, Manchester Academic Health Science Centre, The University of Manchester, Oxford Rd, Manchester M13 9PT, UK. [2]Department of Medicine, The University of Adelaide, Adelaide, SA 5005, Australia. [3]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, 29 Grafton Street, Manchester M13 9WU, UK. [4]Health e-Research Centre, Farr Institute for Health Informatics Research, Manchester Academic Health Science Centre, The University of Manchester, Oxford Rd, Manchester M13 9PL, UK. [5]Department of Rheumatology, The Basil Hetzel Institute for Translational Health Research, Woodville Rd, Woodville South, SA 5011, Australia. [6]Department of Rheumatology, Salford Royal NHS Foundation Trust , Stott Lane, Salford M6 8HD, UK.

Received: 8 October 2015 Accepted: 10 December 2015
Published online: 24 December 2015

References

1. Hench PS, Kendall EC, Slocumb CH, Polley HF. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions - a study in clinical physiology. Arch Intern Med. 1950;85:545–666.
2. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007;1:CD006356.
3. Nassar K, Janani S, Roux C, Rachidi W, Etaouil N, Mkinsi O. Long-term systemic glucocorticoid therapy: patients' representations, prescribers' perceptions, and treatment adherence. Joint Bone Spine. 2014;81:64–8.

4. Da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Ines LB, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis. 2006;65:285–93.
5. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004;329:15–9.
6. National Institute of Health and Clinical Excellence. NICE clinical guideline 79. Rheumatoid arthritis. The management of rheumatoid arthritis in adults. London: NICE; 2009.
7. Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis. 2012;71:1128–33.
8. The Royal Australian College of General Practitioners (RACGP) clinical guidelines for the diagnosis and management of early rheumatoid arthritis. http://www.racgp.org.au/your-practice/guidelines/musculoskeletal/rheumatoidarthritis. Accessed November 2015.
9. Luqmani R, Hennell S, Estrach C, Birrell F, Bosworth A, Davenport G, et al. British Society for Rheumatology and British health professionals in rheumatology guideline for the management of rheumatoid arthritis (the first two years). Rheumatology (Oxford). 2006;45:1167–9.
10. Luqmani R, Hennell S, Estrach C, Basher D, Birrell F, Bosworth A, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). Rheumatology (Oxford). 2009;48:436–9.
11. van der Linden MP, le Cessie S, Raza K, van der Woude D, Knevel R, Huizinga TW, et al. Long-term impact of delay in assessment of patients with early arthritis. Arthritis Rheum. 2010;62:3537–46.
12. Henkel G: Glucocorticoid use in rheumatoid arthritis management focus of ongoing debate. In: The Rheumatologist. vol. March 2015: ACR and ARHP; 2015.
13. Saag KG. Resolved: low-dose glucocorticoids are neither safe nor effective for the long-term treatment of rheumatoid arthritis. Arthr Care Res. 2001;45:468–71.
14. Conn DL. Resolved: Low-dose prednisone is indicated as a standard treatment in patients with rheumatoid arthritis. Arthr Care Res. 2001;45:462–7.
15. Clinical Practice Research Datalink. UK. http://www.cprd.com/home, Accessed August 2015.
16. Lawson DH, Sherman V, Hollowell J. The General Practice Research Database. Scientific and Ethical Advisory Group. QJM. 1998;91:445–52.
17. García Rodríguez LA, Pérez GS. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol. 1998;45:419–25.
18. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010;69:4–14.
19. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract. 2010;60:e128–36.
20. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf. 2012;3:89–99.
21. Health and Social Care Information Centre-Read Codes. http://systems.hscic.gov.uk/data/uktc/readcodes. Accessed August 2015.
22. Thomas SL, Edwards CJ, Smeeth L, Cooper C, Hall AJ. How accurate are diagnoses for rheumatoid arthritis and juvenile idiopathic arthritis in the general practice research database? Arthritis Rheum. 2008;59:1314–21.
23. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Lund Hetland M, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis. 2007;66:1491–6.
24. Buttgereit F, Da Silva JAP, Boers M, Burmester G-R, Cutolo M, Jacobs J, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis. 2002;61:718–22.
25. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. N Engl J Med. 1995;333:142–6.
26. Hickling P, Jacoby RK, Kirwan JR. Joint destruction after glucocorticoids are withdrawn in early rheumatoid arthritis. Arthritis and Rheumatism Council Low Dose Glucocorticoid Study Group. Br J Rheumatol. 1998;37:930–6.
27. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2005;52:3371–80.
28. van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, Bijlsma JWJ. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Ann Intern Med. 2002;136:1–12.
29. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010;69:964–75.
30. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum. 2006;55:420–6.
31. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. Am J Med. 1994;96:115–23.
32. Innala L, Berglin E, Moller B, Ljung L, Smedby T, Sodergren A, et al. Age at onset determines severity and choice of treatment in early rheumatoid arthritis: a prospective study. Arthr Res Ther. 2014;16:R94.
33. Villa-Blanco JI, Calvo-Alen J. Elderly onset rheumatoid arthritis: differential diagnosis and choice of first-line and subsequent therapy. Drugs Aging. 2009;26:739–50.
34. Wei L, MacDonald TM, Walker BR. Taking glucocorticoids by prescription is associated with subsequent cardiovascular disease. Ann Intern Med. 2004;141:764–70.
35. Wallberg-Jonsson S, Johansson H, Ohman ML, Rantapaa-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol. 1999;26:2562–71.
36. Quinn MA, Emery P. Window of opportunity in early rheumatoid arthritis: possibility of altering the disease process with early intervention. Clin Exp Rheumatol. 2003;21:S154–157.
37. Naumann L, Huscher D, Detert J, Spengler M, Burmester GR, Buttgereit F. Anti-tumour necrosis factor {alpha} therapy in patients with rheumatoid arthritis results in a significant and long-lasting decrease of concomitant glucocorticoid treatment. Ann Rheum Dis. 2009;68:1934–6.
38. Seror R, Dougados M, Gossec L. Glucocorticoid sparing effect of tumour necrosis factor alpha inhibitors in rheumatoid arthritis in real life practice. Clin Exp Rheumatol. 2009;27:807–13.
39. Nilsson AC, Christensen AF, Junker P, Lindegaard HM. Tumour necrosis factor-alpha inhibitors are glucocorticoid-sparing in rheumatoid arthritis. Dan Med Bull. 2011;58:A4257.
40. Fortunet C, Pers YM, Lambert J, Godfrin-Valnet M, Constant E, Devilliers H, et al. Tocilizumab induces corticosteroid sparing in rheumatoid arthritis patients in clinical practice. Rheumatology (Oxford). 2015;54:672–7.

4 GC Use in RA in Australia (ARAD)

This chapter also addresses the first aim of the thesis, in a second cohort in Australia:

> *To describe the use of oral glucocorticoids and explore patient and prescriber factors that influence their use in rheumatoid arthritis in the UK (Chapter 3) and Australia (Chapter 4)*

4.1 Introduction

This chapter includes a published manuscript describing the epidemiology of oral GC use among Australian patients with RA enrolled in ARAD. It explores patient factors that influence GC use in a second population as well as expanding this question to look at patient factors associated with the commencement and the cessation of GC use. ARAD does not collect information on GC dose, however the registry format has the benefit of collecting the same data at consistent time intervals longitudinally. This study looked at how GC use has changed over time as well as at factors influencing GC current use, commencement and cessation. Potential influencing patient factors explored in this work included demographics, concurrent medications, Health Assessment Questionnaire (HAQ) and visual analogue scale (VAS) measures of pain and arthritis activity in the past week. Previous studies have shown bDMARDS to have a steroid-sparing effect in RA in terms of dose reduction (212-216), however the question of whether bDMARD use leads to GC cessation or prevents GC commencement has not previously been addressed in the literature. This study used transition state analysis in order to specifically assess this, and found that while bDMARD use was associated with reduced commencement of GCs, it did not influence the cessation of GCs. Unlike the CPRD cohort, the findings of this study were that GC use was less likely with increasing age. The transition state analysis added to this finding, showing that while older patients were less likely to commence GCs, they were less likely to cease GC treatment, once started.

The selection of appropriate statistical analyses was an important aspect of the methodology of this paper. In order to ensure the analyses were answering the research questions posed, whilst maximising the use of the data available, we moved away from traditional regression models and instead used panel regression and transition state analyses. These types of statistical models are well described in the statistical literature but less commonly seen in the medical literature. As described by Douglas Altman in

1994, there is a recognised delay in the translation of new bio-statistical methods to medical research (217). In the dataset used for this work, the GC outcome variable, along with many of the predictor variables, was time-varying. Most traditional models are unable to deal with the time-varying nature of these variables and require a cross-sectional snapshot, ignoring large amounts of the data available. Cox regression analysis is traditionally used when time- varying variables are present, however a time-to-event analysis would not have addressed the research questions in this scenario, given the repeated episodic nature of patterns of GC use.

In summary, this section of work expanded on the work carried out in CPRD in understanding how GCs are used in RA. In particular, it provided an Australian perspective of how GC use has changed over time and looked at factors influencing GC commencement and cessation as well as current use.

4.2 Manuscript: Factors associated with Oral Glucocorticoid Use in Patients with Rheumatoid Arthritis: A Drug Utilisation Study from a Prospective National Biologics Registry

Statement of Authorship

Title of Paper	Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Black RJ, Lester S, Buchbinder R, Barrett C, Lassere M, March L, Whittle S, Hill CL: Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry. *Arthritis research & therapy* 2017, 19(1):253.

Principal Author

Name of Principal Author (Candidate)	Rachel Black		
Contribution to the Paper	Responsible for the design and conception of the work, data preparation including data cleaning, data analysis and interpretation, preparation of the manuscript and acted as corresponding author.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24/04/2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Susan Lester		
Contribution to the Paper	Supervised the design and conception of the work including the selection of appropriate analyses, interpretation of analyses and critically reviewed the manuscript, with approval of the final version prior to publication.		
Signature		Date	24/04/2019

Name of Co-Author	Rachelle Buchbinder
Contribution to the Paper	Contributed to the interpretation of analyses and critically reviewed the manuscript, with approval of the final version prior to publication.

Signature		Date	17 July 2018

Name of Co-Author	Claire Barrett		
Contribution to the Paper	Contributed to the interpretation of analyses and critically reviewed the manuscript, with approval of the final version prior to publication.		
Signature		Date	24/09/19

Name of Co-Author	Marissa Lassere		
Contribution to the Paper	Critically reviewed the manuscript, with approval of the final version prior to publication.		
Signature		Date	28/4/18

Name of Co-Author	Lyn March		
Contribution to the Paper	Contributed to the interpretation of analyses and critically reviewed the manuscript, with approval of the final version prior to publication.		
Signature		Date	24-7-18

Name of Co-Author	Samuel Whittle		
Contribution to the Paper	Supervised the design and conception of the work, contributed to the interpretation of analyses and critically reviewed the manuscript, with approval of the final version prior to publication.		
Signature		Date	24 April 2019

Name of Co-Author	Catherine Hill		
Contribution to the Paper	Supervised the design and conception of the work, including selection of appropriate analyses, contributed to the interpretation of analyses and critically reviewed the manuscript, with approval of the final version prior to publication.		
Signature		Date	24/04/2019

Black et al. Arthritis Research & Therapy (2017) 19:253
DOI 10.1186/s13075-017-1461-3

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry

Rachel J. Black[1,2*], Susan Lester[2,3], Rachelle Buchbinder[4,5], Claire Barrett[6], Marissa Lassere[7], Lyn March[8], Samuel Whittle[3] and Catherine L. Hill[1,2,3]

Abstract

Background: Glucocorticoids (GCs) are used in ~ 60% of patients with rheumatoid arthritis (RA). Although disease-modifying, they also have significant adverse effects. Understanding factors associated with GC use may help minimise exposure. The aims of the present study were to describe oral GC use in RA; determine any change in use over time; and determine factors associated with oral GC use, commencement or cessation.

Methods: Adult patients with RA were identified in the Australian Rheumatology Association Database (ARAD), a national Australian registry that collects long-term outcome data from patients with inflammatory arthritis. Patients were categorised by their ARAD date of entry (DOE), with population-averaged logistic regression and transition state analysis used to determine any change in GC use over time. Fixed-effects panel regression was used to examine whether GC current use was associated with pain/arthritis activity/Health Assessment Questionnaire (HAQ) scores or medication use. Transition state analysis was used to assess whether these factors influenced the commencement or cessation of GCs.

Results: A total of 3699 patients with RA completed a baseline ARAD questionnaire (73% female, mean age 57 years). The probability of GC use decreased over time according to ARAD DOE: September 2001 to March 2005, 55% (95% CI 52–58%); March 2005 to September 2008, 47% (45–49%); September 2008 to March 2012, 42% (39–45%); and March 2012 to October 2015, 39% (34–43%) ($p < 0.001$). Conventional synthetic disease-modifying anti-rheumatic drugs (OR 10.13; 95% CI 8.22–12.47), non-steroidal anti-inflammatory drugs (1.18; 1.02–1.37) and opioids (2.14; 1.84–2.48) were associated with GC current use, as were lower pain scores (0.94; 0.90–0.98), higher arthritis activity scores (1.09; 1.05–1.14) and poorer HAQ scores (1.52; 1.30–1.79). Use of biologic disease-modifying anti-rheumatic drugs (bDMARDs) was not associated with GC current use (0.98; 0.83–1.15) or GC cessation (HR 0.87; 95% CI 0.75–1.01), but it was associated with GC commencement (0.54; 0.47–0.62).

Conclusions: The probability of oral GC use decreased over time, with reduced commencement and increased cessation of GCs. The modest effect of bDMARDs on GC cessation was not statistically significant.

Keywords: Glucocorticoids, Rheumatoid arthritis, Epidemiology, Drug use

* Correspondence: rachel.black2@sa.gov.au
[1]Rheumatology Unit, Royal Adelaide Hospital, North Terrace, Adelaide 5000, Australia
[2]Division of Medicine, The University of Adelaide, Adelaide, Australia
Full list of author information is available at the end of the article

Background

Glucocorticoids (GCs) are used in ~ 60% of patients with rheumatoid arthritis (RA) globally [1]. Although they have been shown to have disease-modifying properties [2], they are also associated with significant adverse effects [3, 4]. For this reason, many international guidelines recommend that the lowest possible dose and duration of GC therapy be used, if prescribed [5, 6]. Understanding the factors that are associated with GC use may help to minimise GC use. The use of GCs in RA may have changed over time with the introduction of biologic disease-modifying anti-rheumatic drugs (bDMARDs). Patients with severe disease resistant to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) prior to the introduction of bDMARDs may have been more likely to receive GCs than those with resistant disease and early access to bDMARDs. Previous studies have shown that bDMARDs can have a GC-sparing effect in RA, with a significant GC dose reduction seen in those commenced on bDMARDs compared with those who are not [7–11]. However, no prior studies have looked at the association between bDMARD use and GC cessation. Arguably, GC cessation rather than reduction should be the goal of therapy.

The following were the aims of the present study:

1. To describe the use of GCs among patients with RA enrolled in the Australian Rheumatology Association Database (ARAD) and any change in use over time
2. To determine factors associated with GC current use, including demographics, patient-reported pain score, arthritis activity score, Health Assessment Questionnaire (HAQ) score and concurrent medication use
3. To determine factors associated with the commencement and cessation of GCs in order to assess whether bDMARDs have a GC-sparing effect in this cohort

Methods

Population (ARAD)

ARAD is a voluntary Australian biologic registry established in 2001 to collect patient-reported long-term safety and other outcome data from patients with inflammatory arthritis, including RA, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis [12]. It includes participants commenced on bDMARDs as well as control subjects on conventional treatments (enrolment of control subjects since February 2007). Rheumatologists refer patients to the registry with minimal baseline information, including diagnosis, as well as rheumatoid factor and anti-citrullinated protein antibody (ACPA) status (ACPA collected since November 2010). All participants may commence, switch or cease bDMARDs at any point during their follow-up. Following written informed consent, participants complete a baseline ARAD questionnaire, with a follow-up questionnaire completed every 6 months for 2 years and then at 12-monthly intervals. The initial questionnaire is defined as the 'baseline' questionnaire, and there are no exclusions for disease duration, prior therapies or associated co-morbidities. The questionnaire was initially available in paper form only, but an electronic version has been available since August 2009. Adult participants with a diagnosis of RA were selected for this analysis, with data censored at October 2015. In order to reflect real-life clinical practice, participants are included in the registry with a diagnosis of RA based on expert clinical opinion (rheumatologist) rather than classification criteria. In Australia, bDMARDs can be prescribed for RA only by rheumatologists, and prescribing is restricted on the basis of the following criteria: (1) The patient has severe, active RA; (2) the patient has failed a 6-month intensive csDMARD trial with a minimum of two agents for a minimum of 3 months each; (3) the patient can demonstrate failure to achieve an adequate response to 6 months of intensive prior treatment by an elevated erythrocyte sedimentation rate > 25 mm/h and/or an elevated C-reactive protein level > 15 mg/L, and the patient has an active joint count of ≥ 20 active (swollen and tender) joints or ≥ 4 major active joints (elbow, wrist, knee, ankle, shoulder and/or hip). In Australia, there is universal access to medications via the Pharmaceutical Benefits Scheme (PBS). bDMARDs have been available on the PBS since August 2004. Prior to this, patients accessed bDMARDs through clinical trials.

Ethics approval for ARAD has been obtained from 18 committees and organisations across Australia (Additional file 1). This study was approved by The University of Adelaide Office of Research Ethics, Compliance and Integrity (approval number H-2015-258).

Outcome measure

For oral GC current use, each questionnaire contains a section 'medications for arthritis' where patients indicate their use of oral GCs (prednisolone/prednisone) since their previous questionnaire as 'never taken', 'currently taking', 'stopped taking' or 'don't know'. Data regarding dosage are not collected. For this analysis, a time-varying 'current use' variable was created for which 'currently taking' was coded as 'yes' and 'never taken', 'stopped taking' and 'don't know' responses were coded as 'no'. The current use variable includes only oral GC use, with injectable GC use described but not included in the analyses.

Predictors

Patient demographics, including age and sex, at baseline/initial questionnaire and a time-varying current age variable were considered as predictors in the analyses.

Current use of bDMARDs and csDMARDs were coded as yes/no time-varying variables using the same method described for current oral GC use. Current use of bDMARDs included use of etanercept, adalimumab, anakinra, infliximab, rituximab, abatacept, tocilizumab, golimumab or certolizumab. Current csDMARD use included use of methotrexate, leflunomide, sulphasalazine, hydroxychloroquine, azathioprine, cyclosporin, intramuscular gold or penicillamine. Current use of non-steroidal anti-inflammatory drugs (NSAIDs) included use of celecoxib, diclofenac, ibuprofen, indomethacin, ketoprofen, meloxicam, naproxen, piroxicam or any other NSAID. Current use of opioids included use of aspirin and codeine, paracetamol and codeine, dextropropoxyphene, oxycodone, OxyContin, morphine or tramadol.

The ARAD questionnaire also contains a global evaluation of disease activity section in which patients are asked to indicate their level of pain and overall arthritis activity in the past week on a 0–100 visual analogue scale (0 indicates no pain/arthritis activity, and 100 indicates pain as bad as it could be/extreme arthritis activity). In addition to other measures of health-related quality of life, the questionnaire contains the HAQ [13]. HAQ scores range from 0 to 3, with higher scores reflecting greater disability [14]. These variables were also time-varying.

Statistical analysis

Descriptive statistics were used to determine the patterns of oral GC use at baseline and throughout follow-up. It was hypothesised that GC use might vary according to the date of the baseline questionnaire. Prior to the availability of bDMARDs, there were limited treatment options for patients with RA with ongoing disease activity despite maximal csDMARD therapy. GC use may have been different in these patients who would have joined ARAD in the years closest to its inception, compared with those who joined in more recent years, when bDMARDs were more readily available. Population-averaged logistic regression (generalised estimating equation model) and transition state analysis were used to assess change in GC use over time, according to the date of baseline questionnaire. Date of entry (DOE) categories were created according to the date of the baseline questionnaire: 12 September 2001–15 March 2005, 15 March 2005–15 September 2008, 15 September 2008–15 March 2012, or 15 March 2012–6 October 2015.

A multivariable fixed-effects panel regression model was used to examine whether oral GC current use was associated with current age; disease duration; self-reported pain score; self-reported arthritis activity score; HAQ score; and current medication use, including bDMARDs, csDMARDs, NSAIDs and opioids. Age, self-reported pain score and self-reported arthritis activity score were transformed (divided by 10) for ease of interpreting the results. A fixed-effects model was chosen over a random effects model on the basis of the Hausman test. The fixed-effects model allows within-patient comparisons so that each patient is effectively acting as his or her own control.

Univariate transition state analysis was used to assess how these same factors influenced the HR of either commencing or ceasing oral GCs, with HRs relative to the first time point. In this analysis, two transition states were of interest: the transition from GC non-use at one visit to GC use at the next visit, and the transition from GC use at one visit to GC non-use at the next visit.

The fixed-effects panel regression model and transition state analyses included all patients with at least one follow-up visit after baseline. The panel regression model excluded those who were either on oral GCs at all visits or off oral GCs at all visits. Regression models were carried out using Stata version 12.1 software (StataCorp, College Station, TX, USA). The transition state analysis was carried out using R version 3.2.3 software (library msm version 1.6.4) [15, 16].

Results

A total of 3699 ARAD participants with a diagnosis of RA completed a baseline questionnaire upon entry to ARAD, 73% of whom were female, with a mean age of 57 years (SD 13). Baseline characteristics of the cohort are shown in Table 1. At baseline 44% were taking an oral GC, 54% were taking a bDMARD, 74% were taking a traditional csDMARD, 43% were taking an NSAID and 32% were taking an opioid. There were 41% on combined bDMARD and csDMARD therapy, 13% on a bDMARD without csDMARDs, and 33% on csDMARDs without a bDMARD. Throughout follow-up (median 4 years, IQR 1.5–7 years), the prevalence of oral GC ever-use was 61%.

Change in GC use over time, according to ARAD date of entry

To test the hypothesis that GC use may vary over time, the probability of GC use throughout follow-up was examined according to DOE categories. The probability of oral GC use throughout follow-up deceased over time: September 2001 to March 2005, 55%; March 2005 to September 2008, 47%; September 2008 to March 2012, 42%; and March 2012 to October 2015, 39%, ($p < 0.001$) (Fig. 1a). In addition, the transition state analysis showed that the HR of commencing oral GCs compared with the first DOE category decreased with date of baseline questionnaire (March 2005 to September 2008 HR 0.42; September 2008 to March 2012 HR 0.30, March 2012 to October 2015 HR 0.20), and the HR of ceasing oral GCs increased (March 2005 to September 2008 HR

Table 1 Baseline characteristics of adult patients with rheumatoid arthritis enrolled in Australian Rheumatology Association Database

Baseline characteristics ($n = 3699$)	No. (%)[a]
Age, years, mean (SD)	57.1 (13.0)
Female sex	2761 (73.4%)
RF-positive[b]	2554/3083 (82.8%)
ACPA-positive[b]	162/239 (67.8%)
Disease duration, years, median (IQR)	10 (1–34)
Duration of ARAD follow-up, years, median (IQR)	4 (1.5–7)
Oral GC use	1641 (44.4%)
GC injection use	740 (20.0%)
bDMARD use	1983 (53.6%)
csDMARD use	2727 (73.7%)
bDMARD and csDMARD combined use	1517 (41.0%)
bDMARD use only (without csDMARD)	466 (12.6%)
csDMARD use only (without bDMARD)	1210 (32.7%)
Neither bDMARD nor csDMARD use	506 (12.7%)
NSAID use	1576 (42.6%)
Opioid use	1174 (31.7%)

Abbreviations: ARAD Australian Rheumatology Association Database, *RA* Rheumatoid arthritis, *RF* Rheumatoid factor, *ACPA* Anti-citrullinated protein antibody, *GC* Glucocorticoid, *bDMARD* Biologic disease-modifying anti-rheumatic drug, *csDMARD* Conventional synthetic disease-modifying anti-rheumatic drug, *NSAID* Non-steroidal anti-inflammatory drug

[a]Unless otherwise stated

[b]In those with known RF/ACPA status

1.60, September 2008 to March 2012 HR 2.38, March 2012 to October 2015 HR 3.56) (Fig. 1b). Data from the transition state analysis can also be expressed as 'sojourn times', which is the average amount of time (in months) patients have spent in each state (Table 2).

Patient factors associated with oral GC current use

In the fixed-effects panel regression model (Table 3), longitudinal within-patient comparisons revealed that increasing age was associated with decreased GC current use (OR 0.24; 95% CI 0.07–0.81), but there was no association with disease duration (OR 1.05; 95% CI 0.93–1.19). Current use of bDMARDs was not associated with GC current use (OR 0.98; 95% CI 0.83–1.15); however, use of csDMARDs (10.13; 8.22–12.47), opioids (2.14; 1.84–2.48) and NSAIDs (1.18; 1.02–1.37) were all associated with increased GC current use. Higher current pain score (OR 0.94; 0.90–0.98) was associated with decreased GC current use, and higher arthritis activity scores (1.09; 1.05–1.14) and poorer HAQ scores (1.52; 1.30–1.79) were associated with increased GC current use.

Patient factors associated with oral GC commencement and cessation

In the transition state analysis (Fig. 2), within-patient comparisons revealed that increasing age was associated with decreased commencement and decreased cessation of oral GCs. Female sex was also associated with increased oral GC cessation. The moderate association between bDMARD use and oral GC cessation did not reach

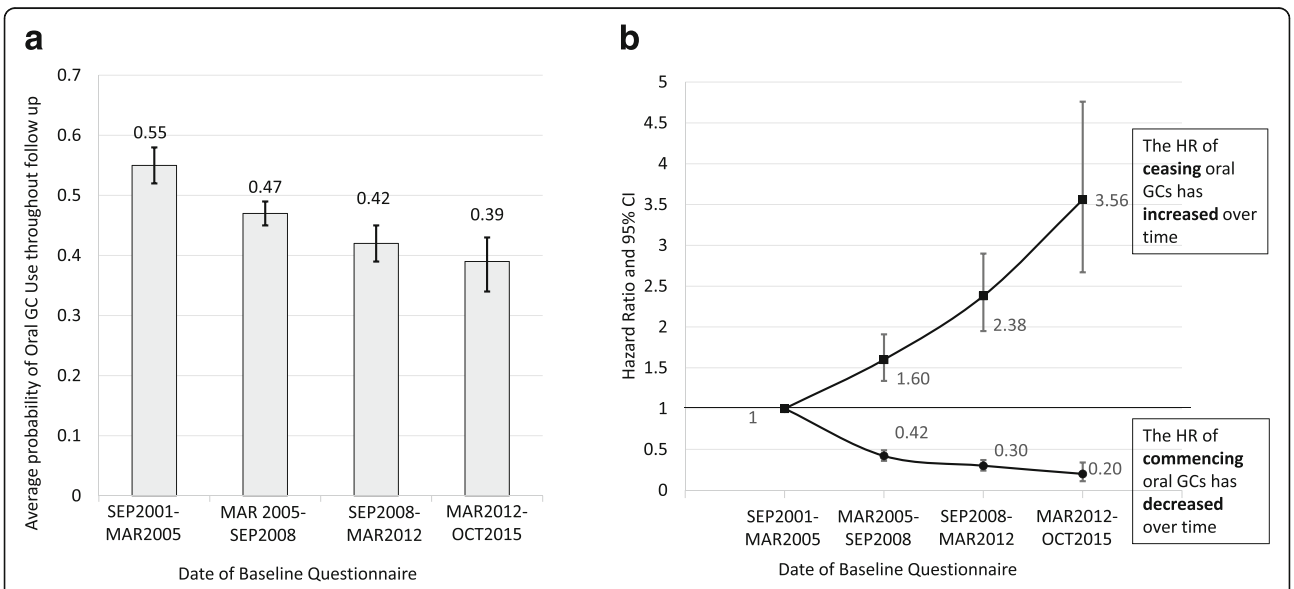


Fig. 1 The association between glucocorticoid (GC) use and date of Australian Rheumatology Association Database baseline questionnaire. **a** Average probability of oral GC use throughout follow-up, according to date of baseline questionnaire. **b** The HR of commencing and ceasing an oral GC according to date of baseline questionnaire (HRs are relative to the first time point)

Table 2 Sojourn times: mean amount of time (in months) spent on and off glucocorticoids, by Australian Rheumatology Association Database date of entry category

ARAD DOE category	State 1 (off GCs)		State 2 (on GCs)	
	Mean	95% CI	Mean	95% CI
12 Sep 2001 to 15 Mar 2005	57	52–63	151	130–175
15 Mar 2005 to 15 Sep 2008	137	123–152	94	86–104
15 Sep 2008 to 15 Mar 2012	193	159–234	63	56–72
15 Mar 2012 to 6 Oct 2015	292	172–493	42	33–54

GC Glucocorticoid

statistical significance. However, bDMARD, csDMARD or NSAID use was associated with a reduced HR of commencing oral GC therapy. Opioid use was associated with a reduced HR of both commencing and ceasing oral GCs. Higher HAQ score (greater disability) was associated with a greater HR of commencing oral GCs and a reduced HR of ceasing GCs. Higher pain scores were associated with an increased HR of commencing GCs, but there was no association between pain score and GC cessation. Higher arthritis activity score was not associated with either commencement or cessation of oral GCs.

Discussion

In this study, we sought to describe the use of GCs amongst patients with RA over time and to determine factors associated with GC current use as well as GC commencement and cessation. In addition, we aimed to determine whether bDMARD use is associated with the cessation of GCs. This was carried out using data from patients with RA enrolled in ARAD, a longitudinal biologic registry.

Table 3 Multivariable fixed-effects panel regression model to determine factors associated with oral glucocorticoid current use at any time point

Factors associated with GC current use	OR	95% CI
Age, decades	0.24	0.07–0.81[a]
Disease duration, years	1.05	0.93–1.19
Current bDMARD use	0.98	0.83–1.15
Current csDMARD use	10.13	8.22–12.47[a]
Current NSAID use	1.18	1.02–1.37[a]
Current opioid use	2.14	1.84–2.48[a]
Self-reported pain score (10)	0.94	0.90–0.98[a]
Self-reported arthritis activity score (10)	1.09	1.05–1.14[a]
HAQ score (3)	1.52	1.30–1.79[a]

Abbreviations: GC Glucocorticoid, *bDMARD* Biologic disease-modifying anti-rheumatic drug, *csDMARD* Conventional synthetic disease-modifying anti-rheumatic drug, *NSAID* Non-steroidal anti-inflammatory drug, *HAQ* Health Assessment Questionnaire

The analysis included patients with rheumatoid arthritis with at least one follow-up visit after baseline and excluded those who were on oral GCs at all visits or off oral GCs at all visits ($n = 1161$). The fixed-effects model uses all available time points and allows for within-patient comparisons where each patient acts as his or her own control

[a]Indicates $p < 0.05$

In this RA cohort, the probability of GC use decreased over time and in recent years, the probability of commencing GCs had reduced, whereas the probability of ceasing GCs had increased. This potentially reflects an increasing awareness of GC-related adverse events (AEs) as well as increased availability of effective disease-modifying agents.

The influence of sex and increasing age on GC use was also of interest. In the panel regression model, increasing age was associated with a reduced HR of current GC use. In keeping with this, in the transition state analysis, we found that increasing age was associated with a reduced HR of commencing GCs, suggesting that clinicians are more cautious about commencing GC treatment in older patients. However, increasing age was also associated with a reduced HR of ceasing GCs, suggesting that, once started, it is more difficult to discontinue GC treatment in older patients. In the transition state analysis, females were more likely to cease GCs, which is in keeping with previous findings that females are more concerned than males about GC use [17].

In the panel regression model, patients had lower pain scores at times when they were on GCs than at times when they were not. Adding to this, the transition state analysis showed that individuals were more likely to commence GCs at times when their pain scores were higher, but that current pain scores had no influence on GC cessation. Given that GCs are effective anti-inflammatory agents in RA, it is not surprising that their use was associated with lower pain scores and that they were more likely to be commenced at times when pain scores were higher. The lack of association between lower pain scores and GC cessation may represent an opportunity for clinicians to reduce GC use; however, this would need to be assessed in the context of traditional disease activity scores.

The panel regression model also showed that patients had greater disability (as indicated by higher HAQ scores) at times when they were on GCs than at times when they were not. This raises the question whether GC use contributes to disability in RA, as has been shown in other rheumatic conditions such as systemic lupus erythematosus and ANCA-associated vasculitis [18–20]. The transition state analysis adds to our understanding of this, showing that patients with greater disability were more likely to commence GC therapy and less likely to cease therapy. Traditional measures of disease activity are not collected in ARAD; however, patients had slightly higher patient-reported arthritis activity scores when they were on GCs than when they were not. When considering the panel regression and

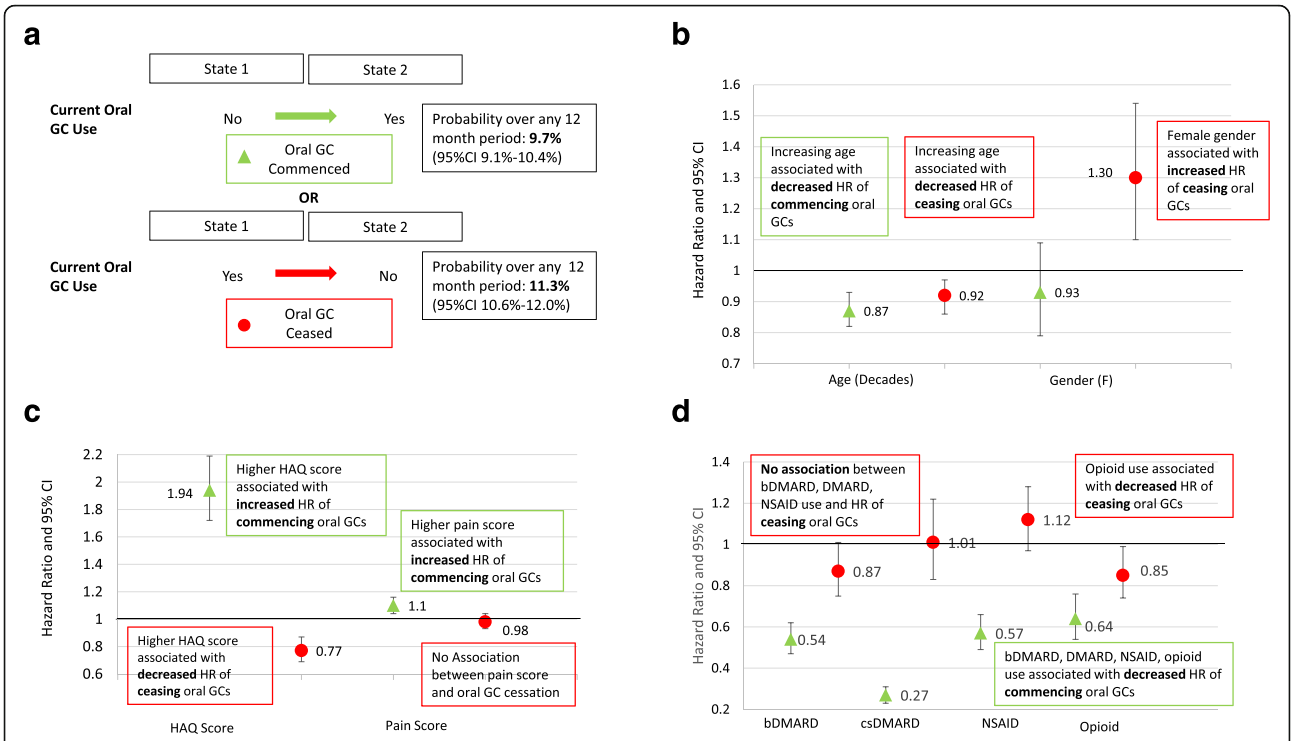


Fig. 2 Transition state analysis of factors associated with the commencement and cessation of an oral glucocorticoid (GC). **a** Two transition states of interest are shown: (1) off oral GC at one time point, then on oral GC at the next time point (*green triangle* = oral GC is commenced), and (2) on oral GC at one time point, then off oral GC at the next time point (*red circle* = oral GC is ceased). The probability of commencing or ceasing an oral GC in any 12-month period is shown. **b** The association between age (decades) and sex (female) and the HR of commencing or ceasing an oral GC. **c** The association between Health Assessment Questionnaire (HAQ) score and pain score and the HR of commencing or ceasing an oral GC. **d** The association between concurrent medication use (biologic disease-modifying anti-rheumatic drug [bDMARD], conventional synthetic disease-modifying anti-rheumatic drug [csDMARD], non-steroidal anti-inflammatory drug [NSAID] and opioid) and the HR of commencing or ceasing an oral GC

transition state analysis together, it appears that the HAQ was a more important driver of oral GC use than pain or self-reported arthritis activity scores.

Patients were more likely to be taking GCs at times when they were also taking csDMARDs, NSAIDs or opioids than at times when they were not using these concurrent medications. However, concurrent bDMARD use was not associated with either increased or decreased current GC use. If it were assumed that current GC use reflects ongoing disease activity, then these findings would suggest that when patients were on csDMARDs, NSAIDs or opioids, their disease was more active than when they were not on these agents. Although this may seem to contradict our knowledge that csDMARDs reduce disease activity, in the setting of bDMARD use ongoing csDMARD use may indeed reflect patients with ongoing disease activity not controlled by bDMARD treatment alone. In the transition state analysis, the moderate association between bDMARD use and GC cessation did not reach statistical significance, suggesting that bDMARDs do not have a significant steroid-sparing effect in regards to GC cessation.

GC use is associated with many AEs, and the likelihood of these developing is influenced by total GC exposure (dose and duration of therapy) [21, 22]. GC cessation is therefore a clinically meaningful outcome when assessing the steroid-sparing effects of bDMARDs and other disease-modifying agents. Use of bDMARDs and csDMARDs was associated with a reduced HR of commencing GCs, which may be due to a reduced need for GCs because these agents are effective at controlling disease activity. NSAID or opioid use was also associated with a reduced HR of commencing GCs, and this may be because use of these agents reflects joint damage rather than active disease. Opioids were associated with a reduced HR of ceasing GCs. Patients on both opioids and GCs may represent a subgroup of patients with ongoing disease activity requiring GCs and joint damage leading to pain treated with opioids. It is plausible that it is more difficult to cease GCs in this subgroup of patients.

The main limitations of this study are that all data in ARAD are patient-reported, and neither GC dosage nor conventional measures of disease activity are collected.

In addition, questionnaires are completed by patients at 6- to 12-monthly intervals and may therefore be associated with a recall bias. Enrolment in ARAD is done on an opt-in basis; therefore, there may be fundamental differences between those who do and do not choose to participate in the database. The ARAD questionnaire asks about GC use in the section 'medications for arthritis', and it is therefore assumed that the GC use reported has been prescribed for RA. However, many patients will have co-morbidities that are also indications for GCs, and it is possible that some of the reported GC use is driven by these co-morbidities. This could potentially bias the results towards the null hypothesis that there is no association between bDMARD use and GC cessation. The mortality in this sample was low, with 8% of the RA cohort recorded as deceased. Only limited data were available regarding cause of death; however, given the analyses made within-patient comparisons, it is unlikely that mortality would have significantly influenced the results.

Strengths of this study include the systematic and consistent way in which data are captured longitudinally in a real-life setting. In the treatment of RA in clinical practice, oral GCs may be given as short- or medium-term courses or used as a long-term therapy. Therefore, treatment may be started and stopped on numerous occasions throughout follow-up. Traditional methods for classifying GC use tend to be cross-sectional and do not capture the dynamic patterns of use that occur in clinical practice. For example, current use is often defined as use at a particular time point, such as at baseline or at the time of a predefined event (i.e., clinical remission or the development of an adverse effect). ARAD is a longitudinal dataset, allowing 'current use' to be defined as a time-varying indicator of whether a patient was taking oral GCs at each questionnaire time point. Most other relevant variables in the dataset were time-varying as well. The primary analyses (fixed-effects panel regression and transition state analysis) were specifically chosen in order to use the longitudinal nature of the data to determine within-patient concomitant predictors of both oral GC use and a change in use (commencement and cessation). This avoids the confounding due to unobserved/unmeasured variables that may occur in cross-sectional analyses.

Conclusions

Oral GC use among Australian patients with RA participating in ARAD has decreased over time. Compared with patients who joined ARAD at its inception, those who joined the registry in more recent years had a lower probability of commencing GCs and a greater probability of ceasing GCs. Care needs to be taken when commencing oral GCs because it is often difficult to cease therapy once started, and bDMARD use has only a modest impact on this. Consideration of intramuscular and intra-articular GCs may help to offset oral GC use.

Additional file

Additional file 1: ARAD list of current ethics approvals across Australia. (DOCX 19 kb)

Abbreviations

ACPA: Anti-citrullinated protein antibody; AE: Adverse event; ARAD: Australian Rheumatology Association Database; bDMARD: Biologic disease-modifying anti-rheumatic drug; csDMARD: Conventional synthetic disease-modifying anti-rheumatic drug; DOE: Date of entry; GC: Glucocorticoid; HAQ: Health Assessment Questionnaire; NSAID: Non-steroidal anti-inflammatory drug; PBS: Pharmaceutical Benefits Scheme; RA: Rheumatoid arthritis; RF: Rheumatoid factor

Acknowledgements

We thank Vibasha Chand, Joanie McPhee and Lyndall Henderson for their contributions to ARAD, as well as the ARAD participants who contribute to the database.

Funding

RJB is supported by an Australian postgraduate award and an Arthritis South Australia/Australian Rheumatology Association (South Australia) postgraduate grant. RB is funded by a National Health and Medical Research Council (NHMRC) senior principal research fellowship. ARAD receives educational grant and project funding from Pfizer Australasia, AbbVie Australia Pty. Ltd, Bristol-Myers Squibb, Celgene and Sanofi.

Availability of data and materials

The data that support the findings of this study are available from the Australian Rheumatology Association Database (ARAD), but restrictions apply to the availability of these data, which were used under license for the present study and so are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of ARAD.

