

Monitoring adverse events of low-dose glucocorticoid therapy: EULAR recommendations for clinical trials and daily practice

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ABSTRACT

Objective To develop recommendations on monitoring for adverse events (AEs) of low-dose glucocorticoid (GC) therapy (≤ 7.5 mg prednisone or equivalent daily) in clinical trials and daily practice.

Methods Literature was searched for articles containing information on incidence and monitoring of GC-related AEs using PubMed, EMBASE and Cochrane databases. Second, the authors searched for broad accepted guidelines on the monitoring of certain AEs (eg, WHO guidelines on screening for diabetes). Available data were summarised and discussed among experts (rheumatologists and patients) of the EULAR Task Force to decide which potential AEs should be monitored, how and at which interval.

Results Data on monitoring proved to be scarce; most articles were focused on therapeutic effects of GCs, not on occurrence and monitoring of AEs. Most recommendations had to be based on consensus. Those for clinical trials aimed at getting insights into incidence, prevalence and clinical relevance of AEs to create a comprehensive and valid AE-profile of GC therapy. The set of AEs to monitor is therefore more extensive, and often consists of assessments at baseline and at end of trials. Recommendations for daily practice are meant to protect patients from real dangers, which can be prevented or treated. Standard care monitoring needs NOT be extended for patients on low-dose GC therapy, except for osteoporosis (follow national guidelines), and baseline assessments of ankle edema, fasting blood glucose and risk factors for glaucoma.

Conclusion Given the incompleteness of literature data, consensus-based recommendations on monitoring for GC-related AEs were created, separately for daily practice and clinical trials.

Since their discovery, glucocorticoids (GCs) are being widely used in different diseases.^{1,2} Their effects are mediated by genomic and non-genomic mechanisms.³ GCs are beneficial in many inflammatory and rheumatic diseases, because of their anti-inflammatory and immunosuppressive actions, reducing disease activity and pain. In the long term, GCs exhibit disease-modifying capacities in rheumatoid arthritis (RA), such as protective effects on joint destruction.⁴ However, their use is restrained by the occurrence of adverse events (AEs).^{5–10}

Despite the established use, there is no definite consensus on the relevant AE-profile of this medication. A common misconception is that AEs

Box 1 Recommendations

Three general recommendations on monitoring in clinical trials

1. Report all monitoring results of trials
2. Report both on the group level (eg, means) and on the individual patient level (eg, numbers)
3. Develop new tools for assessing specific adverse events

of high-dose GC therapy (>30 mg prednisone or equivalent daily) occur in low-dose therapy (≤ 7.5 mg prednisone or equivalent daily) to the same extent. In the past years this Task Force put effort in standardizing nomenclature¹¹ and producing an overview of AEs associated with low-dose GC therapy in RA.¹² Furthermore, recommendations on the management of systemic GC therapy in rheumatic diseases were formulated.¹³ Recently, an exercise to explore the perspectives of patients and rheumatologists on GCs showed that recommendations on the monitoring of GC-related AEs were desired, but lacking.¹⁴ Since many of the GC-related AEs are – at least in part – preventable or treatable, the identification of an AE can be important in daily practice. Currently, great efforts are being made to develop innovative GCs or GC receptor ligands that have an improved therapeutic effect/AE ratio.^{15,16} So for obtaining a true AE-profile of (conventional) GCs and for comparing AEs of innovative GCs with those of conventional GCs, clear guidance and consensus on the monitoring of AEs are desirable.

The aim of this study was to develop recommendations for the monitoring of GC-related AEs of low-dose GC treatment in rheumatic diseases (1) in clinical trials for obtaining high-quality data on the occurrence of AEs and (2) in daily practice for treating patients safely. These recommendations should state *which* AEs to monitor, *how* to monitor them and *in what frequency*.

