Toward safer treatment with glucocorticoids: via patient and rheumatologist perspectives to recommendations on monitoring for adverse events

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Received and accepted on July 27, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 68): S116-S120.

Key words: glucocorticoids, drug toxicity, safety, patient preference, rheumatic diseases, drug monitoring, guidelines

Competing interests: M.C. van der Goes is a speaker for Mundipharma; J.W.G. Jacobs has been a speaker for Mundipharma on two occasions; J.W.J. Bijlsma has served as consultant and speaker for Nitec, Mundipharma and Horizon.

ABSTRACT

Glucocorticoids (GCs) play an important role in the treatment of rheumatic diseases, but adverse events (AEs) are common, particularly at high doses. By identifying perspectives of patients and rheumatologists on GC therapy reasons for concerns about GC therapy and resistance to this treatment were evaluated. Both patients and rheumatologists expressed concerns about AEs like osteoporosis, diabetes and cardiovascular diseases. These concerns and the fact that many GC-related AEs are – at least in part – preventable or treatable, underline the importance of identification of AEs.

The EULAR Task Force on Glucocorticoids developed recommendations for monitoring of AEs during low-dose GC therapy in daily practice and clinical trials, which were based on literature, perspectives of patients and rheumatologists and issues such as clinical relevance. Safe treatment with low-dose GCs in daily practice can be enhanced with use of a limited set of recommendations. In clinical trials, monitoring of a more comprehensive set of AEs is recommended, because this will also contribute to the identification of the relevant AE-profile of GC therapy.

Introduction

Glucocorticoids (GCs) have been widely used in inflammatory rheumatic diseases for over sixty years, because of their capacity to reduce symptoms such as pain and stiffness (1-3). Moreover, it has been demonstrated that GCs have disease-modifying capacities and retard the progression of erosive joint damage in early rheumatoid arthritis (RA) (4-10). GCs are frequently used in the treatment of RA at this time (11-13) and play an important role in combination therapy and treatment strategies such as 'tight control' for the treatment of patients with RA (4, 14-17).

Renewed debate about benefits and risks resulted in the formation of the European League Against Rheumatism (EULAR) Task Force on GC therapy. The Task Force addressed standardising nomenclature (18) and identifying safety issues by exploring the literature on safety of low-dose (≤7.5 milligrams prednisone or equivalent daily) GC therapy in RA (19). Evidence-based recommendations on the management of systemic low-dose to high-dose GC therapy in rheumatic diseases have been developed subsequently (20).

Despite the established use and the position of GCs in modern treatment, there is no certainty on the occurrence of relevant adverse events (AEs) of this medication. It has been shown that the occurrence of AEs is dose-dependent to a large extent (21, 22). A common misconception is that AEs of high-dose GC therapy (>30 mg prednisone or equivalent daily) occur to a similar extent during low-dose therapy (19). This confusion is seen among many doctors and patients. The patients recognise beneficial effects such as pain relief and improved function, but on the other hand they have serious concerns about AEs, which sometimes even lead to refusal to take GCs (23-25). The perceptions and preconceptions of both rheumatologists and patients can in daily practice affect the choice for specific medication, including GC therapy (26).

In order to develop recommendations on monitoring for AEs, the EULAR Task Force on GC therapy explored perspectives of patients and rheumatologists on GC therapy (27). With help of these perspectives and of available literature data, recommendations on monitoring for AEs during low-dose GC therapy have been developed (28).

This review presents the general opinion of patients and rheumatologists towards GC therapy and the consequences for education and safety monitoring. Finally, the process of developing recommendations for safety monitoring in daily practice and clinical trials will be described.

Perspectives

By identifying the opinions of patients and rheumatologists on GC therapy, we aimed to unravel reasons for concerns about and resistance to GC therapy, evaluate the need for recommendations on safety monitoring and identify monitoring issues. Therefore, separate meetings were arranged for patients and rheumatologists in seven rheumatology departments of university medical centres in Europe and one in the United States of America. Rheumatic patients who visited the outpatients' clinic were invited to attend a patient meeting focused on GC therapy, provided that they were acquainted with this treatment. Current use of GCs was not compulsory. Also rheumatologists from the participating centres and surrounding non-university hospitals were invited to participate.