Authors' contributions

RJB, SL, SW and CLH made substantial contributions to the conception and design of the study. RB, CB, ML, LM and CLH made substantial contributions to the acquisition of data. RJB, SL and CLH analysed and interpreted the patient data. RJB was a major contributor to the writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval for ARAD has been obtained from 18 committees and organisations across Australia (Additional file 1). This study was approved by The University of Adelaide Office of Research Ethics, Compliance and Integrity (approval number H-2015-258). Written informed consent was obtained from all participants prior to their enrolment in ARAD.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Rheumatology Unit, Royal Adelaide Hospital, North Terrace, Adelaide 5000, Australia. [2]Division of Medicine, The University of Adelaide, Adelaide, Australia. [3]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia. [4]Monash Department of Clinical Epidemiology, Cabrini Institute, Melbourne, Australia. [5]Department of Epidemiology & Preventive Medicine,

School of Public Health and Preventative Medicine, Monash University, Melbourne, Australia. [6]Redcliffe Hospital, Redcliffe, Australia. [7]School of Public Health and Community Medicine, University of New South Wales, Sydney, Australia. [8]Northern Clinical School, Institute of Bone and Joint Research, University of Sydney, Department of Rheumatology, Royal North Shore Hospital, Sydney, Australia.

Received: 9 March 2017 Accepted: 26 October 2017
Published online: 15 November 2017

References

1. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Lund Hetland M, Naranjo A, Baecklund E, Herborn G, Rau R, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Ann Rheum Dis. 2007;66(11):1491–6.
2. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane Database Syst Rev. 2007;1, CD006356.
3. Da Silva JAP, Jacobs JWG, Kirwan JR, Boers M, Saag KG, Ines LBS, de Koning EJP, Buttgereit F, Cutolo M, Capell H, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis. 2006;65(3):285–93.
4. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, Kovac SH, Spettell CM, Saag KG. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis Rheum. 2006;55(3):420–6.
5. Luqmani R, Hennell S, Estrach C, Basher D, Birrell F, Bosworth A, Burke F, Callaghan C, Candal-Couto J, Fokke C, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). Rheumatology (Oxford). 2009;48(4):436–9.
6. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, Gorter S, Knevel R, Nam J, Schoels M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis. 2010;69(6):964–75.
7. Naumann L, Huscher D, Detert J, Spengler M, Burmester GR, Buttgereit F. Anti-tumour necrosis factor α therapy in patients with rheumatoid arthritis results in a significant and long-lasting decrease of concomitant glucocorticoid treatment. Ann Rheum Dis. 2009;68(12):1934–6.
8. Seror R, Dougados M, Gossec L. Glucocorticoid sparing effect of tumour necrosis factor α inhibitors in rheumatoid arthritis in real life practice. Clin Exp Rheumatol. 2009;27(5):807–13.
9. Kawai VK, Grijalva CG, Arbogast PG, Curtis JR, Solomon DH, Delzell E, Chen L, Ouellet-Hellstrom R, Herrinton L, Liu LY, et al. Changes in cotherapies after initiation of disease-modifying antirheumatic drug therapy in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2011;63(10):1415–24.
10. Nilsson AC, Christensen AF, Junker P, Lindegaard HM. Tumour necrosis factor-α inhibitors are glucocorticoid-sparing in rheumatoid arthritis. Dan Med Bull. 2011;58(4):A4257.
11. Fortunet C, Pers YM, Lambert J, Godfrin-Valnet M, Constant E, Devilliers H, Gaudin P, Jorgensen C, Prades BP, Wendling D, et al. Tocilizumab induces corticosteroid sparing in rheumatoid arthritis patients in clinical practice. Rheumatology (Oxford). 2015;54(4):672–7.
12. Buchbinder R, March L, Lassere M, Briggs AM, Portek I, Reid C, Meehan A, Henderson L, Wengier L, van den Haak R. Effect of treatment with biological agents for arthritis in Australia: the Australian Rheumatology Association Database. Intern Med J. 2007;37(9):591–600.
13. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum. 1980;23(2):137–45.
14. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol. 1993;20(3):557–60.
15. R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2015. http://www.R-project.org/.
16. Jackson CH. Multi-state models for panel data: the msm package for R. J Stat Softw. 2011;38(8):1–29. http://www.jstatsoft.org/v38/i08/.
17. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. NPJ Prim Care Respir Med. 2015;25:15026.
18. Apostolopoulos D, Kandane-Rathnayake R, Raghunath S, Hoi A, Nikpour M, Morand EF. Independent association of glucocorticoids with damage accrual in SLE. Lupus Sci Med. 2016;3(1), e000157.
19. Ruiz-Arruza I, Ugarte A, Cabezas-Rodriguez I, Medina JA, Moran MA, Ruiz-Irastorza G. Glucocorticoids and irreversible damage in patients with systemic lupus erythematosus. Rheumatology (Oxford). 2014;53(8):1470–6.
20. Robson J, Doll H, Suppiah R, Flossmann O, Harper L, Hoglund P, Jayne D, Mahr A, Westman K, Luqmani R. Glucocorticoid treatment and damage in the anti-neutrophil cytoplasm antibody-associated vasculitides: long-term data from the European Vasculitis Study Group trials. Rheumatology (Oxford). 2015;54(3):471–81.
21. Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, Sylvestre MP. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis. 2012;71(7):1128–33.
22. Movahedi M, Beauchamp ME, Abrahamowicz M, Ray DW, Michaud K, Pedro S, Dixon WG. Risk of incident diabetes associated with dose and duration of oral glucocorticoid therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2016;68(5):1089–98.

HUMAN RESEARCH ETHIC COMMITTEES THAT HAVE APPROVED ARAD

ACT Health & Community Care HREC (EC 00100)

AIHW - Australian Institute of Health & Welfare Ethics Committee (EC 00103)

Australian Government Department of Health HREC (EC 00106)

Cabrini Hospital HREC (EC 00239)

Cancer Council NSW – Cancer Institute Ethics Committee (EC 00345)

DOHWA – Dept. of Health WA HREC (EC 00422)

DVA - Dept. of Veterans' Affairs HREC (EC 00366)

Monash University HREC (EC 00234)

North Sydney Local Health District HREC (Hawkesbury) (EC 00132)

NT HREC - NT Dept. of Health & Families & Menzies Sc (EC 00153)

Queensland HREC (EC 00334)

Royal Children's Hospital HREC (EC 00238)

SAC – Southern Adelaide Clinical HREC - SA Dept. of Health (EC 00188)

Southern Metropolitan Health Service HREC, Government of WA

St Vincent's Hospital (Melbourne) Ltd. HREC (EC 00344)

Tasmania Health & Medical HREC (EC 00337)

The Cancer Council Victoria HREC (EC 00203)

Women's & Children's Hospital SA Health Network HREC (EC 00197)

In Progress:
Royal Perth Hospital

No Longer active:
Princess Margaret Hospital, WA HREC (EC 00268) – no longer active 2007-2016

Updated 14/2/2017

5 GC Use- The Patient Perspective

This chapter addresses the second aim of the thesis:

> *To better understand the benefits and harms of glucocorticoid use from the patient perspective*

5.1 Introduction

In this chapter, the focus of the work moves from investigating how GCs are used in RA, to examining the benefits and harms of treatment from the patient perspective. As a starting point, it explores the need for a patient reported outcome measure (PRO) to capture the benefits and harms of GC use from the patient perspective, by searching the literature for whether a GC PRO has already been developed. Having established that such a PRO has not already been reported in the literature, the chapter goes on to explore the benefits and harms of GC use from the patient perspective with a descriptive exercise to establish the types of GC AEs reported in RCTs, and a quantitative survey presented as a published manuscript. The work in this section of the thesis has also contributed to the OMERACT GC working group, described in more detail in the Thesis Introduction. Complementary work undertaken by other members of the OMERACT GC working group is described in the OMERACT 2016 (218) and 2018 (83) conference papers, which are included in Appendix and Appendix.

Establishing whether a GC PRO has already been developed

As an initial step, a systematic literature review (SLR) was performed to determine if a PRO for capturing the effects of GC use had already been published. This involved a librarian-assisted search, which was carried out in OVID MEDLINE (1946 to February, Week 3, 2016) and OVID EMBASE (1974 to February 26, 2016). The search terms are shown in Table 5.1, with the search (1 OR 2 OR 3 OR 4 OR 5) AND 6 AND (7 OR 8 OR 9 OR 10 OR 11) performed in both databases.

Table 5.1: Search terms used to identify any pre-existing PROMs for GC AEs

OVID MEDLINE	OVID EMBASE
1. exp Adrenal Cortex Hormones/	1. exp corticosteroid/
2. corticosteroid*.mp.	2. corticosteroid*.mp.
3. glucocorticoid*.mp.	3. glucocorticoid*.mp.
4. glucocorticosteroid*.mp.	4. glucocorticosteroid*.mp.
5. steroid*.mp.	5. steroid*.mp.
6. patient report*.mp.	6. patient report*.mp.
7. (adverse adj2 effect*).mp.	7. (adverse adj2 effect*).mp.
8. (adverse adj2 event*).mp.	8. (adverse adj2 event*).mp.
9. (adverse adj2 outcome*).mp.	9. (adverse adj2 outcome*).mp.
10. (adverse adj2 reaction*).mp.	10. (adverse adj2 reaction*).mp.
11. (side adj2 effect*).mp.	11. (side adj2 effect*).mp.

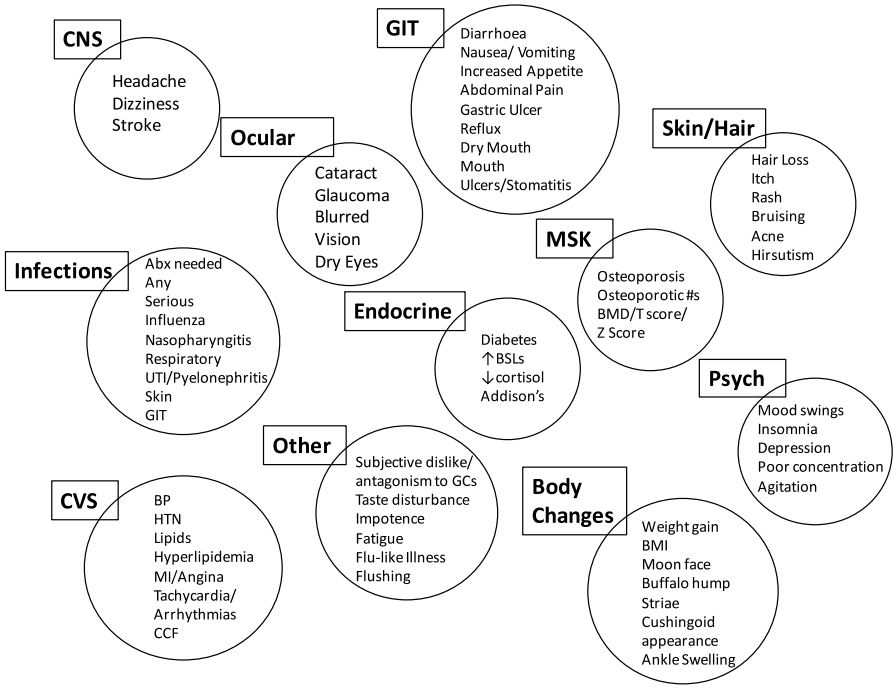
Titles and abstracts of 146 articles were screened, and seven papers were chosen for full-text review. No PRO for systemic GC use was identified; however, two articles described the Inhaled Corticosteroid Questionnaire (ICQ)(219, 220), a PRO for inhaled GC use (218). The ICQ contains 57 items across 15 categories; 38 items identified inhalation-related AEs affecting the oropharynx, taste, and voice, and 19 items were related to systemic AEs of inhaled GC including mood, skin/hair/nails, perspiration, and tiredness, among others. Given many of the items in the ICQ were specific to inhaled GC preparations, it was felt that a PRO to capture the effects of systemic GC exposure is still required.

Exploring GC AEs reported in selected RCTs

Having established that a GC PRO has not yet been published, it was deemed important to look more closely at which AEs have been reported in published randomised controlled trials (RCTs) of GC use and whether there are differences according to the disease population being studied. Together with another member of the OMERACT GC working group (L. Lai), an exploratory exercise was carried out, using the studies included in four SLRs of chronic inflammatory diseases for which GC treatment is commonly used: 1. polymyalgia rheumatica (PMR; 9 RCTs)(221), 2. Crohn's disease (14 RCTs)(222), 3. ulcerative colitis (UC; 6 RCTs) (223) and 4. RA (28 RCTs) (224). Each study included in the four SLRs was reviewed and GC AEs were extracted by two reviewers (R. Black & L. Lai). There were 63 different AEs, fitting into 11 different categories reported across all the RCTs reviewed (Figure 5.1) (218). The percentage of RCTs in each SLR that reported at least one GC AE from each category was determined (Figure 5.2). There were no central nervous system AEs reported in the PMR RCTs and no cardiovascular or

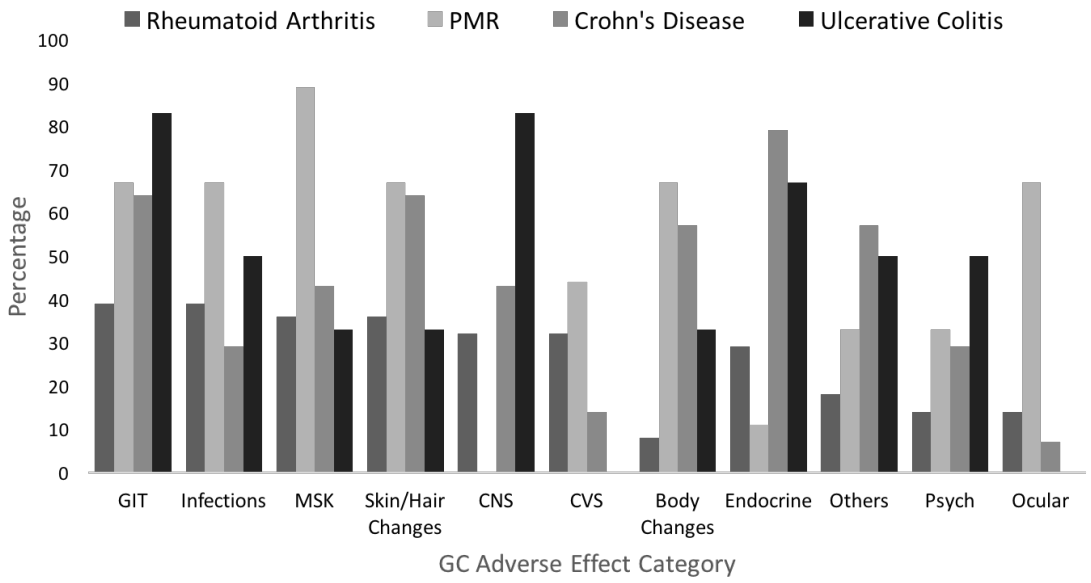
ocular AEs reported in the UC RCTs. The collection of GC AEs in published RCTs looking at GC use in inflammatory diseases was inconsistent, again demonstrating the need for a GC PRO.

Figure 5.1: AEs reported in RCTs of GC use in inflammatory conditions



GIT=gastrointestinal tract, MSK=musculoskeletal, CNS=central nervous system, Psych= psychiatric, Abx=antibiotics, UTI=urinary tract infection, BP=blood pressure, HTN=hypertension, MI=myocardial infarction, CCF=congestive cardiac failure, BSLs=blood sugar levels, #s=fractures, BMD=bone mineral density

Figure 5.2 Percentage of RCTs reporting each GC AE Category in 4 Inflammatory Diseases



PMR=polymyalgia rheumatica, GIT=gastrointestinal tract, MSK=musculoskeletal, CNS=central nervous system, Psych= psychiatric

A cross-sectional patient survey of the benefits and harms of GC use

Having established that a GC PRO has not yet been developed and that published RCTs are inconsistent in their collection of GC AEs, the next stage was to explore the benefits and harms of GC use from the patient perspective. This work also investigates whether the symptoms patients attribute to GC use are likely to be due to GC use rather than the disease being treated or other medications. This section is presented as a published manuscript and describes a cross-sectional survey looking at GC AEs experienced by two international patient populations. It captured which AEs are considered the 'worst' by patients, whether patients feel the benefits of GCs outweigh the AEs, and whether GCs help their disease "a lot," "a little," "not sure," or "not at all". The survey was initially administered to an Australian cohort of rheumatology outpatients who had used GCs within the past 12 months and included patients with various rheumatic diagnoses. In order to assess whether the AEs patients attribute to GC use might actually be due to other medications or the underlying disease, the survey was also administered to a US cohort of RA patients who were both users and non-users of GCs, allowing for a comparison of reported AEs between these groups. AEs identified as "worst" by GC users included skin thinning/easy bruising, sleep disturbance, mood disturbance, and change in facial shape. The comparison of AEs between GC users and non-users confirmed that most GC AEs are more frequently reported by GC users, suggesting that patients are reliably attributing AEs to GC use. It was noted that many of the AEs that

are important to patients are not easily measured in the clinic or research setting, reinforcing the need for a GC PRO.

A large body of research, including the author's work described above, has now been carried out by the OMERACT GC working group in preparation for developing a core domain set, which is the first step in the development of a GC PRO (83, 218). This work, including that presented in the manuscript below (225), has shed light on the patient perspective of GC use. Many of the AEs that are important to patients, occur commonly but are not easily measured. Reassuringly, AEs commonly attributed to GCs are significantly more frequent in those exposed to GCs compared to those unexposed, suggesting that patients are correctly attributing their symptoms to GC use. In addition to the physical and psychological symptoms commonly identified in quantitative studies, qualitative work carried out by other members of the OMERACT GC working group has revealed outcomes relating to participation and contextual factors are also very important to patients (83, 218).

5.2 Manuscript: A Survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases: The Patient Perspective

Statement of Authorship

Title of Paper	A Survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases: The Patient Perspective
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Black RJ, Goodman SM, Ruediger C, Lester S, Mackie SL, Hill CL: A Survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases: The Patient Perspective. *J Clin Rheumatol* 2017.

Principal Author

Name of Principal Author (Candidate)	Rachel Black		
Contribution to the Paper	Responsible for the design and conception of the work, data preparation including data cleaning, data analysis and interpretation, preparation of the manuscript and acted as corresponding author.		
Overall percentage (%)	60%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24 April 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Susan Goodman		
Contribution to the Paper	Responsible for administering the survey to the US cohort, collecting data from the US cohort and critically reviewing the manuscript, with final approval of the version to be published.		
Signature		Date	July 19, 2018

Name of Co-Author	Carlee Ruediger
Contribution to the Paper	Responsible for administering the survey to the AUS cohort, collecting data from the AUS cohort and critically reviewing the manuscript, with final approval of the version to be published.

Signature		Date	26/4/2019

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Susan Lester		
Contribution to the Paper	Supervised the design and conception of the work including appropriate analyses and critically reviewed the manuscript, with final approval of the version to be published.		
Signature		Date	24 April 2019

Name of Co-Author	Sarah Mackie		
Contribution to the Paper	Supervised the design and conception of the work and critically reviewed the manuscript, with final approval of the version to be published.		
Signature		Date	03-MAY-2019

Name of Co-Author	Catherine Hill		
Contribution to the Paper	Supervised the design and conception of the work including development of the questionnaire and analyses and critically reviewd the manuscript, with final approval of the version to be published.		
Signature		Date	24 April 2019

A Survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases

The Patient Perspective

Rachel J. Black, MBBS,† Susan M. Goodman, MD,‡ Carlee Ruediger, PhD,§ Susan Lester, BSc (Hons),§ Sarah L. Mackie, PhD,|| and Catherine L. Hill, MD*†§*

Objective: The aim of this study was to explore, from the patient's perspective, the beneficial and adverse effects (AEs) of glucocorticoids (GCs) in patients with rheumatic diseases, to be used in the development of a patient-reported outcome measure.

Methods: A cross-sectional survey, capturing benefits and AEs of GC use, was administered to 2 groups of patients: (1) those attending a tertiary rheumatology clinic with various rheumatic diseases who had used GCs within the past year and (2) patients from the Hospital for Special Surgery rheumatoid arthritis database.

Results: Cohort 1 had 55 GC users, and cohort 2 had 95 GC users and 29 nonusers. The majority of GC users in both cohorts reported at least 1 AE (100%, 86%). The AE prevalence per person was 50% higher in cohort 1 compared with GC users in cohort 2 (7.7 vs. 5.3; AE ratio, 1.5; 95% confidence interval, 1.3–1.7) and 2-fold greater in cohort 2 GC users compared with GC nonusers (5.3 vs. 2.6; AE ratio, 2.0; 95% confidence interval, 1.6–2.6). In both cohorts, AEs identified as "worst" by GC users included skin thinning/easy bruising, sleep disturbance, mood disturbance, and change in facial shape. Most felt GCs helped their disease "a lot" (78%/62%) and that the benefits were greater than the AEs (55%/64%). Many AEs were more frequent in GC users than in nonusers.

Conclusions: Patients receiving GC therapy for rheumatic conditions report a large number of AEs and those that have the greatest life impact are often difficult for physicians to measure. These results will inform the development of a patient-reported outcome measure to capture the effects of GCs from the patient's perspective.

Key Words: adverse events, glucocorticoids, patient-reported outcomes, rheumatic diseases, rheumatoid arthritis

(*J Clin Rheumatol* 2017;23: 416–420)

Glucocorticoids (GCs) are frequently used to treat rheumatic conditions including inflammatory arthritis, connective tissue disorders, vasculitis, and polymyalgia rheumatica.[1] Although they are effective anti-inflammatory agents, they are also associated with many potential adverse effects (AEs) such as skin thinning, easy bruising, weight gain, osteoporosis, diabetes, hypertension, infection, and cataract. However, not all patients exposed to GCs will develop AEs, and there is currently no standardized measure of the benefits and AEs that are important to patients. The European League Against Rheumatism (EULAR) Taskforce on GC therapy has published 2 systematic reviews concluding that there is a need to systematically capture GC AEs in a standardized manner.[2,3] The EULAR recommendations for monitoring GC AEs in clinical trials and daily practice suggested that new tools be developed for assessing adverse events.[4] This has led to the very recent development of the Glucocorticoid Toxicity Index (GTI), which measures the physiological AEs (clinical signs and biomarkers) of GC use.[5] The GTI focuses on items that are measurable in the clinic such as glucose tolerance, body mass index, and blood pressure.

Increasingly, a patient's experience of treatment and care has been recognized as an important quality indicator. This has led to an expansion in the development and application of questionnaires to measure health and illness from the patient's perspective. Patient-reported outcome measures (PROMs) provide unique insight into the way patients perceive their health and the impact that treatments have on their quality of life.[6,7] Patient-reported outcome measures involve patients in clinical decision making, can improve doctor-patient communication about treatment, and ultimately lead to better patient outcomes.[7] At present, there is no PROM to measure the risks, benefits, and experience of systemic GC use from the patient's perspective.[8] Patients may perceive important effects differently than physicians,[9] making it important to understand both the impact of GC use from the patient's perspective and the physiological impact measured by the GTI.

The first step in developing a PROM for the impact of GCs is to undertake qualitative and quantitative pilot work that provides insight into the aspects of GC treatment that are important to patients, so that these can be captured as items in any future measurement tool. The aim of this pilot study was to determine the AEs related to GCs in 2 groups of GC users and to explore which GC effects are important to patients. A secondary aim was to compare AEs reported by rheumatoid arthritis patients exposed and not exposed to GCs.

METHODS

A cross-sectional, questionnaire-based survey was carried out in 2 cohorts, in Australia and the United States. In Australia, the study was approved by The Queen Elizabeth Hospital Human Research Ethics Committee (reference no. HREC/14/TQEHLMH/209). In the United States, the cohort was approved by the Hospital for Special Surgery Ethics Review Board (reference no. 2014-234-CR2).

Participants

Participants in cohort 1 (Australian cohort) attended a tertiary rheumatology clinic with various rheumatic diseases and

From the *Discipline of Medicine, The University of Adelaide; and †Rheumatology Unit, Royal Adelaide Hospital, Adelaide, South Australia, Australia; ‡Hospital for Special Surgery, New York, NY; §Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, South Australia, Australia; and ||The University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom.

This study was supported by the Weill Cornell Clinical Translational Science Center (UL1-TR000457-06). R.J.B. is supported by an Australian Postgraduate Award and an Arthritis South Australia/Australian Rheumatology Association Postgraduate Grant.

The authors declare no conflict of interest.

Correspondence: Rachel J. Black, MBBS, Rheumatology Unit, Royal Adelaide Hospital, North Terrace, Adelaide, South Australia, Australia 5000. E-mail: Rachel.black2@sa.gov.au.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.jclinrheum.com).

ISSN: 1076-1608
DOI: 10.1097/RHU.0000000000000585

were taking an oral GC currently or within the past 12 months. Potential participants were identified from the departmental electronic outpatient letters, which are sent to the patient's general practitioner after each outpatient visit and include a summary of the diagnoses and medications. All letters from the past 12 months were assessed by 2 reviewers (R.J.B., C.R.), and a random selection of eligible patients was mailed out a participant information sheet, consent form, and a copy of the questionnaire with a reply paid return envelope. Cohort 2 (US cohort) was from the Hospital for Special Surgery rheumatoid arthritis (RA) database and included both GC users and nonusers. Cases included in the database were identified from the Hospital for Special Surgery practice records by *International Classification of Diseases, Ninth Revision* code 714.0 and confirmed by chart review. Cases meeting the American College of Rheumatology/EULAR criteria for RA were recruited at a clinic visit or via mail and were included after giving consent, at which time they completed a brief survey and agreed to be contacted for further studies. The questionnaire was distributed to patients on the database with a valid e-mail address.

Questionnaire

A pilot questionnaire was developed in order to explore patient-reported GC AEs and assess the risks and benefits of GCs from the patient's perspective. It included a checklist of 19 known AEs and an open-ended question about presence of "other GC side effects." The questionnaire was designed to be as inclusive as possible, while balancing the burden of data entry by keeping the checklist relatively concise. Checklist items included AEs cited frequently in the literature, as well as those occurring frequently in the authors' clinical experience. In addition, all participants were asked to rate the 3 "worst" AEs. Participants exposed to GCs were asked to indicate whether GC therapy helped "a lot," "a little," "not sure," or "not at all" and whether the AEs they experienced were worse than the benefits of treatment (yes/no/not sure). The questionnaire was not developed to be a PROM itself, but rather as a format by which to capture information that will inform the development of a PROM in the future.[8] (A copy of the questionnaire can be found in file, Supplemental Digital Content 1, http://links.lww.com/RHU/A76.)

Analysis

Descriptive statistics were used to summarize cohort demographics and the frequency of the individual AEs on the checklist as well as those considered to be the worst AEs. The median number of AEs experienced by each patient (AE prevalence) was compared between cohorts using Poisson regression, and the number of patients to report at least 1 AE was analyzed using χ^2 analysis. The degree to which participants felt GCs helped their condition was assessed by comparing the ordinal trend between groups using the Cochran Armitage exact test. A χ^2 analysis was carried out for the comparison of GC AEs and benefits. Within cohort 2, AEs reported by GC users and GC nonusers were compared by Fisher exact test. All analyses were carried out in R version 3.2.3.[10]

RESULTS

In cohort 1 (Australia), 88 questionnaires were distributed, and 55 (63%) were returned. In cohort 2 (United States), there were 227 questionnaires distributed to those with a valid e-mail address, with 124 (55%) returned. All patients in cohort 1 were GC users, and in cohort 2, 95 (77%) had ever used GCs (GC users), and 29 (23%) had never used GCs (GC nonusers). Demographics and diagnoses are summarized in Table 1. For cohort 1, the 33 patients who declined to participate were younger (median age, 63 years [interquartile range {IQR}, 51–75 years vs. 68 years [IQR, 60–-76 years]), and a greater proportion was female (27/33 [82%] vs. 39/55 [71%]). For cohort 2, the 103 patients who did not participate were also slightly younger (median, 60 years [IQR, 52–-70 years] vs. 63 [IQR, 53–71 years]), with a similar proportion of females (91/103 [88%] vs. 103/124 [83%]). Rheumatoid arthritis duration was similar in nonparticipants (median, 9.5 years [IQR, 4.5–18.0 years] vs. 9.6 years [IQR, 5.5–17.5 years]), and there were fewer GC users at the time of the survey (23/103 [22%] vs. 35/124 [28%]).

The AE prevalence per person was 50% higher in cohort 1 compared with GC users in cohort 2 (7.7 vs. 5.3; AE ratio, 1.5; 95% confidence interval, 1.3–1.7) and 2-fold greater in cohort 2 GC users compared with GC nonusers (5.3 vs. 2.6; AE ratio, 2.0; 95% confidence interval, 1.6–2.6). All patients in cohort 1 reported at least 1 GC AE compared with 86% of GC users in cohort 2 ($P = 0.002$).

The frequency of patient-reported AEs and worst AEs are shown in the Figure 1. The most frequent AEs were similar among patients in cohort 1 (thin skin/easy bruising, weight gain, sleep disturbance, and stomach upset/gastric reflux) and GC users in cohort 2 (sleep disturbance, thin skin/easy bruising, and weight gain). The most frequent AEs in cohort 2 GC nonusers were sleep disturbance, stomach upset/gastric reflux, and muscle weakness. Worst AEs were dependent on the AE frequency and included thin skin/easy bruising (9/45), weight gain (9/36), and sleep disturbance

TABLE 1. Baseline Demographics and Diagnoses

Demographics	Cohort 1 (n = 55) (Australia)	Cohort 2 (n = 124) (United States)	
		GC Users (n = 95)	GC Nonusers (n = 29)
Age, median (IQR), y	68 (33–89)	63 (52–72)	63 (53–70)
Sex, female, n (%)	39 (71)	77 (81)	26 (90)
Diagnosis n (%)			
Connective tissue disease	14 (25)		
RA	14 (25)	95 (100)	29 (100)
Polymyalgia rheumatica	14 (25)		
Giant cell arteritis	5 (9)		
Other vasculitis	3 (5)		
Other inflammatory arthritis	2 (4)		
Other	3 (5)		

(9/30) in cohort 1. The worst AEs for GC users in cohort 2 included weight gain (13/40), sleep disturbance (8/49), stomach upset/gastric reflux (8/38), and muscle weakness (8/34). Glucocorticoid nonusers noted swelling of the feet or ankles (4/6), weakness of muscles (3/8), increased appetite (2/3), and thrush in the mouth (2/2) as the worst AEs. Additional AEs attributed to GCs in either cohort are shown in the Figure, Supplemental Digital Content 2, http://links.lww.com/RHU/A77.

In both GC use cohorts, most (78% cohort 1/62% cohort 2 GC users) felt GCs helped their disease "a lot," 11%/21% felt they helped "a little," 9%/8% were "not sure," and 2%/8% felt GCs did not help at all, with no difference between groups (ordinal $P = 1.0$). Most participants in cohorts 1 (55%) and 2 (64%) felt the benefits of treatment were greater than the AEs, with no difference between groups ($P = 0.67$). In cohort 2, AEs including weight gain, thin skin or easy bruising, high blood sugars, broken bones, change in shape of face, change in shape of body, and increased appetite were more frequently reported by GC users compared with GC nonusers ($P < 0.05$) as shown in Table 2.

DISCUSSION

This study has demonstrated that many AEs that are important to patients are more common in GC users compared with nonusers and include symptoms that are difficult to capture using conventional physiological measures. In addition, a difference in the AE rate among cohort 1 (mixed rheumatic diagnoses) and GC users in cohort 2 (RA) was detected, possibly reflecting the different demographics, diagnoses, and unmeasured differences in the dose and duration of GC treatment.

Many studies looking at GC AEs have focused on AEs that are easier to measure such as osteoporosis, fractures, and infection. However, few studies have also captured patient-reported GC AEs. In a cross-sectional study of UK patients with asthma (n = 233), 88% reported 1 or more AEs, with bruising (67%) and weight gain (67%) being the most common.[11] In a French cohort study of 80 participants on long-term systemic GCs, 71% reported 1 or more AEs, with change in face shape reported as the most distressing (39%).[12] A cross-sectional study of UK patients with asthma, chronic obstructive pulmonary disease, and fibrosing

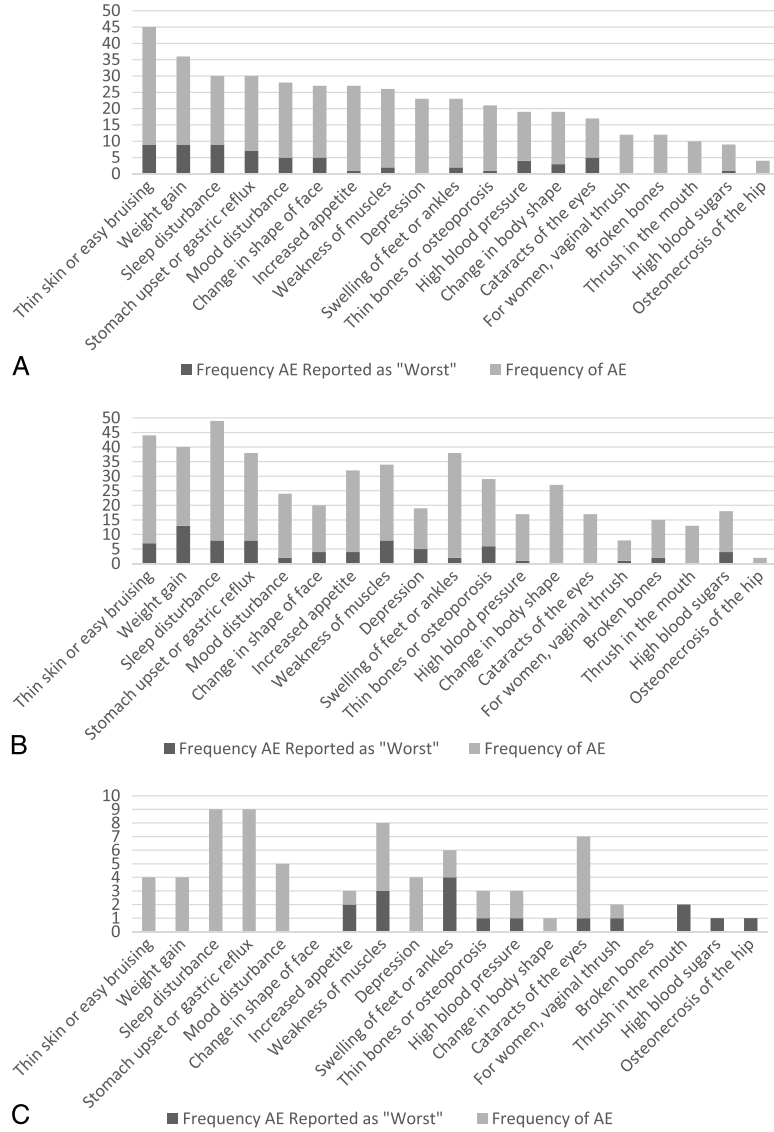


FIGURE 1. Frequency of glucocorticoid adverse effects and worst adverse effects in (A) cohort 1 GC users, n = 55, and (B) cohort 2 GC users, n = 95, and (C) cohort 2 GC nonusers, n = 29.

TABLE 2. Differences Between AEs Reported by GC Users and GC Nonusers in Cohort 2

	Cohort 2 GC Users (n = 95)		Cohort 2 GC Nonusers (n = 29)		
	No. Reporting as AE	No. Not Reporting as AE	No. Reporting as AE	No. Not Reporting as AE	*P*
Weight gain	40	55	4	25	0.007[a]
Thin skin or easy bruising	44	51	4	25	0.002[a]
High blood sugars	18	77	1	28	0.043[a]
Weakness of muscles	34	61	8	21	0.050
High blood pressure	17	78	3	26	0.400
Depression	19	76	4	25	0.590
Mood disturbance	24	71	5	24	0.460
Thin bones or osteoporosis	29	66	3	26	0.031
Broken bones	15	80	0	29	0.021[a]
Change in shape of face	20	75	0	29	0.004[a]
Change in body shape	27	68	1	28	0.004[a]
Sleep disturbance	49	46	9	20	0.059
Increased appetite	32	63	3	26	0.017[a]
Stomach upset or gastric reflux	38	57	9	20	0.510
Swelling of feet or ankles	38	57	6	23	0.076
Thrush in the mouth	13	82	2	27	0.520
Cataracts of eyes	17	78	7	22	0.440
Osteonecrosis of the hip	2	93	1	28	0.550
For women, vaginal thrush	8	69	2	24	1.000

[a]Statistically significant difference between GC users and GC nonusers ($P < 0.05$).

alveolitis (n = 367) found that bruising (73%) and muscle weakness (60%) were the most common GC AEs.[13] A United Kingdom–based case-control study of polymyalgia rheumatica and giant cell arteritis found that 23 (66%) of 35 participants reported 1 or more AEs, with weight gain (26%) and skin changes (26%) being the most common.[14]

In the largest study to date, Curtis et al.[15] included a population cohort of 2167 long-term GC users from the United States, of which 90% reported at least 1 from a list of 8 potential AEs. The most common GC AEs included weight gain, skin bruising or thinning, and sleep problems, similar to the current study. However, the current study examined 19 rather than 8 items, in addition to a free-text question to capture additional AEs attributed to GC use by patients. The current study also differed from the previous study in its comparison of AEs reported by RA patients with and without GC therapy and in that patients were asked to prioritize the 3 "worst" AEs. Lastly, in the current study, the survey was administered in 2 different English-speaking countries, which is important for cross-cultural generalizability.

Another cross-sectional study looking at GC AEs that are important to patients was recently carried out in a novel cohort of online health users in the United Kingdom.[16] In this population, weight gain was deemed the most important AE, followed by insomnia and moon face. The design and unique setting of this study provide additional insight into the patient experience of GC AEs. The results complement the findings of this study and will also be useful in the development of a future PROM.

Limitations of the study include potential biases associated with survey-based research. There may be a response bias, with fundamental differences in the experience of responders and nonresponders; indeed, in cohort 2, fewer GC nonusers responded to the survey. Also in cohort 2, only those with valid e-mail addresses were included, and there may be differences between people who use technologies and those who do not. There is also the potential for recall bias, with those who received more recent GC therapy more likely to recall a greater number of AEs. Other limitations of this study include the small sample size and that the questionnaire was available only in English. Although the checklist was created to capture many common GC AEs, some AEs, such as infections other than oral and vaginal thrush, were not included in order to minimize any burden of data entry. The free-text section was included to capture other AEs not on the checklist; however, these may have been reported less than those visible on the checklist.

Strengths of this study include its inclusion of 2 different cohorts and its comparison of AEs among GC users and nonusers from the same cohort. The results of this study will be used, in conjunction with ongoing qualitative work in different disease cohorts, to develop potential items for inclusion in a PROM. These potential items will then be compiled, and patient and clinician experts will be engaged to determine the most appropriate items to be included in the final PROM, which will then be properly developed and validated. Such a PROM will provide patients with an effective means by which to communicate with their treatment team about the impact of GC treatment.

CONCLUSIONS

This cross-sectional study has increased our understanding of the impact of GC therapy from the patient's perspective and is the first step in the development of a PROM. Patient-reported GC AEs were common among GC users; however, the benefits of treatment were felt to outweigh the AEs. In addition, many patient-reported AEs were more frequent among RA GC users than nonusers.

KEY POINTS

- Patient-reported GC AEs occurred in 86% to 100% of GC users.

- Many GC AEs that are important to patients are poorly captured by current physiological measures, including thin skin and easy bruising, sleep disturbance, and stomach upset/gastric reflux.
- Most patients felt that GCs are effective at controlling their disease and that the benefits of treatment outweigh the AEs.
- Many patient-reported AEs were more frequent among RA GC users than nonusers.

REFERENCES

1. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. *Rheumatology (Oxford)*. 2011;50:1982–1990.
2. Hoes JN, Jacobs JW, Boers M, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis*. 2007;66:1560–1567.
3. Duru N, Van Der Goes MC, Jacobs JW, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis*. 2013;72:1905–1913.
4. van der Goes MC, Jacobs JW, Boers M, et al. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. *Ann Rheum Dis*. 2010;69:1913–1919.
5. Miloslavsky EM, Naden RP, Bijlsma JW, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. *Ann Rheum Dis*. 2016;76:543–546.
6. Weldring T, Smith SM. Patient-reported outcomes (PROs) and patient-reported outcome measures (PROMs). *Health services insights*. 2013;6:61–68.
7. van Tuyl LH, Boers M. Patient-reported outcomes in core domain sets for rheumatic diseases. *Nat Rev Rheumatol*. 2015;11:705–712.
8. Black RJ, Robson JC, Goodman SM, et al. A Patient-reported outcome measure for effect of glucocorticoid therapy in adults with inflammatory diseases is needed: report from the OMERACT 2016 Special Interest Group [published online ahead of print April 1, 2017]. *J Rheumatol*. 2017.
9. van der Goes MC, Jacobs JW, Boers M, et al. Patient and rheumatologist perspectives on glucocorticoids: an exercise to improve the implementation of the European League Against Rheumatism (EULAR) recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. *Ann Rheum Dis*. 2010;69:1015–1021.
10. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2015. Available at: http://www.R-project.org/. Accessed December 2016.
11. Cooper V, Metcalf L, Versnel J, et al. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim Care Respir Med*. 2015;25:15026.
12. Fardet L, Flahault A, Kettaneh A, et al. Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. *Br J Dermatol*. 2007;157:142–148.
13. Walsh LJ, Wong CA, Oborne J, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax*. 2001;56:279–284.
14. Kyle V, Hazleman BL. Treatment of polymyalgia rheumatica and giant cell arteritis. II. Relation between steroid dose and steroid associated side effects. *Ann Rheum Dis*. 1989;48:662–666.
15. Curtis JR, Westfall AO, Allison J, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum*. 2006;55:420–426.
16. Costello R, Patel R, Humphreys J, et al. Patient perceptions of glucocorticoid side effects: a cross-sectional survey of users in an online health community. *BMJ Open*. 2017;7:e014603.

