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

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Abstract (100 words)

Background: 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/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

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). The most common inflammatory indications for GCs include respiratory conditions (COPD) and asthma), rheumatic conditions (polymyalgia rheumatica (PMR), giant cell arteritis (GCA) RA), dermatological conditions (atopic dermatitis, eczema, other dermatoses) and gastrointestinal conditions (ulcerative colitis (UC) and Crohn's disease) (2). While GC Adverse Effects (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 patient reported outcome measures to assess the impact of GC therapy across a wide range of indications.

Often GC dose and duration are reported as a proxy for the "burden" of GC therapy, but this is a poor surrogate measure, without a clear link to impact on patients' quality of life. Discordance between rheumatologists and patients regarding GC AEs (15), suggests patients may perceive GC AEs very differently from doctors.

The need for a standardised measure to report GC AEs has become more pressing given many RCTs of novel therapies are designed to show non-inferiority to standard therapy, which is frequently GCs. It is particularly important to develop and validate instruments that measure the impacts of GCs on patients' lives. The aim of the Glucocorticoid SIG was to review current knowledge and using our pilot study, define a research agenda for measuring the life impact of GCs in the context of previous and ongoing work regarding the medical monitoring of GC AEs.

Systematic Literature Review (SLR) of Patient Reported Outcome Measures 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). Titles and abstracts of 146 articles were screened, and seven papers were chosen for full-text review. There were no papers describing a PRO for GC AEs associated with systemic administration, however two articles described the Inhaled Glucocorticoid Questionnaire (ICQ) PRO (16, 17). 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. No tool for capturing AEs of oral GCs from the patients' perspective was identified, confirming the need for an instrument to be developed.

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 RA (28 RCTs), PMR (9 RCTs), Crohn's Disease (14RCTs) and UC (6 RCTs) (18) (19, 20). 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. The most frequently reported AE categories were gastrointestinal (GIT), infections (in RA), musculoskeletal (in PMR), endocrine (in Crohn's disease), central nervous system (CNS) and GIT (in UC). 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 the AEs related to GCs from the patient perspective. Participants attended a tertiary rheumatology clinic (n=55) and were currently taking oral prednisone or had taken it within the past 12 months. The survey included questions about known AEs and an open-ended question about presence of 'other GC side effects'. Participants were asked to rate the three 'worst' AEs and indicate whether GC therapy helped 'not at all', 'a little', 'a

lot' or 'not sure'. Participants were also asked whether the AEs they experienced were worse than the benefits of treatment (Yes/No/Not sure).

There were 88 questionnaires distributed and 55 completed 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 (40/55) felt GCs helped their disease 'a lot', 6/55 felt they helped 'a little', 5/55 were 'not sure' and no patients 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 the remainder were undecided.

Apart from weight gain, AEs that are important to patients are poorly captured using current physiological measures.

A qualitative assessment of GC use in ANCA associated vasculitis

Patients with ANCA associated vasculitis (AAV) from the United Kingdom, United States and Canada were interviewed about their disease and treatment (21). Themes related to GC use were extracted and analysed with preliminary results presented for discussion during the GC SIG. Patients reported a range of physical and psychological AEs in keeping with previous findings in other diseases. Positive aspects of treatment with GCs included rapid onset and effectiveness in controlling symptoms. SIG patient participants (underlying diagnoses included RA and PMR) confirmed GC positive effects and emphasised difficulties they experienced with dose reduction. Some reported a perceived value judgement 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 Polymyalgia Rheumatica and Giant Cell Arteritis

Patients attending rheumatology clinics at a tertiary hospital, with a diagnosis of PMR or GCA were invited to participate in a qualitative study (supported by Arthritis Australia). Fifteen participants attended one of four discussion groups (3 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 analyse 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 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 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) and doses.
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.

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