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

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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

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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

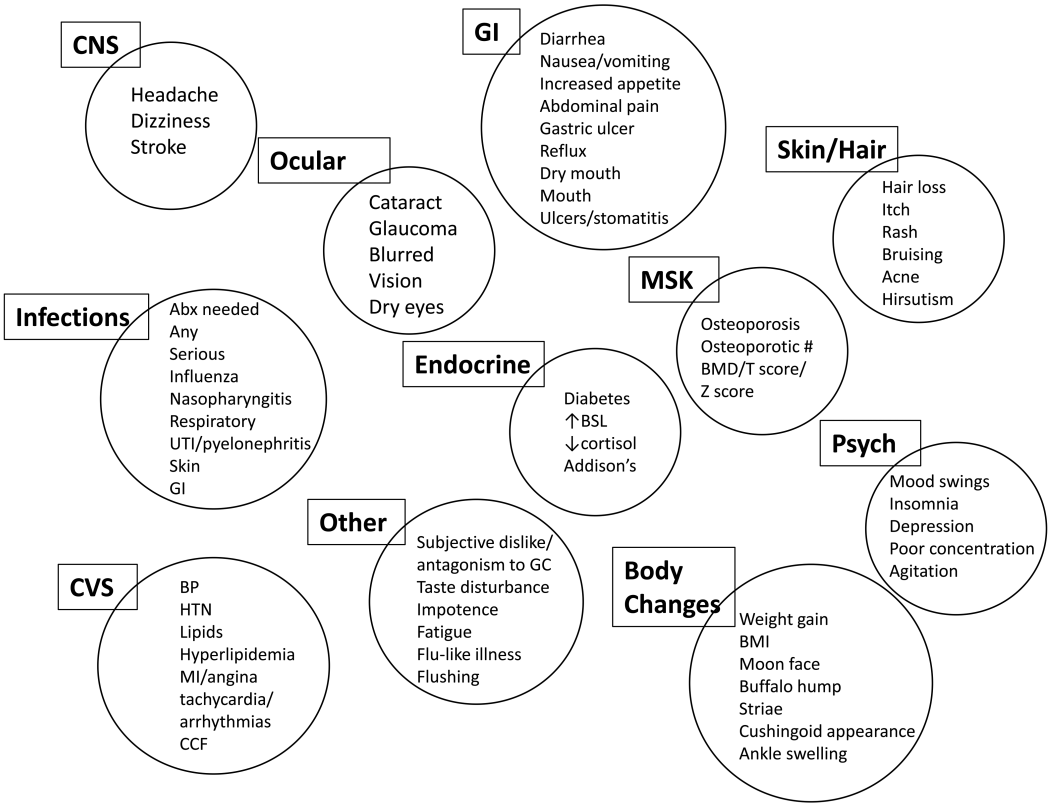

Figure 1. Categories of glucocorticoid adverse effects reported in randomized controlled trials. CNS: central nervous system; Abx: antibiotics; UTI: urinary tract infection; GI: gastrointestinal; CVS: cardiovascular system; BP: blood pressure; HTN: hypertension; MI: myocardial infarction; CCF: congestive 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.

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