METHODS

Literature search

A review of the published evidence on GC-related AEs in rheumatic diseases was performed using the bibliographic databases PubMed, EMBASE and Cochrane Library in order to provide data for group discussions and make the recommendations as

evidence-based as possible. The search was focused on prospective studies in rheumatic diseases reporting AEs of GC therapy. Synonyms and plurals of the search terms were used and MESH terms were added for the PubMed search (all search terms are listed in Online Appendix 1). Studies were included if (1) they were prospective, (2) focused on inflammatory rheumatic diseases, (3) GCs were used in dosages up to 10 mg prednisone or equivalent daily and (4) AEs were reported. Although the focus of these recommendations is on low-dose therapy, studies up to 10 mg prednisone or equivalent were included to enlarge the dataset. Many studies reported AEs for GC dosages up to 10 mg daily and we considered the difference between 7.5 and 10 mg daily not to result in misinterpretations. Exclusion criteria were non-European languages, animal studies and case reports.

Data extraction

After applying inclusion and exclusion criteria and reading full-text articles, characteristics of relevant studies were recorded. Important items were the study population (number of patients, disease) and GC therapy (preparation, dose and duration). Information about the reporting of AEs was collected, such as the definition of AEs, the method of monitoring, the frequency of monitoring and blinding of investigator. The reported data on occurrence of each AE were recorded.

Summarizing and critically appraising the available data

The results of the literature search were separated for outcomes of randomised controlled trials (RCTs) and outcomes of prospective cohort studies. If available, information from RCTs was preferred over that from cohort studies, since randomization prevents from possible confounding by indication and data can be compared with a control group without GC treatment. If no RCTs were available for a certain AE, information

from cohort studies was used. Regarding the quality of reporting AEs, main problems in interpreting data were described for each AE.

Decisions on monitoring

The available data were presented to the Task Force consisting of rheumatologists and rheumatic patients and possible monitoring methods were discussed until consensus was reached on the need for monitoring, the method and frequency. For all AEs considered to be candidate for monitoring, it was checked whether broad accepted guidelines (WHO, American Heart Association etc.) on monitoring or screening in the general population were available. For as far as possible, the methods in these broad accepted guidelines were incorporated in this project. The final decision on monitoring was based on evidence on occurrence of each AE, feasibility of its monitoring and importance as valued by participating rheumatic patients and rheumatologists.

RESULTS

Literature search

The literature search resulted in 6226, 3654 and 15 hits in PubMed, EMBASE and Cochrane Library, respectively (figure 1). After filtering doubles and screening all titles and abstracts with respect to selection criteria, 348 articles were deemed potentially relevant. After reading the full text, 31 articles were included. Relevant data on occurrence of AEs were extracted from RCTs.^{17–32} There were no data from low-dose studies for six AEs. An additional search for literature on medium to high-dose therapy resulted in 14 articles reporting about occurrence of psychosis, osteonecrosis or myopathy.^{33–46}

For each AE the available data are summarised in table 1 (an extensive overview is shown in Online Appendix 2). This table also mentions the difficulties in interpreting the available data.