Patient's perceptions of glucocorticoid therapy
QUESTIONNAIRE

Thank you for completing this questionnaire about steroid (prednisolone) treatment.
It is important to remember that not all patients experience side effects with steroids, and steroids are never commenced unless required to treat your illness.
If you have any questions, the study co-ordinator is happy to help you fill in the questionnaire.
If you are unsure about exact dates, please fill in as much as you are able (for example, month and year or year alone).

NAME ……...

Date …… / /
DD/MM/YYYY

DEMOGRAPHICS

Date of Birth …….. / /
DD/MM/YYYY

Gender ……..... Female
Male

Steroids		
When did you start on prednisolone tablets?		
START DATE: / / DD/MM/YYYY		
STOP DATE: / / DD/MM/YYYY OR still taking		
What dose of prednisolone tablets did you start on?	……mg/day OR don't know	
Were you given any steroids through a drip?	Yes	No
What is your current dose of prednisolone?	……mg/day	
Why are you taking prednisolone?		

Are you currently taking a tablet to lower your cholesterol?	Yes	No	Don't know
Are you currently taking a tablet for diabetes?	Yes	No	Don't know

Are you currently taking any medications to treat osteoporosis?	Yes	No	Not sure
Alendro, Fosamax (alendronate)			
Fosamax Plux (Alendronate + Vitamin D)			
Caltrate, Citrocal (Calcium)			
Calcijex, Calcitriol, Kosteo, Rocaltrol, Sitriol (calcitriol)			
Vitamin D (Ostelin)			
Didrocal, Didronel (etidronate)			
Actonel (risedronate)			
Actonel combi (Risedronate + calcium)			
Evista (raloxifene)			
Protos (Strontium ranelate)			
Forteo (teriparatide)			
Aclasta (Zoledronate injection/infusion)			

Have you ever been told by a doctor that you have had any of the following?			
	Yes	No	Not sure
Diabetes			
Osteoporosis			
High blood pressure			
Asthma			
Emphysema/Chronic Bronchitis			
Ischaemic heart disease			
Heart attack			
Stroke			
Angina			
High cholesterol			
Cataracts			
Glaucoma			

Do you think that your steroid treatment (prednisolone) has helped you? (please circle)			
Not at all	A little	A lot	Not sure

HAVE YOU HAD ANY OF THE FOLLOWING SIDE EFFECTS SINCE COMMENCING ON STEROID (PREDNISOLONE) TREATMENT?			
	Yes	No	Don't know
Weight gain			
Thin skin or easy bruising			
High blood sugars			
Weakness of muscles			
High blood pressure			
Depression			
Mood disturbance			
Thin bones or osteoporosis			
Broken bones Which bone was broken?.....			
Change in shape of face			
Change in body shape			
Sleep disturbance			
Increased appetite			
Stomach upset or gastric reflux			

Swelling of feet or ankles			
Thrush in the mouth			
Cataracts of eyes			
Hip problem (also called avascular necrosis of the hip)			
For women, vaginal thrush			
None of the above			

If you have other side effects, while on steroid treatment please list them below:

_____

_____

_____

If you have had side effects, while on steroid treatment, which were the worst side effects that you had and why. Please list them below:

1. _____

   _____

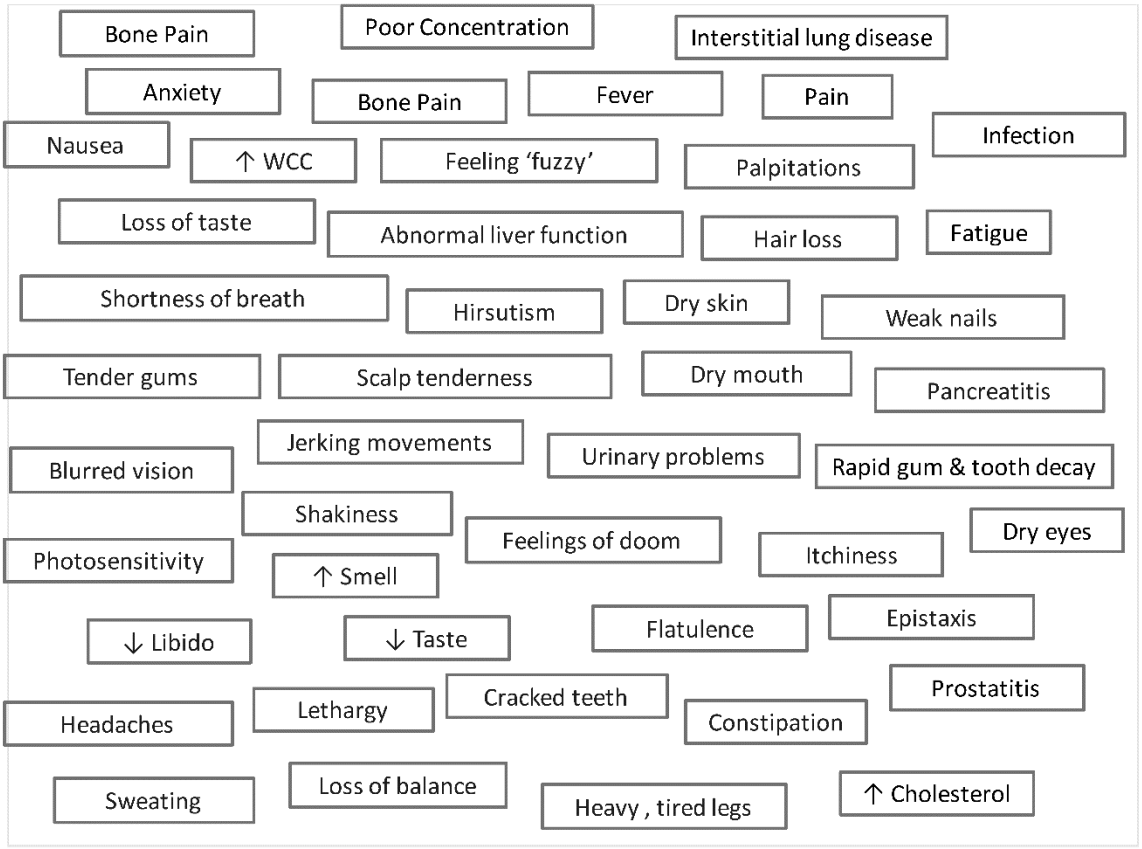
2. _____

   _____

3. _____

With regard to steroid treatment, do you think the side effects were worse than the benefit from the steroids?		
Yes	No	Not sure

SUPPLEMENTAL DIGITAL CONTENT 2



6 GC Use- The Risk of Developing Cataract and Glaucoma in RA

This chapter addresses aims 3 and 4 of the thesis:

> *To determine whether the risk of cataract and glaucoma associated with glucocorticoid use in patients with rheumatoid arthritis has been adequately quantified in the current literature*

> *To quantify the risk of GC exposure and the development of cataract and glaucoma in RA and to explore the risk associated with different patterns of GC exposure, including dose, timing of dose and cumulative dose*

6.1 Introduction

GC related eye disease is a potential harm of GC use that has previously received limited attention. This chapter looks at cataracts and glaucoma, with the aim of better quantifying the risks associated with GC use, dose, timing of dose and cumulative dose. These vision-threatening conditions are highly prevalent worldwide and account for >50% of blindness (96). They can have a significant impact on the lives of those affected and are associated with significant financial costs to the healthcare system (97). The extent to which systemic GC use contributes to the development of cataracts and glaucoma is not clear, with conflicting results among studies which try to quantify this. RA was selected as an ideal population in which to explore this question, as 60% of patients with this inflammatory condition are exposed to GCs, with different patterns of use seen.

The first manuscript in this section of work describes a systematic literature review (SLR) and meta-analysis addressing the association between systemic GC use and the risk of developing cataract and glaucoma in patients with RA. There were three RCTS reporting cataract and glaucoma, five cohort studies reporting cataract, one reporting PSCs specifically, and two reporting glaucoma. There were also five cross-sectional studies reporting PSCs. Data on the effects of dose and duration of therapy were very limited. The study concluded that the association between GC use and the development of cataract and glaucoma in RA is not clear from the current literature and that future well designed observational studies are needed to address this evidence gap.

The second manuscript goes on to address the evidence gaps identified in the SLR and describes a longitudinal cohort study which uses data from CPRD to quantify the risk of

developing cataract and glaucoma associated with GC use. In addition, it investigates the influence of the timing of GC dose and cumulative dose using different time-varying models of GC exposure. As shown in Chapter 3, GC use in RA varies greatly and it was therefore important to select models that capture different time-varying patterns of GC use in order to properly understand the risk of these potential harms. This work quantifies the risk of developing cataract and glaucoma associated with GC use in RA. Current GC use was associated with a 60% increased risk of glaucoma, and double the risk of cataracts, with risk increasing with age. It also investigates the timing of GC dose, with a current dose of 10mg associated with a 16% increased risk of developing cataracts, compared to no GC use. A dose of 10mg (compared to no GC use) six-months prior to cataract diagnosis was associated with a 13% increased risk, with the greatest risk of 26% seen with a 10mg dose one-year prior to diagnosis. Current dose was not associated with the development of glaucoma, whereas a 10mg dose compared to no GC use at three-months and one-year prior to glaucoma diagnosis was associated with a 4% and 5% increased risk respectively. Cumulative doses of more than 1000mg were associated with a 60% increased risk of cataracts compared to no GC use and cumulative doses more than 4000mg were associated with a 3-fold increased risk of cataracts and a 50% increased risk of glaucoma compared to no GC exposure.

As the first study to accurately quantify the risk of cataracts and glaucoma in RA patients treated with oral GCs, these results make a significant contribution to the existing literature, which was previously sparse and inconclusive for RA populations and conflicting in other diseases. Careful consideration was given to the study design and selection of analyses, with CPRD chosen as a large real-life longitudinal cohort, in which time-varying analyses could be performed. The results expand current knowledge regarding GC-associated eye diseases, quantifying the risks related to GC use, dose, timing of dose and also cumulative dose, as a combined measure of both dose and duration.

6.2 Manuscript 1: The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Statement of Authorship

Title of Paper	The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis
Publication Status	☒ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Black RJ, Hill CL, Lester S, Dixon WG. **The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis**. PLoS One. 2016;11:e0166468.

Principal Author

Name of Principal Author (Candidate)	Rachel Black		
Contribution to the Paper	Responsible for the design and conception of the work, creation of search strategy, databse search, review of titles, abstracts and full-text articles at the different stages of the review, quality assessment, data analysis, preparation of the manuscript and acted as corresponding author.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	24 April 2019

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Catherine Hill		
Contribution to the Paper	Responsible for full-text review of articles, quality assessment of included articles and critically reviewing the manuscript, with final approval of the version to be published.		
Signature		Date	24 April 2019

Name of Co-Author	Susan Lester
Contribution to the Paper	Supervised and assisted with the data analysis and critically reviewed the manuscript, with final approval of the version to be published.

Signature		Date	24 April 2019

Please cut and paste additional co-author panels here as required.

Name of Co-Author	William Dixon		
Contribution to the Paper	Responisble for the design and conception of the work, supervised the different stages of the search and critically reviewed the manuscript, with final approval of the version to be published.		
Signature		Date	22 July 2018

PLOS ONE

RESEARCH ARTICLE

The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

Rachel J. Black[1,2¤]*, Catherine L. Hill[2,3], Susan Lester[3], William G. Dixon[1,4,5]

1 Arthritis Research UK Centre for Epidemiology, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, United Kingdom, **2** Discipline of Medicine, The University of Adelaide, Adelaide, Australia, **3** Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia, **4** Health e-Research Centre, Farr Institute for Health Informatics Research, Manchester Academic Health Sciences Centre, The University of Manchester, Manchester, United Kingdom, **5** Department of Rheumatology, Salford Royal NHS Foundation Trust, Salford, United Kingdom

¤ Current address: Rheumatology Unit, The Royal Adelaide Hospital, Adelaide, Australia
* rachel.black2@sa.gov.au

OPEN ACCESS

Citation: Black RJ, Hill CL, Lester S, Dixon WG (2016) The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. PLoS ONE 11(11): e0166468. doi:10.1371/journal.pone.0166468

Editor: Graham R. Wallace, University of Birmingham, UNITED KINGDOM

Received: May 23, 2016

Accepted: October 28, 2016

Published: November 15, 2016

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: RJB was the recipient of the 2013 Ken Muirden Overseas Training Fellowship, an educational research grant jointly funded by Arthritis Australia and Roche Products Pty Ltd. RJB was also supported by an Australian Postgraduate Award (The University of Adelaide) and an Arthritis South Australia/Australian Rheumatology Association (South Australian Branch)

Abstract

Objective

Glucocorticoids (GCs) are often used to treat Rheumatoid Arthritis (RA) despite their many side effects and the availability of other effective therapies. Cataract and glaucoma are known side effects of GCs but the risk of them developing in the setting of GC use for RA is unknown. The aim was to perform a systematic review and meta-analysis to determine the association between GCs and the risk of developing cataract and/or glaucoma in RA.

Methods

A systematic search was carried out using MEDLINE, EMBASE, and Web of Science. All RCTs comparing GC use to non-use in RA populations were sought. Observational studies reporting cataract and/or glaucoma amongst GC users and non-users were also included. Data extracted included incidence/prevalence of cataract and/or glaucoma in each arm, dose and duration of therapy. Two independent reviewers performed quality assessment.

Results

28 RCTs met eligibility criteria, however only 3 reported cataracts and glaucoma, suggesting significant under-reporting. An association between GC use and the development of cataracts in RA patients was seen in observational studies but not RCTs. There was no statistically significant association between GC use and the development of glaucoma, although data were sparse. There were insufficient data to determine the impact of dose and duration of therapy.

Postgraduate Grant. WGD was supported by a MRC Clinician Scientist Fellowship (G0902272). We thank the Arthritis Research UK for their support: Arthritis Research UK grant number 20380. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: RJB was the recipient of the 2013 Ken Muirden Overseas Training Fellowship, an educational research grant jointly funded by Arthritis Australia and Roche Products Pty Ltd. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Conclusion

The current literature suggests a possible association between GC use and the development of cataract. However, this risk cannot be accurately quantified in RA from the available evidence. RCTs have not adequately captured these outcomes and well-designed observational research is required.

Introduction

Cataract and glaucoma were first described as side effects of systemic GC therapy as early as 1953[1, 2]. In particular, posterior subcapsular cataracts (PSCs) are a subtype of cataracts that occur more frequently in GC-exposed patients [1]. Similarly, GC exposure can lead to steroid-induced glaucoma, a type of open angle glaucoma. These conditions can lead to visual impairment, resulting in significant disability and cost to the healthcare system [3]. As GCs remain widely prescribed in rheumatoid arthritis (RA) and many other inflammatory diseases [4, 5], any increased risk might lead to a significant public health burden.

EULAR guidelines advocate that clinicians inform their patients of the risk of side effects associated with GCs before commencing treatment [6]. However, for cataract and glaucoma, the magnitude of risk is rarely reported and current literature has not been reviewed to determine if the risk can be accurately quantified. Specific questions, such as how this is influenced by dose and duration of therapy, also have not yet been addressed. RA was the first condition to be treated with GCs in 1948 [7] and it was also the first condition in which PSCs were described as AEs of GC use in 1950 [1]. There are multiple randomised controlled trials (RCTs) of GC use in RA, and long-term use has been looked at in many observational studies, making it an ideal setting to explore these questions.

The aim was to perform a systematic literature review and meta-analysis of RCTs and observational studies examining the association between GC use and the risk of cataract and glaucoma in patients with RA compared to patients with RA not exposed to GCs. Secondary aims were to determine whether there is an association with dose and duration of GC therapy.

Materials and Methods

Search strategy

A systematic search was conducted using MEDLINE, EMBASE and Web of Science for articles published to January 2016. There was no review protocol for this systematic review. Separate search strategies were conducted for RCTs and observational studies. RCTs fulfilling the following criteria were included: 1) RA population 2) Exposure to systemic (oral, intramuscular or intravenous) GC therapy in one arm and non-exposure (no treatment or placebo) in at least one comparator arm. Studies comparing DMARD(s) plus GC in one arm and the same DMARD(s) without GC in the comparison arm were also included. Inclusion criteria for observational studies were: 1) RA population, 2) Use of a cross-sectional, case-control or cohort study design 3) Reporting of the number or rate of cataracts and/or glaucoma in GC-exposed and non-exposed patients. Although cross-sectional studies do not provide information on causality, they were included in this review in order to capture information from about PSCs from early studies conducted in the 1960s. Studies conducted exclusively in populations other than RA (including early inflammatory arthritis, undifferentiated polyarthritis and JIA) were excluded. If RA was one of several indications reported, the study was only included if

the RA population was reported separately from the other populations. Exposure was restricted to systemic GC therapy (oral, intramuscular, intravenous), and studies reporting only topical, intra-articular, intra-ocular or other non-systemic routes of steroid administration were excluded. In instances where two studies reported on the same cohort, the earlier of the two studies was retained unless the latter reported on cataracts and/or glaucoma.

Search terms are listed in the online supporting information (S1 Table). Search filters for RCTs were based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version [8].The search filters for observational studies was based on the Scottish Intercollegiate Guidelines Network search filters for observational studies [9].

Study Selection and Data extraction

The initial study selection was based on review of title and abstract. Studies in non-RA populations were excluded at this stage, as were those with designs other than RCTs, cohort, case control or cross-sectional studies. Only articles published in English were selected due to lack of access to a translation service. Full text manuscripts of all remaining articles were reviewed for eligibility based on the inclusion and exclusion criteria. Hand searching of references of all papers obtained through the above search and relevant review articles was also carried out. Abstract only publications and unpublished studies were not considered. A random sample of 20 RCTs was selected for independent full-text review by the second reviewer (CH). Each study was assessed in regards to eligibility criteria and the rate of agreement with the first reviewer (RB) was then determined.

Data extraction was performed by a single reviewer using an electronic data collection form. Information was extracted regarding: 1. The RA population including age, gender and disease duration, 2. The exposure including the definition of GC use, dose and duration of therapy, 3. The comparator arm including whether this was placebo or non-GC exposure, and 4. The outcome of cataract and glaucoma in each arm, how this was obtained and whether this was reported as point prevalence, prevalence, incidence or incidence rate.

Quality Appraisal

Both reviewers (RB, CH) performed an independent assessment of the quality of all included studies. Discrepancies were discussed and resolved by consensus. The Cochrane Risk of Bias Assessment tool [10] was used to assess the quality of all included RCTs reporting cataract and/or glaucoma. Cohort studies were assessed using the Newcastle Ottawa Scale[11] and each of the cross-sectional studies was assessed for selection bias, detection bias, attrition bias, and reporting bias, based on the Cochrane Handbook common classification scheme for bias[12]. No case control studies meeting eligibility criteria were identified in the search. The RCTs and cross-sectional studies were assessed as low, high or uncertain risk, however the cohort studies were assessed as either being low or high risk due to differences in the scales used.

Meta analysis

Although data were limited, meta-analyses were performed as a means of summarising the data available. Cross sectional studies were not considered in the meta-analysis due to their inability to assess causality. Random effects meta-analyses were performed for each outcome: all cataracts and glaucoma. While other methodologies for dealing with zero events and sparse data were considered [13–15], risk difference (RD) was selected as the effect size because many studies had zero events in one arm, and odds ratios and relative risks are not defined in this

setting. Statistical heterogeneity was assessed using the I^2 statistic, where $I^2>50\%$ represents significant heterogeneity. Meta analyses were carried out using the Metafor package in R [16].

Effect of dose and duration of GC exposure and visual outcomes

A description, rather than formals analysis of the effect of dose and duration of GC use on the development of cataract and glaucoma was carried out due to the scarcity of studies addressing this.

Comparing the reporting of cataracts in RCTs, to population-based incidence of cataracts

Concerns that cataracts were not being captured or reported in RCTs, early in the course of this review, led to a secondary aim to compare the RCT incidence with the expected incidence of cataracts based on general population rates derived from The Blue Mountains Eye Study (BMES) [17]. For comparison with RA RCTs, the expected population cumulative incidence of cataracts over 1 and 2 years was estimated for patients aged less than 75 years from the reported BMES 5-year incidence, under the constant hazards assumption.

Results

Randomised Controlled Trials

95 RCTs were identified for full-text review and 28 RCTs were ultimately included after applying eligibility criteria (Fig 1). There was initial agreement for 19/20 articles selected for assessment by the second reviewer. Disagreement occurred for one article because the results of this study had already been reported earlier in another paper that had not been included in the random sample. Once this issue was made known to the second reviewer, there was full consensus for all articles. These papers are summarised in the supporting information (S2 Table).

Cataracts and glaucoma were reported in only 3 of the 28 RCTs (Table 1), each of 2 years' duration. The initial 28 RCTs evaluated treatment with oral, intramuscular and intravenous GCs, however the final three studies all assessed oral exposure. These three studies reported all cataracts rather than the PSC subtype. One study, Williams et al [18], was excluded because it did not report whether the single observed glaucoma case occurred in the GC or control group. The remaining 24 RCTs did not mention cataracts and/or glaucoma in either the methods or the results. The protocols for all three RCTs reporting incident eye disease included either recording specific known GC-associated AEs using a standardised list [19, 20] or ophthalmological examinations [20, 21]. There were no significant differences in the risk of developing cataracts for GC-exposed versus unexposed RA patients, either individually by trial, or collectively in the meta-analysis (RD 0.01 events/patient, 95% CI -0.01–0.03), Fig 2 (A RD of 0.01 equates to an additional 10 cataracts for every 1000 patients exposed to GCs compared to those unexposed). Similarly, there were no significant differences in the risk of developing glaucoma for GC-exposed versus unexposed RA patients, either individually by trial, or collectively in the meta-analysis (RD 0.01 events/patient, 95% CI -0.02–0.04), Fig 2.

Comparing the reporting of cataracts in RCTs to population-based incidence of cataracts

Of the 28 RCTS comparing GC use to non-use in RA, there were a total of 13 cataracts reported in only 3/28 studies (11%). The remaining 25 studies did not report cataracts in their results, nor did they set out to do so in the their methods. Across all 28 RCTs there was a total

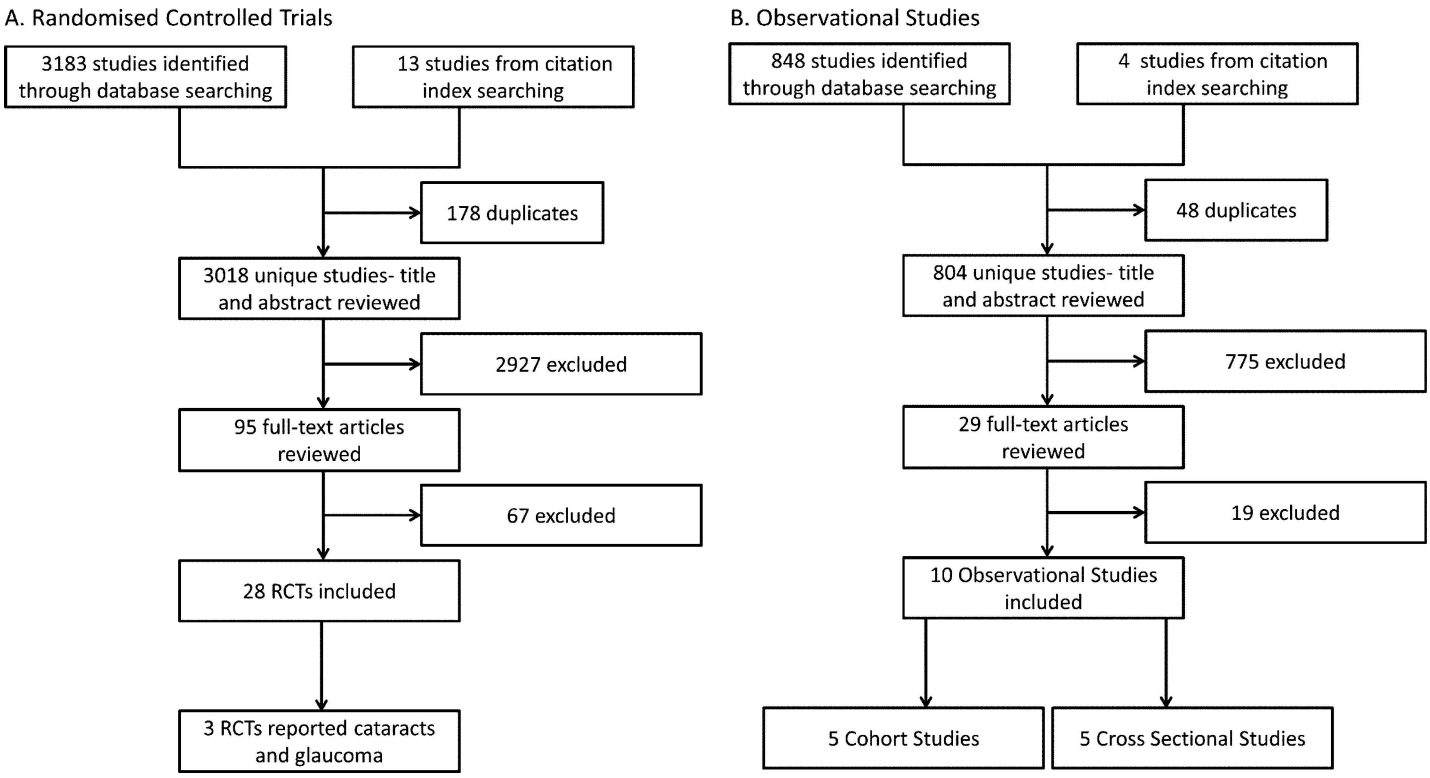


Fig 1. Flow charts depicting selection of A. Randomised Controlled Trials and B. Observational Studies.

doi:10.1371/journal.pone.0166468.g001

of 4604 person years, giving a combined cataract incidence rate of 2.8 per 1000 person years (pyr).

Considering incidence only in the three studies that reported cataracts, the random effects estimate of the combined incidence rate (IR) was 11/1000pyr (95%CI 3-43/1000pyr), although the IRs ranged considerably from 2.1/1000pyr [19] to 12.3/1000pyr [20] to 26.5/1000pyr [21]. This heterogeneity is likely related to the different methods used to detect cataract, with ophthalmological examination detecting a greater prevalence of cataracts.

Table 1. RCTs comparing GC use to non-use in RA and number of reported cataracts and glaucoma.

First Author, Year	Duration of study	Country	Mean Age (% Female)	Arms of RCTs (n)	Outcome Reported & method of detection
Bakker [19],	2 years	The Netherlands	54	MTX + PNL 10mg (117)	Incident cataract and glaucoma-standard list of AEs
2012			(60%)	MTX + placebo (119)	
van Everdingen [20],	2 years	The Netherlands	62	PNL 10mg (40)	Incident cataract and glaucoma- standardised list of AEs, ophthalmologic expertise requested when necessary
2002			(64%)	Placebo (41)	
Wassenberg [21],	2 years	Germany, Austria, Switzerland	52	Gold or MTX + PNL 5mg (93)	Incident cataract and glaucoma- ophthalmologic exams at the beginning and end of the study
2005			(70%)	Gold or MTX + placebo (96)	

RCTs = Randomised Controlled Trials, GC = glucocorticoid, RA = rheumatoid arthritis, n = number, PNL = prednisolone, MTX = methotrexate, AEs = Adverse Events

doi:10.1371/journal.pone.0166468.t001

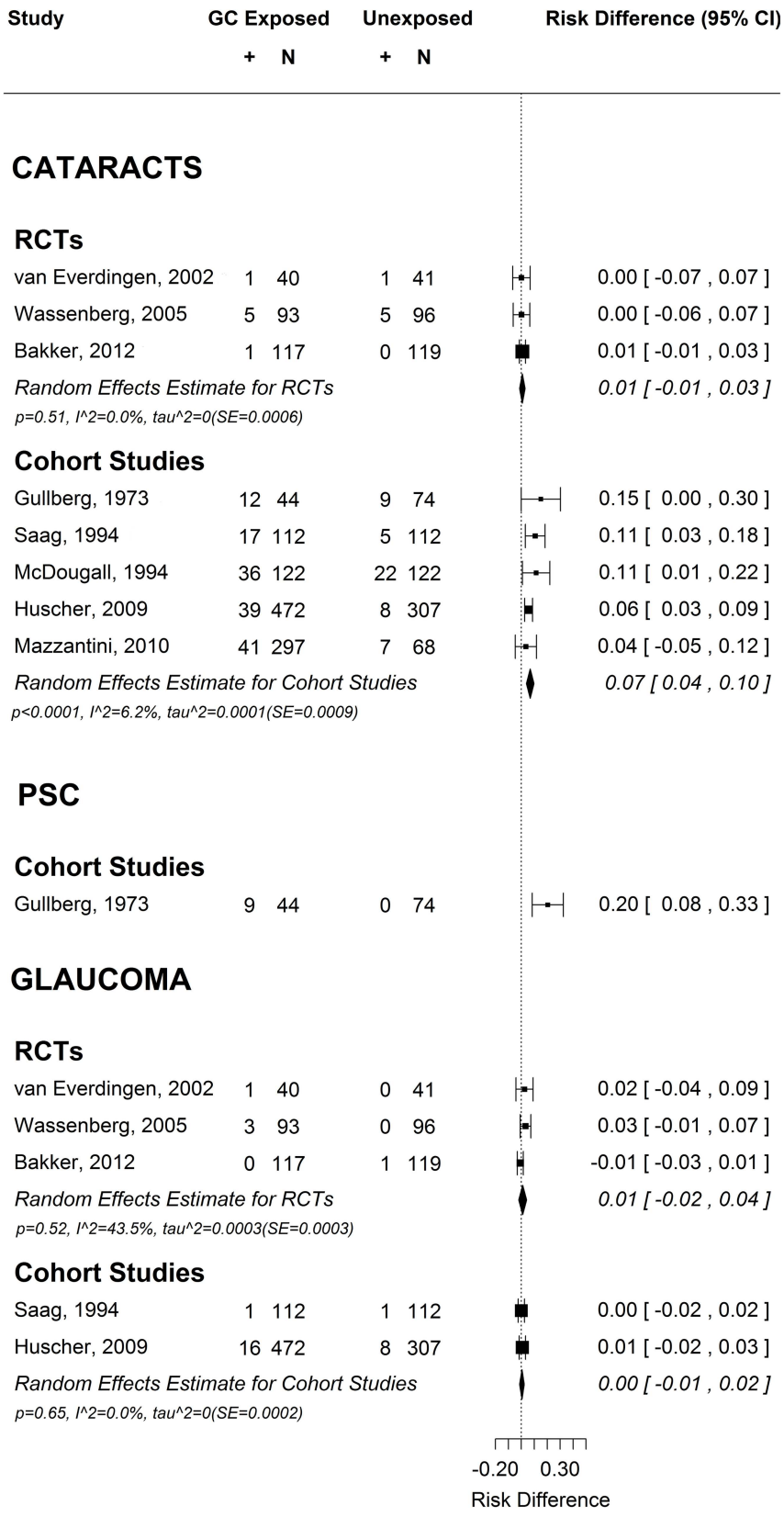


Fig 2. Meta analysis forest plots of RCTs and cohort studies reporting all cataracts, cohort studies reporting PSCs and RCTs and cohort studies reporting glaucoma.

doi:10.1371/journal.pone.0166468.g002

The cumulative two-year incidence in the 3 studies of this duration reporting cataract was 2.0% (95% CI 0.6–6.6). The expected population cumulative incidence (in participants younger than 75 years), estimated from the BMES population [17], is 6% over 1 year and 12% over two years. Given that the median duration of the 27 RCTs was one year, this suggests that cataracts were expected in RCTS in which they were not reported, suggesting a substantial six-fold under-reporting of cataracts in the clinical trials.

Observational studies

A total of 10 observational studies met eligibility criteria for the final review. Five were cohort studies, of which two were prospective and three retrospective. The remaining five were cross-sectional (Fig 1).

a) All Cataracts (Reported in 5 cohort studies). Amongst the cohort studies, Gullberg *et al* [22] reported PSCs as well as all cataracts. However, the remaining cohort studies reported all cataracts only and not PSCs [23–26]. The methods for identifying and defining cataracts varied between studies, as did the definitions of GC use (Table 2).

In contrast to RCTs, four of the five cohort studies reported a significantly increased risk of cataracts in GC-exposed patients, and collectively the combined risk difference was 0.07 events per person (95%CI 0.04–0.10), Fig 2, which is equivalent to an additional 70 cataracts seen per 1000 patients in those exposed to GCs. The odds ratio, which could also be meaningfully estimated from this data, was 2.1 (95%CI 1.5–2.9). While there was considerable variation in age, disease duration, dose and duration on GCs between these studies (Table 2), there was surprisingly little statistical evidence of heterogeneity between the effect sizes (RD $I^2 = 6.2\%$).

In regards to dose and duration of therapy, Huscher *et al* [25] looked at patterns of glucocorticoid induced side effects and found two distinct patterns including 'linear risk', where risk of developing an AE increased with dose in a linear fashion and 'threshold risk' where the increased risk only occurred after a threshold dose was reached. They found that both cataract and glaucoma fit the threshold pattern with a threshold dose of 5mg per day for cataract and 7.5mg per day for glaucoma in patients on GCs for more than 6 months. Mazzantini *et al* [26] did not find any difference in cataract prevalence between those treated with GCs for <2 years, 2–5 years or >5years.

b) Posterior Supcapsular Cataracts (PSCs) (Reported in 5 cross-sectional studies and 1 cohort study). PSCs were reported in five cross-sectional studies published between 1960 and 1969. In all five studies, an RA population, including those exposed and unexposed to GC treatment, underwent ophthalmological examination. In 4/5 of these studies[1, 27–29], PSCs were only seen in those exposed to GCs, and in the remaining study by Williamson et al [30], 1 PSC was seen amongst 159 unexposed to GCs compared to 10/148 exposed (Table 3). PSCs were also reported in a retrospective cohort study by Gullberg et al [22], with a risk difference of 0.20 events per patient (95%CI 0.08–0.33), equivalent to an additional 200 PSCs for every 1000 patients exposed to GCs.

In regards to dose and duration of GC therapy, Black *et al* reported that PSCs were not seen in six patients who took prednisolone equivalent doses of <10mg per day or in nine patients who had been taking GCs for less than one year [1]. Giles *et al* [27] also found that PSCs did not occur in three patients that received GCS for less than one year. However they did occur in four of the 19 patients taking <10mg per day for ≥ 6 months. The prevalence of PSCs increased with GC dose, with PSCs seen in 4/12 patients on 10-15mg/day and in 6/7 patients on >15mg per day. Furst *et al* compared the prednisolone equivalent average daily dose and duration of therapy in those with PSCs to those without and found no significant difference in duration of therapy but a higher average dose of 11.5mg in those that developed PSCs

Table 2. Observational Studies comparing rates of cataracts amongst GC uses and non-users.

First Author, Year	Study Design, Outcome reported (number patients)	Age	Gender (Percentage Female)	RA disease duration	Definition of GC use	Duration on GCs	Prednisolone equivalent dose/d	Cataract Type and Method of Detection
Black [1],	Cross-sectional,	<30 = 3, 30–39 = 9,	37/67	1-3y = 20,	Not defined	<1y = 9,	<10mg = 6,	PSC
1960		40–49 = 24,	(55%)	4-6y = 13,		1-4y = 22,	10-15mg = 22,	Ophthalmologist
	Point prevalence	50–59 = 16,		7-9y = 12,		>4y = 13	>15mg = 16	
	(63)	≥60 = 11		>9y = 18				
Giles [27],	Cross-sectional,	<30 = 3,	45/62	1-3y = 15,	Sustained GC	<1y = 3,	<10mg = 19,	PSC
1962		30–39 = 8,	(73%)	4-6y = 12,	use for	1-4y = 18,	10-15mg = 12,	Ophthalmologist
	Point prevalence	40–49 = 20,		7-9y = 11,	≥6months	>4y = 17	>15mg = 7	
		50–59 = 26,		>9y = 24				
	(62)	≥60 = 5						
Crews [28],	Cross-sectional,	**Patients with PSC**	Not Reported	Range 3-38y	Being treated with GCs	**Patients with**	**Patients with**	PSC
1963		40–49 = 2, 50–59 = 7,				**PSC**	**PSC**	Ophthalmologist
	Point prevalence	60–69 = 8, 70–79 = 1				Mean 4.5y	Mean 10.5mg	
		Without PSC				**Without PSC**	**Without PSC**	
	(86)	Not Reported				Not reported	Not reported	
Furst [29],	Cross-sectional,	Not Reported	Not Reported	Not reported	GC use for	**Patients with**	**Patients with**	PSC
1966					minimum of	**PSC**	**PSC**	Ophthalmologist
	Point prevalence				1year	Mean 4.5y	Mean 12.2mg	
						Without PSC	**Without PSC**	
	(105)					Mean 4.75y	Mean 9.5mg	
Williamson [30],	Cross-sectional*,	**GC-users**	243/307	**GC-users**	Not defined	Mean 3.15y	Mean	PSC
1969		Mean 52.5	(79%)	Mean 8.95y		SD +/-2.45	10.89mg	Ophthalmologist
	Point prevalence	SD +/-11.5		SD +/- 6.35			SD +/-4.8	
		Range 18–80		**Non-users**				
	(307)	**Non-users**		Mean 6.55y				
		Mean 49.3		SD +/-5.9				
		SD +/-15						
		Range 18–83						
Gullberg [22],	Retrospective cohort,	Mean 58	100/130	Mean 11 y	Not defined	**Patients with**	**Patients with**	PSC and all
1973		Range 18–80	(77%)	Range <1-38y		**PSC**	**PSC**	cataracts
	Prevalence					Mean 1640d	Mean 7.6mg	Ophthalmologist
	(118)					**Without PSC**	**Without PSC**	
						Mean 1360d	Mean 7.0mg	

(*Continued*)

Table 2. (*Continued*)

First Author, Year	Study Design, Outcome reported (number patients)	Age	Gender (Percentage Female)	RA disease duration	Definition of GC use	Duration on GCs	Prednisolone equivalent dose/d	Cataract Type and Method of Detection
McDougall [24],	Prospective cohort,	**GC-users**	170/244	**GC-users**	Received GC	Mean 6.9y	Mean 8.0mg	Not Stated
1994		Mean 55.9	(70%)	Mean 14.1y	after study	Range 0.3–21.8y	Range 1.0-	Rheumatologist
	Prevalence	Range 17.1–81.3		**Non-users**	enrolment		23.4	ophthalmoscope
	(244)	**Non-users**		Mean 13.8y	(excluded if			examination at each
		Mean 56.0			prior			visit, ophthalmology
		Range 18.1–82.0			exposure)			referral if needed
Saag [23],	Retrospective cohort,	**GC-users**	168/224	**GC-users**	Near	Not reported	Mean 6.1mg	Not Stated
1994		Mean 51.8	(75%)	Mean 4.9y	continuous		SD +/-3.1mg	Clinical records
	Incidence	SD +/-12.7		SD+/-6.3,	(<1mth off)			
	(224)	**Non-users**		**Non-users**	steroids			
		Mean 51.7		Mean4.9y	for>1y at			
		SD +/-12.5		SD +/-6.7	≤15mg/d			
Huscher [25],	Prospective cohort,	No GC = 58.4	No GC = 79%	No GC = 10.8y,	Any GC use in	Not reported	<5mg = 101,	Not Stated
2009		<5mg = 60.9	<5mg = 82%	<5mg = 9.7y,	the past 12m		5–7.5mg = 281,	Self reported
	Point prevalence	5–7.5mg = 60.4	5–7.5mg = 77%	5–7.5mg = 13.2y,	for >6m		>7.5mg = 90	
	(779)	>7.5mg = 61.5	>7.5mg = 72%	>7.5mg = 10.7y				
Mazzantini [26],	Retrospective cohort,	**GC-users**	**GC-users**	**GC-users**	GC use	Mean 8y	Mean 4.1mg	Not Stated
2010		Mean 66.7	65%	Mean 16.8y	continuously	SD +/-6y	SD+/-1.2mg	Clinical records
	Prevalence	SD +/-11.7	**Non-users**	SD +/-6.3y	for >6m and	Range 1-20y	Range 4-6mg	
	(365)	Range 26–89	74%	**Non-users**	<10y			
		Non-users		Mean 16.3y				
		Mean 66.1		SD +/-6.1y				
		SD+/-12.3						
		Range 28–90						

*Some patients followed up prospectively with repeat ophthalmological examinations performed two or more times at 3 or 6 months intervals.

n = number, PSC = posterior supcapsular cataract, GC = glucocorticoid, d = day, m = month, y = year, SD = standard deviation

doi:10.1371/journal.pone.0166468.t002

compared to 8.8mg in those that did not. However, they did not report whether this difference was significant. Williamson also reported an increased prevalence with longer duration of therapy, with no PSCs seen in the 65 patients on GCs for less that two years compared to seven of the 52 patients on GCs for more than two years ($p<0.01$) [30].

c) Glaucoma (Reported in2 cohort studies and 1 cross-sectional study). Of the observational studies that fulfilled the eligibility criteria for this search, three studies reported glaucoma [23, 25, 30]. No significant association was seen between GC use and glaucoma amongst the 2 cohort studies [23, 25] with a combined risk difference of 0.00 (95% CI -0.01–0.02). In the cross-sectional study, Williamson *et al* [30] reported 1 case of glaucoma amongst 148 GC users and 1 case amongst 159 non-users.

Table 3. Cross-sectional Studies Reporting Posterior Subcapsular Cataracts (PSCs).

