Article:
Black, RJ, Goodman, SM, Ruediger, C et al. (3 more authors) (2017) A Survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases: The Patient Perspective. JCR: Journal of Clinical Rheumatology, 23 (8). pp. 416-420. ISSN 1076-1608

https://doi.org/10.1097/RHU.0000000000000585

A survey of Glucocorticoid Adverse Effects and Benefits in Rheumatic Diseases: The Patient Perspective

Rachel J Black[1, 2], Susan M Goodman[3], Carlee Ruediger[4], Susan Lester[4], Sarah L Mackie[5], Catherine L Hill[1, 2, 4]

[1]The University of Adelaide, Discipline of Medicine, Adelaide, SA, Australia

[2]Royal Adelaide Hospital, Rheumatology Unit, Adelaide, SA, Australia

[3]Hospital for Special Surgery, New York, NY, United States of America

[4]The Queen Elizabeth Hospital, Rheumatology Unit, Woodville, SA, Australia

[5]The University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom

Running Head

Glucocorticoid Adverse Effects

Author Names/ Degrees

Rachel J Black, MBBS

Susan M Goodman, MD

Carlee Ruediger, PhD

Susan Lester, BSc (Hons)

Sarah L Mackie, PhD

Catherine L Hill, MD

Corresponding Author

Dr Rachel Black

Royal Adelaide Hospital

Rheumatology Unit

North Terrace

Adelaide SA, AUSTRALIA 5000

Email: Rachel.black2@sa.gov.au

Phone: +61 8 8222 5190

Fax: +61 8 82225895

Financial Support

RJB is supported by an Australian Postgraduate Award and an Arthritis South Australia/Australian Rheumatology Association (SA) Postgraduate Grant.

This study was supported by the Weill Cornell Clinical Translational Science Center, (UL1-TR000457-06).

Indexing Terms

Glucocorticoids

Patient Reported Outcomes

Adverse Events

Rheumatoid Arthritis

Rheumatic Diseases

Abstract

Objective: To explore, from the patient-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 (PROM).

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

Results: Cohort 1 had 55 GC-users and cohort 2 had 95 GC-users and 29 non-users. The majority of GC-users in both cohorts reported ≥1 AE (100%, 86%). The AE prevalence per person was 50% higher in cohort 1 compared to GC-users in cohort 2 (7.7 vs 5.3, AE ratio 1.5, 95%CI 1.3-1.7) and 2-fold greater in cohort 2 GC-users compared to GC non-users (5.3 vs 2.6, AE ratio 2.0, 95%CI 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 non-users.

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 PROM to capture the effects of GCs from the patient-perspective.

Introduction

Glucocorticoids (GCs) are frequently used to treat rheumatic conditions including inflammatory arthritis, connective tissue disorders, vasculitis and polymyalgia rheumatica [1]. Whilst 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 standardised measure of the benefits and AEs that are important to patients. The 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 [2, 3]. 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, BMI and blood pressure.

Increasingly, a patient's experience of treatment and care has been recognised 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]. PROMs 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 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 perspective in addition to 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 two groups of GC users and to explore which GC effects are important to patients. A secondary aim was to compare AEs reported by RA patients exposed and not exposed to GCs.

Methods

A cross-sectional, questionnaire-based survey was carried out in two cohorts, in Australia and the USA. In Australia, the study was approved by The Queen Elizabeth Hospital Human Research Ethics Committee, reference number: HREC/14/TQEHLMH/209. In the USA, the cohort was approved by the Hospital for Special Surgery Ethics Review Board, reference number: 2014-234-CR2.

Participants

Participants in cohort 1 (Australian cohort) attended a tertiary rheumatology clinic with various rheumatic diseases and 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 a patient's GP after each outpatient visit and include a summary of the diagnoses and medications. All letters from the

past 12 months were assessed by two reviewers (RJB, CR), and a random selection of eligible patients were mailed out a participant information sheet, consent form and a copy of the questionnaire with a reply paid return envelope. Cohort 2 (USA cohort) was from the Hospital for Special Surgery (HSS) rheumatoid arthritis (RA) database and included both GC users and non-users. Cases included in the database are identified from the HSS practice records by ICD-9 code 714.0 and confirmed by chart review. Cases meeting ACR/EULAR criteria for RA are recruited at a clinic visit or via mail and are included after giving consent, at which time they complete a brief survey and agree to be contacted for further studies. The questionnaire was distributed to patients on the database with a valid email 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 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, whilst 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 three '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)

Analysis

Descriptive statistics were used to summarise cohort demographics, 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 one AE was analysed using chi-square. The degree to which participant's felt GCs helped their condition, was assessed by comparing the ordinal trend between groups using the Cochran Armitage exact test. A chi-square analysis was carried out for the comparison of GC AEs and benefits. Within cohort 2, AEs reported by GC users and GC non-users were compared by Fisher's 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 (US), there were 227 questionnaires distributed to those with a valid email 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 non-users). Demographics and diagnoses are summarized in Table 1. For Cohort 1, the 33 patients who declined to participate were younger (median age 63, IQR 51-75 vs median age 68 IQR 60-76), 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, IQR 52-70 vs median 63, IQR 53-71), with a similar proportion of females (91/103, 88% vs 103/124, 83%). RA duration was similar in non-participants (median 9.5 years, IQR 4.5-18.0 vs. median

9.6 years, IQR 5.5-17.5) and fewer were glucocorticoid users at the time of the survey (23/103, 22% vs 35/124, 28%).