In total, 140 patients and 110 rheumatologists attended the meetings. Seventy-eight percent of the patients were women and 80 percent of the patients were currently taking GC therapy (mean dose of 6 mg prednisone or equivalent). A minority of the patients had experience with medium to high-dose therapy. Their most frequent diagnosis was RA (61%), followed by systemic lupus erythematosus (11%) and polymyalgia rheumatica (5%).

Patient meetings started with open-ended group discussions. Attention was paid to positive and negative aspects of GC therapy. Participants introduced their attitude to GC therapy and their experiences with this treatment. This resulted in statements, varying from very positive to negative, of which some were remarkable. Some examples of these statements:

- *It worked considerably faster than other drugs.*
- *When I read all those information leaflets I think 'I should have already died'.* (Concern about toxicity.)
- *You get really hungry.* (Concern about weight gain.)
- *I frequently feel I have to defend myself for my use of GC therapy, not only in front of family and friends but also to doctors such as the general practitioner.*

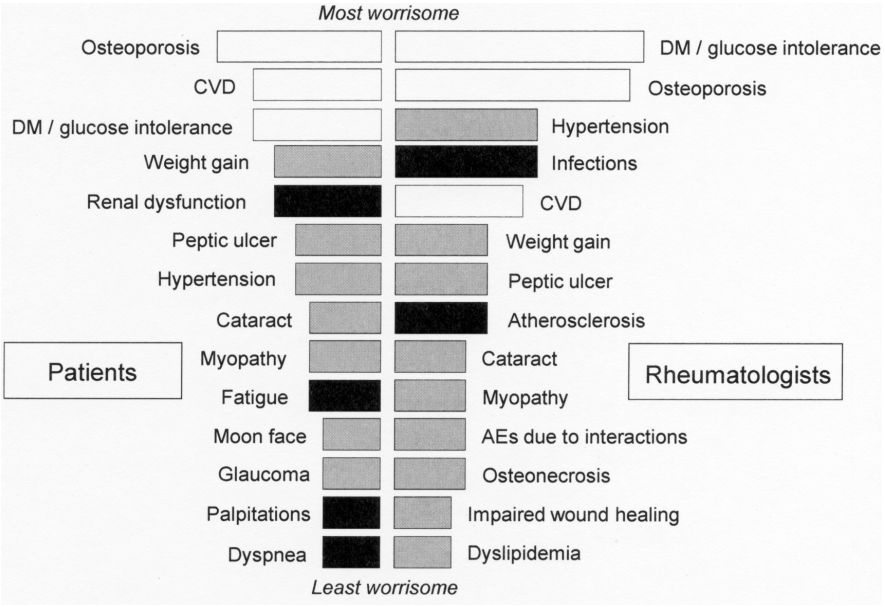

Fig. 1. Most worrisome AEs.
The most worrisome AEs according to 140 patients (left) and 110 rheumatologists (right). All AEs receiving at least 3% of the total score per group are depicted. Scores are corrected for the different numbers of participants per country. Similar scores for AEs by patients and rheumatologists are depicted in white and discordant scores, defined as a difference of at least 3%, are depicted in black.
CVD: cardiovascular disease; DM: diabetes mellitus; AEs: adverse events.

Although concerns about AEs were to a certain degree expected, some of the experiences were surprising. For example, the negative attitude towards the patients' GC therapy from close family, friends and doctors (except the prescribing rheumatologist) reflected the poor image of GCs.

In the second part of the meeting, the participants were asked to choose the 10 most worrisome AEs from a list with 37 items of previously in literature described possibly GC-related AEs. In general, there was conformity among patients and rheumatologists about the most worrisome AEs: osteoporosis, diabetes and cardiovascular diseases were ranked within the top five by both groups (Fig. 1).

There was more concordance in ranking within the group of rheumatologists compared to the group of patients. This could be explained by two important factors. First, rheumatologists gain knowledge about the frequency of occurrence of specific AEs from similar sources, and may therefore have more homogeneous views. Moreover, they can make estimations of the potential clinical impact due to the severity of AEs. It seemed that by integrating these two factors serious AEs known to be very rare were in general not scored as very worrisome. Apparently, frequently occurring problems in clinical practice like diabetes, osteoporosis, hypertension, infections and atherosclerosis (which can also occur without GC therapy) received a higher percentage of the total score in the group of rheumatologists than in the group of patients.