Study	GC-Exposed		GC-Unexposed	
Author, Year	**Number of patients**	**Number of PSCs**	**Number of patients**	**Number of PSCs**
Black [1], 1960	44	17	19	0
Giles [27], 1962	38	14	24	0
Crews [28], 1963	52	18	34	0
Furst [29], 1966	57	6	48	0
Williamson [30], 1969	148	10	159	1

GC = glucocorticoid, PSCs = Posterior Subcapsular Cataracts

doi:10.1371/journal.pone.0166468.t003

Quality Assessment

The quality assessment of all studies is shown in Fig 3. Among RCTs, the risk of bias was low for most criteria (Fig 3A). Conversely, for the cohort studies, there was a high risk of bias in some categories, particularly regarding the exclusion of prevalent eye disease (Fig 3B). Amongst the cross-sectional studies, the risk of bias was uncertain for most categories (Fig 3C).

Discussion

RA is an ideal patient group in which to look for long term adverse effects of GCs. RA was the first condition to be treated with GCs [7]and it was also the first condition in which PSCs were described as AEs of GC use [1]. More recently GCs have been shown to have a disease modifying effect in RA [31], resulting in more continuous patterns of use compared to other indications such as asthma and IBD for which GCs are often used intermittently. RA patients may differ in their risk of developing GC induced eye diseases compared to other populations such as those with IBD and spondyloarthropathies, which are more frequently associated with uveitis and topical GC use, other known risk factors for developing cataract and glaucoma [32]. It is therefore important to understand how systemic GC use affects the risk of developing cataract and glaucoma in RA patients.

This review has found that there is limited literature addressing the association between systemic glucocorticoid use and the risk of cataract and glaucoma in patients with RA. In contrast to the RCTs which showed no association between GC use and all cataracts (RD 0.01, 95%CI -0.01–0.03), an association was observed in the observational cohort studies [22–26], with a estimated risk difference of 0.07, 95%CI 0.04–0.10. The RCT and observational literature regarding glaucoma was particularly limited as was that addressing the effect of dose and duration of GC therapy. There were no studies addressing the impact of comorbidities known to be associated with increased risk of cataract or glaucoma, or the visual outcome of GC-induced cataract or glaucoma. PSCs often require surgery at an earlier stage than other cataract types [33] and whilst this has not been addressed in the context of GC use, it certainly raises concern and highlights the need for future studies in this area.

Although well described as side effects of GC use in review articles and books [34–38], cataracts have been reported in only three of the 28 RCTs comparing GC use and non-use in RA populations (in either arm of the study). Through comparison to general population cumulative incidence rates derived from the BMES, it is apparent there is significant under-reporting of cataracts in RA glucocorticoid clinical trials, making any estimates of GC-associated risk less reliable. Ideally, future RCTs comparing GC use to non-use would endeavour to accurately capture this information with regular ophthalmology assessments.

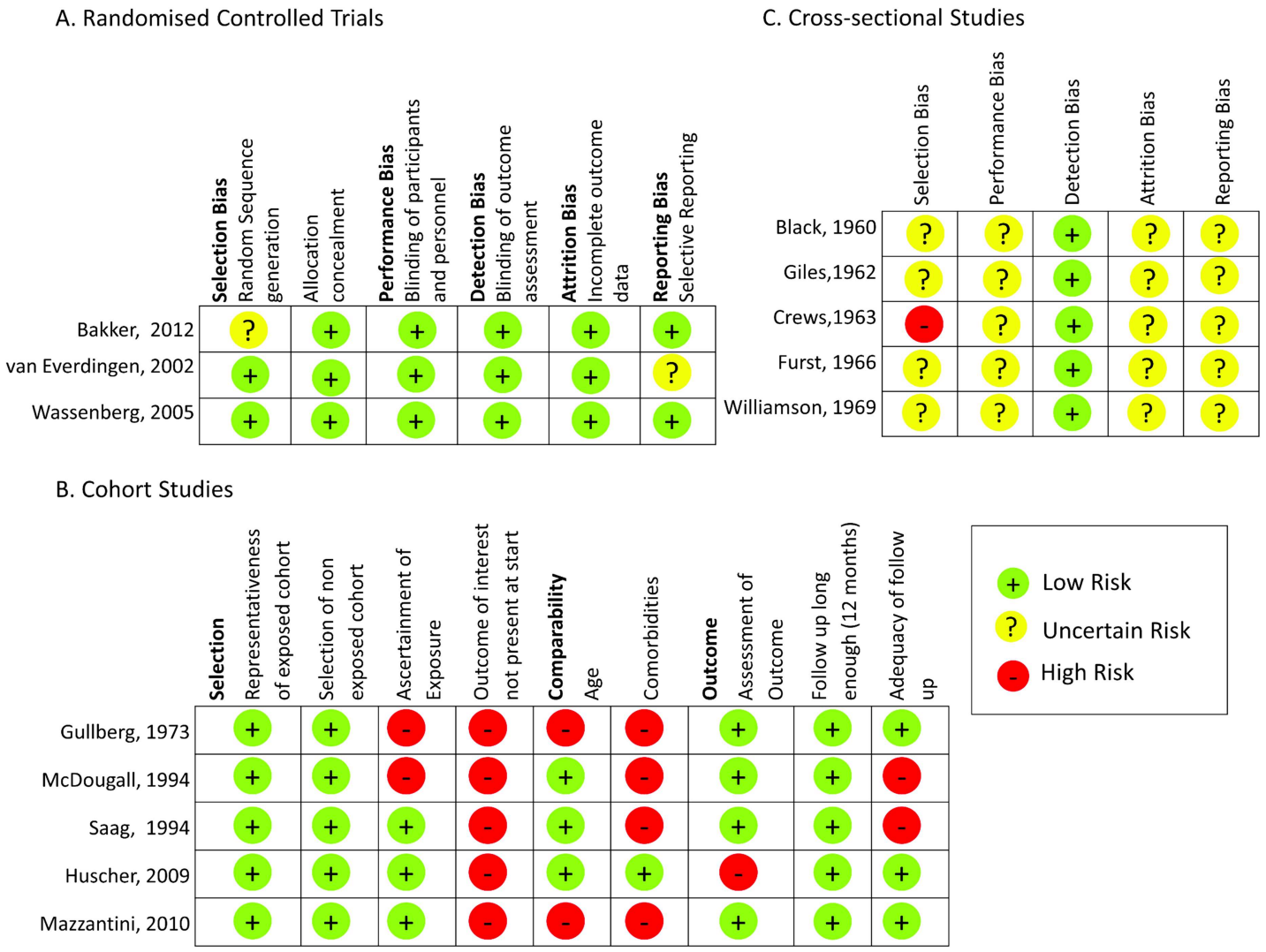


Fig 3. Quality Assessment of A. Randomised controlled trials and C. Cross sectional studies using the Cochrane Risk of Bias Assessment Tool (high risk, low risk of uncertain risk) and B. Cohort studies using the Newcastle Ottawa Scale (high risk or low risk).

doi:10.1371/journal.pone.0166468.g003

Whilst this review focussed specifically on studies in RA populations, it is interesting to consider how the extent of GC-associated risk compares with studies in other populations, and between the sub-types of cataract. In the BMES Australian general population there was an association between current GC use and PSCs (OR 4.11, 95%CI 1.67–10.08) and nuclear cataracts (OR 3.45, 95% CI 1.26–9.43) but not cortical cataracts (OR 1.08, 95%CI 0.44–2.64) [33]. In comparison, the Beaver Dam Eye Study found an increased incidence of cortical cataracts associated with GC use in the American general population (OR 2.59, 95%CI 1.45–4.62) but not PSCs (OR 1.27, 95%CI 0.42–3.86) or nuclear cataracts (OR 1.41, 95%CI 0.77–2.56) [39]. This is in contrast to other studies that have shown a strong association between GC use and PSCs in other populations including asthma and renal transplantation [33, 40–43]. Unfortunately, despite the observation that PSCs occurred with GC use reported in earlier cross-sectional studies, more recent RA studies have not reported specific cataract type.

Impact of Dose and Duration of GC Therapy

The impact of dose and duration of GC therapy on the development of cataract and glaucoma remains unanswered. Whilst some of the observational studies in this review suggest an association between GC use and dose and duration of therapy, they do not adequately quantify the risk in a way that can be translated into clinical practice when discussing the risks and benefits of GC treatment for RA. Many of the observational studies that comment on dose and duration were insufficiently powered, or not appropriately designed, to determine an accurate association between different doses and durations of therapy. A striking association between GC use and the development of PSCs was described in early cross-sectional studies carried out in the 1960s, however an association with cataracts was not seen in more recent RCTs. Whilst under-reporting partly accounts for this, another possible explanation is that GC exposure (dose and duration of therapy) has declined over time with the increasing use of concurrent DMARDs, highlighting the need for this to be explored in future studies.

Strengths and limitations

The main strength of this review is the systematic approach used to identify all relevant studies published since 1950 and the use of two reviewers to confirm eligibility criteria. The main limitation of this review is the small number of studies meeting eligibility criteria, making it impossible to draw meaningful conclusions. Although cross-sectional studies cannot assess causality, their inclusion allowed a comprehensive summary of the complete literature on this subject. The results are reported by study design and thus this does not detract from the study findings. The heterogeneity of studies was significant, particularly in regards to the methods used to detect cataracts and glaucoma. Only one of the RCTs and two of the cohort studies used examinations to detect cataracts, and the remainder relied on patient reports or case note review. There was additional heterogeneity in the definitions of GC exposure. This heterogeneity made it impossible to draw any quantitative conclusions regarding the risk of GC use and the development of cataract and glaucoma in RA patients. The observational studies had a high risk of bias, with only one [25] controlling for comorbidities known to be associated the development of cataract and glaucoma and potentially associated with GC exposure [44–46].

The current literature leaves many questions unanswered in regards to GC use and the development of cataract and glaucoma. Although RCTs often represent the highest level of evidence for efficacy, they are not ideal for examining long-term drug adverse effects. They also do not reflect the patterns of GC use seen in routine practice. In order to adequately address the questions in this review, a well designed observational study that is large enough and of sufficient duration to capture rare events is required. Ideally, such a study would be conducted in a real-life setting so that the impact of age and comorbidities could also be determined. Data on dose and duration of GC use would need to be accurately captured and appropriate methodologies employed to fully understand the interactions between dose, duration and recentness of treatment. Cataracts and glaucoma become increasingly prevalent with age and commonly occur without exposure to systemic GCs. They range in severity from asymptomatic to visually disabling, making it important to clearly define the clinical relevance of cataract/glaucoma in future studies.

Conclusions

In conclusion, observational studies, but not RCTs, suggest an association between GC use and the development of cataracts in RA patients. This relationship has not been adequately quantified, nor have the effect of dose and duration of therapy, visual outcomes and the impact of comorbidities been addressed. Confidence in RCT and observational estimates are limited

by under-reporting, and heterogeneity and bias, respectively. There is no robust literature regarding GC use and the development of glaucoma in RA patients. These findings highlight the need for future well conducted observational studies targeting the unanswered questions as well as improved capture of these outcomes in future RCTs.

Supporting Information

S1 Table. Search terms used for RCTs and Observational Studies in each of the databases.
(DOCX)

S2 Table. RCTs comparing GC use to non-use in RA and number of reported cataract and glaucoma.
(DOCX)

S3 Table. PRISMA 2009 Checklist.
(DOC)

Author Contributions

Conceptualization: RJB WGD.

Formal analysis: RJB SL.

Investigation: RJB CLH.

Methodology: RJB CLH SL WGD.

Supervision: CLH WGD.

Visualization: RJB SL.

Writing – original draft: RJB.

Writing – review & editing: RJB CLH SL WGD.

References

1. Black RL, Oglesby RB, Von Sallmann L, Bunim JJ. Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. JAMA. 1960; 174:166–71. Epub 1960/09/10. PMID: 13801171.
2. Stern JJ. Acute glaucoma during cortisone therapy. American journal of ophthalmology. 1953; 36 (3):389–90. PMID: 13030647.
3. Taylor HR, Keeffe JE, Vu HT, Wang JJ, Rochtchina E, Pezzullo ML, et al. Vision loss in Australia. The Medical journal of Australia. 2005; 182(11):565–8. Epub 2005/06/09. PMID: 15938683.
4. Black RJ, Joseph RM, Brown B, Movahedi M, Lunt M, Dixon WG. Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study. Arthritis research & therapy. 2015; 17(1):375. doi: 10.1186/s13075-015-0895-8 PMID: 26702817; PubMed Central PMCID: PMC4718024.
5. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology (Oxford). 2011; 50(11):1982–90. doi: 10.1093/rheumatology/ker017 PMID: 21393338.
6. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Annals of the rheumatic diseases. 2007; 66(12):1560–7. Epub 2007/07/31. doi: 10.1136/ard.2007.072157 PMID: 17660219; PubMed Central PMCID: PMC2095301.
7. Hench PS, Kendall EC, Slocumb CH, Polley HF. Effects of Cortisone Acetate and Pituitary Acth on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions—A Study in Clinical Physiology. Archives of internal medicine. 1950; 85(4):545–666. PMID: 15411248

8. The Cochrane highly sensitive search strategies for identifying randomized trials in PubMed [cited 2015 October]. Available from: http://work.cochrane.org/pubmed.
9. Scottish Intercollegiate Guidelines Network Search Filters [cited 2015 October]. Available from: http://www.sign.ac.uk/methodology/filters.html.
10. Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of bias [cited 2015 October]. Available from: http://www.handbook.cochrane.org.
11. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [cited 2015 October]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
12. Table 8.4.a: A common classification scheme for bias. [cited 2015 Oct]. Available from: http://www.handbook.cochrane.org.
13. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Statistics in medicine. 2010; 29 (29):3046–67. doi: 10.1002/sim.4040 PMID: 20827667.
14. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Statistics in medicine. 2004; 23(9):1351–75. doi: 10.1002/sim.1761 PMID: 15116347.
15. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Statistics in medicine. 2007; 26(1):53–77. doi: 10.1002/sim.2528 PMID: 16596572.
16. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. [cited 2016 July]. Available from: http://www.R-project.org/.
17. Kanthan GL, Wang JJ, Rochtchina E, Tan AG, Lee A, Chia EM, et al. Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. Ophthalmology. 2008; 115(5):808–14 e1. Epub 2007/09/29. doi: 10.1016/j.ophtha.2007.07.008 PMID: 17900695.
18. Williams IA, Baylis EM, Shipley ME. A double-blind placebo-controlled trial of methylprednisolone pulse therapy in active rheumatoid disease. Lancet. 1982; 2(8292):237–40. Epub 1982/07/31. PMID: 6124671.
19. Bakker MF, Jacobs JWG, Welsing PMJ, Verstappen SMM, Tekstra J, Ton E, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. Annals of internal medicine. 2012; 156(5):329–39. doi: 10.7326/0003-4819-156-5-201203060-00004 PMID: 22393128.
20. van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, Bijlsma JWJ. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial. Annals of internal medicine. 2002; 136(1):1–12. PMID: 11777359.
21. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis and rheumatism. 2005; 52(11):3371–80. doi: 10.1002/art.21421 PMID: 16255011.
22. Gullberg R, Elman A. Posterior subcapsular cataract in rheumatoid arthritis patients after long-term, low-dosage paramethasone therapy. Scand J Rheumatol. 1973; 2(3):113–8. PMID: 4769063.
23. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. The American journal of medicine. 1994; 96(2):115–23. Epub 1994/02/01. PMID: 8109596.
24. McDougall R, Sibley J, Haga M, Russell A. Outcome in patients with rheumatoid arthritis receiving prednisone compared to matched controls. The Journal of rheumatology. 1994; 21(7):1207–13. PMID: 7966059.
25. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. Annals of the rheumatic diseases. 2009; 68(7):1119–24. Epub 2008/08/08. doi: 10.1136/ard.2008.092163 PMID: 18684744.
26. Mazzantini M, Talarico R, Doveri M, Consensi A, Cazzato M, Bazzichi L, et al. Incident Comorbidity Among Patients with Rheumatoid Arthritis Treated or Not with Low-dose Glucocorticoids: A Retrospective Study. The Journal of rheumatology. 2010; 37(11):2232–6. doi: 10.3899/jrheum.100461 PMID: WOS:000284301900007.
27. Giles CL, Mason GL, Duff IF, McLean JA. The association of cataract formation and systemic corticosteroid therapy. JAMA. 1962; 182:719–22. PMID: 13947854.

28. Crews SJ. Posterior subcapsular lens opacities in patients on longterm corticosteroid therapy. British medical journal. 1963; 1(5346):1644–7. Epub 1963/06/22. PMID: 14023840; PubMed Central PMCID: PMC2124356.

29. Furst C, Smiley WK, Ansell BM. Steroid cataract. Annals of the rheumatic diseases. 1966; 25(4):364–8. Epub 1966/07/01. PMID: 5947583; PubMed Central PMCID: PMC2453341.

30. Williamson J, Paterson RW, McGavin DD, Jasani MK, Boyle JA, Doig WM. Posterior subcapsular cataracts and glaucoma associated with long-term oral corticosteroid therapy. In patients with rheumatoid arthritis and related conditions. The British journal of ophthalmology. 1969; 53(6):361–72. Epub 1969/06/01. PMID: 5794952; PubMed Central PMCID: PMC1214577.

31. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane database of systematic reviews. 2007;(1:):CD006356. Epub 2007/01/27. doi: 10.1002/14651858.CD006356 PMID: 17253590.

32. Rothova A, Suttorp-van Schulten MS, Frits Treffers W, Kijlstra A. Causes and frequency of blindness in patients with intraocular inflammatory disease. The British journal of ophthalmology. 1996; 80(4):332–6. PMID: 8703885; PubMed Central PMCID: PMC505460.

33. Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. Ophthalmology. 2009; 116(4):652–7. Epub 2009/02/27. doi: 10.1016/j.ophtha.2008.12.001 PMID: 19243828.

34. Hodge WG, Whitcher JP, Satariano W. Risk factors for age-related cataracts. Epidemiologic reviews. 1995; 17(2):336–46. Epub 1995/01/01. PMID: 8654515.

35. Caldwell JR, Furst DE. The efficacy and safety of low-dose corticosteroids for rheumatoid arthritis. Seminars in arthritis and rheumatism. 1991; 21(1):1–11. Epub 1991/08/01. PMID: 1948096.

36. Carnahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. Current opinion in ophthalmology. 2000; 11(6):478–83. Epub 2001/01/06. PMID: 11141645.

37. Da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Ines LB, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Annals of the rheumatic diseases. 2006; 65(3):285–93. Epub 2005/08/19. doi: 10.1136/ard.2005.038638 PMID: 16107513; PubMed Central PMCID: PMC1798053.

38. Jacobs JWG, Bijlsma JWJ. Glucocorticoid Therapy. In: Firestein GS, Budd RC, Gabriel S, McInnes I, O'Dell JR, editors. Kelley's Textbook of Rheumatology. 1. 9th Edition ed. Philadelphia: Elsevier Saunders; 2013. p. 894–916.

39. Klein BE, Klein R, Lee KE, Danforth LG. Drug use and five-year incidence of age-related cataracts: The Beaver Dam Eye Study. Ophthalmology. 2001; 108(9):1670–4. PMID: 11535471.

40. Leske MC, Chylack LT Jr., Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. Arch Ophthalmol. 1991; 109(2):244–51. PMID: 1993036.

41. Group TI-ACS. Risk factors for age-related cortical, nuclear, and posterior subcapsular cataracts. American journal of epidemiology. 1991; 133(6):541–53. PMID: 1672483.

42. Toogood JH, Markov AE, Baskerville J, Dyson C. Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. The Journal of allergy and clinical immunology. 1993; 91(2):571–9. PMID: 8436773.

43. Matsunami C, Hilton AF, Dyer JA, Rumbach OW, Hardie IR. Ocular complications in renal transplant patients. Aust N Z J Ophthalmol. 1994; 22(1):53–7. PMID: 8037915.

44. Delcourt C, Cristol JP, Tessier F, Leger CL, Michel F, Papoz L. Risk factors for cortical, nuclear, and posterior subcapsular cataracts: the POLA study. Pathologies Oculaires Liees a l'Age. American journal of epidemiology. 2000; 151(5):497–504. PMID: 10707918.

45. Leske MC, Connell AM, Wu SY, Hyman LG, Schachat AP. Risk factors for open-angle glaucoma. The Barbados Eye Study. Arch Ophthalmol. 1995; 113(7):918–24. PMID: 7605285.

46. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. Eye. 2006; 20(4):407–16. Epub 2005/05/07. doi: 10.1038/sj.eye.6701895 PMID: 15877093.

S1 Table. Search terms used for RCTs and Observational Studies in each of the databases.

MEDLINE and EMBASE- Observational studies and RCTs	**Web of Science- Observational studies and RCTs**
exp Adrenal Cortex Hormones/	corticosteroid$
corticosteroid$.mp.	glucocorticoid$
glucocorticoid$.mp.	glucocorticosteroid$
glucocorticosteroid$.mp.	steroid$
steroid$.mp.	rheumatoid arthritis
exp Arthritis, Rheumatoid/	inflammatory arthritis
Rheumatoid Arthritis.mp.	inflammatory polyarthritis
inflammatory arthritis.mp.	
inflammatory polyarthritis.mp.	
MEDLINE and EMBASE- Observational studies only	**Web of Science- Observational studies only**
exp Cataract/	cataract$
cataract.mp.	lens opac$
lens opacity.mp.	glaucoma
(lens adj3 opacity).mp.	ocular hypertension
(lens adj3 opacification).mp.	
glaucoma.mp.	
exp Glaucoma/	
ocular adj3 hypertension).mp.	

S2 Table. RCTs comparing GC use to non-use in RA and number of reported cataract and glaucoma.

First Author, Year	Duration of study	Country	Mean Age* (%Female)	Arms of RCTs (n)
Bakker(1), 2012	2 years	The Netherlands	54 (60%)	MTX + PNL 10mg/d (117) MTX + placebo (119)
Buttgereit(2), 2013	12 weeks	North America, Europe	57.2 (84%)	MR-PNL 5mg/d (231) Placebo (119)
Capell(3), 2004	2 years	United Kingdom	Median 56 (65%)	SSZ + PNL 7mg (84) SSZ + placebo (83)
Chamberlain(4), 1976	2 years	United Kingdom	Range 28-75 (85%)	PNL 5mg (20) PNL 3mg (10) PNL 0mg (19)
Choy(5), 2005	2 years	United Kingdom	58 (78%)	IM Depomedrone 120mg (48) Saline placebo (43)
Choy(6), 2008	2 years	United Kingdom	54 (70%)	MTX (117) MTX + Ciclosporin (119) MTX + PNL (115) MTX + Ciclosporin + PNL (116)
Ciconelli(7), 1996	26 weeks	Brazil	44 (100%)	SSZ + IV MP 5mg/kg month 0,1 +2 (20) SSZ + IV placebo (saline) month 0, 1+2 (18)
Corkill(8), 1990	24 weeks	United Kingdom	54 (64%)	Gold + IM MP 120mg week 0,4 + 8 (35) Gold + IM placebo (saline) week 0,4 + 8 (24)
Durez(9), 2007	46 weeks	Belgium	51 (66%)	MTX (14) MTX + IV MP 1g (15) MTX + infliximab (15)
Emery(10), 2006	24 weeks	International	51 (81%)	RTX placebo + IV MP (42) RTX placebo + IV MP + PO PNL (44) RTX placebo + placebo (63) RTX 500mg + IV MP (41) RTX 500mg + IV MP + PO PNL (42) RTX 500mg + placebo (41) RTX 1000mg + IV MP (62) RTX 1000mg + IV MP + PO PNL (65) RTX 1000mg + placebo (55)
Gerlag(11), 2004	2 weeks	The Netherlands	53 (62%)	PNL 60mg week 1, 40mg week 2 (10)

First Author, Year	Duration of study	Country	Mean Age* (%Female)	Arms of RCTs (n)
				Placebo (11)
Gough(12), 1994	1 year	United Kingdom	54 (80%)	SSZ + IM MP 120mg week 0, 4 + 12 (11) SSZ + IM placebo (saline) week 0,4 + 12 (9)
Hansen(13), 1990	1 year	Denmark	60 (73%)	DMARD (AZA or PEN) + IV MP week 0,4,8,12,16 + 20 (31) DMARD (AZA or PEN) + placebo (26)
Hansen(14), 1999	1 year	Denmark	62 (NR)	DMARD + PNL (42) DMARD only (34)
Kirwan(15), 1995	2 years	United Kingdom	49 (64%)	PNL 7.5mg (61) Placebo (67)
Kirwan(16), 2004	12 weeks	Belgium, Sweden, United Kingdom	55 (71%)	Budesonide 3mg (37) Budesonide 9mg (36) PNL 7.5mg (39) Placebo (31)
Laan(17), 1993	44 weeks	The Netherlands	55 (70%)	Gold + PNL mean dose 7.5mg for 20 weeks (20) Gold + placebo for 20 weeks (20)
Lee(18), 1973	2 weeks	United Kingdom	NR	PNL 5mg tds (45) Aspirin 975mg qid (42) Placebo qid (41)
Montecucco(19), 2012	1 year	Italy	60 (64%)	MTX + PNL 12.5mg/d for 2 weeks then 6.25mg/d (96) MTX alone (90)
Sheldon(20), 2003	4 weeks	United Kingdom	57 (62%)	Budesonide CR (14) Placebo (12)
Svensson(21), 2005	2 years	Sweden	55 (64%)	DMARD + PNL 7.5mg (119) DMARD alone, no placebo (131)
Todoerti(22), 2010	2 years	Italy	60 (74%)	MTX + PNL 12.5mg for 2 weeks, then 6.25mg (105) MTX + placebo (105)
van der Veen(23), 1993	1 year	The Netherlands	56 (80%)	MTX + placebo (10) MTX + PNL 100mg day 1,3+5 (10) MTX + 1g IV MP day 1,3+5 (10)
van Everdingen(24), 2002	2 years	The Netherlands	62 (64%)	PNL 10mg (40) Placebo (41)
Verschueren(25), 2015	16 weeks	Belgium	51 (79%)	MTX (47) MTX + PNL 30mg tapered to 5mg

First Author, Year	Duration of study	Country	Mean Age* (%Female)	Arms of RCTs (n)
				at week 6 (43)
Wassenberg(26), 2005	2 years	Germany, Austria, Switzerland	52 (70%)	Gold or MTX + PNL 5mg (93) Gold or MTX + placebo (96)
Williams(27), 1982	6 weeks	United Kingdom	56 (90%)	1g IV MP (10) Placebo (10)
Wong(28), 1990	24 weeks	Australia	64 (38%)	Gold + 1g IV MP week 0,4+8 (20) Gold + placebo (20)

* mean age, unless otherwise stated

**Williams et al reported one open angle glaucoma but did not state whether it occurred in the GC or control group

GC=glucocorticoid, pyr= person years at risk, NR= not reported, No.=number, PNL=prednisolone, MR-PNL= modified release prednisolone, MTX= methotrexate, SSZ=sulfasalazine, MP=methylprednisolone, RTX=rituximab

1. Bakker MF, Jacobs JWG, Welsing PMJ, Verstappen SMM, Tekstra J, Ton E, et al. Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial.[Summary for patients in Ann Intern Med. 2012 Mar 6;156(5):I18; PMID: 22393145]. Annals of internal medicine. 2012;156(5):329-39. PubMed PMID: 22393128.
2. Buttgereit F, Mehta D, Kirwan J, Szechinski J, Boers M, Alten RE, et al. Low-dose prednisone chronotherapy for rheumatoid arthritis: a randomised clinical trial (CAPRA-2). Annals of the rheumatic diseases. 2013;72(2):204-10. PubMed PMID: 22562974. Pubmed Central PMCID: PMC3553491.
3. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Annals of the rheumatic diseases. 2004;63(7):797-803. PubMed PMID: 15194574. Pubmed Central PMCID: PMC1755058.
4. Chamberlain MA, Keenan J. The effect of low doses of prednisolone compared with placebo on function and on the hypothalamic pituitary adrenal axis in patients with rheumatoid arthritis. Rheumatology and rehabilitation. 1976 Feb;15(1):17-23. PubMed PMID: 766142. Epub 1976/02/01. eng.
5. Choy EH, Kingsley GH, Khoshaba B, Pipitone N, Scott DL, Intramuscular Methylprednisolone Study G. A two year randomised controlled trial of intramuscular depot steroids in patients with established rheumatoid arthritis who have shown an incomplete response to disease modifying antirheumatic drugs. Annals of the rheumatic diseases. 2005 Sep;64(9):1288-93. PubMed PMID: 15760929. Pubmed Central PMCID: 1755652. Epub 2005/03/12. eng.
6. Choy EH, Smith CM, Farewell V, Walker D, Hassell A, Chau L, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Annals of the rheumatic diseases. 2008 May;67(5):656-63. PubMed PMID: 17768173. Epub 2007/09/05. eng.
7. Ciconelli RM, Ferraz MB, Visioni RA, Oliveira LM, Atra E. A randomized double-blind controlled trial of sulphasalazine combined with pulses of methylprednisolone or placebo in the treatment of rheumatoid arthritis. British journal of rheumatology. 1996;35(2):150-4. PubMed PMID: 8612028.

8. Corkill MM, Kirkham BW, Chikanza IC, Gibson T, Panayi GS. Intramuscular depot methylprednisolone induction of chrysotherapy in rheumatoid arthritis: a 24-week randomized controlled trial. British journal of rheumatology. 1990;29(4):274-9. PubMed PMID: 2198977.
9. Durez P, Malghem J, Nzeusseu Toukap A, Depresseux G, Lauwerys BR, Westhovens R, et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. Arthritis and rheumatism. 2007 Dec;56(12):3919-27. PubMed PMID: 18050189. Epub 2007/12/01. eng.
10. Emery P, Fleischmann R, Filipowicz-Sosnowska A, Schechtman J, Szczepanski L, Kavanaugh A, et al. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis & Rheumatism. 2006;54(5):1390-400. PubMed PMID: 16649186.
11. Gerlag DM, Haringman JJ, Smeets TJ, Zwinderman AH, Kraan MC, Laud PJ, et al. Effects of oral prednisolone on biomarkers in synovial tissue and clinical improvement in rheumatoid arthritis. Arthritis and rheumatism. 2004 Dec;50(12):3783-91. PubMed PMID: 15593225. Epub 2004/12/14. eng.
12. Gough A, Sheeran T, Arthur V, Panayi G, Emery P. Adverse interaction between intramuscular methylprednisolone and sulphasalazine in patients with early rheumatoid arthritis. A pilot study. Scandinavian Journal of Rheumatology. 1994;23(1):46-8. PubMed PMID: 7906428.
13. Hansen TM, Kryger P, Elling H, Haar D, Kreutzfeldt M, Ingeman-Nielsen MW, et al. Double blind placebo controlled trial of pulse treatment with methylprednisolone combined with disease modifying drugs in rheumatoid arthritis. Bmj. 1990;301(6746):268-70. PubMed PMID: 2202458. Pubmed Central PMCID: PMC1663457.
14. Hansen M, Podenphant J, Florescu A, Stoltenberg M, Borch A, Kluger E, et al. A randomised trial of differentiated prednisolone treatment in active rheumatoid arthritis. Clinical benefits and skeletal side effects. Annals of the rheumatic diseases. 1999;58(11):713-8. PubMed PMID: 10531077. Pubmed Central PMCID: PMC1752793.
15. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. The New England journal of medicine. 1995 Jul 20;333(3):142-6. PubMed PMID: 7791815. Epub 1995/07/20. eng.
16. Kirwan JR, Hallgren R, Mielants H, Wollheim F, Bjorck E, Persson T, et al. A randomised placebo controlled 12 week trial of budesonide and prednisolone in rheumatoid arthritis. Annals of the rheumatic diseases. 2004 Jun;63(6):688-95. PubMed PMID: 15140776. Pubmed Central PMCID: 1755023. Epub 2004/05/14. eng.
17. Laan R, Vanriel P, Vandeputte LBA, Vanerning L, Vanthof MA, Lemmens JAM. LOW-DOSE PREDNISONE INDUCES RAPID REVERSIBLE AXIAL BONE LOSS IN PATIENTS WITH RHEUMATOID-ARTHRITIS - A RANDOMIZED, CONTROLLED-STUDY. Annals of internal medicine. 1993 Nov;119(10):963-8. PubMed PMID: WOS:A1993MG67200001.
18. Lee P, Jasani MK, Dick WC, Buchanan WW. Evaluation of a functional index in rheumatoid arthritis. Scand J Rheumatol. 1973;2(2):71-7. PubMed PMID: 4584370. Epub 1973/01/01. eng.
19. Montecucco C, Todoerti M, Sakellariou G, Scire CA, Caporali R. Low-dose oral prednisone improves clinical and ultrasonographic remission rates in early rheumatoid arthritis: results of a 12-month open-label randomised study. Arthritis research & therapy. 2012;14(3):R112. PubMed PMID: 22584017. Pubmed Central PMCID: PMC3446489.
20. Sheldon P. Ileum-targeted steroid therapy in rheumatoid arthritis: double-blind, placebo-controlled trial of controlled-release budesonide. Rheumatology international. 2003 Jul;23(4):154-8. PubMed PMID: 12856138. Epub 2003/07/12. eng.
21. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafstrom I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year

randomized trial. Arthritis and rheumatism. 2005 Nov;52(11):3360-70. PubMed PMID: 16255010. Epub 2005/10/29. eng.
22. Todoerti M, Scire CA, Boffini N, Bugatti S, Montecucco C, Caporali R. Early disease control by low-dose prednisone comedication may affect the quality of remission in patients with early rheumatoid arthritis. Annals of the New York Academy of Sciences. 2010;1193:139-45. PubMed PMID: 20398020.
23. van der Veen MJ, Bijlsma JW. The effect of methylprednisolone pulse therapy on methotrexate treatment of rheumatoid arthritis. Clinical rheumatology. 1993;12(4):500-5. PubMed PMID: 8124913.
24. van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, Bijlsma JWJ. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial.[Summary for patients in Ann Intern Med. 2002 Jan 1;136(1):I-26; PMID: 11777372]. Annals of internal medicine. 2002;136(1):1-12. PubMed PMID: 11777359.
25. Verschueren P, De Cock D, Corluy L, Joos R, Langenaken C, Taelman V, et al. Methotrexate in combination with other DMARDs is not superior to methotrexate alone for remission induction with moderate-to-high-dose glucocorticoid bridging in early rheumatoid arthritis after 16 weeks of treatment: the CareRA trial. Annals of the rheumatic diseases. 2015 Jan;74(1):27-34. PubMed PMID: 25359382.
26. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis and rheumatism. 2005 Nov;52(11):3371-80. PubMed PMID: 16255011. Epub 2005/10/29. eng.
27. Williams IA, Baylis EM, Shipley ME. A double-blind placebo-controlled trial of methylprednisolone pulse therapy in active rheumatoid disease. Lancet. 1982 Jul 31;2(8292):237-40. PubMed PMID: 6124671. Epub 1982/07/31. eng.
28. Wong CS, Champion G, Smith MD, Soden M, Wetherall M, Geddes RA, et al. Does steroid pulsing influence the efficacy and toxicity of chrysotherapy? A double blind, placebo controlled study. Annals of the rheumatic diseases. 1990 Jun;49(6):370-2. PubMed PMID: 2116773. Pubmed Central PMCID: 1004102. Epub 1990/06/01. eng.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1 Table
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4 & 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7 (Fig1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1 & 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Fig 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Fig 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

6.3 Manuscript 2: The association between systemic glucocorticoid use and the risk of cataract and glaucoma in CPRD patients with incident rheumatoid arthritis

Statement of Authorship

Title of Paper	Oral glucocorticoid use and the development of cataracts and glaucoma in patients with incident rheumatoid arthritis.
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☒ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Black RJ, Lester S, Hill CL, Dixon WG. Manuscript ready for submission but not yet submitted.

Principal Author

Name of Principal Author (Candidate)	Rachel Black		
Contribution to the Paper	Responsible for the design and conception of the work, data preparation including data cleaning, data analysis and interpretation, preparation of the manuscript and will act as corresponding author.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	16/05/2015

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Susan Lester		
Contribution to the Paper	Supervised and assisted with the selection of appropriate analyses, interpretation of analyses and critically reviewed the manuscript, with approval of the final version prior to publication.		
Signature		Date	16/05/2019

Name of Co-Author	Catherine Hill
Contribution to the Paper	Supervised and assisted with the interpretation of analyses and critically reviewed the manuscript, with final approval of the version to be published.

Signature		Date	16/05/2015

Please cut and paste additional co-author panels here as required.

Name of Co-Author	William Dixon		
Contribution to the Paper	Supervised the conception and design of the work, including interpretation of analyses and critically reviewd the manuscript, with approval of the final version to be published.		
Signature		Date	15th May 2019

Oral glucocorticoid use and the development of cataracts and glaucoma in patients with incident rheumatoid arthritis.

Rachel J. Black[1, 2, 3,4], Susan Lester[2, 3], Catherine L. Hill[1, 2, 3], William G. Dixon[4,5,6]

[1]The Royal Adelaide Hospital, Rheumatology Unit, Adelaide, Australia
[2]The Queen Elizabeth Hospital, Rheumatology Unit, Adelaide, Australia
[3] Faculty of Health and Medical Sciences, The University of Adelaide, Adelaide, Australia
[4]Arthritis Research UK Centre for Epidemiology, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK
[6] NIHR Manchester Biomedical Research Centre, Manchester University, NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK

Corresponding Author
Dr Rachel Black, MBBS, FRACP
Rheumatology Unit 8E300
Royal Adelaide Hospital
Port Road, Adelaide, SA
AUSTRALIA 5000
Email: rachel.black2@sa.gov.au

Abstract

Background: Cataracts and glaucoma are recognised glucocorticoid (GC) adverse effects. However, the impact of GC use, dose and timing of dose on the development of cataracts and glaucoma has not been well quantified.

Objectives: To determine the association between: 1. GC use 2. GC dose and the lag effect of GC dose, and 3. Cumulative GC dose and the development of incident cataract and glaucoma in patients with incident RA.

Methods: Data were used from the Clinical Practice Research Datalink (CPRD), a large UK primary care database derived from electronic medical records (Jan 1992- Dec 2017). Incident RA patients were identified using a validated algorithm. Three GC exposure models assessed the impact of: 1. Current GC exposure, 2. Current dose (prednisolone daily dose equivalent) and lagged dose (at 1, 3, 6 months, 1 & 2 years) and 3. Cumulative dose, all as time-varying covariates. Each outcome was analysed separately using parametric log-logistic and Weibull survival models respectively. To improve the model fit, a square root (sqrt) transformation of dose was used for cataract Model 2. Smoking, gender and uveitis were included as covariates in the model and age was used as the timescale. Comorbidities on the causal pathway, such as diabetes, obesity and hypertension, were not included.

Results: There were 22607 patients with incident RA (median age 66, IQR 37, 84, 68% female), of whom 241 had cataracts and 164 had glaucoma on or before baseline and were thus excluded. Median duration of follow up was 8.7 years (IQR 1.8, 19.8) and 39% were ever GC users during follow up. The incidence rate, per 1000 patient-years, was 12.3 (95% CI 11.8, 12.9) for cataracts and 3.1 (95% CI 2.8, 3.4) for glaucoma, which increased with age. GC use was associated with both cataracts (OR 2.25, 95%CI 1.89, 2.68) and glaucoma (HR 1.60, 95%CI 1.26, 2.02). In the multivariable lagged dose analysis, an increase in current dose from 0-10mg was associated with an increased risk of cataract (OR 1.59, 95%CI 1.08, 2.33), with dose 1-year prior having the greatest effect size for cataracts (OR 2.08, 95%CI 1.45- 3.00). For glaucoma, each 10mg increase in GC dose at 3-months prior (HR 1.54, 95% CI 1.13, 2.10) and 1-year prior (HR 1.60, 95% CI 1.20, 2.14) were important. Compared to no GC use, cumulative GC doses more than 1000mg were associated with cataracts (OR 1.63, 95%CI 1.26, 2.10), with an increased risk seen with higher cumulative doses more than 4000mg (OR3.15, 95%CI 2.56, 3.88). Compared to no GC use, there was an increased risk of glaucoma associated with cumulative doses greater then 4000mg (HR 1.47, 95%CI 1.07, 2.02).

Conclusions: The quantification of the risk associated with GCs and the development of cataract and glaucoma is of clinical utility in daily practice. EULAR guidelines recommend patients are informed of the risks and benefits of GC treatment prior to

commencement, however the risk of these potential side effects had not previously been quantified. This information will allow patients to make better informed treatment choices in conjunction with their treating doctor.

Introduction

Cataracts and glaucoma are well recognised as the main ophthalmic adverse effects (AEs) associated with glucocorticoid (GC) use. These conditions can lead to visual loss and account for significant disability and cost to the healthcare system(1, 2). Multiple mechanisms linking GC use to the development of cataracts and glaucoma have been proposed (3, 4), however much of the literature focuses on topical GC use, with less understood about the effects of systemic GC use on the eye. The impact of oral GC use on the development of cataracts, but not glaucoma, has been previously reported in disease-specific and general populations (5-10). However, the estimates in these studies ranged from a less than three-fold increase in risk to a greater than eight-fold increased risk due to significant heterogeneity in the design of the studies, including different definitions of cataracts and differing methods for identifying them. The impact of dose, the timing of when a dose is given and the cumulative effects of dose also remain unquantified (11).

GCs are frequently used in the treatment of rheumatoid arthritis (RA), with approximately 50-60% of RA patients found to be ever-users(12-14). International guidelines recommend the risks and benefits of GC treatment are discussed with patients prior to therapy (15), however an informed risk-benefit assessment is difficult when the risks have not been adequately quantified. Dosing patterns have been shown to vary greatly for patients with RA (12), making it necessary to explore the impact of differing GC exposure patterns on the development of cataracts and glaucoma.

The primary aim of this study was to examine the association between GC use and the development of cataracts and glaucoma in RA patients. Specific objectives were to examine time-varying models of: 1) current GC use (yes/no), 2) current or lagged GC dose, and 3) cumulative dose as a combination of dose and timing.

