A Patient Reported Outcome Measure for Impact of Glucocorticoid Therapy In Adults with Inflammatory Diseases Is Needed: Report from the OMERACT 2016 Special Interest Group

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Abstract

Objective: The need for a standardised instrument to measure the impact of glucocorticoid (GC) therapy has been well documented in the literature. The aim of the first GC SIG was to define a research agenda around the development of a patient reported outcome measure (PRO) in this area.

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

Results: It was agreed that there is a need for a data driven PRO that captures both positive and negative effects of GC use, 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 impact of GCs across different groups including: different indications for GC use, different age groups, different dosages and duration of treatment.

Conclusion: There was agreement on the need for a PRO in this area and a research agenda was set.

Key Indexing Terms

Glucocorticoids, Adverse Effects, Outcomes

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Running Footline

Glucocorticoid impact measure needed

Introduction

Glucocorticoids (GCs) have had a prominent role in the treatment of inflammatory diseases for over 60 years, with 0.5-1% of adults considered current long-term users(1-3). They are effective anti-inflammatory agents, however they have many known associated adverse effects (AEs). While GC-AEs have been well documented(4-8), the absolute risk of many GC-AEs has not been quantified(5, 9). This may be because AEs are poorly captured in RCTs, or may reflect differences in AEs when GCs are prescribed for different indications and doses(10-14). 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(10, 12). In addition, EULAR recommendations for GC monitoring suggest new tools are required(13), supporting the need for the development of outcome measures to assess the impact of GC therapy across a wide range of indications.

The recently developed glucocorticoid toxicity index (GTI) measures the physiological AEs of systemic glucocorticoid use, and includes items such as BMI, glucose tolerance, blood pressure, lipids and bone density, amongst others. (15). However, it is not a patient reported outcome measure (PRO). Discordance between rheumatologists and patients regarding GC-AEs(16) suggests patients may perceive GC-AEs very differently from doctors. Therefore, development of a PRO that specifically addresses the positive and negative impact of GCs on patients' quality of life and experience, would complement the GTI. The aim of the Glucocorticoid SIG was to review current knowledge and define a research agenda for measuring the life impact of GCs in order to identify relevant domains. Items achieved on the OMERACT Master Checklist are indicated in supplementary file S1.

Main findings

A literature search revealed a PRO that measures the effects of inhaled GCs, but no PRO for the effects of systemic GCs was found. The preliminary results of a pilot survey and two 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

PRO for the impact of GCs.

What is novel?

The GC SIG met for the first time at OMERACT 2016 and all data presented was new. In addition, the first OMERACT research agenda in this area was defined, with a focus on the need to further understand the impact of GCs amongst patients of different ages and with different diagnoses and GC exposure. The aim of this research agenda is to identify relevant domains.

WHAT IS NEW?

- No patient reported outcome measure for assessing the impact of systemic glucocorticoid therapy was identified in a review of the literature
- RCTs identified in SLRs of RA, PMR and IBD reported 63 different GC AEs, with differences in reporting according to the indication for GC use
- Preliminary data from cross-sectional and qualitative studies suggest that patients feel GCs are an effective treatment and that the benefits outweigh the adverse effects
- It was agreed that a PRO for measuring the positive and negative impact of GC use is needed
- A research agenda was established to assist in the identification of potential domains

How this advances published research to date

The findings presented confirm the need for a standardized instrument to measure the unrecognized impact of GCs from the patient perspective.

The work presented in this paper has not previously been published elsewhere.

Systematic Literature Review of Patient Reported Outcome Measures (PROs) for Glucocorticoid Adverse Effects

A librarian-assisted search was carried out in OVID MEDLINE (1946-Feb week3 2016) and OVID EMBASE (1974- 26 Feb 2016) (Supplementary Table S1). Titles and abstracts of 146 articles were screened, and seven papers were chosen for full-text review. No PRO for capturing the effects of systemic GC use was identified, however two articles described the Inhaled Corticosteroid Questionnaire (ICQ)(17, 18), a PRO for inhaled GC use (Supplementary Figure S1). The ICQ contains 57 items across 15 categories; 38 items capture inhalation related AEs affecting the oropharynx, taste and voice and 19 items are related to systemic AEs of inhaled GCs including mood, skin/hair/nails, perspiration and tiredness amongst others (Figure 1).