The scores of patients were more distributed over all AEs. Patients probably used their own experiences with GCs and weighed the severity of an AE largely without knowledge on the chance of occurrence. This resulted in scoring of very rare items without a clear relation with GC therapy, considered by them to be serious, as very worrisome. The same occurred for AEs experienced by themselves or acquainted patients. This resulted in their scoring of renal dysfunction, fatigue, palpitations and dyspnoea as more worrisome compared to rheumatologists.

Box 1. Example of an information card for patients.

Patient information

Ten important things to know about low-dose glucocorticoid therapy in rheumatic diseases

Glucocorticoids are medicines, which are commonly called steroids, corticosteroids or cortisone and include prednisone, prednisolone, medrol and deflazacort. This leaflet mentions ten important things to know about glucocorticoid therapy. It is applicable for all patients on treatment with low dosages (7.5 mg prednisone or less).

1. Benefits
Glucocorticoids are effective, simple to use and they work rapidly.

2. Risks
The possible side-effects depend on the dose, the duration of use and the presence of other diseases and medication you may have. The side-effects are usually mild on low doses. The most important are osteoporosis, worsening of diabetes and worsening of glaucoma. Some patients may experience weight gain, skin thinning, bruising, flushing, cataract, or worsening of hypertension.

3. Monitoring of side-effects
Contact your doctor if you are experiencing serious problems with glucocorticoid therapy. Side-effects will also be monitored by your rheumatologist.

4. Adjusting the dose and stopping
Your rheumatologist will review your individual benefits and risks regularly and will change dosage if needed. Your rheumatologist can also advise you about the timing of intake. It is important to remember that glucocorticoid therapy should not be stopped suddenly on your own.

5. Acute illness
Always mention you are on glucocorticoid therapy. Glucocorticoids should not be stopped suddenly on your own. Actually, extra glucocorticoids may be needed.

6. Surgery
If you need surgery inform the doctor about your glucocorticoid therapy. Extra glucocorticoids may be needed.

7. Pregnancy and lactation
Low-dose glucocorticoids are relatively safe during pregnancy; nevertheless, notify your rheumatologist if you are pregnant, planning to get pregnant or breastfeeding your child.

8. Bone protection
Measures to protect bone are often recommended. Your rheumatologist will evaluate this for your individual case.

9. General information
[Website]

10. Contact information
[Name, address and phone number of rheumatology department]

Disclaimer: This patient information leaflet does not replace the regular information leaflet or explanation by the prescribing rheumatologist.

Rheumatologists should explain the benefits and risks of glucocorticoid therapy to their patients. Additionally, an information card could be issued to patients. This figure shows an example of such a card with 10 important items about the treatment with low-dose glucocorticoids.

Consequences for education and safety monitoring

In the recommendations on systemic GC therapy, it was stated that AEs should be discussed with patients before the start of therapy and that information regarding GC management should be given (20). The work on perspectives showed that concerns about AEs exist in the group of patients as well as rheumatologists; patients clearly expressed the need for information and education about the true effects of GCs. The recommendation can be followed and the request can be met by explaining benefits and risks of GC therapy to patients when treatment is started. It is essential to adapt the explanation to the prescribed GC dose and the corresponding risk of developing AEs. This information could be supported by an information card with the most important items of the therapy, which can be issued to patients. An example of such an information card for low-dose therapy is given in Box 1.

Patients mentioned the negative attitude of other doctors than the prescribing rheumatologist. This indicates that other doctors may need to be educated about the relatively mild risks of treatment with low-dose GCs. Unfortunately, clear evidence from literature about the mildness of AEs is limited and therefore a solid basis for risk communication with them is lacking.

The need for information about the relevant concerns and unfounded fears about AEs is clear. Beside this, it is important to realise that many of the GC-related AEs are – at least in part – preventable or treatable, which means that the identification of AEs can be extremely important. Therefore, effort was put into developing recommendations for the monitoring of AEs.

In the project of developing recommendations, a couple of patient representatives stayed involved, what is in agreement with the EULAR recommendations on this item (29). The focus was on low-dose GC therapy, because these dosages are often used as chronic treatment in RA. Available literature was used as much as possible. In case of absence of literature, expert opinion was applied. Separate recommendations were developed for clinical trials and daily practice because of different purposes of monitoring.