Methods

Setting

Clinical Practice Research Datalink (CPRD) is an automated database that contains pseudonymised, prospectively collected electronic medical records (EMRs) from registered UK general practices. In the UK, healthcare is centralised through general practice and EMRs are maintained and updated within practices. The EMRs contain all primary care details as well as information about referrals. Studies have found the

data held by CPRD to be representative of the UK population in terms of age and gender structure (16, 17). Validation studies have demonstrated good completeness and accuracy of the data, particularly for chronic diseases (18, 19). CPRD has its own internal quality measures at the patient and practice level, including acceptability flags based on contiguity and quality of patient data, and an up to standard date for practices based on continuity of data recording (20). UK primary care electronic medical records use a unique coding system with Read codes identifying medical diagnoses and Product codes to identify medications (21). Medical and Product Browsers available to generate Read and Product code lists.

Data were obtained from CPRD for the period from 1st January 1992- 31st December 2017. Patients with RA were identified using a validated algorithm, shown to have a sensitivity of 84% and a specificity of 86% when compared to the American College of Rheumatology 1987 revised RA classification criteria (22). The RA diagnosis date was defined as the date of the first RA code in patients with validated RA. Each patient had a cohort entry date defined as the date at which all of the following criteria were met: their practice was classified as up to standard, the patient was currently registered with the practice and the study period had started (1st Jan 1992). Patients with incident RA were identified as those with an RA diagnosis date on or after their cohort entry date, at least 12 months of data recorded prior to diagnosis and no record of disease modifying anti-rheumatic drug (DMARD) use, including prior to their RA diagnosis date. Those aged less than 18 years were excluded.

Outcome variables

Cataract and Glaucoma codes were identified using the Read code dictionary. A number of cataract and glaucoma codes have been previously validated (23), however these validated code lists included 13 cataract codes and 13 glaucoma codes, far fewer than those identified in Medical Browser search. Therefore, an expanded list was selected for this study. Codes for cataract and glaucoma with congenital, post traumatic and surgical causes were excluded as well as those identified as being secondary to another medical condition. Code lists are available in data supplement Table S1. Those with a cataract code on or before baseline were excluded from the cataract analyses, with the same process applied to the glaucoma analyses.

Glucocorticoid use exposure variables

Oral GC use was identified using the Product codes for prednisolone, cortisone, hydrocortisone, triamcinolone, methylprednisolone, dexamethasone, bethamethasone, budesonide and deflazacort. A previously developed prescription

algorithm was used to prepare the data for analysis(12, 24, 25). Dosages were converted to a prednisolone-equivalent (PEQ) daily dose. Those with a GC prescription greater than a pre-defined maximum PEQ dose of 100mg per day were excluded. For each patient, episodes on and off GCs were created for the complete follow up period, with a prednisolone equivalent daily dose for each episode on GCs. A binary indicator of GC use (on/off) and a continuous measure of GC dose (mg PEQ) were therefore time varying variables.

Analyses

All analyses were performed in Stata v13 (StatCorp LLC, Texas, USA). Descriptive statistics were used to determine the characteristics of the incident RA cohort. Cataract and glaucoma analyses were run separately. The incidence rate per 1000 patient years by age and gender was tabulated, and cumulative incidence (Kaplan-Meier failure function) and the smoothed hazard function were plotted for both cataract and glaucoma.

The relationships between GC exposure and cataract or glaucoma outcome were analysed by time-to-event (survival) regression analysis. Follow up began on the date of RA diagnosis and ended when the patient first developed the outcome of interest, or censored when the patient left the practice, died, the study period finished (31st Dec 2017) or on the date data was last collected from the practice, whichever occurred first. Age was used as the timescale in all analyses.

Non-parametric Cox regression models were initially considered for the analysis, but the proportional hazards assumption was clearly violated for the glaucoma data, and ultimately parametric survival models were selected for the analysis. Selection of the appropriate model was based on the shape of the underlying hazard function, and both the Akaike information criterion (AIC) and Bayesian information criterion (BIC).

Three separate GC exposure models were analysed for both cataracts and glaucoma: 1. Current GC use (on/off), 2. GC dose at pre-specified lagged intervals, and 3. Cumulative GC dose. The lagged dose multivariable models looked at current PEQ dose, dose at 1 month, 3 months, 6 months, 1 year and 2 years prior to the development of cataract or glaucoma. Prior to this analysis, the relationship between current dose and outcome was evaluated using Tukey ladder of powers fractional polynomial transformations, and the square root of dose was selected as an appropriate transformation to linearize the relationship between GC dose and cataracts. However, no transformation was needed for glaucoma as the relationship between dose and glaucoma was linear. The cumulative dose models looked at the

total additive GC exposure from the date of diagnosis. For ease of interpreting the results, the cumulative dose was categorised (0mg, 1-125mg, 126-250mg, 251-500mg, 501-1000mg, 1001-2000mg, 2001-4000mg and >4000mg PEQ).

Covariates

Risk factors for cataract and glaucoma were identified from the literature. Many, including diabetes mellitus, hypertension and obesity were not included as covariates in the analysis as they are on the causal pathway for the association between exposure and outcome. For example, hypertension is a risk factor for cataract and glaucoma, however GC use can lead to hypertension, which can in turn increase the risk of developing cataracts or glaucoma. Risk factors not on the causal pathway, that were included as covariates in all analyses were gender, uveitis and baseline smoking status.

Results

Data Description

Of the 36,000 patients identified using the RA validation algorithm, 22,607 met criteria for incident RA, with Figure 1 depicting how the cohort was derived. Characteristics of the incident RA cohort (median age 66; 68.2% female) are shown in Table 1. The overall incidence rate of cataracts was 12.33 (11.75, 12.94) per 1000 patient years, with a lower incidence rate of 3.10 (2.82, 3.40) per 1000 patient years seen for glaucoma. The incidence rate increased with age for both cataracts and glaucoma as shown in data supplement Table S2.

The cumulative incidence and smoothed hazards function by age for both cataracts and glaucoma are shown in Figure 2. The cumulative incidence curve may be interpreted as the probability that a patient will develop cataracts or glaucoma by a certain age. For cataracts (Figure 2A), the cumulative incidence rises steeply from age 65, reaching ~50% by age 80. For glaucoma (Figure 2B), the steepest part of the curve also occurs from age 60, however the cumulative incidence is far less than that of cataract, reaching just over 10% by age 80. The smoothed hazards function was unimodal for both cataracts (Figure 2C) and glaucoma (Figure 2D).

Model Selection

Initial analysis was performed by semi-parametric cox proportional hazards regression, with GC use as the exposure variable (Model 1). However, there was evidence of violation of the proportional hazards assumption for the cataract data ($p = 0.0007$),

but not for glaucoma (p = 0.13). Based on the AIC and BIC criteria (Table S3), the log-logistic parametric survival model was the best fitting parametric survival model for the cataract data, which was also consistent with the shape of the hazards function (Figure 2C). The loglogistic survival model is an accelerated failure time (AFT) model in which the exponentiated coefficients represent the time (in this case, age) ratio at outcome onset between comparator groups. This model also has the property of proportional odds, and therefore the odds ratio for survival (or cumulative failure) between comparator groups is constant over time. There was no evidence that the proportional odds assumption was violated for any of the model covariates, as assessed by covariate interaction with the gamma (shape) parameter.
Because the proportional hazards assumption held for the glaucoma data, a Weibull parametric survival model was used for the glaucoma data. In addition to a proportional hazards model, this also has representation as an AFT model, and therefore results for glaucoma can be compared to those for cataracts.

The suitability of the models selected for the analyses is shown in data supplement Figure S1, where the predicted survival from the log logistic model (with no covariates) is plotted against the observed Kaplan Meier (KM) survival curve for cataract, and the predicted survival from the Weibull model is plotted against the observed KM curve for glaucoma. For both the cataract and glaucoma models, there was a good fit, with the predicted models lying within the 95% confidence intervals of the observed plot.

GC Exposure Models- Cataracts

The results of the three different exposure models for cataracts are shown in Table 2. In the first model, current GC use was associated with cataracts (OR 2.25, 95%CI 1.89, 2.68), as was baseline uveitis (OR 8.73, 95% CI 4.11, 18.52). The AFT $\log_e$ coefficient, which for small values is approximately equal to the proportional reduction in age of onset, was -0.098 (95% CI 0.12, -0.076) for GC use, indicating that cataracts occurred at a 10% earlier age in GC users compared to non-users. The second model examined the effect of current and lagged GC dose, for which a square root transformation was performed, as described in the methods. For ease of interpretation, the results are presented as ORs for an increase in dose from 0-10mg. There was an association between current GC dose (OR 1.59, 95%CI 1.08, 2.33), meaning that an increase in GC dose from 0-10mg PEQ was associated with a 60% increase in the odds of developing cataracts. There was also a significant association with an increase in GC dose from 0-10mg at 6 months (OR 1.49, 95%CI 1.02, 2.17), with the greatest association seen at 1 year prior to the diagnosis of cataracts (OR 2.08, 95%CI 1.45, 3.00). In the third model, prior cumulative GC dose was analysed, showing that cumulative doses 1000-2000mg

were associated with the development of cataracts (OR 1.63, 95%CI 1.26, 2.10), with similar odds for 2000-4000mg, whereas the odds increased further with cumulative doses greater than 4000mg (OR 3.15, 95%CI 2.56, 3.88).

GC Exposure Models-Glaucoma

The results of the three GC exposure models for glaucoma are shown in Table 3. In Model 1, current GC use (HR 1.60, 95%CI 1.26, 2.02) and baseline uveitis (HR 4.69, 95%CI 2.42, 9.09) were associated with glaucoma. The AFT for GC use was -0.122 (95%CI -0.188, -0.055), indicating that glaucoma developed at a 12% younger age in GC users compared to non-users. In Model 2, glaucoma risk was associated with a 0-10mg increase in GC dose at 3 months (HR 1.54, 95%CI 1.13, 2.10) and 1 year (HR 1.60, 95%CI 1.20, 2.14), but not at 6 months. In Model 3, cumulative doses greater than 4000mg were associated with the development of glaucoma (HR 1.47, 95%CI 1.07, 2.02), however there was no association with lower cumulative doses below 4000mg.

Mean difference in Age of Onset with GC Use

The results of the AFT models can be expressed in different ways, one of which is the mean age difference (in years) for the outcome onset. For example, in Model 1, the mean age of onset of cataract or glaucoma with GC use was estimated by prediction of the marginal effects, averaged over all covariates (Figure 3). Cataracts occurred an average of 8.4 years (95%CI -10.3, -6.6) earlier with GC use compared to non-use. The effect of GC use on glaucoma age of onset was even greater, occurring an average of 15.2 years (95%CI -23.6, -6.9) earlier with GC use compared to non-use. Uveitis had the greatest impact on age of onset for both cataract and glaucoma, bringing forward the average age of diagnosis by 20 years for cataract and 40 years for glaucoma.

Discussion

This study confirms that oral GC use is associated with the development of cataracts and glaucoma in patients with RA. For cataracts, the results of Model 1 have shown an OR of 2.25 (95%CI 1.89, 2.68) for current exposure, which is comparable to the results of a previous meta-analysis, where the OR for GC exposure in RA observational studies was found to be 2.1 (95%CI 1.5–2.9)(11). The same meta-analysis, found no such association between GC exposure and cataracts in randomised controlled trials, reinforcing the message that long-term observational studies in real-life populations play an essential role in quantifying safety outcomes.

The relationship between GC use and the development of cataracts has previously been explored in general and diseases specific populations, but with significant heterogeneity in estimates and study design. Many of these studies used ophthalmic examination to define cataracts, dividing them into three common subtypes including posterior subcapsular cataracts (PSCs), nuclear cataracts and cortical cataracts. In The Blue Mountains Eye Study (BMES) 3654 Australians aged 49 years or older were examined between 1992– 1994, 2335 were re-examined after five years and 1952 were re-examined after 10 years. Current oral GC users at baseline had a greater risk of developing PSCs(OR 4.11; 95% CI 1.67–10.08) and nuclear cataracts (OR 3.45, 95% CI 1.26 –9.43) but not cortical cataracts (5). Conversely, in the Beaver Dam Eye Study (BDES) adults aged 43 to 86 years were examined between 1988-1990 and again 5 years later. In contrast to the BMES, oral GC use was associated with an increased risk of cortical cataracts (OR 2.59, 95%CI 1.45-4.62) but not nuclear cataracts or PSCs (6). In the Lens Opacities Study, cases (cataracts) and controls were taken from a general ophthalmology outpatient clinic, with oral GCs found to be a risk factor for PSCs only (OR 5.73, 95%CI 2.14, 15.3) (7). In the Italian-American Cataract Study Group, patients were recruited from the three ophthalmic clinics in Parma, Italy, from 1987 -1989. They did not analyse oral and topical GCs separately, and cortisone given orally or as eye drops was associated with an increased risk or PSCs (OR 8.39, 95%CI 3.42-20.61) but not with other cataract types (8). In a cross sectional disease-specific study of asthma patients, PSCs diagnosed by at an ophthalmological examination were associated with current prednisolone dose (coef 0.43, $P<0.002$) but non-PSC opacities were not (9). Renal transplant recipients at Princess Alexandra Hospital, Australia between 1982-1988 were examined before and after treatment. High dose versus low dose GC treatment was associated with an increased risk of cataracts ($\chi^2= 8.097$; df= 1, $P<0.01$)(10).

Current knowledge about the relationship between oral GC dose and the development of cataracts and glaucoma has been extended by the results of Models 2 & 3. In Model 2, the effect of current dose on the development of cataracts was quantified, with a 60% increase in risk associated with a dose increase from 0-10mg PEQ. This model also demonstrated that doses taken 1 and 3-months prior to diagnosis were not associated with cataract development but a dose increase from 0-10mg PEQ 6-months prior was associated with a 50% increase in risk, with a doubling of the risk seen wat 12-months prior. The lack of association with doses at 1 and 3-months may be due to a correlation between current dose and dose at these time points, such that they are not significant when included in the same multivariable model. It is also interesting to consider how current dose and doses 6 and 12 months prior could mechanistically

lead to cataract development. One explanation might be that current dose is important in accelerating cataract development in patients who already have pre-clinical cataracts, not yet diagnosed. However prior dose might be playing a role in the development of de-novo cataracts. Cumulative doses greater than 1000mg PEQ were associated with a 30% increased risk of developing cataracts, whereas cumulative exposure greater than 4000mg PEQ had the greatest impact, with a threefold increase in risk. A dose of 4000mg PEQ equates to a daily dose of 5mg for just over 2 years, a dose often reported to be safe for long-term use (26). Cumulative dose has previously been shown to be important in the development of cataracts in other cohorts with giant cell arteritis (GCA)(27) and systemic lupus erythematosus (SLE)(28). Broder et al (27) found that the effects of cumulative dose on the development of cataracts increased with age (up to age 80), with a HR of 2.88 (95%CI 2.34, 3.54) for PEQ cumulative dose in those aged 70-79. However, by categorising cumulative dose, we have added to this knowledge by demonstrating levels at which cumulative dose becomes a concern. Compared to patients with RA, patients with GCA are expected to be older and to be exposed to greater cumulative doses, with no patients expected to be unexposed to GCs post diagnosis.

When compared to cataracts, there was less prior knowledge regarding oral GC use and the development of glaucoma, with a recent systematic literature review of RA studies concluding that there is a lack of robust evidence in this area (11). A case-control study using data from the Quebec universal health insurance program for the elderly, looked at the risk of developing ocular hypertension or OAG associated with oral GC use in patients aged 65 years or older (29). It found that GC current use (in the past 14 days) was associated with an increased risk of developing glaucoma (OR 1.41, 95%CI 1.22-1.63), but former use in the past 15-45 days (OR 1·18, 95% CI 0·87–1·62) or 46-365 days (OR 0·92, 95%CI 0·78–1·08) was not. It also showed that the risk increased with average daily dose (PEQ daily dose 0.4- <10mg OR 1.26, 10- <20mg OR 1.40, ≥20mg 1.88) and duration of continuous GC therapy of 3 months or more (3-5 months OR 1.63, 6-11 months OR 1.87, ≥12 months OR 1.52). Another recently published study using CPRD data looked at GC use and the development of glaucoma and other GC AEs in patients with and without RA (30). This study did not find an association between GC use in the past 180 days and glaucoma (OR 1.27, 95%CI 0.87–1.84) but did show an increased risk of glaucoma associated with cumulative prednisolone equivalent doses of 700- <3500mg (OR 1.53, 1.10-2.13) and ≥7000mg (OR 1.71, 95%CI 1.07- 2.72).While there were some similarities with our study, the nested case-control design was very different, comparing GC associated AEs in both RA and non-RA

patients. While a nested case control design should give comparable results to a Cox regression analysis, our study found that this was not the most appropriate model.

This is the first study to quantify the risk of developing glaucoma associated with time-varying models of GC exposure, and all three models extend current knowledge substantially. Previous studies looking at oral rather than topical or intraocular GC use date back to the 1970s, and demonstrated an increase in intra-ocular pressure (IOP) in patients treated with long-term GCs of varying doses and durations (31, 32). In contrast to our study, in these studies dose and duration of therapy were not found to be associated with the rise in IOP, but rather the important factor was whether or not the treated patient was a steroid responder. The concept of a steroid responder relates to whether IOP rises in response to topical dexamethasone in a given individual, and is well described in the literature relating to topical GC use(33, 34).

Uveitis is a recognised risk factor for the development of cataract and glaucoma(35, 36), and was significantly associated with both outcomes in all three models. Although not investigated specifically, it is assumed that the risk associated with uveitis captures both the inherent risk of the inflammatory eye disease, as well as the increased risk associated with topical GC use, which is commonly used as first line therapy for uveitis. Contrary to the literature (37, 38), there was no clear association seen with female gender and the development of cataracts. In the third GC exposure model, male gender was shown to be associated with the development of glaucoma, which is in keeping with the literature (39, 40). Smoking is often cited as a risk factor for both cataract and glaucoma(7, 41-44), however this was not found to be the case in our RA cohort.

The time varying exposure models selected for this study provide clinically useful results, which will enable better informed risk-benefit discussions between doctors and patients. These models capture the effects of current exposure (yes/no), current dose, lagged dose and cumulative dose. More complex, weighted cumulative dosing (WCD) models of GC exposure have been used in recent studies to capture differences in the importance of recent versus distant dosing (24, 45, 46). These WCD models could be considered as the current gold-standard of exposure models, however they are also based on the proportional hazards assumption, which was not met for our cataracts dataset. Furthermore, the WCD models require the outcome to be accurately recorded on the date of onset. For cataracts and glaucoma, the onset of disease may pre-date the first code by months. Therefore, we instead opted for models that could provide certain similar information to that obtained using a WCD

approach. A systematic approach was taken when selecting the appropriate parametric time to event survival models and models were shown to fit the data well.

The incidence of cataracts in our cohort was 12.3 per 1000 patient years (equivalent to 12.3% per 10 years), which is substantially lower than the 38-54% incidence over 10 years reported in general population cohorts in the Blue Mountains Eye study (BMES) and the Beaver Dam Eye Study (BDES) (37, 38). Similar to these studies, the incidence of cataract increased with age in our cohort, however the magnitude was lower, with an incidence rate of 31/34 (Males/Females) per 1000 patient years for those aged over 75 years, compared to a 10-year cumulative incidence of 87% in those aged over 75 years in the BBMES and BDES. This is likely due to the fact that the general population studies diagnosis was based on eye examinations rather than primary care records, which is likely to capture a greater number of cases. Regular eye examinations are recommended for patients with SLE receiving GCs (47-49) and may also be beneficial in older RA patients. The incidence of glaucoma of 3.1 per 1000 patient years was in keeping with previous reports of 3.5 per 1000 person years (39) and a cumulative incidence of 1.1% (probable or definite OAG) over 5 years (50) and 2.2% over 4 years (51).

The main limitation of this study is that it uses prescription data, with no information available on dispensing or adherence. A recent small study comparing patient reported GC use as 'true exposure' to prescription data in CPRD, found that although the misclassification of current GC use was low, with 86% correctly classified as currently on/off GCs, this was sufficient to impact the observed OR (52). However, this limitation is countered by the fact that CPRD is a large dataset that captures meaningful information from real-life practice. As this is a primary care dataset, there is no collection of formal measures of RA disease activity. Unlike other outcomes related to GC use, such as infection risk, there is no evidence that disease activity is linked to the development of cataracts and glaucoma, outside of the uveitis pathway. Therefore, no surrogate for disease activity was included in the models. Traditional models of drug exposure often include duration of therapy. We chose not to directly look at duration of GC use because individuals in our cohort were followed up for differing lengths of time, which would bias the duration of time available for GC exposure. Instead, duration of treatment was indirectly captured, using cumulative dose. We did not account for GC use that occurred prior to cohort entry. An incident RA cohort was selected in order to minimise the chance of prior exposure. However, because there are many other indications for GC use, some prior use would still be expected.

Conclusion

This study has demonstrated that current GC exposure is associated with a two-fold increased risk of developing cataracts and a 60% increased risk of developing glaucoma in patients with RA, and that the risk associated with GC use increases with age. Our models have also shown that doses given at the time of diagnosis and 6-12 months prior to the diagnosis of cataracts are important, with this bimodal effect perhaps reflecting that GCs can accelerate cataracts that have already developed but not yet been diagnosed, as well as precipitate de-novo cataract development. Doses given 3-12 months prior to the diagnosis of glaucoma are important but current dose is not, perhaps reflecting a lower background incidence of glaucoma compared to cataract. For cataracts, cumulative doses greater than 1000mg PEQ are associated with increased risk, more so at doses above 4000mg PEQ, whereas for glaucoma, the risk is seen only with higher cumulative doses greater than 4000mg. It is hoped that the quantification of these risks will lead to better informed risk-benefit discussions in the clinic setting. In the future, health economic modelling could be used to assess whether screening for cataracts and glaucoma in patients with RA prior to GC use is cost-effective, particularly in older patients

References

1. Rao GN, Khanna R, Payal A. The global burden of cataract. Current opinion in ophthalmology. 2011;22(1):4-9.
2. Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5(12):e1221-e34.
3. James ER. The etiology of steroid cataract. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics. 2007;23(5):403-20.
4. Jones R, 3rd, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. Current opinion in ophthalmology. 2006;17(2):163-7.
5. Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. Ophthalmology. 2009;116(4):652-7.
6. Klein BE, Klein R, Lee KE, Danforth LG. Drug use and five-year incidence of age-related cataracts: The Beaver Dam Eye Study. Ophthalmology. 2001;108(9):1670-4.
7. Leske MC, Chylack LT, Jr., Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. Arch Ophthalmol. 1991;109(2):244-51.
8. Group TI-ACS. Risk factors for age-related cortical, nuclear, and posterior subcapsular cataracts. . American journal of epidemiology. 1991;133(6):541-53.
9. Toogood JH, Markov AE, Baskerville J, Dyson C. Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. The Journal of allergy and clinical immunology. 1993;91(2):571-9.
10. Matsunami C, Hilton AF, Dyer JA, Rumbach OW, Hardie IR. Ocular complications in renal transplant patients. Aust N Z J Ophthalmol. 1994;22(1):53-7.
11. Black RJ, Hill CL, Lester S, Dixon WG. The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. PloS one. 2016;11(11):e0166468.
12. Black RJ, Joseph RM, Brown B, Movahedi M, Lunt M, Dixon WG. Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study. Arthritis research & therapy. 2015;17(1):375.
13. Black RJ, Lester S, Buchbinder R, Barrett C, Lassere M, March L, et al. Factors associated with oral glucocorticoid use in patients with rheumatoid arthritis: a drug use study from a prospective national biologics registry. Arthritis research & therapy. 2017;19(1):253.
14. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Lund Hetland M, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Annals of the rheumatic diseases. 2007;66(11):1491-6.
15. Duru N, Van Der Goes MC, Jacobs JWG, Andrews T, Boers M, Buttgereit F, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Annals of the rheumatic diseases. 2013;72(12):1905-13.

16. Lawson DH, Sherman V, Hollowell J. The General Practice Research Database. Scientific and Ethical Advisory Group. QJM : monthly journal of the Association of Physicians. 1998;91(6):445-52.
17. García Rodríguez LA, Pérez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. British journal of clinical pharmacology. 1998;45(5):419-25.
18. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. British journal of clinical pharmacology. 2010;69(1):4-14.
19. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Brit J Gen Pract. 2010;60(572):199-206.
20. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Therapeutic Advances in Drug Safety. 2012;3(2):89-99.
21. Health and Social Care Information Centre-Read Codes [cited 2015 August]. Available from: http://systems.hscic.gov.uk/data/uktc/readcodes.
22. Thomas SL, Edwards CJ, Smeeth L, Cooper C, Hall AJ. How accurate are diagnoses for rheumatoid arthritis and juvenile idiopathic arthritis in the general practice research database? Arthritis and rheumatism. 2008;59(9):1314-21.
23. Kang EM, Pinheiro SP, Hammad TA, Abou-Ali A. Evaluating the validity of clinical codes to identify cataract and glaucoma in the UK Clinical Practice Research Datalink. Pharmacoepidemiology and drug safety. 2015;24(1):38-44.
24. Movahedi M, Beauchamp ME, Abrahamowicz M, Ray DW, Michaud K, Pedro S, et al. Risk of Incident Diabetes Mellitus Associated With the Dosage and Duration of Oral Glucocorticoid Therapy in Patients With Rheumatoid Arthritis. Arthritis Rheumatol. 2016;68(5):1089-98.
25. Robinson DE, van Staa TP, Dennison EM, Cooper C, Dixon WG. The limitations of using simple definitions of glucocorticoid exposure to predict fracture risk: A cohort study. Bone. 2018;117:83-90.
26. Strehl C, Bijlsma JW, de Wit M, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Annals of the rheumatic diseases. 2016;75(6):952-7.
27. Broder MS, Sarsour K, Chang E, Collinson N, Tuckwell K, Napalkov P, et al. Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis. Seminars in arthritis and rheumatism. 2016.
28. Alderaan K, Sekicki V, Magder LS, Petri M. Risk factors for cataracts in systemic lupus erythematosus (SLE). Rheumatology international. 2015;35(4):701-8.
29. Garbe E, LeLorier J, Boivin JF, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. Lancet. 1997;350(9083):979-82.
30. Wilson JC, Sarsour K, Gale S, Petho-Schramm A, Jick SS, Meier CR. Incidence and Risk of Glucocorticoid-Associated Adverse Effects in Patients With Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2019;71(4):498-511.

31. Godel V, Feiler-Ofry V, Stein R. Systemic steroids and ocular fluid dynamics. I. Analysis of the sample as a whole. Influence of dosage and duration of therapy. Acta Ophthalmol (Copenh). 1972;50(5):655-63.
32. Godel V, Feiler-Ofry V, Stein R. Systemic steroids and ocular fluid dynamics. II. Systemic versus topical steroids. Acta Ophthalmol (Copenh). 1972;50(5):664-76.
33. Becker B. Intraocular Pressure Response to Topical Corticosteroids. Invest Ophthalmol. 1965;4:198-205.
34. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced Glaucoma: An Avoidable Irreversible Blindness. Journal of Current Glaucoma Practice. 2017;11(2):67-72.
35. Dick AD, Tundia N, Sorg R, Zhao C, Chao J, Joshi A, et al. Risk of Ocular Complications in Patients with Noninfectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis. Ophthalmology. 2016;123(3):655-62.
36. Tomkins-Netzer O, Talat L, Bar A, Lula A, Taylor SRJ, Joshi L, et al. Long-Term Clinical Outcome and Causes of Vision Loss in Patients with Uveitis. Ophthalmology. 2014;121(12):2387-92.
37. Kanthan GL, Wang JJ, Rochtchina E, Tan AG, Lee A, Chia EM, et al. Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. Ophthalmology. 2008;115(5):808-14 e1.
38. Klein BE, Klein R, Lee KE. Incidence of age-related cataract over a 10-year interval: the Beaver Dam Eye Study. Ophthalmology. 2002;109(11):2052-7.
39. de Voogd S, Ikram MK, Wolfs RC, Jansonius NM, Hofman A, de Jong PT. Incidence of open-angle glaucoma in a general elderly population: the Rotterdam Study. Ophthalmology. 2005;112(9):1487-93.
40. Leske MC, Connell AM, Wu SY, Hyman LG, Schachat AP. Risk factors for open-angle glaucoma. The Barbados Eye Study. Arch Ophthalmol. 1995;113(7):918-24.
41. Pérez-de-Arcelus M, Toledo E, Martínez-González MÁ, Martín-Calvo N, Fernández-Montero A, Moreno-Montañés J. Smoking and incidence of glaucoma: The SUN Cohort. Medicine. 2017;96(1):e5761-e.
42. Law SM, Lu X, Yu F, Tseng V, Law SK, Coleman AL. Cigarette smoking and glaucoma in the United States population. Eye. 2018;32(4):716-25.
43. Hodge WG, Whitcher JP, Satariano W. Risk factors for age-related cataracts. Epidemiologic reviews. 1995;17(2):336-46.
44. Seddon J, Fong D, West SK, Valmadrid CT. Epidemiology of risk factors for age-related cataract. Survey of Ophthalmology. 1995;39(4):323-34.
45. Abrahamowicz M, Bartlett G, Tamblyn R, du Berger R. Modeling cumulative dose and exposure duration provided insights regarding the associations between benzodiazepines and injuries. Journal of clinical epidemiology. 2006;59(4):393-403.
46. Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Annals of the rheumatic diseases. 2012;71(7):1128-33.
47. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Brey R, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Annals of the rheumatic diseases. 2010;69(7):1269-74.

48. Mosca M, Tani C, Aringer M, Bombardieri S, Boumpas D, Cervera R, et al. Development of quality indicators to evaluate the monitoring of SLE patients in routine clinical practice. Autoimmun Rev. 2011;10(7):383-8.
49. Mosca M, Bombardieri S. Disease-specific quality indicators, guidelines, and outcome measures in systemic lupus erythematosus (SLE). Clinical and experimental rheumatology. 2007;25(6 Suppl 47):107-13.
50. Mukesh BN, McCarty CA, Rait JL, Taylor HR. Five-year incidence of open-angle glaucoma: the visual impairment project. Ophthalmology. 2002;109(6):1047-51.
51. Leske MC, Connell AM, Wu SY, Nemesure B, Li X, Schachat A, et al. Incidence of open-angle glaucoma: the Barbados Eye Studies. The Barbados Eye Studies Group. Arch Ophthalmol. 2001;119(1):89-95.
52. Joseph RM, van Staa TP, Lunt M, Abrahamowicz M, Dixon WG. Exposure measurement error when assessing current glucocorticoid use using UK primary care electronic prescription data. Pharmacoepidemiology and drug safety. 2018.

Tables

Table 1: Patient Demographics/Descriptors

Incident RA Cohort Characteristics	**n (%)[1]**
N	22,607
Age- years median (IQR)	66 (37-84)
Female gender	15,421 (68.2%)
Duration of follow up- years median (IQR)	8.7 (1.8-19.8)
Baseline GC use	2,488 (11.0%)
Ever GC use	8,746 (38.7%)
GC dose-mg median IQR[2]	5 (2-15)
Baseline Cataracts	241 (1.1%)
Ever Cataracts[3]	1671/22,365 (7.5%)
Baseline Glaucoma	164 (0.7%)
Ever Glaucoma[3]	436/22,442 (1.9%)
Uveitis	122 (0.5%)
Baseline smoking status	
Never	9105 (40.2%)
Former	6729 (29.8%)
Current	5339 (23.6%)
Missing	1434 (6.3%)

[1]unless otherwise stated

[2]prednisolone equivalent daily dose in GC users throughout follow up

[3]baseline RA cases excluded

Table 2: Log-logistic parametric survival models for cataracts, with age as the time scale. Three models for glucocorticoid (GC) use were estimated, with covariates (1): GC use (2) GC dose (with a square root transformation derived from fractional polynomial power analysis and (3) Cumulative GC dose. Results are expressed as Accelerated Failure Time (AFT) $\log_e$ coefficients and odds ratios.

Variable	AFT Coefficient (95% CI)[1]	Odds Ratio (95% CI)[2]	p-val
Model 1			
Female	-0.016 (-0.033, 0.001)	1.14 (0.99, 1.31)	0.067
Uveitis	-0.261 (-0.352, -0.171)	8.73 (4.11, 18.52)	< 0.001
Smoking (base: Never)			
former	-0.008 (-0.027, 0.011)	1.07 (0.91, 1.25)	0.40
current	0.003 (-0.018, 0.024)	0.97 (0.82, 1.16)	0.76
missing	0.011 (-0.018, 0.039)	0.92 (0.72, 1.16)	0.46
GC use	-0.098 (-0.12, -0.076)	2.25 (1.89, 2.68)	< 0.001
constant	4.518 (4.499, 4.536)		
gamma	0.121 (0.115, 0.126)		
Model 2			
Female	-0.017 (-0.034, 0.000)	1.15 (1.00, 1.32)	0.055
Uveitis	-0.259 (-0.35, -0.168)	8.55(4.01, 18.24)	< 0.001
Smoking (base: Never)			
former	-0.008 (-0.027, 0.011)	1.07 (0.91, 1.25)	0.43
current	0.006 (-0.015, 0.027)	0.95 (0.8, 1.13)	0.57
missing	0.012 (-0.017, 0.040)	0.91 (0.72, 1.15)	0.42
10mg GC: lag 0d	-0.056 (-0.102, -0.009)	1.59 (1.08, 2.33)	0.019
10mg GC: lag 1m	0.019 (-0.033, 0.070)	0.86 (0.56, 1.31)	0.47
10mg GC: lag 3m	-0.001 (-0.048, 0.046)	1.01 (0.68, 1.49)	0.97
10mg GC: lag 6m	-0.048 (-0.094, -0.002)	1.49 (1.02, 2.17)	0.039
10mg GC: lag 1y	-0.089 (-0.133, -0.044)	2.08 (1.45, 3.00)	< 0.001
10mg GC: lag 2y	-0.040 (-0.082, 0.001)	1.39 (0.99, 1.96)	0.059
constant	4.522 (4.504, 4.541)		
gamma	0.121 (0.115, 0.127)		
Model 3			
Female	-0.016 (-0.033, 0.001)	1.14 (0.99, 1.31)	0.066
Uveitis	-0.259 (-0.350, -0.167)	8.51 (3.98, 18.19)	< 0.001
Smoking (base: Never)			
former	-0.008 (-0.027, 0.011)	1.06 (0.91, 1.25)	0.44
current	0.008 (-0.013, 0.029)	0.94 (0.79, 1.12)	0.47
missing	0.015 (-0.014, 0.043)	0.88 (0.70, 1.12)	0.31
Cumulative Dose (base:0)			
1-125mg	-0.003 (-0.061, 0.055)	1.02 (0.63, 1.65)	0.925
126-250mg	-0.027 (-0.068, 0.013)	1.26 (0.89, 1.76)	0.188
251-500mg	-0.031 (-0.067, 0.006)	1.29 (0.96, 1.74)	0.097
501-1000mg	-0.011 (-0.046, 0.024)	1.10 (0.82, 1.46)	0.535
1001-2000mg	-0.059 (-0.090, -0.028)	1.63 (1.26, 2.10)	< 0.001
2001-40000mg	-0.062 (-0.094, -0.030)	1.67 (1.29, 2.17)	< 0.002
>40000mg	-0.139 (-0.165, -0.112)	3.15 (2.56, 3.88)	< 0.003
constant	10.428 (10.409, 10.448)		
gamma	0.121 (0.115, 0.127)		

[1]Accelerated Failure Time (AFT) $\log_e$ coefficients. The coefficients represent the approximate proportional change in age associated with each predictor variable level and exponentiation gives the age ratio.
[2]The odds ratio is derived from the cumulative failure probability associated with each predictor variable level

Table 3: Weibull parametric survival models for glaucoma, with age as the time scale. Three models for glucocorticoid (GC) use were estimated, with covariates (1): GC use (2) GC dose and (3) Cumulative GC dose. Results are expressed as Accelerated Failure Time (AFT) $\log_e$ coefficients and hazards ratios.

Variable	AFT Coefficient (95% CI)	Hazards Ratio (95% CI)	p-val
Model 1			
Females	0.042 (-0.011, 0.096)	0.85 (0.69, 1.04)	0.12
Uveitis	-0.403 (-0.582, -0.225)	4.69 (2.42, 9.09)	< 0.001
Smoking (base: Never)			
former	0.006 (-0.054, 0.067)	0.98 (0.77, 1.23)	0.84
current	-0.001 (-0.067, 0.065)	1.00 (0.78, 1.29)	0.98
missing	0.086 (-0.014, 0.186)	0.72 (0.49, 1.05)	0.093
GC use	-0.122 (-0.188, -0.055)	1.60 (1.26, 2.02)	< 0.001
constant	4.947 (4.865, 5.029)		
p	3.83 (3.336, 4.397)		
Model 2[1]			
Females	0.089 (-0.033, 0.212)	0.85 (0.70, 1.05)	0.15
Uveitis	-0.711 (-1.215, -0.207)	3.51 (1.81, 6.79)	0.006
Smoking (base: Never)			
former	0.004 (-0.128, 0.135)	0.99 (0.79, 1.25)	0.96
current	0.122 (-0.030, 0.274)	0.81 (0.63, 1.03)	0.12
missing	0.139 (-0.100, 0.378)	0.78 (0.53, 1.15)	0.25
10mgGC dose: lag 0d	-0.112 (-0.325, 0.102)	1.22 (0.84, 1.76)	0.30
10mgGC dose: lag 1m	-0.079 (-0.299, 0.141)	1.15 (0.78, 1.69)	0.48
10mgGC dose: lag 3m	-0.244 (-0.453, -0.034)	1.54 (1.13, 2.10)	0.022
10mgGC dose: lag 6m	-0.143 (-0.348, 0.062)	1.29 (0.91, 1.81)	0.17
10mgGC dose: lag 1y	-0.268 (-0.473, -0.062)	1.60 (1.20, 2.14)	0.011
10mgGC dose: lag 2y	0.117 (-0.166, 0.399)	0.81 (0.50, 1.33)	0.42
constant	11.149 (10.760, 11.538)		
p	1.765 (1.106, 2.817)		
Model 3			
Females	0.065 (0.006, 0.124)	0.77 (0.61, 0.97)	0.030
Uveitis	-0.261 (-0.484, -0.037)	2.83 (1.17, 6.88)	0.022
Smoking (base: Never)			
former	0.009 (-0.061, 0.079)	0.96 (0.73, 1.28)	0.80
current	-0.056 (-0.127, 0.015)	1.25 (0.94, 1.67)	0.12
missing	-0.008 (-0.110, 0.093)	1.03 (0.69, 1.55)	0.87
Cumulative Dose (base:0)			
1-125mg	-0.072 (-0.225, 0.081)	1.33 (0.73, 2.45)	0.36
126-250mg	0.033 (-0.101, 0.168)	0.87 (0.51, 1.5)	0.63
251-500mg	-0.065 (-0.173, 0.042)	1.30 (0.85, 1.99)	0.23
501-1000mg	-0.014 (-0.123, 0.094)	1.06 (0.69, 1.63)	0.79
1001-2000mg	-0.072 (-0.17, 0.026)	1.33 (0.91, 1.96)	0.15
2001-4000mg	-0.063 (-0.162, 0.036)	1.29 (0.87, 1.90)	0.21
>4000mg	-0.096 (-0.18, -0.013)	1.47 (1.07, 2.02)	0.024
constant	10.848 (10.739, 10.956)		
p	3.998 (3.381, 4.729)		

[1]FP analysis indicated that no transformation of GC dose was necessary for glaucoma data

Figures

Figure 1. Steps taken to derive the final incident RA cohort used in the cataract and glaucoma analyses

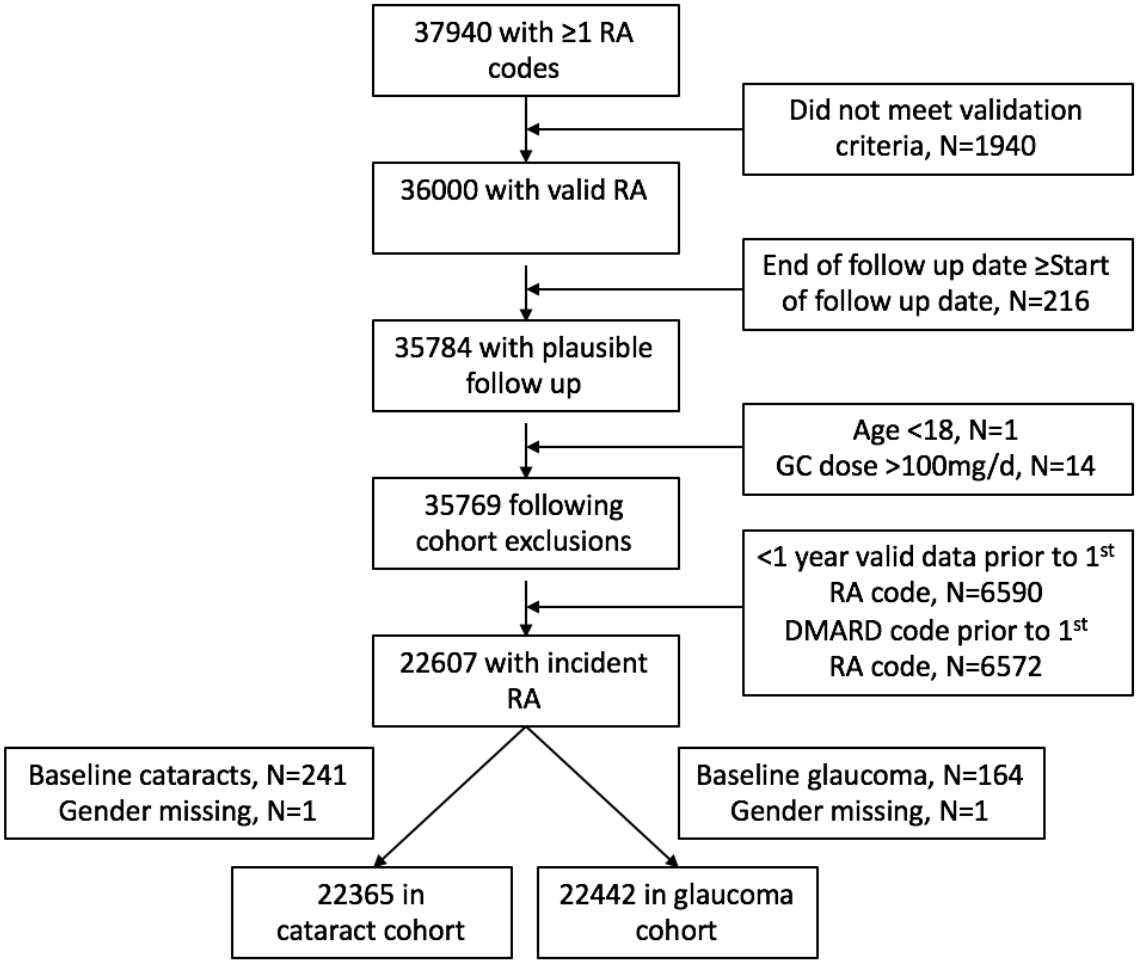


Figure 2. Cumulative incidence (Kaplan-Meier failure function) for A. Cataracts B. Glaucoma and smoothed hazard function for C. Cataracts and D. Glaucoma. Shaded areas represent 95% confidence intervals. Age was used as the timeline in the analyses.

