EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases

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ABSTRACT
To develop recommendations for the management of medium to high-dose (ie, >7.5 mg but ≤100 mg prednisone equivalent daily) systemic glucocorticoid (GC) therapy in rheumatic diseases.

A multidisciplinary EULAR task force was formed, including rheumatic patients. After discussing the results of a general initial search on risks of GC therapy, each participant contributed 10 propositions on key clinical topics concerning the safe use of medium to high-dose GCs. The final recommendations were selected via a Delphi consensus approach. A systematic literature search of PubMed, EMBASE and Cochrane Library was used to identify evidence concerning each of the propositions. The strength of recommendation was given according to research evidence, clinical expertise and patient preference.

The 10 propositions regarded patient education and informing general practitioners, preventive measures for osteoporosis, optimal GC starting dosages, risk-benefit ratio of GC treatment, GC sparing therapy, screening for comorbidity, and monitoring for adverse effects. In general, evidence supporting the recommendations proved to be surprisingly weak. One of the recommendations was rejected, because of conflicting literature data.

Nine final recommendations for the management of medium to high-dose systemic GC therapy in rheumatic diseases were selected and evaluated with their strengths of recommendations. Robust evidence was often lacking; a research agenda was created.

INTRODUCTION
Glucocorticoids (GCs) are a cornerstone in the treatment of rheumatic diseases for many decades. Detailed information on the capacity of GCs to retard the progression of joint damage in rheumatoid arthritis (RA) has been published.[1–7] GCs are also used, often in higher dosages, for many other rheumatic diseases such as polymyalgia, lupus and vasculitis. Medium/high-dose GC therapy (ie, >7.5 mg but ≤100 mg prednisone equivalent daily) generates non-genomic effects next to genomic effects, which occur already at lower dosages, indicating that the risk-benefit profile for these higher dosages might be different from that for low dosages.[8] General recommendations on the management of GC therapy have been developed by

the EULAR task force on GC therapy,[9] but these were mainly based on evidence and experience with low-dose GC therapy (ie, ≤7.5 mg prednisone equivalent daily). Proper advice on balancing advantages and disadvantages of medium/high-dose GC therapy is lacking. Therefore, this task force set out to develop recommendations for the use and management of systemic medium/high-dose GC therapy in rheumatic diseases.

METHODS
Participants
The EULAR task force on GC therapy is a multidisciplinary committee consisting of 16 experts from 7 European countries (8 rheumatologists, 1 endocrinologist, 1 rheumatologist/epidemiologist, 4 rheumatic patients as patients' representatives and 2 research fellows). The objective was to formulate 10 recommendations on the management of medium/high-dose systemic GC therapy in rheumatic diseases by identifying and critically appraising evidence in the literature. The strength of each recommendation was evaluated.

Experts' consensus and Delphi rounds
As a first step, a general systematic literature search was performed aiming at identifying prospective follow-up studies in which medium/high-dose GC therapy was administered systemically. This search was not limited to rheumatic diseases (see online supplementary appendix 1 for details on this search). We used the databases PubMed, EMBASE and Cochrane Library; search results on adverse events (AEs) were expressed in events per patient year and odds ratios (ORs) (not corrected for disease activity or comorbidity) and summarised in tables (see online supplementary appendix 2), using the software Comprehensive Meta Analysis V2. The results were presented at the first group meeting to initiate group discussions identifying important topics. After the first meeting, each task force member independently formulated 10 propositions related to management of medium/high-dose GC use in rheumatic diseases. The Delphi technique was used to reach consensus on the propositions as follows. The initial propositions were listed and overlapping propositions were amalgamated. The list was returned to the members with the request to select the 10 most important

propositions in this first round. A proposition was accepted if over three-quarters of the members selected it in the first round, two-thirds in the second round, and half in the third and fourth rounds. A proposition was removed if it was selected by one-quarter of the participants or less in the first round, one-third or less in the second round, and half or less in the third and fourth rounds. After 4 rounds, 10 propositions of which the text had been optimised by an English native speaker remained and were agreed upon by all participants.