The AE prevalence per person was 50% higher in in cohort 1 compared to GC users in cohort 2 (7.7 vs 5.3, AE ratio 1.5, 95%CI 1.3-1.7) and 2-fold greater in cohort 2 GC-users compared to GC non-users (5.3 vs 2.6, AE ratio 2.0, 95%CI 1.6-2.6). All patients in cohort 1 reported at least one GC AE compared to 86% of GC-users in Cohort 2 (p=0.002).

The frequency of patient reported AEs and worst AEs are shown in Figure 1. The most frequent AEs were similar amongst 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 non-users 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 (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). GC non-users 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 Figure, Supplemental Digital Content 2.

In both GC use cohorts, the majority (78%/62%) 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 cohort 1 (55%) and cohort 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 to GC non-users ($p<0.05$) 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 to non-users, 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 focussed 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 one or more AEs, with bruising (67%) and weight gain (67%) most common [11]. In a French cohort study of 80 participants on long term systemic GCs, 71% reported one or more AEs, with change in face shape reported as the most distressing (39%) [12]. A cross-sectional study of UK patients with asthma, COPD and fibrosing alveolitis (n=367) found that bruising (73%) and muscle weakness (60%) were the most common GC AEs [13]. A UK based case-control study of PMR and GCA found that 23/35 (66%) participants reported one or more AEs, with weight gain (26%) and skin changes (26%) most common [14].

In the largest study to date, Curtis et al. included a population cohort of 2167 long-term GC users from the US, of which 90% reported at least one from a list of eight

potential AEs [15]. 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 prioritise the three 'worst' AEs. Lastly, in the current study, the survey was administered in two 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 UK[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 non-responders; indeed, in Cohort 2, fewer glucocorticoid non-users responded to the survey. Also in cohort 2, only those with valid email addresses were included and there may be differences between people who use technologies and those who don't. 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 only available in English. Whilst 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 minimise 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 two different cohorts and its comparison of AEs amongst GC users and non-users 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.

Conclusion

This cross-sectional study has increased our understanding of the impact of GC therapy form the patient perspective and is the first step in the development of a PROM. Patient-reported GC AEs were common amongst 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 non-users.

Key Points

- Patient-reported glucocorticoid (GC) adverse effects (AEs) occurred in 86-100% 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 non-users

Tables

Table 1. Baseline Demographics and Diagnoses

Table 2. Differences between AEs reported by GC Users and GC Non-Users in Cohort 2

Figure Legends

Figure 1. Frequency of Glucocorticoid Adverse Effects and Worst Adverse Effects in A. Cohort 1, n=55, B. Cohort 2 GC-users, n=95 and C. Cohort 2 GC Non-users, n=29.

Supplemental Digital Content

Supplemental Digital Content 1: File. Glucocorticoid Adverse Effects Questionnaire

Supplemental Digital Content 2: Figure. Other AEs attributed to GC use by patients

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(11):1982-90.
2. 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.
3. 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.
4. 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.
5. 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.
6. Weldring T, Smith SM. Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs). *Health services insights*. 2013;6:61-8.
7. van Tuyl LH, Boers M. Patient-reported outcomes in core domain sets for rheumatic diseases. *Nature reviews Rheumatology*. 2015;11(12):705-12.
8. 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.
9. 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.
10. R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. Available at: http://www.R-project.org/. Accessed December, 2016.
11. 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 primary care respiratory medicine*. 2015;25:15026.
12. Fardet L, Flahault A, Kettaneh A, Tiev KP, Genereau T, Toledano C, et al. Corticosteroid-induced clinical adverse events: frequency, risk factors and patient's opinion. *The British journal of dermatology*. 2007;157(1):142-8.
13. Walsh LJ, Wong CA, Oborne J, Cooper S, Lewis SA, Pringle M, et al. Adverse effects of oral corticosteroids in relation to dose in patients with lung disease. *Thorax*. 2001;56(4):279-84.
14. Kyle V, Hazleman BL. Treatment of polymyalgia rheumatica and giant cell arteritis. II. Relation between steroid dose and steroid associated side effects. *Annals of the rheumatic diseases*. 1989;48(8):662-6.
15. 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.
16. 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.