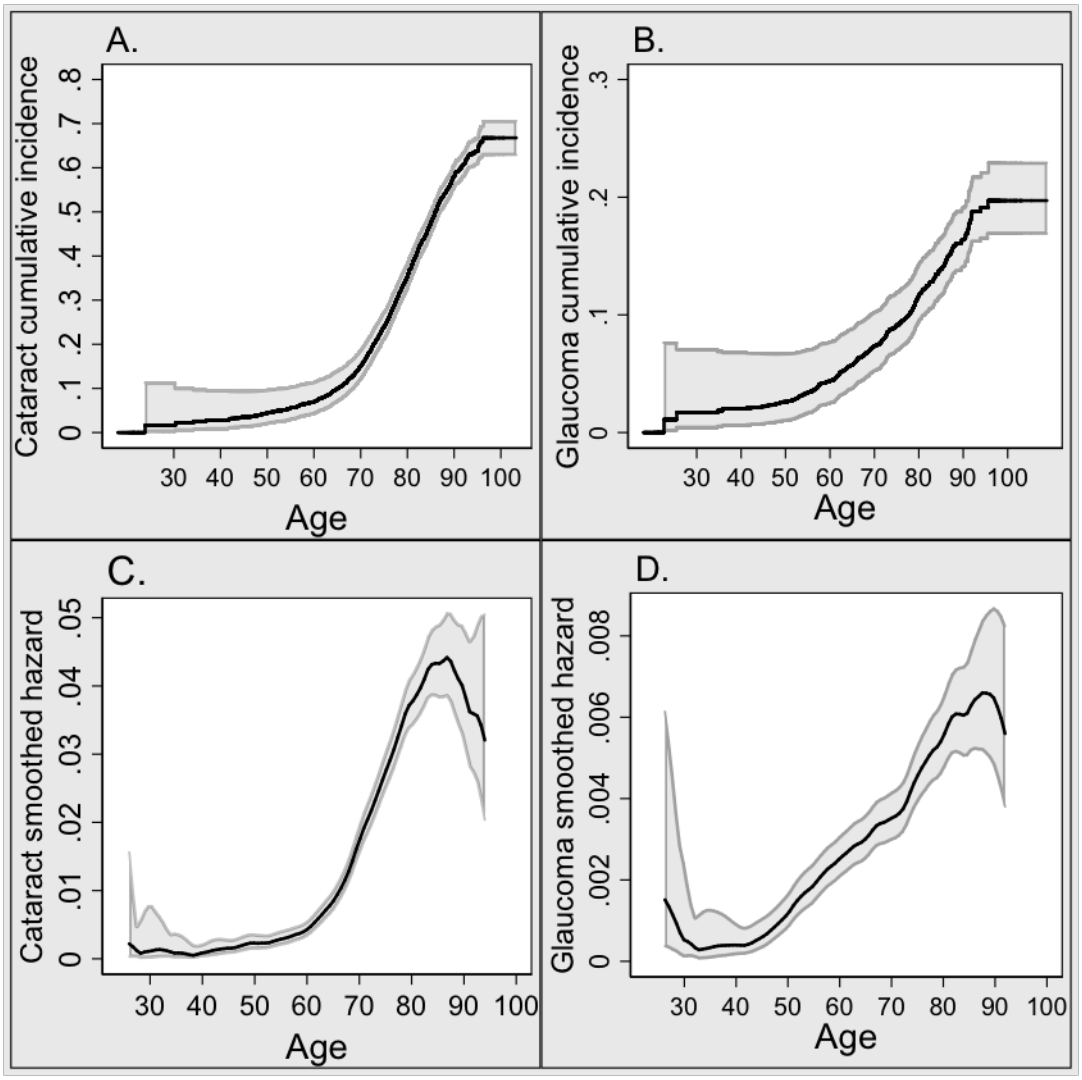
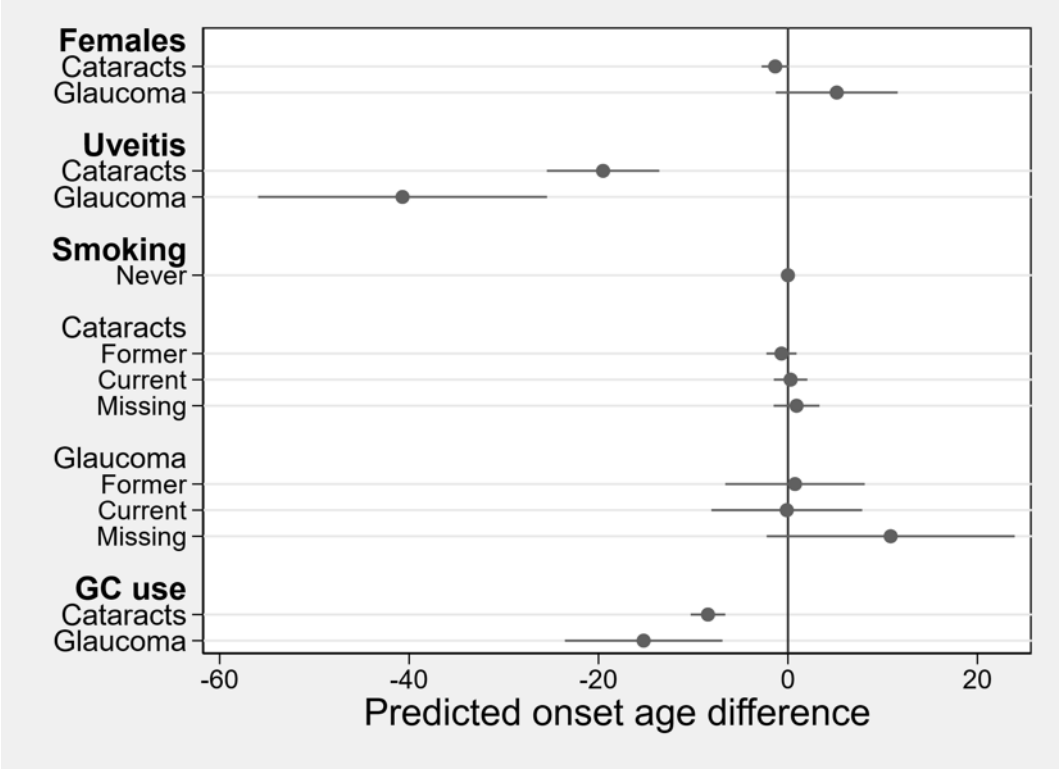


Figure 3. Predicted mean difference in age of onset of cataracts and glaucoma (marginal effects), averaged over all covariates) for the GC-use model (Model 1)



Supplementary Data

Table S1. Read codes used to define cataracts and glaucoma.

Medical code	Read term
296	Cataract
703	Bilateral cataracts
1622	O/E - cataract present
4242	Posterior subcapsular polar cataract
4260	Intracapsular extraction of cataract
4358	Other cataract
4439	O/E - lens opacity
4459	[V]State following cataract extraction
5325	Posterior subcapsular polar senile cataract
5361	Other extraction of cataract
5518	H/O: cataract
6317	Cataract NOS
6330	Extracapsular extraction of cataract
6547	O/E - Right cataract present
6876	Nuclear senile cataract
7257	Cortical cataract
7793	Nuclear cataract
9931	O/E - Left cataract present
10010	Senile cataract
10659	Diabetic cataract
11255	Subcapsular cataract
11767	Referral for cataract extraction
11941	Referral to cataract clinic
11970	H/O: Bilateral cataract extraction
15589	Other cataract NOS
16751	O/E lens - early opacity
17545	Type I diabetes mellitus with diabetic cataract
18089	Capsular cataract
22022	Cortical senile cataract
23631	Immature cataract NOS
23883	Needling of lens for cataract
24467	Unspecified secondary cataract
26097	Punctate cataract
26850	After-cataract with vision obscured
28513	H/O: R cataract extraction
28515	H/O: L cataract extraction
29770	Senile cataract NOS
33482	After cataract
33793	Total, mature senile cataract
38641	Discission of cataract
41668	Infantile, juvenile and presenile cataracts

42452	Vitreous syndrome following cataract surgery
44260	Insulin dependent diabetes mellitus with diabetic cataract
44294	Immature cortical cataract
44487	After cataract NOS
44779	Type 2 diabetes mellitus with diabetic cataract
44982	Type 2 diabetes mellitus with diabetic cataract
47566	Unspecified senile cataract
48148	Incipient cataract NOS
48192	Type II diabetes mellitus with diabetic cataract
49085	Other senile cataract
49554	Type 1 diabetes mellitus with diabetic cataract
51162	Hypermature cataract
57805	Unspecified presenile cataract
58078	Nonsenile cataract NOS
58120	Drug induced cataract
58625	Cataract associated with other syndromes
59125	Anterior subcapsular polar cataract
59914	Capsular and subcapsular cataract
61325	Cataract with neovascularization
62188	Unspecified cataracta complicata
63640	Morgagni cataract
64196	Cataract observation
69278	Non-insulin depend diabetes mellitus with diabetic cataract
70201	[X]Other specified cataract
70257	Combined senile cataract
70403	Other nonsenile cataract
88738	Capsular or subcapsular cataract NOS
89585	Other after cataract with vision normal
92358	Anterior subcapsular polar senile cataract
93727	Type II diabetes mellitus with diabetic cataract
94348	Cataract operation planned
94430	Cataract due to other disorder NOS
94474	Combined nonsenile cataract
96385	Cortical and zonular cataract
98962	Cortical or zonular cataract NOS
100770	Insulin dependent diabetes mellitus with diabetic cataract
101939	[X]Other senile cataract
103508	Cataract extraction and insertion of intraocular lens
104553	Keratopathy following cataract surgery
105971	Bullous aphakic keratopathy following cataract surgery
110400	Type 1 diabetes mellitus with diabetic cataract
1611	Ocular hypertension
1798	Open-angle glaucoma
2074	Glaucoma
2399	Glaucoma monitoring

4581	Primary open-angle glaucoma
8001	Glaucoma NOS
8132	Low tension glaucoma
8955	H/O: glaucoma
8971	Borderline glaucoma
9260	Borderline glaucoma NOS
9469	Low tension glaucoma
10070	Open angle glaucoma with borderline intraocular pressure
11059	Pan retinal photocoagulation for glaucoma
24860	Unspecified preglaucoma
28189	Open-angle glaucoma NOS
30649	Simple chronic glaucoma
35528	Steroid-induced glaucoma
36737	Borderline glaucoma steroid responder
42447	Unspecified open-angle glaucoma
44295	Other specified glaucoma NOS
44338	Glaucoma - absolute
46069	Operations following glaucoma surgery
48132	Steroid-induced glaucoma NOS
53879	Normal pressure glaucoma
65079	Needling of bleb following glaucoma surgery
68094	Steroid-induced glaucoma residual stage
70195	[X]Other glaucoma
72394	Open-angle glaucoma residual stage
88142	Other specified operations following glaucoma surgery
88595	Revision of bleb NEC following glaucoma surgery
89934	Injection of bleb following glaucoma surgery
91442	Removal of releasable suture following glaucoma surgery
93967	Laser suture lysis following glaucoma surgery
94229	Suspected glaucoma
95852	Operations following glaucoma surgery NOS

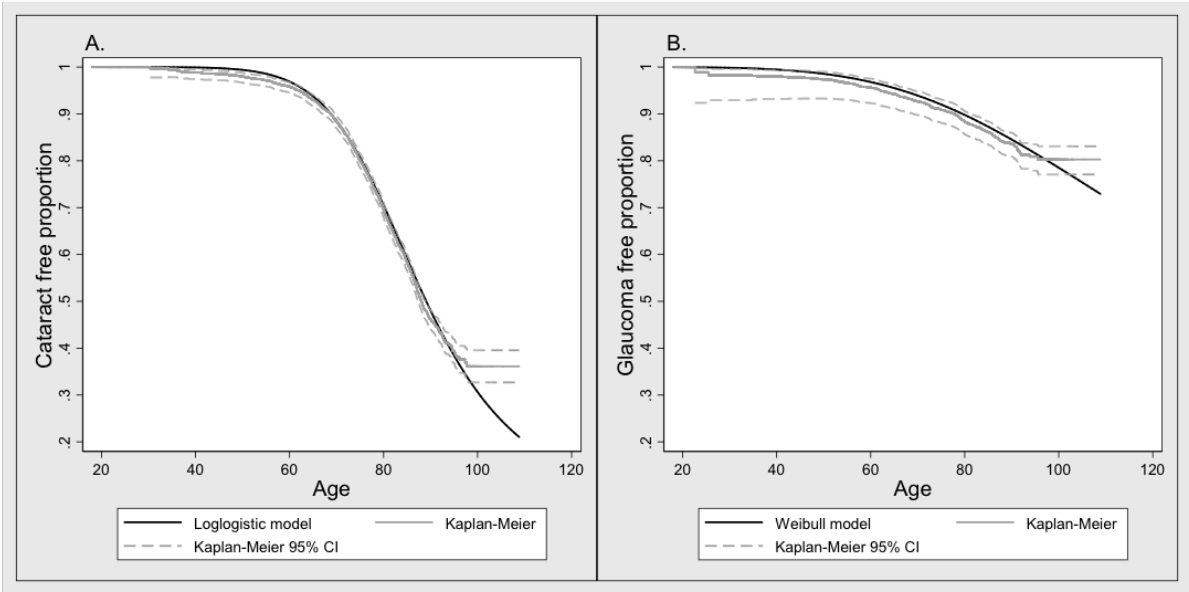
Table S2. Cataracts and glaucoma incidence rates by age and gender

Group	CATARACTS			GLAUCOMA		
	person-time	failures	rate (95% CI)[1]	person-time	failures	rate (95% CI)[1]
Males						
<55 yrs	10394.19	11	1.06 (0.59, 1.91)	10366.56	8	0.77 (0.39, 1.54)
55-65 yrs	10482.68	48	4.58 (3.45, 6.08)	10544.07	26	2.47 (1.68, 3.62)
65-75 yrs	11507.85	155	13.47 (11.51, 15.77)	11797.17	49	4.15 (3.14, 5.50)
>75 yrs	8656.82	271	31.3 (27.79, 35.26)	9499.3	63	6.63 (5.18, 8.49)
Females						
<55 yrs	27758.39	34	1.22 (0.88, 1.71)	27768.75	28	1.01 (0.70, 1.46)
55-65 yrs	23561.51	107	4.54 (3.76, 5.49)	23532.48	59	2.51 (1.94, 3.24)
65-75 yrs	22606.31	338	14.95 (13.44, 16.63)	23400.23	78	3.33 (2.67, 4.16)
> 75 yrs	20540.64	707	34.42 (31.97, 37.05)	23794.96	125	5.25 (4.41, 6.26)
Total	135508.38	1671	12.33 (11.75, 12.94)	140703.52	436	3.10 (2.82, 3.40)

Table S3. AIC and BIC, for both cataract and glaucoma data, showing the fit of different parametric survival models

Model	df	CATARACTS		GLAUCOMA	
		AIC	BIC	AIC	BIC
Exponential	6	3337.5	3410.6	2166.4	2240.1
Weibull	7	1866.0	1949.6	2034.2	2118.3
Gompertz	7	1915.0	1998.5	2037.9	2122.1
Log normal	7	1870.3	1953.9	2082.7	2116.9
Log-logistic	*7*	1804.1	1887.7	*2032.3*	*2116.4*
Generalised Gamma	8	1835.2	1929.2	2034.1	2128.8

Figure S1. Comparison of the predicted survival functions estimated by parametric regression with the observed Kaplan-Meier survival function for A. Cataracts (loglogistic survival model) and B. Glaucoma (Weibull survival model)



7 Discussion, conclusions and future directions

7.1 Discussion

GCs remain important therapeutic options in the treatment of many chronic inflammatory diseases. Although they have been available for more than 60 years, there are still many unanswered questions surrounding optimal use and harm minimisation. In the literature, and in clinical practice, opinions around GCs are strikingly divided and discussion often provokes emotive responses (82). This thesis has furthered current knowledge with regard to glucocorticoid use and adverse effects in clinical practice, particularly in the field of rheumatology. The three main sections of this thesis addressed different aspects of GC use: Firstly, it investigated how GCs are used among patients with RA, secondly it looked at GC AEs from the patient perspective and thirdly it evaluated the risk of GC exposure associated with the development of cataracts and glaucoma. In addition, the thesis describes the research databases and methodologies used to explore these sections of work.

Dataset strengths and limitations

For the epidemiological components of this work, two different datasets were used. CPRD is a large UK-based dataset derived from primary care EMRs and ARAD is an Australian-based rheumatology biologics registry, which collects patient-reported data. There were pros and cons to using each of these datasets. CPRD is a very large dataset, which has been validated and shown to be representative of the UK population (203, 204). It also has its own internal validation processes to ensure logical consistency of patient registration data and longitudinal records that are complete, continuous and plausible. It contains real-life data that reflects real-life practises, with long-term follow up over many years, and is therefore an ideal setting for exploring safety outcomes. Data is provided as a number of different files with common variables, which allow them to be merged together using statistical software. However, the data available is dependent on what is entered into the EMR, and as a consequence significant data cleaning and preparation is required to deal with missing, duplicate and implausible data in order to achieve an analysis-ready dataset. Using CPRD to explore medication use relies on prescription data, with no dispensing or adherence information available.

Although not on the same scale as CPRD, ARAD is also a large database that provides information about patients followed prospectively over many years in Australia. As a

registry, there is consistent and streamlined data collection with standardised fields, which makes the data cleaning process significantly easier compared to CPRD. It uses patient reported medication exposure, which potentially reflects actual use more closely than prescription data although, like CPRD, it does not collect information on adherence. A recent study comparing patient reported GC use as 'true exposure' to prescription data in CPRD, found the misclassification of current GC use to be low with 86% correctly classified as currently on/off GCs (226). As with CPRD, ARAD provides data from a real-life population with real-life medication exposures in which to study long-term safety outcomes, as opposed to the more artificial setting of clinical trials. There are, however, potential biases related to the ARAD data collection processes. These include a potential recall bias with patient reported data collected at 6 to 12 month intervals. There is also a potential selection bias due to voluntary 'opt-in' participation, and it is not known if those who join and continue to contribute to ARAD are fundamentally different from those who do not. ARAD is also limited by what fields are collected, for example it does not collect standard measures of disease activity or medication dosages. Data linkage with Australian pharmaceutical (Pharmaceutical Benefits Scheme, PBS) and medical (Medicare Benefits Schedule, MBS) billing databases has recently become available and will help to address some of these limitations in the future.

Glucocorticoid use in Rheumatoid arthritis

RA is a chronic inflammatory disorder often treated with GCs, for which there are many alternative therapeutic options, making it an ideal setting in which to explore GC use. The first section of work in this thesis has extended current knowledge about how GCs are used in RA and the factors than can influence this. A greater understanding of how GCs are used in a condition for which other therapeutic options are available, allows us to identify areas which might be targeted to improve the balance between the benefits and harms of treatment.

In a primary care based cohort of RA patients in the UK, it was shown that nearly 50% of RA patients were ever prescribed GCs, with nearly 40% receiving doses greater than 20mg per day and nearly 20% receiving doses greater than 30mg per day (227). International guidelines recommend low dose GCs (<=10mg ACR, <=7.5mg EULAR) for 6 months or less (42, 43), indicating that doses far greater than recommended are used in clinical practice. Further analyses suggested that this may in part reflect GC use for other comorbidities such as asthma (OR 1.63, 95%CI 1.33–1.99), COPD (OR 1.58, 95%CI 1.42–1.76) or lower respiratory tract infections (OR 1.22, 95%CI 1.11–1.34) (227). However, it may also reflect use of high dose GC protocols such as COBRA (Dutch

acronym for COmbinatietherapie Bij Reumatoide Artritis) (228) and COBRA-Light (229), which include prednisolone doses starting at 60mg and 30mg per day respectively. GC prescribing was also more likely in patients who were older (OR 1.17, 95%CI 1.14–1.20), current smokers (OR 1.22, 95%CI 1.13–1.32) and/or had cardiovascular disease (OR 1.25, 95%CI 1.03–1.51) at baseline. While these patient factors may be associated with more severe disease necessitating GC therapy, they are also characteristics that may predispose to GC AEs. These findings can therefore be translated to the clinical setting as they identify patient characteristics that may alert clinicians to the need for a more careful risk-benefit assessment.

This study also explored whether the factors that influence GC prescribing differ according to prescriber. Prescribers were classified as either high or low GC prescribers according to their GC prescribing habits across all patients. This analysis revealed that high prescribers were more likely to prescribe to higher risk patients including those who were older (OR 1.26, 95%CI 1.23–1.29, P<0.001) and those with hypertension (OR 1.29, 1.17–1.41, P=0.039). GC use prior to follow up was the most important predictor of GC ever use during follow up in high prescribers compared to low prescribers (OR 11.76, 95%CI 10.24–13.51, P<0.001). These findings again provide an opportunity for clinical translation, as they suggest that those who are more frequent GC prescribers are using GCs in patients who may be at increased risk of AEs. In the future, this information could be used to formulate guidelines for risk benefit assessments.

To expand this knowledge further, factors affecting GC use were also explored in an Australian RA cohort using ARAD. In this group, patient-reported GC ever use was higher than the CPRD cohort at 60%. GC use over time was only examined within the ARAD cohort and was shown to be decreasing over time. This finding was in keeping with our hypothesis that GC use was likely to be higher in those who joined ARAD in the initial years following its inception and reduce over time as bDMARDS became more readily available and accepted as standard care. In contrast to the UK based population, increasing age was associated with reduced GC use (OR 0.24, 95%CI 0.07–0.81) in the ARAD cohort. It is possible that this reflects different practices in the UK compared to Australia, or perhaps even differences in GC use between a primary care based cohort and a cohort referred from rheumatologists. However, the analyses were also carried out differently with the impact of baseline characteristics on GC ever use explored in CPRD, compared to the impact of current characteristics on GC current use evaluated in the ARAD cohort, making direct comparisons difficult.

Panel regression was used in the ARAD analysis to compare current characteristics with current GC use. While the results of this analysis can only be interpreted as an association, rather than causation, the most likely direction of an association needs to be carefully considered within the clinical context, when interpreting the results. For example, GC use in ARAD patients was associated with lower pain scores (less pain) (OR 0.94, 95%CI 0.90–0.98), and is in keeping with current knowledge that GCs rapidly reduce inflammatory joint pain. However, GC use was associated with higher HAQ scores (poorer quality of life) (OR 1.52, 95%CI 1.30–1.79), suggesting that poorer quality of life may predispose to increased GC use, but any improvement in quality of life is delayed compared to the improvement in pain.

Factors that influence whether a patient commences or comes off GC therapy were explored, with poorer quality of life (higher HAQ scores) (HR 1.94) and higher levels of pain (HR1.1) associated with an increased HR for commencing GCs. Factors associated with a reduced HR for commencing GCs included older age (HR 0.87) and use of other medications including bDMARDs (HR 0.54), csDMARDs (HR 0.27), NSAIDs (HR 0.57) and opioids (HR 0.64). Female gender was associated with an increased HR for ceasing GCs (HR 1.30), while increasing age (HR 0.92) and poorer quality of life (HR 0.77) were associated with a reduced HR for ceasing GCs.

The use of transition state analysis to explore GC use in terms of commencement and cessation was a novel approach to understanding GC use in more detail. Of particular interest were factors that had an impact on both commencement and cessation of GCs. The effect of increasing age was an example of this, with older patients less likely to commence GCs but also less likely to come off GC treatment, once started. It was hypothesised that bDMARD use would have a steroid-sparing effect and although those using bDMARDs were less likely to commence GCs, their use did not affect GC cessation. Similarly, there was no association seen between GC cessation and other concomitant medications including csDMARDS, NSAIDs and opioids. Female gender was in fact the only factor found to be associated with GC cessation in all of the transition state analyses. This reflects the phenomenon often described by rheumatologists in clinical practice, that once GCs are commenced, they are often difficult to cease. This suggests that there may be some discordance between how patients perceive the benefits and harms of GC treatment, versus the benefits and harms deemed important by clinicians.

The impact of glucocorticoid use from the patient perspective

Having shown that GC use is common in the first section of this thesis, the second section examined at how patients perceive both the wanted and unwanted effects of

GCs. The patient perspective is well recognised as an important quality measure and it has previously been shown that doctor's and patient's opinions differ in regards to the importance of GC AEs (94). This thesis has shown that many GC AEs that are important to patients, occur commonly and are not easily measurable in the clinic setting. In addition, most patients feel that GCs help their disease 'a lot' and that the benefits of treatment outweigh the harms. Many GC AEs were more frequent in RA patients who had used GCs compared to those who had not, confirming that these symptoms are appropriately attributed to GC use. This work contributes to a broader body of work being undertaken by the OMERACT GC SIG, which aims to develop a GC PRO for use across all systemic inflammatory diseases.

Since this work began, other GC outcome measures have been published, including the GTI (93) which consists mainly of physician measured outcomes, a disease specific PRO for SLE (230), a PRO for inhaled corticosteroids (219) and a PRO for IV methylprednisolone (231). However, a recent systematic review found that a PRO for measuring the effects of systemic GCs across all inflammatory diseases has not yet been developed (83). In a soon to be published systematic review of qualitative and quantitative studies, patient-reported GC outcomes were found to fall into four main categories including physical and psychological symptoms, participation and contextual factors (83). The participation and contextual factors categories were identified in the qualitative studies, with participation including the impact on work, family and friends and contextual factors including negative attitudes of family, friends and the wider community as well as the concept of management and mastery of disease.

The work in this thesis is a step towards the development of a GC PRO, for use in future clinical trials and observational studies which include GC use. A PRO will lead to better quality data collection and help fill the remaining gaps in the literature more efficiently and effectively. This knowledge needs to be translatable into clinical practice and capturing the patient perspective is a means of ensuring research outcomes are relevant to patients' needs.

Glucocorticoid use and the risk of developing cataracts and glaucoma

In addition to understanding the benefits and harms of GC use from the patient perspective, it is also important to be able to communicate the potential risks of treatment, which requires us to know both the probability that an AE will occur as well as how important this may be to the patient(47). Knowing that GC use is high and that GC AEs are common, the third section of this work focused on the need to better quantify the risks of specific GC AEs and in particular ophthalmic AEs, including cataract

and glaucoma. These were selected as AEs of interest, as they have been shown to be important to patients when they occur(225, 232) and the frequency at which they occur in the setting of oral GC use is not well understood. RA was again selected as an ideal setting to explore these risks. There were two components to this section of work, including a systematic literature review (SLR) with meta-analysis and an observational study, which used data from CPRD. The SLR included observational studies looking at GC use and the development of cataracts and glaucoma in RA and all RCTs looking at GC use in RA. It found that the majority of RCTs (25/28) did not report cataracts and glaucoma, an indication that these outcomes are under-reported in the literature. This observation was explored further, by comparing the 2% two-year cumulative incidence of cataracts reported in the three RCT cohorts to the much higher 12% general population cumulative incidence seen in the BMES over two years. This under-reporting may in part reflect that many of the RCTs dated back to the 1990s, and lacked the rigorous reporting of outcomes that would be expected of more contemporary studies. This factor drove the development of the CONSORT extension for better reporting of harms in RCT which was published in 2004 (233).

In the three RCTs that did report cataracts, no association was seen between GC use and their development, which differed from the meta-analysis of observational cohort studies where the odds of developing cataracts doubled with GC use. No association was seen between GC use and the development of glaucoma in the meta-analysis of RCTs or cohort studies. However, data were very limited and the review concluded that the GC-associated risk of developing cataracts and glaucoma in patients with RA could not be accurately quantified, based on the existing literature. More so, no conclusions about the effect of dose and duration of GC treatment could be drawn from these studies.

In order to address the gaps in the literature identified in the SLR, an observational study using CPRD data was carried out. Different models of GC exposure were used to explore the effect of current GC use (yes/no), GC dose (current prednisolone equivalent daily dose (PEQ) and lagged dose) and cumulative dose. In keeping with the findings of the SLR, current GC exposure was shown to be associated with a two-fold increased risk of developing cataracts. However, unlike the SLR in which no association could be found between GC use and glaucoma, this study found there to be a 60% increased risk of developing glaucoma in patients with RA currently using GCs. This study was able to extend existing knowledge, finding that doses given 12 months prior to the diagnosis of cataracts and 3-12 months prior to the diagnosis of glaucoma were of greatest importance. However, the lag between the onset of disease and diagnosis/date of first

CPRD code is not defined. For cataracts, cumulative doses greater than 1000mg PEQ and 4000mg PEQ were associated with a 60% and 3-fold increased risk respectively, whereas for glaucoma the risk was increased by approximately 50% with cumulative doses greater than 4000mg.

These findings directly address the need to better quantify the risk of GC AEs so that patients can be informed of the risks and benefits of GCs prior to treatment as per international guidelines (91). The study also found that the cumulative incidence of cataracts and glaucoma rises steeply from around age 60-65, which is in keeping with previous studies (99, 100). The smoothed hazard also increased steeply between the ages of approximately 60 and 85 for cataract and around 50 and 85 for glaucoma. This information could be used to inform future guidelines regarding the need to screen for cataracts and glaucoma in patients exposed to GCs, particularly older patients who are likely to be exposed to higher cumulative doses. It is well recognised that screening for AEs is only worthwhile if there is the opportunity to modify the outcome with early detection. The current literature suggests that GC cessation or dose reduction should be part of the management of GC induced cataracts and glaucoma, and may necessitate the addition of a steroid-sparing agent. A future study comparing screening to routine care could help to determine if there is a role for screening for these GC AEs.

Challenges to overcome and skills developed

There were a number of challenges to overcome to create the body of work included in this thesis, particularly when working with CPRD data. Clinical knowledge and experience were essential when making decisions in the data cleaning process. However, significant skill acquisition in the field of epidemiology and statistics was required together with statistical coding skills to create complex data cleaning scripts. Stata statistical software was used for data preparation and analyses throughout the thesis. The statistical code created for both data preparation and analysis needed to be saved in a format that allowed for large sections to be re-run efficiently if changes had to be made. This was achieved in Stata by creating do-files with text descriptors between code, so it was clear what each section was coding for. These descriptors were most useful when kept concise but frequent throughout the do-files. The logical naming of do-files according to their purpose was also important. Simple macros were used to refer to the different data files used throughout the do-files, making it simpler to update the code with newer versions of the dataset, when required. It is accepted that there should be transparency in research, and there is increasing recognition that data and code should be made available for results to be replicated and validated. Creating clearly labelled do-files is also good practice for sharing code.

The size of the CPRD dataset meant that errors could be difficult to detect and care had to be taken to check how the data were affected by each section of the data cleaning script. Following the outcomes of different decisions in a small selection of patients was a useful solution for checking for errors. The size of the dataset also meant that adequate secure data storage space was required and complex analyses could take a long time to run. CPRD data had to be accessed and analysed remotely from Australia using a secure server in the UK. This required IT skills development to troubleshoot problems as they arose. My candidature has required the acquisition and integration of clinical, epidemiological, coding and statistical skills necessary for a clinician-researcher to work with large datasets derived from real-life clinical practice. As EMRs are increasingly being used in hospitals and well as primary care, future research opportunities using these skills as a clinician researcher are likely to be vast.

Unanswered questions and future directions

The overarching theme of this PhD was to extend current knowledge about the use and impact of GCs in order to promote the safer, better use of these agents, which are important therapeutic options for chronic inflammatory disorders and remain essential in the management of many life or organ threatening complications. An assessment of the benefits and harms underlies any treatment decision in clinical practice (47). There are a number of foreseeable ways in which the work in this thesis can be translated into clinical practice to help both patients and clinicians make a clearer assessment of the benefits and harms of GC treatment. The first section of work provided insights into the factors associated with GC use and identified situations where increased caution might be needed when prescribing GCs, particularly in older patients and those with comorbidities that could potentially put them at increased risk of harm from GC AEs. Future work is needed to expand on these results by developing predictive algorithms to inform guidelines or prescribing alerts within EMRs.

The second section of work is based on current knowledge that the patient perspective of medication benefits and harms is different but complementary to the clinician perspective (95, 234-236). In identifying GC AEs that are important to patients, and demonstrating that patients are correctly attributing these effects to GC use, this work has contributed to the early phases of developing of a GC PRO. With subsequent work for the OMERACT GC SIG, we have already added to these initial findings and are a stage closer to the development of such a PRO (83, 218). The next step will be to decide on a Core Domain Set, which will include items that are important to measure in all studies. From there, the OMERACT GC working group will look in more detail at existing

instruments that measure GC use and then the process of developing a new instrument will begin. This will include decisions about which items should be binary measures of whether an outcome has occurred or not, and for which items it will also be important to measure effect size or severity. The aim is to develop a PRO that will have utility in both clinical and research settings, and consideration will need to be given to how it is administered and the results disseminated. Ideally, it would be available digitally with the option for remote reporting so that it can be completed by patients outside of the time constraints of clinic or research visits. Further work will see the development of this PRO completed and then validated in different cohorts. If risk-benefit discussions about GC use are to be properly informed in the future, it is essential that a PRO is developed so that patient-relevant aspects of GC use can be accurately and consistently measured in clinical trials and observational studies.

In the final section of work for this thesis, the risks of developing cataracts and glaucoma associated with exposure to GCs was quantified. These findings can be directly translated into the clinic setting, allowing patients and clinicians to better understand the risk of developing these ophthalmic AEs with different exposure to GCs. Further exploration of how these risks are best communicated to patients is warranted. It is recognised that many patients, as well as clinicians, will find it difficult to conceptualise common statistical risks such as relative and absolute risks, odds ratios, hazard ratios and number needed to treat or harm (47, 237). It has instead been suggested that natural frequencies (1 person out of 10 treated with GCs will develop 'x') are a better understood descriptor (238, 239). The use of visual aids such as the 1000 person Paling pallete (240) can greatly improve the communication of risk (48, 241). Future work is still needed to make this information readily available to patients and clinicians. Consideration will need to be given to how this information is provided in the context of also needing to communicate many other GC AEs. This can be a time-consuming process, taking over two hours per subject in a research study (85). In order to meet the needs of a broad range of patients, this information could be made available in different formats including printable handouts, online recourses and as part of eHealth apps. Novel modalities for helping patients to understand the experience of the benefits and harms of GCs could be considered, such as short videos of patients describing their own different experiences. Communicating risk is also complicated by the fact that risk varies according to age, gender, comorbidities and differing GC exposure patterns (48). This has led to the development of personalised risk calculators to guide clinical decision making, including the risk of developing cardiovascular disease (242) and fracture risk in osteoporosis(243, 244), and future work could see the development of similar risk calculators for GC AEs.

While this work has quantified the risk of developing incident cataracts and glaucoma associated with GC use in RA, future work is still needed to determine the impact of GC use on RA patients with pre-existing cataracts and glaucoma. Another planned expansion of this work is to explore the GC-associated risks of developing cataracts and glaucoma in other disease groups, and ISAC approval has already been obtained to do this in CPRD. This should also be explored in an Australian population, which may be at increased risk of GC related eye disease due to greater exposure to UV radiation. This would be possible using ARAD data linked to dispensing data from the PBS and MBS codes for cataract surgery.

International collaboration was a key component to this thesis, beginning with a year spent at the University of Manchester in the Arthritis Research UK Centre for Epidemiology. This collaboration provided initial training in epidemiology, statistics and statistical coding required for the body of work undertaken in the thesis. It also provided the opportunity to work with CPRD data, a unique dataset with no real Australian equivalent. Ongoing collaboration, mentorship and supervision continued for the duration of the thesis and the working relationships formed will pave the way for ongoing collaboration in the future. International collaboration was also an important aspect of the patient-perspective section of work. Along with patient participation, international collaborative research underpins the principles of OMERACT and it is a requirement that each SIG has representation from at least three continents. Working together with colleagues from the UK, US and Australia has highlighted some of the challenges of international collaboration, including long-distance communication, time-zone differences and the need to make the most of often limited opportunities for face-to-face contact with collaborators. However, these challenges are far outweighed by the benefits of collaborative research, including access to a wider range of facilities and resources, the opportunity to work with field-leaders and contribute to some of the highest impact research activity (245). Other benefits include the range of skills and different international experiences, meaning that research outcomes are more likely to be relevant to a broader range of patients.

Benefits and harms- the broader perspective

In an online essay, Herxheimer (47) identifies four dimensions of any benefit or harm: "1. Its nature, described by its quality, its intensity, and its time course (onset, duration, and reversibility). 2. The probability that it will occur. 3. Its importance to the person experiencing it. 4. How the benefit can be maximised, or the harm prevented or minimized.". This thesis has tried to address each of these issues to differing extents: 1. In the introduction, a description of the literature summarises relevant aspects of what

is known about the nature of the benefits and harms of GC use, 2. The probability of developing ophthalmic harms of GC use is addressed in the cataract and glaucoma section of work, 3. The importance of GC benefits and harms to the person experiencing them is explored in the patient perspective section and 4. The work on GC use in RA identifies factors associated with GC use that might be targeted to minimise of prevent harm related to GC use in the future.

Shared decision making is well recognised as an important aspect of best-practice clinical care (246). It relies on the clinician and patient having sufficient information about a disease and treatment options to be able to make an informed assessment of the benefits and harms. This will often include quantifiable measures, such as the risk of the disease worsening without treatment and the likelihood of the treatment being effective. These need to be weighed against quantifiable harms such as the development of AEs.

In addition to quantifiable risks, contextual factors also play an important role in clinician and patient decision making (47). Contextual factors may include clinician, patient and family attitudes to GCs and prior experience with GCs (247). Patients are also likely to weight positive and negative treatment outcomes differently, depending on their individual circumstances. For example, the risk of visual impairment from cataracts or glaucoma may be weighted more highly by someone who already has visual loss in one eye or has experienced recurrent falls. Conversely, an older patient may be less worried about developing an AE if they know that this takes years to develop and is unlikely to occur within their life expectancy. Whether a patient has experienced a particular GC AE also influences how important that AE is to them, with serious GC AEs such as diabetes, cardiovascular disease or eye disease being very important to patients who have experienced them but less important to those who have not (232). How best to include these contextual factors in shared decision making discussions is an ongoing challenge for the medical community.

7.2 Conclusions

In conclusion, this thesis has extended current knowledge about the benefits and harms of GC use in three key ways. It has identified patient and prescriber characteristics associated with GC use and in doing so uncovered situations for potential harm minimisation, such as increasing age. It has captured further knowledge about which GC AEs are most important to patients and identified that many of these are not easily

measured, while also confirming that the majority of patients consider GCs are effective treatments, with benefits outweighing harms. Finally, it has quantified the risk of developing cataracts and glaucoma associated with different patterns of GC exposure in RA for the first time, having identified this as a gap in the literature by means of a SLR and meta-analysis.

Following on from this work, there are a number of planned next steps to both expand this research and mobilise the new knowledge obtained. Further development of a GC PRO is already under way within the OMERACT GC working group. The next steps will include the completion of a Delphi exercise to confirm a core domain set and then the process of selecting and developing appropriate measurement instruments will begin. To expand the cataract and glaucoma work, ISAC approval has already been obtained for similar analyses to be conducted in other disease populations within CPRD. In addition, there are plans to explore this in an Australian population, who may be at increased risk of GC related eye disease due to increased exposure to UV radiation. This can be done within ARAD, using PBS and MBS data linkage. Further work is also needed to determine whether screening for cataract and glaucoma prior to or during periods of GC exposure would alter outcomes. This will require a collaborative approach involving ophthalmologists, and will need to take into consideration other factors that affect risk such as increasing age.

Future work will also include making this knowledge accessible to patients and clinicians in different formats. This translational process will require a collaborative approach involving patient and clinician focus groups to develop materials that are accessible and useful to a wide range of patients. It will be important to engage with patient-focussed organisations such as Arthritis Australia, who are frequently the providers of risk-benefit information and are therefore able to offer experience, advice and resources. This work would also be strengthened by collaboration with colleagues who have expertise in digital health, in order to develop this information in different electronic formats. It would also be informative to incorporate electronic patient feedback into these resources, to allow for ongoing development.

The underlying aim of this body of work was to improve clinical practice by adding to current knowledge, allowing for better-informed discussions about the benefits and harms of GC treatment. The work was designed with 'clinical-translatability' in mind, and it is hoped that the results may have a positive impact on the lives of patients in the future.

Appendices

The Journal of Rheumatology Volume 44, no. 11

A Patient-reported Outcome Measure for Effect of Glucocorticoid Therapy in Adults with Inflammatory Diseases Is Needed: Report from the OMERACT 2016 Special Interest Group

Rachel J. Black, Joanna C. Robson, Susan M. Goodman, Elizabeth Hoon, Lana Y.H. Lai, Lee S. Simon, Eileen Harrison, Lorna Neill, Pam Richards, Linda M. Nelsen, J. Michael Nebesky, Sarah L. Mackie and Catherine L. Hill

J Rheumatol 2017;44;1754-1758
http://www.jrheum.org/content/44/11/1754

A Patient-reported Outcome Measure for Effect of Glucocorticoid Therapy in Adults with Inflammatory Diseases Is Needed: Report from the OMERACT 2016 Special Interest Group

Rachel J. Black, Joanna C. Robson, Susan M. Goodman, Elizabeth Hoon, Lana Y.H. Lai, Lee S. Simon, Eileen Harrison, Lorna Neill, Pam Richards, Linda M. Nelsen, J. Michael Nebesky, Sarah L. Mackie, and Catherine L. Hill

ABSTRACT. ***Objective.*** The need for a standardized instrument to measure the effect of glucocorticoid (GC) therapy has been well documented in the literature. The aim of the first GC Special Interest Group was to define a research agenda around the development of a patient-reported outcome measure (PROM) in this area.