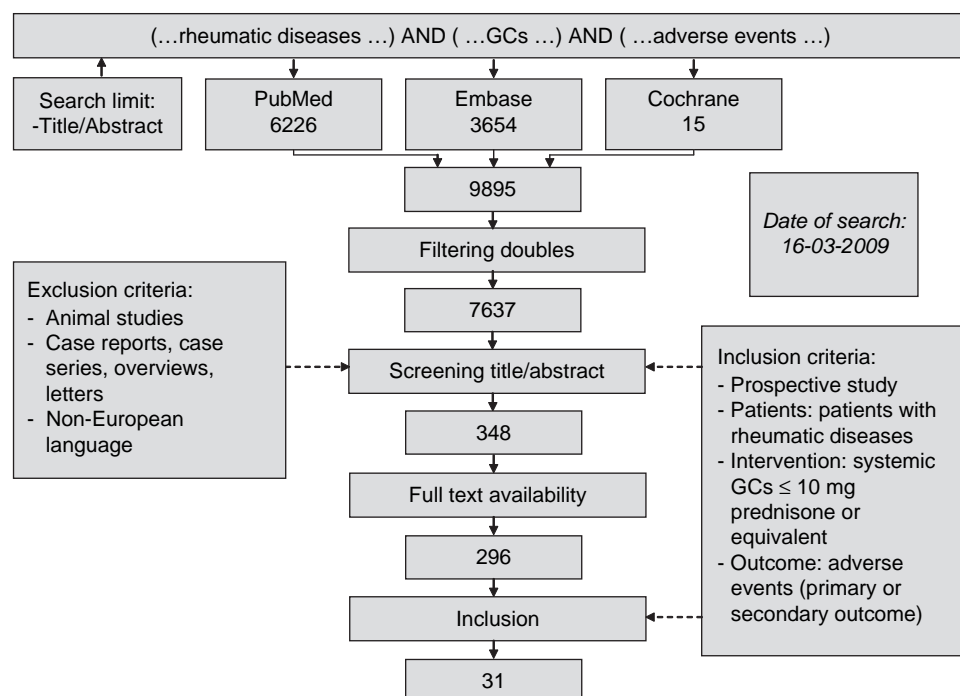


Figure 1 Flow chart of search strategy. The literature search was performed with the databases PubMed, EMBASE and Cochrane Library. After filtering doubles, screening all titles and abstracts with respect to selection criteria and reading the full text versions, 31 articles were included. Relevant data were recorded from these articles.

Table 1 Monitoring recommendations

Adverse event	Increased risk in RCTs	Difficulties in interpreting results from RCTs	Increased risk in prospective cohort studies	Status and relevance of AE	Feasible method for monitoring purpose available	Monitoring advised
	N/A, data not available	c, conflicting data; s, small numbers; e, endpoint inaccurately defined	N/A, data not available	c (LE), clinical endpoint (life expectancy); c (QoL), clinical endpoint (quality of life); s, surrogate endpoint; b, biomarker		–, not indicated; c, in clinical trials; d, in daily practice
Cardiovascular						
Dyslipidemia	No	e	–	s	Yes	c
Electrolyte disturbances	N/A	–	No	b	Yes	c
Edema	No	s e	–	c (QoL)	Yes	c d
Renal dysfunction (creatinine clearance)	N/A	–	N/A	b	Yes	–
Heart failure	No	s e	–	c (LE, QoL)	No	–
Hypertension	No	e	–	s	Yes	c d (standard care)
Ischemic CVD / atherosclerosis	No	s	–	c (LE, QoL)	No	c d (standard care)
Infectious						
Infections	Possibly	c e	–	c (LE, QoL)	No	c
Gastro-intestinal						
Peptic ulcer disease	Possibly	c s	–	c (LE, QoL)	Yes	c d (standard care)
Pancreatitis	N/A	–	N/A	c (LE)	Yes	–
Psychological						
Mood disturbances	Possibly	c s e	–	c (QoL)	No	c
Psychosis	N/A	–	Yes*	c (QoL)	No	c
Endocrine & metabolic						
Diabetes / glucose intolerance	Possibly	c e	–	s	Yes	c d
Body weight and fat redistribution	Possibly	c	–	c (QoL)	Yes	c d (standard care)
Interference with hormone secretion	Yes	s e	–	b	No	c
Dermatological						
Skin atrophy	N/A	–	N/A	c (QoL)	No	c
Acne, hirsutism, alopecia, bruising	No	s e	–	c (QoL)	Yes	c
Musculo skeletal						
Osteoporosis (BMD)	Possibly	c e	–	s	Yes	c d
Osteonecrosis	N/A	–	Yes*	c (QoL)	No	c
Myopathy	N/A	–	Yes*	c (QoL)	No	c
Ophthalmological						
Cataract	No	s e	–	c (QoL)	Yes	c
Glaucoma (intra-ocular pressure)	Yes	s e	–	s	Yes	c d

*Data indicating that risk may be increased with high-dose glucocorticoid therapy.

The 'increased risk' columns describe the risk of occurrence for all adverse events (AEs). Preferably, data from randomised controlled trials (RCTs) were used. If lacking, data from prospective cohort studies were included. Difficulties in interpreting results from RCTs are mentioned. 'Endpoint inaccurately defined' means there are problems with the definition of an AE (eg, What is 'diabetes'? Cut off values?). In case of 'small numbers' only a few studies (or: limited number of patients included) report an AE and therefore drawing firm conclusions is impossible. 'Conflicting data' mean that different studies show opposite outcomes on occurrence of an AE. The relevance of AEs is split in three different levels. A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention. A surrogate endpoint is a biomarker intended to substitute for a clinical endpoint, that is, a biomarker that is expected to predict presence or lack of clinical benefit or harm. A clinical endpoint is a characteristic or variable that reflects how a patient feels or functions (QoL, quality of life), or how long a patient survives (LE, life expectancy).