Systematic literature search of the 10 propositions

After agreement on 10 propositions, additional proposition-specific searches were performed using PubMed, EMBASE and Cochrane Library by two research fellows (see online supplementary appendix 3 for details on inclusion and exclusion per search). Results of the different databases were combined and duplicates were excluded; issues regarding inclusion or exclusion of articles were resolved by discussion and consensus. Articles evaluating the value of a recommendation were selected and in case of lack of evidence, circumstantial evidence was looked for. References of articles found were screened for additional evidence.

Categorising evidence and strength of recommendations

The quality of evidence based on study design was categorised according to the EULAR hierarchy (table 1). [10]

After the proposition-specific literature searches, evidence regarding each of the recommendations was subjected to group discussion; the final recommendations were approved by all members. For each proposition, the strength of recommendation (SOR) was graded using an A–E ordinal scale (A=fully recommended, B=strongly recommended, C=moderately recommended, D=weakly recommended and E=not recommended) and a visual analogue scale (VAS, 0–100 mm, 0=no agreement and 100=maximal agreement). The members were asked to consider both the quality of evidence presented and their own clinical experience while grading. For each proposition, the mean VAS and 95% CI, and the percentage of strongly to fully recommended (A–B) propositions were calculated. This grading method has not been fully evaluated, but is, in our view, valuable to give SOR for recommendations which cannot be or have not been assessed in randomised controlled trials (RCT); SOR has been used for other EULAR recommendations too. [9 11]

During the meetings, members were asked to discuss items which should be the focus of future research. These items were combined into a research agenda.

RESULTS
General literature search

The general search on AEs of medium/high-dose GCs (see online supplementary appendix 1) yielded a total of 1104 hits (461 in PubMed, 427 in EMBASE and 216 in Cochrane database), reduced to 916 hits excluding duplicates. Of these studies, only 53 met the inclusion criteria. [2 3 7 12–61] Online supplementary appendix 2 gives an overview of the estimated incidence of different AEs derived from the studies reporting on dichotomous AE outcomes, or mean values derived from the studies reporting mean outcomes. Major limitations of these search results are the lack of sufficient GC-naive control groups, the incompleteness of defining and reporting AEs, and the probability of selective reporting of some AEs.

Experts' opinion approach

After discussing the results of the general literature search, the Delphi exercise was initiated. At start, 126 (partly overlapping) propositions were produced, and after four anonymous Delphi rounds, 10 propositions were agreed upon, of which one was rejected after evaluating the available evidence (table 2).

RECOMMENDATIONS

The recommendations can be classified in the main issues of education and prevention, dosing and the risk-benefit ratio, and monitoring.

Explain to patients (and their family and/or carers, including healthcare professionals) the aim of medium/high-dose GC treatment and the potential risks associated with such therapy

The goals of this education are to correctly inform especially patients about GC therapy, reassuring them if there would be unfounded worries about the treatment, increasing vigilance for AEs and improving adherence to treatment. The search retrieved one cross-sectional and one retrospective study in rheumatic diseases evaluating the need for informing patients on the benefits and risks of GC treatment. [62 63] The first study showed that worries about potential AEs–often caused by ineffective communication–may lead to termination of DMARD therapy (among which GC therapy). [62] A study on patients' views on GC therapy indicated that information should be given in a structured manner in small steps over time. [63]

Circumstantial evidence: RCTs in asthma and chronic obstructive pulmonary disease often showed better adherence to (inhaled) GC treatment after patient education, [64–71] and fewer exacerbations and reduced hospitalisation in some but not all studies. [72–74] An RCT focused on GC-induced osteoporosis education in patients with different diseases showed improved calcium intake after verbal and written information given by pharmacists. [75] This is in line with other studies showing that patients' knowledge about GCs is best served by written information combined with verbal instructions. [75–78] In educating, items such as communicative skills (eg, the use of non-technical language, adapted to the patient's education level) and cultural aspects are important. [62 79–82]

To guide education on AEs of GCs, those that concern patients and rheumatologists most are shown in table 3. [63]

Discuss measures to mitigate such risks, including diet, regular exercise and appropriate wound care