There were several factors of importance in the decision making on which AEs to monitor (Table I). The more positive answers to the questions from Table I, the stronger was the indication for monitoring. The importance of monitoring increased in case literature was not conclusive, concerns of patients and rheumatologists were present and impact on quality of life or life expectancy was substantial. The burden of monitoring should preferably be low due to applicability of an easy and accurate monitoring test and the consequence of monitoring should be clear: actions or measures should be possible in order to prevent or treat an AE.

The ultimate goal of monitoring in daily practice is ensuring safe treatment, to protect patients from real dangers, and therefore it is justified to limit this monitoring to clinically important and not

Table I. Important items for the decision making whether to monitor or not a certain AE.

Literature	Are there indications for increased risk on developing the AE during low-dose GC therapy? If not: Is there uncertainty about the occurrence of the AE?
Perspectives	Are there concerns about the AE by patients or rheumatologists?
Severity	Is there substantial impact of the AE on quality of life or life expectancy?
Methodological issues	Is there an accurate method available for monitoring of the AE?
Burden of monitoring	Is the burden of monitoring low for patients?
Consequence of monitoring	Is prevention or treatment of the AE possible? if not: Is reversibility of the AE to be expected?
Economic	Are economic benefits of monitoring for the AE to be expected? (cost-effectiveness, low number needed to screen) if not: Do costs outweigh the clinical consequence of this AE?

This table shows several important aspects, which should be considered before making decisions on monitoring of an AE.
As an example skin atrophy: The frequency and severity of skin atrophy during low-dose GC therapy have not been prospectively studied nor described in literature. However, it could be a relevant problem. Skin atrophy does not affect life expectancy, but interferes with quality of life. It could be accurately measured with sonography, of which the burden for patients is low, or with skin biopsies, of which the burden for patients is higher. Unfortunately, skin atrophy cannot be prevented or treated and economic benefits of screening are not to be expected.
Weighing these facts, regular monitoring in daily practice of skin atrophy was not recommended, but monitoring by means of sonography was recommended for clinical trials to get clear data on frequency and severity.
GC: glucocorticoid; AE: adverse event.

Box 2. Monitoring for adverse events with low-dose glucocorticoid therapy in daily practice.

1. Osteoporosis:
Monitor for osteoporosis according to national guidelines and take the appropriate preventive measures.

2. Diabetes:
Evaluate the fasting blood glucose value before start of therapy. Repeat this measurement during follow-up in case impaired fasting glucose is identified at baseline.

3. Oedema:
Look for the presence of ankle oedema before the start of therapy. Perform follow-up measurements in case of presence.

4. Glaucoma:
Assess the risk factors for glaucoma (family history, presence of high myopia or diabetes) and refer to an ophthalmologist in case these factors are present.

Recommendations on monitoring for adverse events before and during low-dose glucocorticoid therapy (≤7.5 mg prednisone or equivalent). Standard care evaluation of hypertension, heart disease, peptic ulcer disease and body weight needs not be extended for patients on low-dose glucocorticoid therapy.

very rare AEs. The recommendations are meant as 'minimum recommendations': specific aspects of individual patients may warrant a higher frequency of monitoring or a more comprehensive set of items to monitor. Moreover, it is important to realise that the recommendations for daily practice do not replace good clinical practice and the normal screening on the presence of frequently occurring disorders (such as hypertension and dyslipidemia) in an aging population with an inflammatory disease and medication involved, which is usually performed by the general practitioner. The main conclusion was that standard care monitoring needs not be expanded for patients on low-dose GC therapy, except the monitoring for osteoporosis (for which national guidelines can be used), and baseline assessments of ankle oedema, fasting blood glucose and risk factors for glaucoma (Box 2). In future clinical trials it would be a great opportunity to obtain high-quality data on the occurrence of AEs. Therefore, a more extensive set of items should be monitored and the results of this monitoring should be reported in literature. Monitoring in this setting will contribute to the identification of the relevant AE profile for GCs. The perspective of patients played an important role in the development of these recommendations. Items for which many concerns were expressed, although generally not severe in clinical practice, such as skin atrophy, were included in this recommended monitoring set.

Conclusion

Views of patients and rheumatologists on benefits and risks of GC therapy have been identified. Recommendations for the monitoring of AEs during low-dose GC therapy have been developed for clinical trials and daily practice.

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