AE, adverse event; BMD, bone mineral density; CVD, cardiovascular disease; RCT, randomised clinical trial.

In general, no definite conclusions can be drawn on the occurrence of most AEs, because there often is a lack of good quality evidence. Most studies had been designed to assess treatment effects, not to assess AEs. Specific problems in interpreting data were addressed. Inadequately defined AEs (eg, what values or parameters for diagnosing diabetes were used?) made it difficult to compare results. In case of small numbers (only a few studies, or limited number of patients included) drawing firm conclusions was impossible. Moreover, often conflicting data were present, meaning that different studies showed opposite outcomes on occurrence of an AE.

Decisions on monitoring

The available evidence was discussed within the Task Force and appropriate monitoring methods were considered. It was decided to develop separate sets of recommendations for clinical trials and daily practice, because of different aims of monitoring in these two situations. For daily practice, monitoring is meant to protect patients from real dangers, which can be prevented or treated. The burden of monitoring should be low and reliable interpretation of the monitoring test needs to be possible. Therefore monitoring was advised for clinically important and not very rare AEs. Monitoring in clinical trials also serves the purpose of gaining

scientific insight into incidence, prevalence and clinical relevance of AEs to create a true AE-profile of GC therapy. Therefore the set of AEs to monitor in clinical trials is more comprehensive.

For some AEs, circadian rhythms play an important role. Monitoring of parameters, such as blood pressure and blood glucose, should preferably be performed at the same time of day (eg, in the morning in fasting state) to optimise the value of the measurements and to allow good comparisons between different assessments and patients.

The decision-making on monitoring is described for a couple of AEs in more detail below. The final recommendations for monitoring are summarised in table 2. Comprehensive data are enclosed in Online Appendix 2.

Monitoring in daily practice and clinical trials: diabetes as an example

Outcomes of RCTs reporting on the development of diabetes and the increase of blood glucose levels during GC therapy are conflicting. Developing diabetes after starting low-dose GC treatment seems rare. Progression of already impaired glucose tolerance to overt diabetes is possible. In *daily practice*, there should be awareness for these possible problems and monitoring should be performed at start of therapy and during follow-up according to standard patient care.

The WHO guidelines state that diabetes can be diagnosed with fasting blood glucose values or oral glucose tolerance tests.⁴⁷ Screening with urinary glucose values is not sensitive and thus not recommended. Therefore we recommend obtaining fasting blood glucose and insulin levels at least at start and end of *clinical trials*. With these parameters and the Homeostasis Model Assessment (HOMA) the steady state β -cell function and insulin sensitivity can be estimated.⁴⁸ In case of overt diabetes before treatment, patients should be instructed to carefully monitor their blood glucose level after starting GC therapy.

Monitoring in clinical trials only: hypertension and skin atrophy as an example

Hypertension: Literature did not show an increased risk for hypertension in patients on low-dose GC treatment. Screening for hypertension is part of standard patient care in daily practice. There is no indication for extra blood pressure monitoring because of GC treatment. In clinical trials, measuring blood pressure is part of good clinical practice. We recommend to measure blood pressure at least at start and end of trials and to report the outcomes in future articles. Reporting should not only be on group level (mean values for treatment groups), but also on patients' level (number of patients with hypertension according to an internationally accepted definition^{49 50}). This will give insight into the clinical relevance of a possible blood pressure increase and will indicate if an increase of the mean group value is based on many small blood pressure increases, or on some severe cases of hypertension.

Skin atrophy: Literature did not report on the occurrence of skin atrophy during oral low-dose GC therapy. Despite the absence of literature data, skin atrophy is thought to be a relatively frequently occurring AE, but not easy to record. Since skin atrophy is not preventable or treatable, monitoring in daily practice is not recommended.

However, it would be valuable to create information about the occurrence of this AE. Patients can be asked for the presence of skin atrophy at start and end of trials. This will give subjective results. In studies with topical GCs, sonography has been used to study (epi)dermal thickness and total skin thickness

objectively, for example at the volar aspect of the arm.^{51 52} We strongly support the idea of measuring the skin thickness in at least one trial (with a study duration of at least 1 year) to get good insight into the occurrence of skin atrophy with low-dose oral GC therapy.