Glucocorticoid Adverse Effects Reported in Randomised Controlled Trials of Inflammatory Disorders

An exploratory exercise to determine which GC-AEs have been reported in RCTs was carried out using the studies reported in SLRs of PMR (9 RCTs), Crohn's Disease (14RCTs) and UC (6 RCTs)(19-21). In addition, 28 RA RCTs comparing systemic GC use in one arm to non-use (placebo or no treatment) in at least one comparator arm were identified in a systematic literature search. GC-AE data was extracted by review of the manuscripts identified. There were 63 different AEs reported in the RCTs distributed amongst 11 categories (Figure 1) that differed between diagnostic groups. AEs in all categories were reported in the RA, PMR and Crohn's disease trials but no UC trials report cardiovascular or ocular AEs.

Glucocorticoid Adverse Effects- The Patient Perspective (Pilot Survey)

A cross-sectional pilot survey was performed to determine GC-AEs 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 AEs 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'whether the AEs they experienced were worse than the benefits of treatment (Yes/No/Not sure).

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

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

A qualitative assessment of GC use in ANCA associated vasculitis

The OMERACT vasculitis working group are key collaborators in the international development of a PRO, for patients with ANCA associated vasculitis (AAV). AAV is a multi-system disease, which can be organ and life threatening unless treated with high-dose GCs and other immunosuppressants, all of which can significantly impact on patients' health related quality of life. During the qualitative phase of this project, fifty individual patient interviews were performed with participants from the United Kingdom, United States and Canada (22). Participants were purposively sampled to include a range of disease features (for example renal disease, versus limited respiratory, ear nose and throat involvement; time since onset of the disease and severity of disease), and demographic features. The interviews were broad ranging in order to capture the full breadth and depth of themes of importance to patients in relation to both the disease itself and its treatment, including symptoms, and impact on function, psychological and emotional health and social interactions. The interviews were semi-structured and used a topic-guide including questions specifically related to GCs 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 in more 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. Patients interviewed reported many positive aspects of treatment with GCs, including rapid onset and effectiveness in controlling organ and life threatening features of vasculitis. They also reported a range of physical and psychological AEs in keeping with previous findings in other diseases. GC SIG patient participants (underlying diagnoses included RA and PMR) confirmed GC positive effects and emphasised 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". Fears surrounding long-term use of GCs was suggested as a driver of patients' and doctors' seemingly emotional response to GC use, but further work is needed to explore 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 one of four discussion groups (two were interviewed by phone as they were unable to attend a group discussion), where exploratory data were gathered using facilitated discussions by non-clinician researchers. Questions focussed on: onset of symptoms, process of diagnosis, treatment, AEs 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 GC use. AEs 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 nature of AEs was also acknowledged, along with difficulties in distinguishing AEs 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-AEs, while concurrently benefitting from the treatment effect.

Summary of the OMERACT 2016 Glucocorticoid SIG

Participants in the inaugural GC SIG agreed on the need for a data driven PRO that captures both positive and negative effects of GC use, 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, as the Filter 2.0 (23) has not been designed to address AEs as an outcome; however, it was felt that the framework would nonetheless be helpful.

A research agenda was developed for development of a GC impact PRO:

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 determine differences from physicians.
4. To explore the sense of conflict patients describe when physicians recommend tapering, while they 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.

Conclusion

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

Figure Legend

Figure 1. Categories of Glucocorticoid Adverse Effects Reported in RCTs

Abx=antibiotics, BMD= bone mineral density, BMI=body mass index, BSL=blood sugar level, CNS=central nervous system, GIT= gastrointestinal, MSK=musculoskeletal, Osteoporotic #s= osteoporotic fractures, Psych=psychiatric, UTI=urinary tract infection.

Data Supplements

Supplementary File S1. OMERACT Master Checklist

Supplementary Table S1. Search strategy used in Systematic Literature Review to identify Patient Reported Outcome Measures for Glucocorticoid Adverse Effects

Supplementary Figure S1. Flow diagram depicting number of articles identified in Systematic Literature Review

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