Methods. The results of a background literature search and the preliminary results of a pilot survey and 2 qualitative studies were presented to facilitate the development of a research agenda.

Results. It was agreed that there was a need for a data-driven PROM that identified both positive and negative effects of GC therapy to be used across all inflammatory indications for systemic GC use in adults. A research agenda was developed, consisting of further qualitative work to assess the effect of GC across different groups including various indications for GC use, different age groups, different dosages, and duration of treatment.

Conclusion. There was agreement on the need for a PROM in this area and a research agenda was set. (First Release April 1 2017; J Rheumatol 2017;44:1754–8; doi:10.3899/jrheum.161083)

Key Indexing Terms:
GLUCOCORTICOIDS ADVERSE EFFECTS OUTCOMES

Glucocorticoids (GC) have had a prominent role in the treatment of inflammatory diseases for over 60 years, with 0.5%–1% of adults considered current longterm users[1,2,3]. They are effective antiinflammatory agents; however, they have many known associated adverse effects (AE). While GC AE have been well documented[4,5,6,7,8], the absolute risk of many GC AE has not been quantified[5,9]. This may be because AE are poorly identified in randomized controlled trials (RCT), or may reflect differences in AE when GC are prescribed for different indications and doses[10,11,12,13,14]. A European League Against Rheumatism (EULAR) taskforce on GC therapy has published 2 systematic reviews

From the Discipline of Medicine, School of Public Health, The University of Adelaide; Rheumatology Unit, The Royal Adelaide Hospital, Adelaide; Rheumatology Unit, The Queen Elizabeth Hospital, Woodville, Australia; Faculty of Health and Applied Sciences, University of the West of England; University of Bristol, Bristol; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds; PMR & GCA UK North East, Kibblesworth; PMR and GCA Scotland, Berwickshire, Foulden, UK; Hospital for Special Surgery, New York, New York; SDG LLC, Cambridge, Massachusetts; Value Evidence and Outcomes, GlaxoSmithKline, Collegeville, Pennsylvania, USA; F. Hoffmann-Roche Ltd., Basel, Switzerland.

RJB is the recipient of an Australian Rheumatology Association Outcome Measures in Rheumatology (OMERACT) Fellowship 2016. EH is supported by a fellowship funded by Arthritis SA and The University of Adelaide Florey Research Fund, with Arthritis Australia providing funding for the qualitative study of GC use in PMR/GCA outlined here. LMN is an employee of GlaxoSmithKline.

R.J. Black, MBBS, PhD Candidate, Consultant Rheumatologist, Clinical Lecturer, Discipline of Medicine, The University of Adelaide, and Rheumatology Unit, The Royal Adelaide Hospital; J.C. Robson, MRCP, PhD, Consultant Senior Lecturer in Rheumatology, University of the West of England, and Honorary Senior Lecturer, University of Bristol, and Honorary Consultant, University Hospitals Bristol UK National Health Service Trust, and Faculty of Health and Applied Sciences, University of the West of England; S.M. Goodman, MD, Associate Professor of Clinical Medicine, Hospital for Special Surgery; E. Hoon, PhD, Arthritis SA Florey Research Fellow, School of Public Health, The University of Adelaide; L.Y. Lai, MSc, PhD Candidate, Board Certified Pharmacotherapy Specialist, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds; L.S. Simon, MD, Principal, SDG LLC; E. Harrison, BSc (Hons Physiology), OMERACT Patient Research Partner, PMR and GCA UK North East; L. Neill, BSc (Hons Nat Phil), OMERACT Patient Research Partner, PMR and GCA Scotland;
P. Richards, HNC (Business Studies), OMERACT Patient Research Partner, University of Bristol; L.M. Nelsen, MHS, Director, Patient Focused Outcomes, Value Evidence and Outcomes, GlaxoSmithKline; J.M. Nebesky, MD, Senior Medical Director, F. Hoffmann-La Roche Ltd.; S.L. Mackie, PhD, Associate Clinical Professor, Honorary Consultant Rheumatologist, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds; C.L. Hill, MD, Clinical Professor, Consultant Rheumatologist, Discipline of Medicine, The University of Adelaide, and Rheumatology Unit, The Royal Adelaide Hospital, and Rheumatology Unit, The Queen Elizabeth Hospital.

Address correspondence to Dr. R.J. Black, Rheumatology Unit, Royal Adelaide Hospital, North Terrace, Adelaide, SA, Australia 5000. E-mail: rachel.black2@sa.gov.au

Accepted for publication February 14, 2017.

concluding that there is a need to systematically identify GC AE in a standardized manner[10,12]. In addition, EULAR recommendations for GC monitoring suggest that new tools are required[13], supporting the need for the development of outcome measures to assess the effect of GC therapy across a wide range of indications.

The recently developed GC toxicity index (GTI) measures the physiological AE of systemic GC use, and includes items such as body mass index, glucose tolerance, blood pressure, lipids, and bone density, among others[15]. However, it is not a patient-reported outcome measure (PROM). Discordance between rheumatologists and patients regarding GC AE[16] suggests that patients may perceive GC AE very differently from doctors. Therefore, development of a PROM that specifically addresses the positive and negative effects of GC on patients' quality of life and experience would complement the GTI. The aim of the GC Special Interest Group (SIG) was to review current knowledge and define a research agenda for measuring the life effect of GC to identify relevant domains. Items achieved on the Outcome Measures in Rheumatology (OMERACT) Master Checklist are available on the OMERACT Website.

Main Findings

A literature search revealed a PROM that measures the effects of inhaled GC, but no PROM for the effects of systemic GC was found. The preliminary results of a pilot survey and 2 qualitative studies demonstrated that patients report outcomes including sleep disturbance, weight gain, and skin fragility that are not typically measured by clinicians. These data facilitated discussion regarding the need for a PROM for the effect of GC.

Systematic Literature Review of PROM for GC AE

A librarian-assisted search was carried out in OVID MEDLINE (1946 to February, Week 3, 2016) and OVID EMBASE (1974 to February 26, 2016; Supplementary Table 1, available with the online version of this article). Titles and abstracts of 146 articles were screened, and 7 papers were chosen for full-text review. No PROM for identifying the effects of systemic GC use was identified; however, 2 articles described the Inhaled Corticosteroid Questionnaire (ICQ)[17,18], a PROM for inhaled GC use (Supplementary Figure 1, available with the online version of this article). The ICQ contains 57 items across 15 categories; 38 items identified inhalation-related AE affecting the oropharynx, taste, and voice, and 19 items were related to systemic AE of inhaled GC including mood, skin/hair/nails, perspiration, and tiredness, among others (Figure 1).

GC AE Reported in RCT of Inflammatory Disorders

An analytical exercise to determine which GC AE have been reported in RCT was carried out using the studies reported in the systematic literature review of polymyalgia rheumatica (PMR; 9 RCT), Crohn disease (14 RCT), and ulcerative colitis (UC; 6 RCT)[19,20,21]. In addition, 28 rheumatoid arthritis (RA) RCT comparing systemic GC use in 1 arm to nonuse (placebo or no treatment) in at least 1 comparator arm were identified in a systematic literature search. GC AE data was extracted by review of the manuscripts identified. There were 63 different AE reported in the RCT distributed among 11 categories (Figure 1) that differed between diagnostic groups. AE in all categories were reported in the RA, PMR, and Crohn disease trials, but no UC trials report cardiovascular or ocular AE.

GC AE: The Patient Perspective (Pilot Survey)

A cross-sectional pilot survey was performed to determine GC AE from the patient perspective. Participants attended an Australian tertiary rheumatology clinic (n = 55) and were currently taking oral prednisone or had taken it within the past 12 months. The survey included a checklist of known AE and participants were asked "Which were the worst side effects you had?" Participants were also asked to indicate whether GC therapy helped "not at all," "a little," "a lot," or "not sure," and whether the AE they experienced were worse than the benefits of treatment (Yes/No/Not sure).

There were 55/88 questionnaires returned. Responders were 71% women, with a median age of 68 years (range 33–89 yrs). The disease range was broad [14 connective tissue disease, 14 RA, 14 PMR, 5 giant cell arteritis (GCA), 3 other vasculitis, 2 other arthritis, 1 retroperitoneal fibrosis]. All patients reported at least 1 GC AE (median 8, range 2–19). The most common AE were thin skin/easy bruising (45/55), weight gain (36/55), stomach upset/gastric reflux (30/55), and sleep disturbance (30/55).

The "worst" AE were weight gain, skin fragility, and sleep disturbance. Most patients (43/55) felt that GC helped their disease "a lot," 6/55 felt they helped "a little," 5/55 were "not sure," and 1/55 felt that GC did not help at all. Most (30/55) felt the benefits of treatment were greater than the AE, 9/55 thought that the AE were greater than the benefits, and 13/55 were undecided. (Data on this question were missing for 3 patients.)

A Qualitative Assessment of GC Use in ANCA-associated Vasculitis (AAV)

The OMERACT vasculitis working group members are key collaborators in the international development of a PROM for patients with AAV. AAV is a multisystem disease that can be organ- and life-threatening unless treated with high-dose GC and other immunosuppressants, all of which can significantly affect patients' health-related quality of life. During the qualitative phase of this project, 50 individual patient interviews were performed with participants from the United Kingdom, United States, and Canada[22]. Participants were purposely sampled to include a range of disease features (for example, renal disease vs limited respiratory, ENT

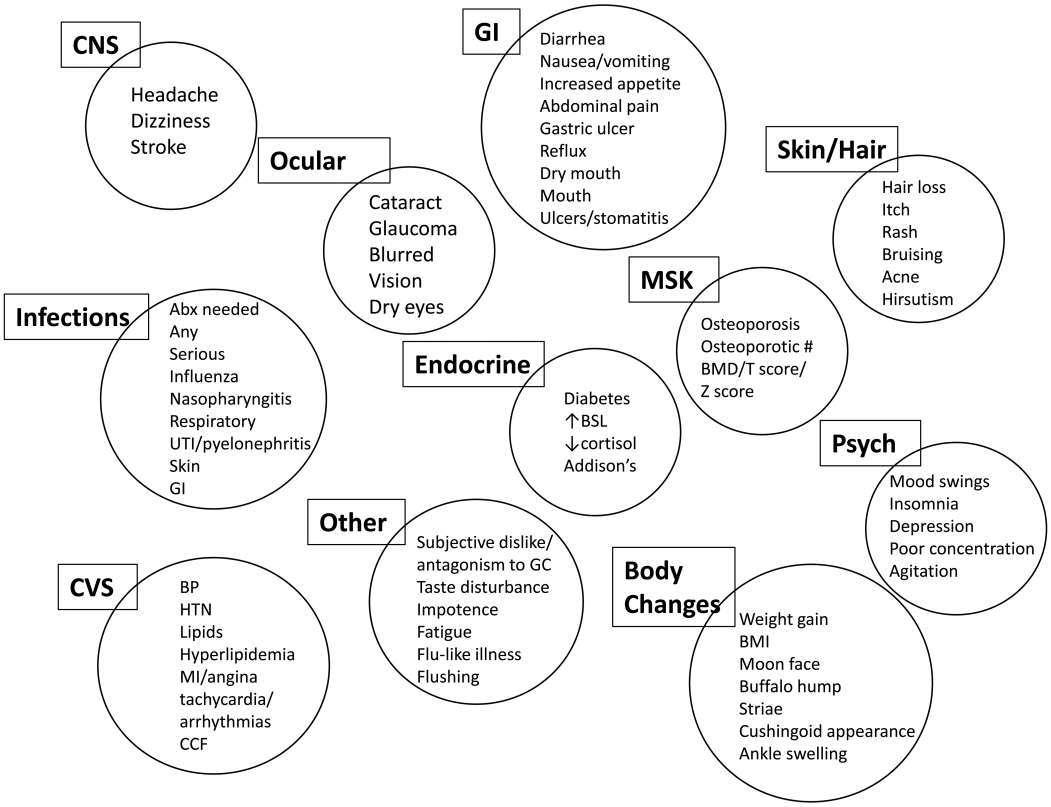


Figure 1. Categories of glucocorticoid adverse effects reported in randomized controlled trials. CNS: central nervous system; Abx: antibiotics; UTI: urinary tract infection; GI: gastrointestinal; CVS: cardiovascular system; BP: blood pressure; HTN: hypertension; MI: myocardial infarction; CCF: congestive cardiac failure; GC: glucocorticoid; MSK: musculoskeletal; osteoporotic #: osteoporotic fractures; BMD: bone mineral density; BSL: blood sugar level; psych: psychiatric; BMI: body mass index.

involvement; time since onset of the disease; and severity of disease) and demographic features. The interviews were broad-ranging to identify the full breadth and depth of themes of importance to patients in relation to both the disease itself and its treatment, including symptoms, effect on function, psychological and emotional health, and social interactions. The interviews were semistructured and used a topic guide including questions specifically related to GC and other treatments. Themes related to the positive and negative aspects of treatment with GC rapidly emerged as being of high importance to patients, with in-depth questioning revealing a range of differing patient perspectives. A detailed analysis across the 50 interviews looking more in depth at cross-cutting themes within the dataset was therefore performed. Inductive analysis was used. Preliminary results were presented for discussion during the GC SIG; the full report will be submitted for separate publication. Interviewed patients reported many positive aspects of GC treatment, including rapid onset and effectiveness in controlling organ- and life-threatening features of vasculitis. They also reported a range of physical and psychological AE in keeping with previous findings in other diseases. GC SIG patient participants (underlying diagnoses included RA and PMR) confirmed GC's positive effects and emphasized difficulties they experienced with dose reduction, including symptom recurrence. Some reported a perceived value judgement from family and friends attached to difficulty reducing their dose, and a feeling of failure if they were unable to "get off steroids." Fear surrounding longterm use of GC was suggested as a driver of patients' and doctors' seemingly emotional response to GC use, but further work is needed to analyze this.

A Qualitative Assessment of GC Use in PMR and GCA

Patients attending rheumatology clinics at an Australian tertiary hospital with a diagnosis of PMR or GCA were invited to participate in a qualitative study (supported by Arthritis Australia). Fourteen participants attended 1 of 4 discussion groups (2 were interviewed by phone because they were unable to attend a group discussion), where analytical data were gathered using facilitated discussions by nonclinician researchers. Questions focused on onset of symptoms, process of diagnosis, treatment, AE of treatment, and ongoing management of their condition(s). All discussion groups were transcribed verbatim and a "framework analysis" was used to analyze and interpret the data (Nvivo 10 software).

Preliminary findings highlight a wide range of experiences related to GC use. AE tended to occur after an initial positive treatment effect and dosage was identified as an influencing factor. Weight gain, changes in shape of face and neck, and insomnia with fatigue were commonly reported. The cumulative characteristic of AE was also acknowledged, along with difficulties in distinguishing AE from symptoms of the condition (e.g., fatigue). Some participants also reported having to manage distrust expressed by clinicians, family, and friends related to GC AE, while concurrently benefiting from the treatment effect.

Summary of the OMERACT 2016 GC SIG

Participants in the inaugural GC SIG agreed on the need for a data-driven PROM that identifies both positive and negative effects of GC therapy to be used across all inflammatory indications for systemic GC use in adults. The participants recognized the difficulty of determining how this might fit within the OMERACT framework because the Filter 2.0[23] has not been designed to address AE as an outcome; however, it was felt that the framework would nonetheless be helpful.

A research agenda was drawn up for development of a GC effect PROM:

1. To conduct further qualitative work in populations with different GC indications to identify relevant domains.
2. To address differences in age groups (adults), GC dose, and duration of use.
3. To define and quantify the value patients place on GC benefits and harms, and to determine differences from physicians.
4. To analyze the sense of conflict patients describe when physicians recommend tapering, while patients feel they need ongoing GC therapy.

In addition, it was agreed that this group would benefit from engagement and collaboration with the OMERACT Drug Safety Group.

When assessing novel therapies for inflammatory conditions treated with GC, it is important to identify the relevant GC-related risks and benefits. Based on the background evidence presented, attendees agreed that a PROM instrument should be developed. A research agenda has been established to broaden our understanding of the positive and negative effect of GC across different indications, ages, and doses. The group will be well placed to develop a preliminary core outcome set at OMERACT 2018.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. BMJ 1996;313:344-6.
2. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology 2011;50:1982-90.
3. van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM 2000;93:105-11.
4. Caldwell JR, Furst DE. The efficacy and safety of low-dose corticosteroids for rheumatoid arthritis. Semin Arthritis Rheum 1991;21:1-11.
5. Da Silva JA, Jacobs JW, Kirwan JR, Boers M, Saag KG, Inês LB, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Ann Rheum Dis 2006;65:285-93.
6. Jacobs JW, Bijlsma JW. Glucocorticoid therapy. In: Firestein GS, Budd RC, Gabriel S, McInnes I, O'Dell JR, editors. Kelley's textbook of rheumatology. 9th ed. Philadelphia: Elsevier Saunders; 2013:894-916.
7. Ruiz-Irastorza G, Danza A, Khamashta M. Glucocorticoid use and abuse in SLE. Rheumatology 2012;51:1145-53.
8. Bijlsma JW, Boers M, Saag KG, Furst DE. Glucocorticoids in the treatment of early and late RA. Ann Rheum Dis 2003;62:1033-7.
9. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van Der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis 2009;68:1833-8.
10. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2007;66:1560-7.
11. Hodkinson A, Kirkham JJ, Tudur-Smith C, Gamble C. Reporting of harms data in RCTs: a systematic review of empirical assessments against the CONSORT harms extension. BMJ Open 2013;3:e003436.
12. Duru N, Van Der Goes MC, Jacobs JW, Andrews T, Boers M, Buttgereit F, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2013;72:1905-13.
13. van der Goes MC, Jacobs JW, Boers M, Andrews T, Blom-Bakkers MA, Buttgereit F, et al. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. Ann Rheum Dis 2010;69:1913-9.
14. Strehl C, Bijlsma JW, de Wit M, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis 2016;75:952-7.
15. Miloslavsky EM, Naden RP, Bijlsma JW, Brogan PA, Brown ES, Brunetta P, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Ann Rheum Dis 2017;76:543-6.
16. van der Goes MC, Jacobs JW, Boers M, Andrews T, Blom-Bakkers MA, Buttgereit F, et al. Patient and rheumatologist perspectives on glucocorticoids: an exercise to improve the implementation of the European League Against Rheumatism (EULAR) recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2010;69:1015-21.
17. Foster JM, Aucott L, van der Werf RH, van der Meijden MJ, Schraa G, Postma DS, et al. Higher patient perceived side effects related to higher daily doses of inhaled corticosteroids in the community: a cross-sectional analysis. Respir Med 2006;100:1318-36.
18. Foster JM, van Sonderen E, Lee AJ, Sanderman R, Dijkstra A, Postma DS, et al. A self-rating scale for patient-perceived side effects of inhaled corticosteroids. Respir Res 2006;7:131.
19. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al. Current evidence for therapeutic interventions and prognostic factors in polymyalgia rheumatica: a systematic literature review

informing the 2015 European League Against Rheumatism/American College of Rheumatology recommendations for the management of polymyalgia rheumatica. Ann Rheum Dis 2015;74:1808-17.
20. Sherlock ME, MacDonald JK, Griffiths AM, Steinhart AH, Seow CH. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database Syst Rev 2015;10:CD007698.
21. Rezaie A, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2015;6:CD000296.
22. Robson J, Milman N, Tomasson G, Dawson J, Cronholm PF, Kellom K, et al. Exploration, development, and validation of patient-reported outcomes in antineutrophil cytoplasmic antibody-associated vasculitis using the OMERACT process. J Rheumatol 2015;42:2204-9.
23. Boers M, Kirwan JR, Gossec L, Conaghan PG, D'Agostino MA, Bingham CO 3rd, et al. How to choose core outcome measurement sets for clinical trials: OMERACT 11 approves filter 2.0. J Rheumatol 2014;41:1025-30.

2 Appendix Manuscript: Toward a Core Domain Set for Glucocorticoid Impact in Inflammatory Rheumatic Diseases: The OMERACT 2018 Glucocorticoid Impact Working Group

The Journal of Rheumatology

Toward a Core Domain Set for Glucocorticoid Impact in Inflammatory Rheumatic Diseases: The OMERACT 2018 Glucocorticoid Impact Working Group

Jonathan T.L. Cheah, Rachel J. Black, Joanna C. Robson, Iris Y. Navarro-Millán, Sarah R. Young, Pamela Richards, Susan Beard, Lee S. Simon, Susan M. Goodman, Sarah L. Mackie and Catherine L. Hill

DOI: 10.3899/jrheum.181082
http://www.jrheum.org/content/early/2019/01/11/jrheum.181082

Toward a Core Domain Set for Glucocorticoid Impact in Inflammatory Rheumatic Diseases: The OMERACT 2018 Glucocorticoid Impact Working Group

Jonathan T.L. Cheah, Rachel J. Black, Joanna C. Robson, Iris Y. Navarro-Millán, Sarah R. Young, Pamela Richards, Susan Beard, Lee S. Simon, Susan M. Goodman, Sarah L. Mackie, and Catherine L. Hill

ABSTRACT. ***Objective.*** To understand the effects of glucocorticoids (GC), which are of importance to patients.
Methods. The results of 2 literature reviews, a patient survey, and a qualitative study were presented.
Results. No validated instrument exists to evaluate GC effect on patients. Survey data revealed skin thinning/bruising, sleep disturbance, and weight gain as the most frequent adverse effects. The qualitative research yielded rich data covering rapid benefits and physical and emotional consequences of GC.
Conclusion. It was agreed that a patient-reported outcome to measure GC effect was required and a research agenda was developed for this goal. (J Rheumatol First Release January 15 2019; doi:10.3899/jrheum.181082)

Key Indexing Terms:
OMERACT GLUCOCORTICOIDS OUTCOME ASSESSMENT
RHEUMATIC DISEASES ADVERSE EFFECTS

From the Division of Rheumatology, Hospital for Special Surgery; Department of Medicine, and the Division of General Internal Medicine, Weill Cornell Medicine, New York; Department of Social Work, Binghamton University, Binghamton, New York; SDG LLC, Cambridge, Massachusetts, USA; Rheumatology Unit, Royal Adelaide Hospital; Discipline of Medicine, The University of Adelaide; Rheumatology Unit, The Queen Elizabeth Hospital, Adelaide, Australia; Faculty of Health and Applied Science, University of the West of England; School of Clinical Science, University of Bristol, Bristol; Leeds Biomedical Research Centre, Leeds Institute of Rheumatic and Musculoskeletal Medicine; Chapel Allerton Hospital, University of Leeds, Leeds, UK.

J.T. Cheah, MBBS, Fellow, Division of Rheumatology, Hospital for Special Surgery, and Department of Medicine, Weill Cornell Medicine; R.J. Black, MBBS, Consultant Rheumatologist, Rheumatology Unit, Royal Adelaide Hospital, and Discipline of Medicine, The University of Adelaide; J.C. Robson, MBBS, PhD, MRCP, Consultant Senior Lecturer in Rheumatology, Faculty of Health and Applied Science, University of the West of England, and School of Clinical Science, University of Bristol; I.Y. Navarro-Millán, MD, MSPH, Assistant Professor of Medicine, Division of General Internal Medicine, Weill Cornell Medicine, and Division of Rheumatology, Hospital for Special Surgery; S.R. Young, PhD, LMSW, Assistant Professor, Department of Social Work, Binghamton University; P. Richards, HNC (Business Studies), OMERACT Patient Research Partner; S. Beard, BMus, OMERACT Patient Research Partner; L.S. Simon, MD, Principal, SDG LLC; S.M. Goodman, MD, Professor of Clinical Medicine, Division of Rheumatology, Hospital for Special Surgery, and Department of Medicine, Weill Cornell Medicine; S.L. Mackie, MB BCh, PhD, MRCP, Leeds Biomedical Research Centre, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, and University of Leeds; C.L. Hill, MBBS, MSc, MD, FRACP, Clinical Professor, Rheumatology Unit, The Queen Elizabeth Hospital, and Rheumatology Unit, Royal Adelaide Hospital, and Discipline of Medicine, The University of Adelaide.

Address correspondence to Dr. J.T. Cheah, Division of Rheumatology, Hospital for Special Surgery, 535 E. 70th St., New York, New York 10021, USA. E-mail: cheahj@hss.edu

Accepted for publication November 27, 2018.

Glucocorticoids (GC) have a substantial role in the treatment of inflammatory diseases[1,2]. However, while adverse effects (AE) are well documented, the absolute risk of many GC AE remains unquantified[3] and the effects of greatest importance to patients are not known. With the aim to define a research agenda for measuring the effect of GC to identify relevant domains, the Outcome Measures in Rheumatology (OMERACT) GC Impact Working Group (WG) held its inaugural meeting at the 2016 OMERACT meeting[4]. The presented work included a literature search that confirmed that there was not an already developed patient-reported outcome (PRO) for the effects of systemic GC use. Additionally, the preliminary results of a pilot survey and 2 qualitative studies identified that patients are concerned and affected by outcomes that are not commonly assessed by their treating clinician, such as skin fragility, sleep disturbance, and weight gain. At that meeting, there was agreement on the need for a data-driven PRO identifying both positive and negative effects of GC therapy to be used across inflammatory conditions. However, it was agreed that further work was required to gain additional understanding of the effects of GC prior to the development of a PRO. Following the steps of the current OMERACT filter[5,6], we sought to generate candidate domains from which to propose a core domain set. To this end, 2 literature reviews, a cross-sectional survey, and a qualitative study were undertaken and presented at OMERACT 2018 to better understand the effect of GC across various patient groups.

MATERIALS AND METHODS/RESULTS

Systematic literature review (SLR) of PRO for the effect of systemic GC. At OMERACT 2016, a systematic review revealed that no PRO had been developed to assess the effect of systemic GC use. We updated the original search, using OVID MEDLINE (2013 to Week 1 of October 2017) and OVID EMBASE (1974 to October 16, 2017). There were 208 unique articles identified and screened. Although no PRO measuring the effects of systemic GC across all inflammatory diseases were identified, 2 disease-specific PRO were found: 1 for multiple sclerosis (MS) and 1 for systemic lupus erythematosus (SLE)[7,8]. The Methylprednisolone Adverse Effects Questionnaire assessed the presence and severity of 15 items including facial flushing, sleep disturbance, and feeling angry or bad tempered in those with MS with a confirmed relapse. However, patients did not clearly participate in the development of the questionnaire and the psychometric properties of the questionnaire were not evaluated. The SLE Steroid Questionnaire measured 50 items across 7 domains. Although patients were involved throughout the development process, this PRO has not been tested across a large population of patients, and psychometric testing and adequate measurement properties have not been demonstrated.

Cross-sectional survey of GC AE from the patient perspective on 2 continents. To complement the survey performed and previously presented within an Australian tertiary rheumatology clinic, the same survey was subsequently administered to both GC users and nonusers from the rheumatoid arthritis (RA) database at the Hospital for Special Surgery (HSS; New York)[9]. The questionnaire included a checklist of 19 known AE and asked participants to rate the 3 "worst" AE. Similar results were found in the HSS GC users when compared with the initial Australian cohort, suggesting that the patient's perception of GC AE appear similar despite cultural and geographic differences. The most frequent AE across the 2 groups of GC users were sleep disturbance, thin skin/easy bruising, and weight gain. Weight gain was described most frequently as the worst AE in both cohorts. Compared to the HSS GC nonusers, many GC AE were significantly more frequent among GC users, suggesting that these AE were due to the use of GC, rather than to other medications or the underlying disease itself.

Qualitative assessment of GC use in RA. Patients with RA at the HSS with experience of GC use were invited to participate in a qualitative study to supplement the qualitative work that had already been conducted and reported on in antineutrophil cytoplasmic antibody-associated vasculitis (AAV), giant cell arteritis, and polymyalgia rheumatica, conditions in which both the dose as well as duration of GC may be significantly different from those in RA[4,10]. Eleven participants with RA (9 female) attended 1-to-1 semistructured interviews to describe the experience (benefits and harm) of taking GC. Ages ranged from 26–83 years. Eight participants were currently taking GC (range 2-20 mg daily of prednisone equivalent). Four themes emerged (Table 1). Overall, GC had been beneficial in the control of RA symptoms such as swelling and pain. However, this had "come at a price," the participants said, referring to the unintended physical and emotional effects of GC, such as weight gain and feelings of anger. Additionally, there was an acknowledgment of the necessity of GC use in certain contexts because of the need to be able to function for family and work purposes. Finally, there was uncertainty over attribution of potential symptoms solely to GC or to other disease-modifying antirheumatic drugs or to RA itself. Compared to the themes that emerged from the interviews conducted in AAV, similarities included the beneficial effects (which were quick), the adverse effects both physical and emotional, as well as the need to balance both in relation to the participants' current life situation. However, those with AAV voiced uncertainty regarding the dose-reduction process, whereas those with RA were at times uncertain whether particular effects were due to GC use.

SLR of the effect of GC from the patient perspective. To establish whether GC therapy carried similar effects in nonrheumatological inflammatory conditions, a further SLR was undertaken to identify the effects of systemic GC in adults across any condition in which systemic GC were used[11]. An academic librarian searched OVID EMBASE, OVID MEDLINE, PsycINFO, and CINAHL for articles published from inception to October 2017, related to 3 concepts: GC, the patient perspective, and AE. Inclusion criteria included systemic GC use for any indication in an adult population and both qualitative and quantitative research methodology. The initial search retrieved 1356 articles, of which 24 (18 quantitative, 6 qualitative) were deemed suitable for quality assessment and data extraction. Studies included the assessment of GC use across a variety of diseases both rheumatological (e.g., RA, vasculitis) and nonrheumatological (including asthma, inflammatory bowel disease, and MS). Four major themes emerged among the 71 discrete outcomes (Table 2): physical symptoms (44), psychological symptoms (18), effect on participation (6), and contextual factors (3). The metasynthesis of the qualitative work was richest for outcomes that had not been as well represented previously, including the effect on work/relationships, the cognitive load of debating the benefits and harm of GC use but also the sense of self-management and mastery of one's own disease, and the appropriate use of GC. Using a qualitative metasummary, frequency and intensity effect sizes will be calculated to identify those outcomes most prominently featured across all reviewed articles.

DISCUSSION

The session was well attended and insightful discussion took

Table 1. Description of themes from thematic analysis of interview transcripts.

Theme	Key Points with Quotes
Benefits	Pain and swelling • "…it does reduce the swelling. And when the swelling is reduced, the joints feel much better." Return to functional activities • "If I can't move my hands, I can't take a shower, I can't wash my hair, I can't brush my teeth. So how do I get to work? For me that was debilitating…the prednisone allowed me to do that because I would feel the effects within 2–3 days..."
Challenges	Physical (e.g., weight gain and recurrent infections) • "I looked like a white whale with a harpoon in my hip… I looked like Moby Dick." "I had a respiratory infection a lot; I seem subject to those. I would get skin infections, I had to be so careful not to break my skin and things." Emotional (e.g., anger and low mood) • "…inside I felt like a terrorist. I really did. I could have killed somebody. I'm not kidding, I had a terrible temper…" "My parents …for them to see me unhappy and just not feeling like myself, in that way, is really hard on them and it's hard on me…"
Necessity	Frustration with need • "I was angry that I had to take them. I did not want to take them, but I had no choice, because they do reduce the inflammation."
Attribution	Unsure whether GC solely responsible • "…when I'm taking all this…it's hard to precisely point to what's working and what's not working, what's good, what's bad…"

GC: glucocorticoid.

Table 2. Outcomes with the most frequently reported outcome per theme.

Theme	Outcome
Physical symptoms	Weight gain
	Sleep problems
	Skin changes
	Upper GI problems
	Cardiopulmonary
Psychological symptoms	Irritability and mood swings
	Depression
	Anxiety
	Hyperactivity and euphoria
	Process of debating GC use
Participation	Effect on sexual relationships
	Effect on work
	Effect on family
Contextual factors	Lack of support from community or media
	Self-management and mastery
	Lack of support from family and friends

GI: gastrointestinal; GC: glucocorticoid.

place among attendees and WG members, who identified issues to consider for future work, including:

1. The ongoing challenge of being able to clearly attribute an outcome to GC, rather than to the underlying disease or other medication(s).

2. How to create a PRO to be used across a broad range of rheumatic diseases in which GC use may be very different regarding dose, duration, and frequency.

3. How to integrate with the work of the Drug Safety WG and whether a generic core set for drug safety in addition to a GC-specific core set would be appropriate.

4. The importance of life context in determining the relative importance of a GC effect and how this can change over time.

5. That 3 main areas should be considered when assessing the effect of GC: the intended effects, the unintended effects, and the life context in which those effects take place.

A summary of both the presentation and subsequent discussion was also identified in cartoon form (Figure 1). Despite these issues, there was overall agreement that a PRO primarily concentrating on measuring the life effect of GC use is needed, and the following research agenda was developed:

1. Complete a Delphi exercise to prioritize outcomes.

2. Assess whether a different approach to the Delphi is needed to prioritize true GC effects (as opposed to the effects of the underlying disease or other medications).

3. Investigate novel ways of incorporating GC outcomes into the OMERACT onion[5,6], because having the effect of a medication as the outcome may require some adaptation.

Figure 1. Summary of the Glucocorticoid Impact Special Interest Group session. OMERACT: Outcome Measures in Rheumatology; GC: glucocorticoid; AE: adverse effects; MS: multiple sclerosis. OMERACT logo from OMERACT; used with permission.

4. Develop a preliminary core domain set to be voted on at OMERACT 2020.

The ability to measure the effect of GC, both positive and negative, is crucial at a time when there are an increasing number of steroid-sparing agents requiring rigorous evaluation in clinical trials. Therefore, there is an unmet need to measure the outcomes of GC use from the patient perspective. Developing a core domain set to create such a PRO remains the goal of the WG.

REFERENCES

1. Laugesen K, Jørgensen JOL, Sørensen HT, Petersen I. Systemic glucocorticoid use in Denmark: A population-based prevalence study. BMJ Open 2017;7:e015237.
2. van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM 2000;93:105-11.
3. Hoes JN, Jacobs JW, Verstappen SM, Bijlsma JW, Van der Heijden GJ. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis 2009;68:1833-8.
4. Black RJ, Robson JC, Goodman SM, Hoon E, Lai LYH, Simon LS, et al. A patient-reported outcome measure for effect of glucocorticoid therapy in adults with inflammatory diseases is needed: Report from the OMERACT 2016 special interest group. J Rheumatol 2017;44:1754-8.
5. Boers M, Kirwan JR, Tugwell P, Beaton D, Bingham CO III, Conaghan PG, et al. The OMERACT Handbook. [Internet. Accessed May 17, 2017.] Available from: https://omeract.org/resources
6. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. J Clin Epidemiol 2014;67:745-53.
7. Jongen PJ, Stavrakaki I, Voet B, Hoogervorst E, van Munster E, Linssen WH, et al. Patient-reported adverse effects of high-dose intravenous methylprednisolone treatment: a prospective web-based multi-center study in multiple sclerosis patients with a relapse. J Neurol 2016;263:1641-51.
8. Mathias SD, Berry P, De Vries J, Askanase A, Pascoe K, Colwell HH, et al. Development of the systemic lupus erythematosus steroid questionnaire (SSQ): a novel patient-reported outcome tool to assess the impact of oral steroid treatment. Health Qual Life Outcomes 2017;15:43.
9. Black RJ, Goodman SM, Ruediger C, Lester S, Mackie SL, Hill CL. A survey of glucocorticoid adverse effects and benefits in rheumatic diseases: the patient perspective. J Clin Rheumatol 2017;23:416-20.
10. Robson JC, Dawson J, Cronholm PF, Ashdown S, Easley E, Kellom KS, et al. Patient perceptions of glucocorticoids in anti-neutrophil cytoplasmic antibody-associated vasculitis. Rheumatol Int 2018;38:675-82.
11. Hill CL, Cheah JT, Goodman SM, Black RJ, Mackie SL. Patient's perspective of glucocorticoid use: A systematic review of quantitative and qualitative studies. PROSPERO 2018 CRD42018081620. [Internet. Accessed November 28, 2018.] Available from: www.crd.york.ac.uk/prospero/display_record.php?RecordID=81620

Bibliography

1. Kumar VMMDF, Abbas AKM, Aster JCMDP. Inflammation and Repair. In: Kumar VMMDF, Abbas AKM, Aster JCMDP, editors. Robbins and Cotran Pathologic Basis of Disease2015. p. 69-111.
2. Kemp WL, Burns DK, Brown TG. Chapter 2. Inflammation and Repair. Pathology : the big picture. New York: McGraw-Hill Medical; 2008.
3. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2017;9(6):7204-18.
4. Schett G, Neurath MF. Resolution of chronic inflammatory disease: universal and tissue-specific concepts. Nature Communications. 2018;9(1):3261.
5. Hench PS, Kendall EC, Slocumb CH, Polley HF. Effects of Cortisone Acetate and Pituitary Acth on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions - A Study in Clinical Physiology. Archives of internal medicine. 1950;85(4):545-666.
6. Kirwan JR, Balint G, Szebenyi B. Anniversary: 50 years of glucocorticoid treatment in rheumatoid arthritis. Rheumatology (Oxford). 1999;38(2):100-2.
7. Gupta P, Bhatia V. Corticosteroid physiology and principles of therapy. Indian J Pediatr. 2008;75(10):1039-44.
8. McKay LI CJ. Physiologic and Pharmacologic Effects of Corticosteroids. In: Kufe DW PR, Weichselbaum RR, et al., editor. Holland-Frei Cancer Medicine 6th edition: Hamilton (ON): BC Decker; 2003.
9. Lecocq FR, Mebane D, Madison LL. The acute effect of hydrocortisone on hepatic glucose output and peripheral glucose utilization. The Journal of clinical investigation. 1964;43:237-46.
10. Kaplan SA, Shimizu CS. Effects of cortisol on amino acids in skeletal muscle and plasma. Endocrinology. 1963;72:267-72.
11. Peckett AJ, Wright DC, Riddell MC. The effects of glucocorticoids on adipose tissue lipid metabolism. Metabolism: clinical and experimental. 2011;60(11):1500-10.
12. Macfarlane DP, Forbes S, Walker BR. Glucocorticoids and fatty acid metabolism in humans: fuelling fat redistribution in the metabolic syndrome. 2008;197(2):189.
13. Lee M-J, Pramyothin P, Karastergiou K, Fried SK. Deconstructing the roles of glucocorticoids in adipose tissue biology and the development of central obesity. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2014;1842(3):473-81.
14. Campbell JE, Peckett AJ, D'souza AM, Hawke TJ, Riddell MC. Adipogenic and lipolytic effects of chronic glucocorticoid exposure. American Journal of Physiology-Cell Physiology. 2011;300(1):C198-C209.
15. Chinenov Y, Rogatsky I. Glucocorticoids and the innate immune system: crosstalk with the toll-like receptor signaling network. Molecular and cellular endocrinology. 2007;275(1-2):30-42.
16. Fan H, Morand EF. Targeting the side effects of steroid therapy in autoimmune diseases: the role of GILZ. Discov Med. 2012;13(69):123-33.
17. De Bosscher K, Vanden Berghe W, Haegeman G. The interplay between the glucocorticoid receptor and nuclear factor-kappaB or activator protein-1: molecular mechanisms for gene repression. Endocr Rev. 2003;24(4):488-522.

18. Ismaili N, Garabedian MJ. Modulation of glucocorticoid receptor function via phosphorylation. Annals of the New York Academy of Sciences. 2004;1024:86-101.
19. Almawi WY, Melemedjian OK. Negative regulation of nuclear factor-kappaB activation and function by glucocorticoids. J Mol Endocrinol. 2002;28(2):69-78.
20. Anderson P, Phillips K, Stoecklin G, Kedersha N. Post-transcriptional regulation of proinflammatory proteins. J Leukoc Biol. 2004;76(1):42-7.
21. Smoak K, Cidlowski JA. Glucocorticoids regulate tristetraprolin synthesis and posttranscriptionally regulate tumor necrosis factor alpha inflammatory signaling. Molecular and cellular biology. 2006;26(23):9126-35.
22. Chikanza IC, Kozaci DL. Corticosteroid resistance in rheumatoid arthritis: molecular and cellular perspectives. Rheumatology (Oxford). 2004;43(11):1337-45.
23. Toh ML, Yang Y, Leech M, Santos L, Morand EF. Expression of mitogen-activated protein kinase phosphatase 1, a negative regulator of the mitogen-activated protein kinases, in rheumatoid arthritis: up-regulation by interleukin-1beta and glucocorticoids. Arthritis and rheumatism. 2004;50(10):3118-28.
24. Yang YH, Toh ML, Clyne CD, Leech M, Aeberli D, Xue J, et al. Annexin 1 negatively regulates IL-6 expression via effects on p38 MAPK and MAPK phosphatase-1. Journal of immunology. 2006;177(11):8148-53.
25. Barnes PJ. Corticosteroids: the drugs to beat. Eur J Pharmacol. 2006;533(1-3):2-14.
26. Gametchu B, Chen F, Sackey F, Powell C, Watson CS. Plasma membrane-resident glucocorticoid receptors in rodent lymphoma and human leukemia models. Steroids. 1999;64(1-2):107-19.
27. Spies CM, Schaumann DH, Berki T, Mayer K, Jakstadt M, Huscher D, et al. Membrane glucocorticoid receptors are down regulated by glucocorticoids in patients with systemic lupus erythematosus and use a caveolin-1-independent expression pathway. Annals of the rheumatic diseases. 2006;65(9):1139-46.
28. Bartholome B, Spies CM, Gaber T, Schuchmann S, Berki T, Kunkel D, et al. Membrane glucocorticoid receptors (mGCR) are expressed in normal human peripheral blood mononuclear cells and up-regulated after in vitro stimulation and in patients with rheumatoid arthritis. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2004;18(1):70-80.
29. Tryc AB, Spies CM, Schneider U, Kunkel D, Berki T, Sieper J, et al. Membrane glucocorticoid receptor expression on peripheral blood mononuclear cells in patients with ankylosing spondylitis. The Journal of rheumatology. 2006;33(11):2249-53.
30. Keating KM, Roess DA, Peacock JS, Barisas BG. Glucocorticoid effects on membrane lipid mobility during differentiation of murine B lymphocytes. Biochimica et biophysica acta. 1985;846(2):305-12.
31. Croxtall JD, Choudhury Q, Flower RJ. Glucocorticoids act within minutes to inhibit recruitment of signalling factors to activated EGF receptors through a receptor-dependent, transcription-independent mechanism. Br J Pharmacol. 2000;130(2):289-98.
32. Talaber G, Boldizsar F, Bartis D, Palinkas L, Szabo M, Berta G, et al. Mitochondrial translocation of the glucocorticoid receptor in double-positive thymocytes correlates with their sensitivity to glucocorticoid-induced apoptosis. Int Immunol. 2009;21(11):1269-76.

33. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. Bmj. 1996;313(7053):344-6.
34. Fardet L, Petersen I, Nazareth I. Prevalence of long-term oral glucocorticoid prescriptions in the UK over the past 20 years. Rheumatology (Oxford). 2011;50(11):1982-90.
35. van Staa TP, Leufkens HG, Abenhaim L, Begaud B, Zhang B, Cooper C. Use of oral corticosteroids in the United Kingdom. QJM : monthly journal of the Association of Physicians. 2000;93(2):105-11.
36. Hoes JN, Jacobs JWG, Verstappen SMM, Bijlsma JWJ, Van Der Heijden GJMG. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: A meta-analysis. Annals of the rheumatic diseases. 2009;68(12):1833-8.
37. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Bmj. 2004;329(7456):15-9.
38. Listing J, Kekow J, Manger B, Burmester G-R, Pattloch D, Zink A, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. 2015;74(2):415-21.
39. Roubille C, Rincheval N, Dougados M, Flipo RM, Daures JP, Combe B. Seven-year tolerability profile of glucocorticoids use in early rheumatoid arthritis: data from the ESPOIR cohort. Annals of the rheumatic diseases. 2017;76(11):1797-802.
40. Del Rincón I, Battafarano DF, Restrepo JF, Erikson JM, Escalante A. Glucocorticoid Dose Thresholds Associated With All-Cause and Cardiovascular Mortality in Rheumatoid Arthritis. Arthritis & rheumatology. 2014;66(2):264-72.
41. National Institute of Health and Clinical Excellence. NICE clinical guideline 79. Rheumatoid arthritis. The management of rheumatoid arthritis in adults. 2009 NICE Clinical Guideline 79.
42. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Annals of the rheumatic diseases. 2014;73(3):492-509.
43. Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis & rheumatology. 2016;68(1):1-26.
44. Dixon WG, Abrahamowicz M, Beauchamp ME, Ray DW, Bernatsky S, Suissa S, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Annals of the rheumatic diseases. 2012;71(7):1128-33.
45. Hoes JN, Jacobs JW, Boers M, Boumpas D, Buttgereit F, Caeyers N, et al. EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Annals of the rheumatic diseases. 2007;66(12):1560-7.
46. Movahedi M, Beauchamp ME, Abrahamowicz M, Ray DW, Michaud K, Pedro S, et al. Risk of Incident Diabetes Mellitus Associated With the Dosage and Duration of Oral Glucocorticoid Therapy in Patients With Rheumatoid Arthritis. Arthritis & rheumatology. 2016;68(5):1089-98.
47. Herxheimer A. Communicating with patients about harms and risks. PLoS Med. 2005;2(2):e42.

48. Ahmed H, Naik G, Willoughby H, Edwards AGK. Communicating risk. BMJ : British Medical Journal. 2012;344:e3996.
49. Symmons D, Turner G, Webb R, Asten P, Barrett E, Lunt M, et al. The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century. Rheumatology. 2002;41(7):793-800.
50. Silman AJ, Pearson JE. Epidemiology and genetics of rheumatoid arthritis. Arthritis research. 2002;4 Suppl 3(Suppl 3):S265-S72.
51. Australian Institute of Health and Welfare Web Report- Rheumatoid Arthritis 2017 [cited 2019 May]. Available from: https://www.aihw.gov.au/reports/chronic-musculoskeletal-conditions/rheumatoid-arthritis/contents/who-gets-rheumatoid-arthritis.
52. Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewe R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Annals of the rheumatic diseases. 2014;73(1):3-5.
53. McInnes IB, Schett G. The Pathogenesis of Rheumatoid Arthritis. New England Journal of Medicine. 2011;365(23):2205-19.
54. Demoruelle MK, Deane KD, Holers VM. When and where does inflammation begin in rheumatoid arthritis? Current opinion in rheumatology. 2014;26(1):64-71.
55. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. The Lancet. 2016;388(10055):2023-38.
56. Feldmann M, Maini SR. Role of cytokines in rheumatoid arthritis: an education in pathophysiology and therapeutics. Immunol Rev. 2008;223:7-19.
57. Tanaka S, Tanaka Y, Ishiguro N, Yamanaka H, Takeuchi T. RANKL: A therapeutic target for bone destruction in rheumatoid arthritis. Modern Rheumatology. 2018;28(1):9-16.
58. Baschant U, Lane NE, Tuckermann J. The multiple facets of glucocorticoid action in rheumatoid arthritis. Nature Reviews Rheumatology. 2012;8(11):645-55.
59. Lundy SK, Sarkar S, Tesmer LA, Fox DA. Cells of the synovium in rheumatoid arthritis. T lymphocytes. Arthritis research & therapy. 2007;9(1):202.
60. Mauri C, Ehrenstein MR. Cells of the synovium in rheumatoid arthritis. B cells. Arthritis research & therapy. 2007;9(2):205.
61. Sokka T, Kautiainen H, Toloza S, Makinen H, Verstappen SM, Lund Hetland M, et al. QUEST-RA: quantitative clinical assessment of patients with rheumatoid arthritis seen in standard rheumatology care in 15 countries. Annals of the rheumatic diseases. 2007;66(11):1491-6.
62. Kirwan JR, Bijlsma JW, Boers M, Shea BJ. Effects of glucocorticoids on radiological progression in rheumatoid arthritis. Cochrane database of systematic reviews. 2007(1):CD006356.
63. Bijlsma JW, Jacobs JW. Glucocorticoids in the treatment of rheumatoid arthritis: still used after 65 years. Annals of the New York Academy of Sciences. 2014;1318:27-31.
64. Hoes JN, Jacobs JWG, Buttgereit F, Bijlsma JWJ. Current view of glucocorticoid co-therapy with DMARDs in rheumatoid arthritis. Nature Reviews Rheumatology. 2010;6(12):693-702.
65. Da Silva JAP, Jacobs JWG, Kirwan JR, Boers M, Saag KG, Ines LBS, et al. Safety of low dose glucocorticoid treatment in rheumatoid arthritis: published evidence and prospective trial data. Annals of the rheumatic diseases. 2006;65(3):285-93.

66. Curtis JR, Westfall AO, Allison J, Bijlsma JW, Freeman A, George V, et al. Population-based assessment of adverse events associated with long-term glucocorticoid use. Arthritis and rheumatism. 2006;55(3):420-6.
67. Luqmani R, Hennell S, Estrach C, Basher D, Birrell F, Bosworth A, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). Rheumatology (Oxford). 2009;48(4):436-9.
68. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Annals of the rheumatic diseases. 2010;69(6):964-75.
69. Conn DL. Resolved: Low-dose prednisone is indicated as a standard treatment in patients with rheumatoid arthritis. Arthritis Care and Research. 2001;45(5):462-7.
70. Saag KG. Resolved: Low-dose glucocorticoids are neither safe nor effective for the long-term treatment of rheumatoid arthritis. Arthritis Care and Research. 2001;45(5):468-71.
71. Kirwan JR. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. The Arthritis and Rheumatism Council Low-Dose Glucocorticoid Study Group. The New England journal of medicine. 1995;333(3):142-6.
72. Boers M, Verhoeven AC, Markusse HM, van de Laar MA, Westhovens R, van Denderen JC, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet. 1997;350(9074):309-18.
73. Goekoop-Ruiterman YPM, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJSM, Hazes JMW, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Annals of internal medicine. 2007;146(6):406-15.
74. Hansen M, Podenphant J, Florescu A, Stoltenberg M, Borch A, Kluger E, et al. A randomised trial of differentiated prednisolone treatment in active rheumatoid arthritis. Clinical benefits and skeletal side effects. Annals of the rheumatic diseases. 1999;58(11):713-8.
75. Mottonen T, Hannonen P, Leirisalo-Repo M, Nissila M, Kautiainen H, Korpela M, et al. Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Lancet. 1999;353(9164):1568-73.
76. van Everdingen AA, Jacobs JWG, Siewertsz Van Reesema DR, Bijlsma JWJ. Low-dose prednisone therapy for patients with early active rheumatoid arthritis: clinical efficacy, disease-modifying properties, and side effects: a randomized, double-blind, placebo-controlled clinical trial.[Summary for patients in Ann Intern Med. 2002 Jan 1;136(1):I-26; PMID: 11777372]. Annals of internal medicine. 2002;136(1):1-12.
77. Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R, et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Lancet. 2004;364(9430):263-9.
78. Capell HA, Madhok R, Hunter JA, Porter D, Morrison E, Larkin J, et al. Lack of radiological and clinical benefit over two years of low dose prednisolone for rheumatoid arthritis: results of a randomised controlled trial. Annals of the rheumatic diseases. 2004;63(7):797-803.

79. Wassenberg S, Rau R, Steinfeld P, Zeidler H. Very low-dose prednisolone in early rheumatoid arthritis retards radiographic progression over two years: a multicenter, double-blind, placebo-controlled trial. Arthritis and rheumatism. 2005;52(11):3371-80.
80. Svensson B, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafstrom I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: a two-year randomized trial. Arthritis and rheumatism. 2005;52(11):3360-70.
81. Choy EH, Smith CM, Farewell V, Walker D, Hassell A, Chau L, et al. Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. Annals of the rheumatic diseases. 2008;67(5):656-63.
82. Dixon WG, Bansback N. Understanding the side effects of glucocorticoid therapy: shining a light on a drug everyone thinks they know. Annals of the rheumatic diseases. 2012;71(11):1761-4.
83. Cheah JTL, Black RJ, Robson JC, Navarro-Millan IY, Young SR, Richards P, et al. Toward a Core Domain Set for Glucocorticoid Impact in Inflammatory Rheumatic Diseases: The OMERACT 2018 Glucocorticoid Impact Working Group. The Journal of rheumatology. 2019.
84. Fraenkel L, Nowell WB, Michel G, Wiedmeyer C. Preference phenotypes to facilitate shared decision-making in rheumatoid arthritis. Annals of the rheumatic diseases. 2018;77(5):678-83.
85. Merlino LA, Bagchi I, Taylor TN, Utrie P, Chrischilles E, Sumner W, et al. Preferences for Fractures and Other Glucocorticoid-Associated Adverse Effects among Rheumatoid Arthritis Patients. Medical Decision Making. 2001;21(2):122-32.
86. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). Health services insights. 2013;6:61-8.
87. van Tuyl LH, Boers M. Patient-reported outcomes in core domain sets for rheumatic diseases. Nature reviews Rheumatology. 2015;11(12):705-12.
88. Cheung PP, de Wit M, Bingham CO, 3rd, Kirwan JR, Leong A, March LM, et al. Recommendations for the Involvement of Patient Research Partners (PRP) in OMERACT Working Groups. A Report from the OMERACT 2014 Working Group on PRP. The Journal of rheumatology. 2016;43(1):187-93.
89. Boers M, Kirwan JR, Wells G, Beaton D, Gossec L, d'Agostino MA, et al. Developing core outcome measurement sets for clinical trials: OMERACT filter 2.0. Journal of clinical epidemiology. 2014;67(7):745-53.
90. OMERACT: Outcome Measures in Rheumatology [cited 2018 Oct]. Available from: https://omeract.org/about.
91. Duru N, Van Der Goes MC, Jacobs JWG, Andrews T, Boers M, Buttgereit F, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Annals of the rheumatic diseases. 2013;72(12):1905-13.
92. van der Goes MC, Jacobs JWG, Boers M, Andrews T, Blom-Bakkers MAM, Buttgereit F, et al. Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice. Annals of the rheumatic diseases. 2010;69(11):1913-9.

93. Miloslavsky EM, Naden RP, Bijlsma JW, Brogan PA, Brown ES, Brunetta P, et al. Development of a Glucocorticoid Toxicity Index (GTI) using multicriteria decision analysis. Annals of the rheumatic diseases. 2016.
94. van der Goes MC, Jacobs JW, Boers M, Andrews T, Blom-Bakkers MA, Buttgereit F, et al. Patient and rheumatologist perspectives on glucocorticoids: an exercise to improve the implementation of the European League Against Rheumatism (EULAR) recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases. Annals of the rheumatic diseases. 2010;69(6):1015-21.
95. Basch E. Patient-reported outcomes in drug safety evaluation. Ann Oncol. 2009;20(12):1905-6.
96. Flaxman SR, Bourne RRA, Resnikoff S, Ackland P, Braithwaite T, Cicinelli MV, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. Lancet Glob Health. 2017;5(12):e1221-e34.
97. Taylor HR, Keeffe JE, Vu HT, Wang JJ, Rochtchina E, Pezzullo ML, et al. Vision loss in Australia. The Medical journal of Australia. 2005;182(11):565-8.
98. Rao GN, Khanna R, Payal A. The global burden of cataract. Current opinion in ophthalmology. 2011;22(1):4-9.
99. Kanthan GL, Wang JJ, Rochtchina E, Tan AG, Lee A, Chia EM, et al. Ten-year incidence of age-related cataract and cataract surgery in an older Australian population. The Blue Mountains Eye Study. Ophthalmology. 2008;115(5):808-14 e1.
100. Klein BE, Klein R, Lee KE. Incidence of age-related cataract over a 10-year interval: the Beaver Dam Eye Study. Ophthalmology. 2002;109(11):2052-7.
101. Mukesh BN, McCarty CA, Rait JL, Taylor HR. Five-year incidence of open-angle glaucoma: the visual impairment project. Ophthalmology. 2002;109(6):1047-51.
102. WHO: Global Data on Visual Impairments 2010: World Health Organisation; 2012 [cited 2018 Oct]. Available from: http://www.who.int/blindness/GLOBALDATAFINALforweb.pdf.
103. Seddon J, Fong D, West SK, Valmadrid CT. Epidemiology of risk factors for age-related cataract. Survey of Ophthalmology. 1995;39(4):323-34.
104. Hodge WG, Whitcher JP, Satariano W. Risk factors for age-related cataracts. Epidemiologic reviews. 1995;17(2):336-46.
105. Frampton G HP, Cooper K, et al. The clinical effectiveness and cost-effectiveness of second-eye cataract surgery: a systematic review and economic evaluation. Southampton (UK):: NIHR Journals Library; 2014 Nov. (Health Technology Assessment, No. 18.68.); 2014 [cited 2018 Oct]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK263908/.
106. Ivers RQ, Cumming RG, Mitchell P, Attebo K. Visual impairment and falls in older adults: the Blue Mountains Eye Study. J Am Geriatr Soc. 1998;46(1):58-64.
107. Admitted patient care 2014–15: Australian hospital statistics. Canberra: AIHW: Australian Institute of Health and Welfare, 2016 16 Mar 2016. Report No.: Contract No.: Cat. No. HSE 172.
108. 4.6 Cataract surgery hospitalisations 40 years and over: Australian Commission on Safety and Quality in Health Care; [cited 2018 Oct]. Available from: https://www.safetyandquality.gov.au/wp-content/uploads/2017/06/4.6-Cataract-surgery.pdf.

109. Leske MC, Chylack LT, Jr., He Q, Wu SY, Schoenfeld E, Friend J, et al. Incidence and progression of cortical and posterior subcapsular opacities: the Longitudinal Study of Cataract. The LSC Group. Ophthalmology. 1997;104(12):1987-93.
110. McCarty CA, Mukesh BN, Dimitrov PN, Taylor HR. Incidence and progression of cataract in the Melbourne Visual Impairment Project. American journal of ophthalmology. 2003;136(1):10-7.
111. McCarty CA, Nanjan MB, Taylor HR. Operated and unoperated cataract in Australia. Clin Exp Ophthalmol. 2000;28(2):77-82.
112. Black RL, Oglesby RB, Von Sallmann L, Bunim JJ. Posterior subcapsular cataracts induced by corticosteroids in patients with rheumatoid arthritis. JAMA. 1960;174:166-71.
113. Cumming RG, Mitchell P, Leeder SR. Use of Inhaled Corticosteroids and the Risk of Cataracts. New England Journal of Medicine. 1997;337(1):8-14.
114. Garbe E, Suissa S, LeLorier J. Association of inhaled corticosteroid use with cataract extraction in elderly patients. JAMA. 1998;280(6):539-43.
115. WEATHERALL M, CLAY J, JAMES K, PERRIN K, SHIRTCLIFFE P, BEASLEY R. Dose–response relationship of inhaled corticosteroids and cataracts: A systematic review and meta-analysis. Respirology. 2009;14(7):983-90.
116. McLean CJ, Lobo RF, Brazier DJ. Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. Lancet. 1995;345(8945):330.
117. Group TI-ACS. Risk factors for age-related cortical, nuclear, and posterior subcapsular cataracts. . American journal of epidemiology. 1991;133(6):541-53.
118. Thompson JT. Cataract Formation and Other Complications of Intravitreal Triamcinolone for Macular Edema. American journal of ophthalmology. 2006;141(4):629-.e10.
119. Çekiç O, Chang S, Tseng JJ, Akar Y, Barile GR, Schiff WM. Cataract Progression After Intravitreal Triamcinolone Injection. American journal of ophthalmology. 2005;139(6):993-8.
120. Chu YK, Chung EJ, Kwon OW, Lee JH, Koh HJ. Objective evaluation of cataract progression associated with a high dose intravitreal triamcinolone injection. Eye. 2007;22:895.
121. Gillies MC, Simpson JM, Billson FA, Luo W, Penfold P, Chua W, et al. Safety of an intravitreal injection of triamcinolone: results from a randomized clinical trial. Arch Ophthalmol. 2004;122(3):336-40.
122. Wang JJ, Rochtchina E, Tan AG, Cumming RG, Leeder SR, Mitchell P. Use of inhaled and oral corticosteroids and the long-term risk of cataract. Ophthalmology. 2009;116(4):652-7.
123. Klein BE, Klein R, Lee KE, Danforth LG. Drug use and five-year incidence of age-related cataracts: The Beaver Dam Eye Study. Ophthalmology. 2001;108(9):1670-4.
124. Toogood JH, Markov AE, Baskerville J, Dyson C. Association of ocular cataracts with inhaled and oral steroid therapy during long-term treatment of asthma. The Journal of allergy and clinical immunology. 1993;91(2):571-9.
125. Matsunami C, Hilton AF, Dyer JA, Rumbach OW, Hardie IR. Ocular complications in renal transplant patients. Aust N Z J Ophthalmol. 1994;22(1):53-7.
126. Broder MS, Sarsour K, Chang E, Collinson N, Tuckwell K, Napalkov P, et al. Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis. Seminars in arthritis and rheumatism. 2016.

127. Alderaan K, Sekicki V, Magder LS, Petri M. Risk factors for cataracts in systemic lupus erythematosus (SLE). Rheumatology international. 2015;35(4):701-8.
128. James ER, Robertson L, Ehlert E, Fitzgerald P, Droin N, Green DR. Presence of a transcriptionally active glucocorticoid receptor alpha in lens epithelial cells. Investigative ophthalmology & visual science. 2003;44(12):5269-76.
129. Gupta V, Wagner BJ. Expression of the functional glucocorticoid receptor in mouse and human lens epithelial cells. Investigative ophthalmology & visual science. 2003;44(5):2041-6.
130. James ER, Fresco VM, Robertson LL. Glucocorticoid-induced changes in the global gene expression of lens epithelial cells. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics. 2005;21(1):11-27.
131. James ER. The etiology of steroid cataract. Journal of Ocular Pharmacology and Therapeutics. 2007;23(5):403-20.
132. Streeten BW, Eshaghian J. Human posterior subcapsular cataract. A gross and flat preparation study. Arch Ophthalmol. 1978;96(9):1653-8.
133. James ER. The etiology of steroid cataract. Journal of ocular pharmacology and therapeutics : the official journal of the Association for Ocular Pharmacology and Therapeutics. 2007;23(5):403-20.
134. Jobling AI, Augusteyn RC. What causes steroid cataracts? A review of steroid-induced posterior subcapsular cataracts. Clinical & experimental optometry : journal of the Australian Optometrical Association. 2002;85(2):61-75.
135. Guo ZJ, Zhu YJ, Gu L, Zhou X, Li LJ, Tian XL, et al. [Inhibition of human lung fibroblast proliferation and the mitogen activated protein kinase pathway by dexamethasone]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2004;26(3):227-31.
136. Jeon JW, Lee SJ, Kim JB, Kang JJ, Lee JH, Seong GJ, et al. Cellular proliferative effect of dexamethasone in immortalized trabecular meshwork cell (TM5) line. Yonsei Med J. 2003;44(2):299-306.
137. Miller AL, Webb MS, Copik AJ, Wang Y, Johnson BH, Kumar R, et al. p38 Mitogen-activated protein kinase (MAPK) is a key mediator in glucocorticoid-induced apoptosis of lymphoid cells: correlation between p38 MAPK activation and site-specific phosphorylation of the human glucocorticoid receptor at serine 211. Mol Endocrinol. 2005;19(6):1569-83.
138. Mikosz CA, Brickley DR, Sharkey MS, Moran TW, Conzen SD. Glucocorticoid receptor-mediated protection from apoptosis is associated with induction of the serine/threonine survival kinase gene, sgk-1. The Journal of biological chemistry. 2001;276(20):16649-54.
139. Andersson M, Honarvar A, Sjostrand J, Peterson A, Karlsson JO. Decreased caspase-3 activity in human lens epithelium from posterior subcapsular cataracts. Experimental eye research. 2003;76(2):175-82.
140. Bucala R, Gallati M, Manabe S, Cotlier E, Cerami A. Glucocorticoid-lens protein adducts in experimentally induced steroid cataracts. Experimental eye research. 1985;40(6):853-63.
141. Bucala R, Fishman J, Cerami A. Formation of covalent adducts between cortisol and 16 alpha-hydroxyestrone and protein: possible role in the pathogenesis of cortisol toxicity and systemic lupus erythematosus. Proceedings of the National Academy of Sciences of the United States of America. 1982;79(10):3320-4.

142. Dickerson JE, Jr., Dotzel E, Clark AF. Steroid-induced cataract: new perspective from in vitro and lens culture studies. Experimental eye research. 1997;65(4):507-16.
143. Jobling AI, Augusteyn RC. Steroid adduct formation with lens crystallins. Clinical & experimental optometry : journal of the Australian Optometrical Association. 1999;82(4):130-6.
144. Bettelheim FA, Li L, Zeng FF. Do changes in the hydration of the diabetic human lens precede cataract formation? Res Commun Mol Pathol Pharmacol. 1998;102(1):3-14.
145. Karim AK, Jacob TJ, Thompson GM. The human lens epithelium; morphological and ultrastructural changes associated with steroid therapy. Experimental eye research. 1989;48(2):215-24.
146. Derfoul A, Robertson NM, Lingrel JB, Hall DJ, Litwack G. Regulation of the human Na/K-ATPase beta1 gene promoter by mineralocorticoid and glucocorticoid receptors. The Journal of biological chemistry. 1998;273(33):20702-11.
147. Kolla V, Robertson NM, Litwack G. Identification of a mineralocorticoid/glucocorticoid response element in the human Na/K ATPase alpha1 gene promoter. Biochemical and biophysical research communications. 1999;266(1):5-14.
148. Wensor MD, McCarty CA, Stanislavsky YL, Livingston PM, Taylor HR. The prevalence of glaucoma in the Melbourne Visual Impairment Project. Ophthalmology. 1998;105(4):733-9.
149. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open-angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology. 1996;103(10):1661-9.
150. Vision 2020 Australia: National Eye Health Survey Report. Available from: http://www.vision2020australia.org.au/resources/national-eye-health-survey-report.
151. European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 2: Classification and terminologySupported by the EGS Foundation: Part 1: Foreword; Introduction; Glossary; Chapter 2 Classification and Terminology. The British journal of ophthalmology. 2017;101(5):73-127.
152. Prum BE, Jr., Lim MC, Mansberger SL, Stein JD, Moroi SE, Gedde SJ, et al. Primary Open-Angle Glaucoma Suspect Preferred Practice Pattern((R)) Guidelines. Ophthalmology. 2016;123(1):P112-51.
153. American Academy of Ophthalmology: The Glaucoma Suspect [cited 2018 Oct]. Available from: https://www.aao.org/bcscsnippetdetail.aspx?id=3267989c-d06f-4faf-8144-fc05139f80cc.
154. Leske MC, Wu S-Y, Hennis A, Honkanen R, Nemesure B. Risk Factors for Incident Open-angle Glaucoma: The Barbados Eye Studies. Ophthalmology. 2008;115(1):85-93.
155. Le A, Mukesh BN, McCarty CA, Taylor HR. Risk factors associated with the incidence of open-angle glaucoma: the visual impairment project. Investigative ophthalmology & visual science. 2003;44(9):3783-9.
156. Coleman AL, Miglior S. Risk Factors for Glaucoma Onset and Progression. Survey of Ophthalmology. 2008;53(6, Supplement):S3-S10.
157. Mclean JM. Use of ACTH and cortisone. Trans Am Ophthalmol Soc. 1950;48:293-6.
158. Francois J. Cortisone et tension oculaire. Ann D'Oculist. 1954;187:805.

159. Bernstein HN, Mills DW, Becker B. Steroid-induced elevation of intraocular pressure. Arch Ophthalmol. 1963;70:15-8.
160. Garbe E, LeLorier J, Boivin JF, Suissa S. Risk of ocular hypertension or open-angle glaucoma in elderly patients on oral glucocorticoids. Lancet. 1997;350(9083):979-82.
161. Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. JAMA. 1997;277(9):722-7.
162. Cubey RB. Glaucoma following the application of corticosteroid to the skin of the eyelids. The British journal of dermatology. 1976;95(2):207-8.
163. Garrott HM, Walland MJ. Glaucoma from topical corticosteroids to the eyelids. Clin Exp Ophthalmol. 2004;32(2):224-6.
164. Kalina RE. Increased intraocular pressure following subconjunctival corticosteroid administration. Arch Ophthalmol. 1969;81(6):788-90.
165. Smithen LM, Ober MD, Maranan L, Spaide RF. Intravitreal triamcinolone acetonide and intraocular pressure. American journal of ophthalmology. 2004;138(5):740-3.
166. Behbehani AH, Owayed AF, Hijazi ZM, Eslah EA, Al-Jazzaf AM. Cataract and ocular hypertension in children on inhaled corticosteroid therapy. J Pediatr Ophthalmol Strabismus. 2005;42(1):23-7.
167. Singh IP, Ahmad SI, Yeh D, Challa P, Herndon LW, Allingham RR, et al. Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. American journal of ophthalmology. 2004;138(2):286-7.
168. Becker B. Intraocular Pressure Response to Topical Corticosteroids. Invest Ophthalmol. 1965;4:198-205.
169. Becker B, Mills DW. Corticosteroids and Intraocular Pressure. Arch Ophthalmol. 1963;70:500-7.
170. Armaly MF. Effect of Corticosteroids on Intraocular Pressure and Fluid Dynamics. I. The Effect of Dexamethasone in the Normal Eye. Arch Ophthalmol. 1963;70:482-91.
171. Cantrill HL, Palmberg PF, Zink HA, Waltman SR, Podos SM, Becker B. Comparison of in vitro potency of corticosteroids with ability to raise intraocular pressure. American journal of ophthalmology. 1975;79(6):1012-7.
172. Bernstein HN, Schwartz B. Effects of long-term systemic steroids on ocular pressure and tonographic values. Arch Ophthalmol. 1962;68:742-53.
173. Francois J. Corticosteroid glaucoma. Ann Ophthalmol. 1977;9(9):1075-80.
174. Williamson J, Paterson RW, McGavin DD, Jasani MK, Boyle JA, Doig WM. Posterior subcapsular cataracts and glaucoma associated with long-term oral corticosteroid therapy. In patients with rheumatoid arthritis and related conditions. The British journal of ophthalmology. 1969;53(6):361-72.
175. Saag KG, Koehnke R, Caldwell JR, Brasington R, Burmeister LF, Zimmerman B, et al. Low dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse events. The American journal of medicine. 1994;96(2):115-23.
176. Huscher D, Thiele K, Gromnica-Ihle E, Hein G, Demary W, Dreher R, et al. Dose-related patterns of glucocorticoid-induced side effects. Annals of the rheumatic diseases. 2009;68(7):1119-24.

177. Armaly MF. Statistical Attributes of the Steroid Hypertensive Response in the Clinically Normal Eye. I. The Demonstration of Three Levels of Response. Invest Ophthalmol. 1965;4:187-97.
178. Armaly MF. The heritable nature of dexamethasone-induced ocular hypertension. Arch Ophthalmol. 1966;75(1):32-5.
179. Armaly MF. Dexamethasone ocular hypertension and eosinopenia, and glucose tolerance test. Arch Ophthalmol. 1967;78(2):193-7.
180. Armaly MF. Effect of Corticosteroids on Intraocular Pressure and Fluid Dynamics. Ii. The Effect of Dexamethasone in the Glaucomatous Eye. Arch Ophthalmol. 1963;70:492-9.
181. Becker B, Chevrette L. Topical Corticosteroid Testing in Glaucoma Siblings. Archives of Ophthalmology. 1966;76(4):484-7.
182. Becker B, Hahn KA. Topical Corticosteroids and Heredity in Primary Open-Angle Glaucoma. American journal of ophthalmology. 1964;57:543-51.
183. Davies TG. Tonographic survey of the close relatives of patients with chronic simple glaucoma. The British journal of ophthalmology. 1968;52(1):32-9.
184. Lam DS, Fan DS, Ng JS, Yu CB, Wong CY, Cheung AY. Ocular hypertensive and anti-inflammatory responses to different dosages of topical dexamethasone in children: a randomized trial. Clin Exp Ophthalmol. 2005;33(3):252-8.
185. Gaston H, Absolon MJ, Thurtle OA, Sattar MA. Steroid responsiveness in connective tissue diseases. The British journal of ophthalmology. 1983;67(7):487-90.
186. Becker B. Diabetes mellitus and primary open-angle glaucoma. The XXVII Edward Jackson Memorial Lecture. American journal of ophthalmology. 1971;71(1 Pt 1):1-16.
187. Podos SM, Becker B, Morton WR. High myopia and primary open-angle glaucoma. American journal of ophthalmology. 1966;62(6):1038-43.
188. Haas JS, Nootens RH. Glaucoma secondary to benign adrenal adenoma. American journal of ophthalmology. 1974;78(3):497-500.
189. Jones R, 3rd, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. Current opinion in ophthalmology. 2006;17(2):163-7.
190. Wordinger RJ, Clark AF. Effects of glucocorticoids on the trabecular meshwork: towards a better understanding of glaucoma. Progress in retinal and eye research. 1999;18(5):629-67.
191. Steely HT, Browder SL, Julian MB, Miggans ST, Wilson KL, Clark AF. The effects of dexamethasone on fibronectin expression in cultured human trabecular meshwork cells. Investigative ophthalmology & visual science. 1992;33(7):2242-50.
192. Wilson K, McCartney MD, Miggans ST, Clark AF. Dexamethasone induced ultrastructural changes in cultured human trabecular meshwork cells. Current eye research. 1993;12(9):783-93.
193. Snyder RW, Stamer WD, Kramer TR, Seftor RE. Corticosteroid treatment and trabecular meshwork proteases in cell and organ culture supernatants. Experimental eye research. 1993;57(4):461-8.
194. Bill A. Editorial: The drainage of aqueous humor. Invest Ophthalmol. 1975;14(1):1-3.
195. Renfro L, Snow JS. Ocular effects of topical and systemic steroids. Dermatol Clin. 1992;10(3):505-12.

196. Im L, Allingham RR, Singh I, Stinnett S, Fekrat S. A prospective study of early intraocular pressure changes after a single intravitreal triamcinolone injection. Journal of glaucoma. 2008;17(2):128-32.
197. Kersey JP, Broadway DC. Corticosteroid-induced glaucoma: a review of the literature. Eye. 2006;20(4):407-16.
198. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced Glaucoma: An Avoidable Irreversible Blindness. Journal of Current Glaucoma Practice. 2017;11(2):67-72.
199. Espildora J, Vicuna P, Diaz E. [Cortisone-induced glaucoma: a report on 44 affected eyes (author's transl)]. J Fr Ophtalmol. 1981;4(6-7):503-8.
200. Forbes H, Bhaskaran K, Smeeth L, Mathur R, Herrett E, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.
201. Franks P, Clancy CM, Nutting PA. Gatekeeping Revisited — Protecting Patients from Overtreatment. New England Journal of Medicine. 1992;327(6):424-9.
202. Greenfield G, Foley K, Majeed A. Rethinking primary care's gatekeeper role. Bmj. 2016;354.
203. Lawson DH, Sherman V, Hollowell J. The General Practice Research Database. Scientific and Ethical Advisory Group. QJM : monthly journal of the Association of Physicians. 1998;91(6):445-52.
204. García Rodríguez LA, Pérez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. British journal of clinical pharmacology. 1998;45(5):419-25.
205. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners. 2010;60(572):e128-36.
206. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. British journal of clinical pharmacology. 2010;69(1):4-14.
207. Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. BMJ open. 2018;8(2):e020738.
208. Dedman D, Lunn D, Booth H, Campbell J, Chapman J, Myles P, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. 2019.
209. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf. 2012;3(2):89-99.
210. Buchbinder R, March L, Lassere M, Briggs AM, Portek I, Reid C, et al. Effect of treatment with biological agents for arthritis in Australia: the Australian Rheumatology Association Database. Internal medicine journal. 2007;37(9):591-600.
211. Pye SR, Sheppard T, Joseph RM, Lunt M, Girard N, Haas JS, et al. Assumptions made when preparing drug exposure data for analysis have an impact on results: An unreported step in pharmacoepidemiology studies. Pharmacoepidemiology and drug safety. 2018;27(7):781-8.

212. Fortunet C, Pers YM, Lambert J, Godfrin-Valnet M, Constant E, Devilliers H, et al. Tocilizumab induces corticosteroid sparing in rheumatoid arthritis patients in clinical practice. Rheumatology (Oxford). 2015;54(4):672-7.
213. Kawai VK, Grijalva CG, Arbogast PG, Curtis JR, Solomon DH, Delzell E, et al. Changes in cotherapies after initiation of disease-modifying antirheumatic drug therapy in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2011;63(10):1415-24.
214. Nilsson AC, Christensen AF, Junker P, Lindegaard HM. Tumour necrosis factor-alpha inhibitors are glucocorticoid-sparing in rheumatoid arthritis. Danish medical bulletin. 2011;58(4):A4257.
215. Naumann L, Huscher D, Detert J, Spengler M, Burmester GR, Buttgereit F. Anti-tumour necrosis factor {alpha} therapy in patients with rheumatoid arthritis results in a significant and long-lasting decrease of concomitant glucocorticoid treatment. Annals of the rheumatic diseases. 2009;68(12):1934-6.
216. Seror R, Dougados M, Gossec L. Glucocorticoid sparing effect of tumour necrosis factor alpha inhibitors in rheumatoid arthritis in real life practice. Clinical and experimental rheumatology. 2009;27(5):807-13.
217. Altman DG, Goodman SN. Transfer of Technology From Statistical Journals to the Biomedical Literature: Past Trends and Future Predictions. JAMA. 1994;272(2):129-32.
218. Black RJ, Robson JC, Goodman SM, Hoon E, Lai LY, Simon LS, et al. A Patient-reported Outcome Measure for Effect of Glucocorticoid Therapy in Adults with Inflammatory Diseases Is Needed: Report from the OMERACT 2016 Special Interest Group. The Journal of rheumatology. 2017.
219. Foster JM, van Sonderen E, Lee AJ, Sanderman R, Dijkstra A, Postma DS, et al. A self-rating scale for patient-perceived side effects of inhaled corticosteroids. Respiratory research. 2006;7:131.
220. Foster JM, Aucott L, van der Werf RH, van der Meijden MJ, Schraa G, Postma DS, et al. Higher patient perceived side effects related to higher daily doses of inhaled corticosteroids in the community: a cross-sectional analysis. Respir Med. 2006;100(8):1318-36.
221. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al. Current evidence for therapeutic interventions and prognostic factors in polymyalgia rheumatica: a systematic literature review informing the 2015 European League Against Rheumatism/American College of Rheumatology recommendations for the management of polymyalgia rheumatica. Annals of the rheumatic diseases. 2015;74(10):1808-17.
222. Rezaie A, Kuenzig ME, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH, et al. Budesonide for induction of remission in Crohn's disease. Cochrane database of systematic reviews. 2015;6:CD000296.
223. Sherlock ME, MacDonald JK, Griffiths AM, Steinhart AH, Seow CH. Oral budesonide for induction of remission in ulcerative colitis. Cochrane database of systematic reviews. 2015;10:CD007698.
224. Black RJ, Hill CL, Lester S, Dixon WG. The Association between Systemic Glucocorticoid Use and the Risk of Cataract and Glaucoma in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. PloS one. 2016;11(11):e0166468.

225. Black RJ, Goodman SM, Ruediger C, Lester S, Mackie SL, Hill CL. A Survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases: The Patient Perspective. J Clin Rheumatol. 2017;23(8):416-20.
226. Joseph RM, van Staa TP, Lunt M, Abrahamowicz M, Dixon WG. Exposure measurement error when assessing current glucocorticoid use using UK primary care electronic prescription data. Pharmacoepidemiology and drug safety. 2018.
227. Black RJ, Joseph RM, Brown B, Movahedi M, Lunt M, Dixon WG. Half of UK patients with rheumatoid arthritis are prescribed oral glucocorticoid therapy in primary care: a retrospective drug utilisation study. Arthritis research & therapy. 2015;17(1):375.
228. Landewe RBM, Boers M, Verhoeven AC, Westhovens R, van de Laar MAFJ, Markusse HM, et al. COBRA combination therapy in patients with early rheumatoid arthritis: long-term structural benefits of a brief intervention. Arthritis & Rheumatism. 2002;46(2):347-56.
229. Konijn NPC, van Tuyl LHD, Boers M, den Uyl D, Ter Wee MM, van der Wijden LKM, et al. Similar efficacy and safety of initial COBRA-light and COBRA therapy in rheumatoid arthritis: 4-year results from the COBRA-light trial. Rheumatology (Oxford). 2017;56(9):1586-96.
230. Mathias SD, Berry P, De Vries J, Askanase A, Pascoe K, Colwell HH, et al. Development of the Systemic Lupus Erythematosus Steroid Questionnaire (SSQ): a novel patient-reported outcome tool to assess the impact of oral steroid treatment. Health and quality of life outcomes. 2017;15:43.
231. Jongen PJ, Stavrakaki I, Voet B, Hoogervorst E, van Munster E, Linssen WH, et al. Patient-reported adverse effects of high-dose intravenous methylprednisolone treatment: a prospective web-based multi-center study in multiple sclerosis patients with a relapse. Journal of neurology. 2016;263:1641-51.
232. Costello R, Patel R, Humphreys J, McBeth J, Dixon WG. Patient perceptions of glucocorticoid side effects: a cross-sectional survey of users in an online health community. BMJ open. 2017;7(4):e014603.
233. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Annals of internal medicine. 2004;141(10):781-8.
234. Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst. 2009;101(23):1624-32.
235. Basch E. The Missing Voice of Patients in Drug-Safety Reporting. New England Journal of Medicine. 2010;362(10):865-9.
236. Weingart SN, Gandhi TK, Seger AC, Seger DL, Borus J, Burdick E, et al. Patient-reported medication symptoms in primary care. Archives of internal medicine. 2005;165(2):234-40.
237. Gigerenzer G, Galesic M. Why do single event probabilities confuse patients? Bmj. 2012;344:e245.
238. Hoffrage U, Gigerenzer G. Using natural frequencies to improve diagnostic inferences. Acad Med. 1998;73(5):538-40.
239. Gigerenzer G. What are natural frequencies? Bmj. 2011;343:d6386.
240. The Risk Communication Institute- Visual Aids [cited 2019 March]. Available from: https://www.riskcomm.com/visualaids/visualaids.html.

241. Paling J. Strategies to help patients understand risks. Bmj. 2003;327(7417):745-8.
242. Australian absolute cardiovascular disease risk calculator [cited 2019 March]. Available from: https://www.cvdcheck.org.au/calculator/.
243. Garvan Institute Fracture Risk Calculator. Available from: https://www.garvan.org.au/promotions/bone-fracture-risk/calculator/.
244. FRAX ® Fracture Risk Assessment Tool [cited 2019 March]. Available from: https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9.
245. Jonathan Adams* KG, Stuart Marshall. Patterns of International Collaboration for the UK and Leading Partners. Science Focus. 2007;2(6):1-19.
246. Legare F, Witteman HO. Shared decision making: examining key elements and barriers to adoption into routine clinical practice. Health Aff (Millwood). 2013;32(2):276-84.
247. Bowling A, Ebrahim S. Measuring patients' preferences for treatment and perceptions of risk. Qual Health Care. 2001;10 Suppl 1:i2-8.