DISCUSSION

It is remarkable that after 60 years of GC use in clinical practice, there is no certainty about the actual incidence of AEs. Therefore, the EULAR Task Force on GCs set out to formulate recommendations for the monitoring of GC-related AEs, based on reports of GC-related AEs in literature.

From studying literature on GC-related AEs to three general recommendations

All GC literature has possible problems with confounding. First, confounding by indication can be assumed present in all observational literature on GCs, including cohort studies. Only the process of randomization prevents this problem and therefore data from randomised studies were preferred data from over non-randomised studies in this project. The underlying disease can also influence the reporting of AEs. For example, psychological symptoms are linked to GC therapy, but also to disease such as systemic lupus erythematosus (SLE).^{53 54} Likewise osteoporosis is linked to GCs, but also to active disease in RA and SLE. Third, comorbidity can be an important factor. Longer RA duration is accompanied by more comorbidity, and more comorbidity could lead to polypharmacy.⁵⁵ Toxicity of other medication could be attributed to GCs. Interactions between medication can increase the occurrence of AEs, such as the combination of GCs and NSAIDs, which may lead to gastric ulcers.

The extensive literature search revealed dose-dependent relations between GC use and occurrence of certain AEs and showed at the same time that for many AEs good quality evidence on occurrence during low-dose therapy is lacking.^{7 9} To enlarge the available dataset, although the project was focused on monitoring of low-dose GC therapy, studies with GCs up to 10 mg prednisone or equivalent were included. However, the studies included were mostly not designed and powered to assess AEs but were primarily focused on treatment effects after 1 or 2 years of treatment, so the reporting on the occurrence of AEs was often limited. Nevertheless, assuming most of the published clinical trials have been performed according to good clinical practice dictating broad safety measures, probably more safety checks have been performed than those reported in the publications. Therefore, our first general recommendation is to report all monitoring results of trials (see box 1).

Furthermore, often reporting turned out to be on the mean group level (glucose levels, weight, blood pressure), which gives no insight into the prevalence of the AEs and only limited insight into clinical relevance, because the actual number of patients with an AE is not known. So our second general recommendation is to report AEs also on the number of patients level (see box 1).

Finally, some AEs are difficult to assess. Regarding psychological and behavioural AEs and appearance or signs of Cushing's syndrome, new tools should be developed to assess them (third general recommendation) (see box 1).

RECOMMENDATIONS ON MONITORING

Separate recommendations were formulated for daily practice and clinical trials. Although the occurrence of AEs is dependent

Table 2 Recommendations on monitoring including method and interval

Adverse event	Assessments and feasible methods of monitoring		Minimal monitoring frequency	
	Clinical trials	Daily practice (if different from clinical trials)	Clinical trials	Daily practice
Cardiovascular				
Dyslipidemia	Blood: fasting lipids	–	Start, end	–
Electrolyte disturbances	Blood: sodium and potassium	–	Start, end	–
Edema	Physical examination: ankle edema	–	Start, end	Start
Hypertension	Blood pressure measurement	–	Start, end	Standard care
Ischemic CVD	1. Questioning 2. Carotid intima-media thickness*	Questioning	1. Start, end 2. Start, end**	Standard care
Infectious				
Infections	Questioning: occurrence, treatment with antibiotics	–	Start, during follow-up	–
Gastro-intestinal				
Peptic ulcer disease	1. Questioning: complaints 2. Blood: haemoglobin	–	1. Start, end 2. Start, end	Standard care
Psychological				
Mood disturbances	Questioning	–	Start, end	–
Psychosis	Active monitoring not indicated; report of occurrence	–	–	–
Endocrine and metabolic				
Diabetes/glucose intolerance	Blood: fasting glucose and insulin (HOMA)	Blood: fasting glucose	Start, end	Start, standard care
Body weight and fat redistribution	1. Height 2. Weight 3. Abdominal circumference	1. Height 2. Weight	1. Start, end 2. Start, during follow-up 3. Start, end	Standard care
Interference with hormone secretion	1. Questioning: menstrual disturbances/loss of libido 2. Blood: ACTH stimulation test*	–	1. Start, end 2. Start, within 48 h after stopping	–
Dermatological				
Skin atrophy	1. Questioning 2. Sonography for skin thickness (volar part of arm)*	–	1. Start, end 2. Start, end**	–
Acne, hirsutism, alopecia, bruisability	Questioning	–	Start, end	–
Hirsutism	Questioning	–	Start, end	–
Musculo skeletal				
Osteoporosis (BMD)	1. DEXA 2. X-rays dorsal spine (if possible) 3. Questioning for fractures	–	1. Start, end** (for newly started GCs: also at six months) 2. Start, end 3. Start, end	Standard care according to local guidelines
Osteonecrosis	Active monitoring not indicated; imaging only in case of complaints	–	–	–
Myopathy	Questioning	–	Start, end	–
Ophthalmological				
Cataract	Ophthalmologic evaluation	–	Start, end**	–
Glaucoma (intra-ocular pressure)	Ophthalmologic evaluation with tonometry	Questioning for risk factors: family history, high myopia, diabetes	Start, end**	Start (ophthalmologic evaluation in case of risk factors)

*This is the preferable monitoring method, but probably less feasible. We ask to incorporate at least one of these items in future trials.

**Monitoring is only indicated for studies with a duration of at least 1 year.

For all adverse events (AEs) feasible monitoring methods are described and preferable monitoring intervals are given. These are minimum recommendations, indicating that they can be intensified for patients with additional risk factors for a certain AE. In most cases monitoring is recommended at start and at the end of trials. In case of drop-out, the 'end'-monitoring should be performed at time of drop-out. Broad explanation about these recommendations is enclosed in Online Appendix 2. In Online Appendix 3 suggestions for questioning are given. ACTH, adrenocorticotrophic hormone; BMD, bone mineral density; CVD, cardiovascular disease; GCs, glucocorticoids; HOMA, homeostasis model assessment.

on the dose and duration of GC therapy and the underlying disease, phase of treatment and co-morbidity also play a role. So the recommendations for daily practice do not replace the 'normal' screening on the presence of frequently occurring disorders in an older-growing population (such as diabetes and hypercholesterolemia), usually performed by the general practitioner. Measurements which should already be part of good clinical care in all rheumatic patients were tagged as 'standard care' in table 2.

Apart from safety, monitoring in clinical trials also serves the purpose of gaining scientific insight into the incidence, prevalence and clinical relevance of AEs to create a true AE-profile of GC therapy. In future clinical trials with GCs there should be extra interest and awareness in not only performing this

monitoring, but also in reporting the results. The results should be reported in a standardised way, even if no problem or increased occurrence of an AE has been found. This would enable future meta-analyses on GC-related AEs. In clinical trials, for most AEs monitoring is recommended at least at baseline and end, for maximal feasibility and because data on the time to develop an AE are lacking. These are meant as 'minimum recommendations': specific aspects of individual patients may warrant a higher frequency of monitoring and/or a more comprehensive set of items to monitor. With relatively few efforts, a large body of data on occurrence of GC-related AEs can be created. In case of drop-out, we would advise to perform the 'end-measurements' immediately.

This exercise has shown that evidence on occurrence is scarce for several AEs, such as ischemic cardiovascular disease, adrenal insufficiency and skin atrophy. We want to emphasise the need for more evidence on these three AEs in particular and want to stimulate identifying at least one of these three items in future clinical trials on GCs with a duration of at least 1 year. Measuring intima-media thickness for the development of atherosclerosis, performing ACTH stimulation tests after stopping GC therapy for the occurrence of adrenal failure and applying sonography for the development of skin atrophy will help to reveal the occurrence and severity of these AEs.

CONCLUSION

Given the incompleteness of literature data, consensus-based recommendations on monitoring of GC-related AEs were created, separately for daily practice and clinical trials. For daily practice, the Task Force recommends that standard care monitoring need NOT be expanded for patients on low-dose GC therapy, with a few exceptions. For clinical trials, the recommendations are more extensive in order to create a comprehensive and valid AE-profile of GC therapy.

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