The risks of some AEs have been proven to be mitigated or counterbalanced by lifestyle interventions. A prospective cohort study in RA with 72% of patients on GC therapy showed that moderate physical activity reduced the risk of osteopenia. [83] Moreover, a cross-sectional study in RA with most patients on GCs showed a positive association between quadriceps muscle strength and femoral neck bone mineral density (BMD). [84]

Table 1	The level of evidence based on study design[10]
Level of evidence	
I-A	Meta-analysis of randomised controlled trials
I-B	Randomised controlled trial
II-A	Controlled study without randomisation
II-B	Quasiexperimental study
III	Descriptive study (comparative, correlation, case-control)
IV	Expert committee report/opinion and/or clinical opinion of respected authority

Table 2 The recommendations with strength of recommendation and level of evidence

Proposition		SOR VAS; mean (95% CI)	A+B %	LoE
Education and prevention				
1	Explain to patients (and their family and/or carers, including healthcare professionals) the aim of medium/high-dose GC treatment, and the potential risks associated with such therapy	91 (81 to 101)	100	III
2	Discuss measures to mitigate such risks, including diet, regular exercise and appropriate wound care	75 (57 to 93)	75	III/IV
3	Patients with, or at risk of, GC-induced osteoporosis should receive appropriate preventive/therapeutic interventions	91 (84 to 99)	100	I-A
4	Patients and the patients' treatment teams should receive appropriate, practical advice on how to manage with GC-induced hypothalamic-pituitary-adrenal axis suppression	84 (67 to 101)	92	IV
5	Provide an accessible resource to promote best practice in the management of patients using medium/high-dose GCs to general practitioners	80 (69 to 91)	75	IV
Dosing/risk-benefit				
6	Before starting medium/high-dose GC treatment consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis. Patients with these comorbidities require tight control to manage the risk/benefit ratio	85 (76 to 94)	83	IV
7	Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment	85 (76 to 95)	92	I-A/IV
8	Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment and development of AEs	82 (72 to 94)	92	IV
9	If long-term medium/high-dose GC therapy is anticipated to be necessary, actively consider GC-sparing therapy	REJECTED		
Monitoring				
10	All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological AEs	85 (79 to 92)	75	IV

A+B %, percentage of the task force members that strongly to fully recommended this proposition based on an A—E ordinal scale (A, fully recommended, B, strongly recommended); AEs, adverse effects; CI, confidence interval; GC, glucocorticoid; LoE, level of evidence (table 1); SOR, strength of recommendation; VAS, visual analogue scale (0–100 mm 0= not recommended at all, 100, fully recommended).

Circumstantial evidence: Physical exercise is in general effective to prevent osteoporosis,[85–87] and is recommended in recent guidelines on prevention of GC-induced osteoporosis.[88] Benefits of exercise training regarding the risk of GC-induced osteoporosis have also been found in organ transplants and pulmonary disease patients.[89–93] Other lifestyle advices for the prevention of osteoporosis include stopping of smoking,[94] limiting alcohol intake,[94] maintaining an adequate dietary calcium intake,[95 96] training muscles for strength,[97] and performing weight-bearing exercises on a daily basis.[88]

Although recommendations on diet and physical activity are broadly endorsed for the general population to prevent cardiovascular disease[85 86] which occurs in a higher frequency in patients with inflammatory rheumatic diseases compared with the general population,[98 99] no supportive information on diet and physical activity mitigating the GC-induced risk of cardiovascular disease, increased appetite, and weight gain was found. Evidence on increasing awareness of wounds or applying appropriate wound care in the context of GC therapy for prevention of wound complications was lacking. Nevertheless, GC-induced skin atrophy and increased risk of infection provide a rationale to discuss prevention and good wound care.[100 101]

Patients with, or at risk of, GC-induced osteoporosis should receive appropriate preventive/therapeutic interventions

Generally, all patients starting medium/high-dose GC therapy are at risk of developing osteoporosis. Several meta-analyses showed efficacy of calcium, (active) vitamin D and bisphosphonates in preventing and treating GC-induced osteoporosis.[96 102–105] Preventive therapy with calcium and vitamin D should be started, because GCs via inhibition of intestinal calcium absorption and renal tubular calcium reabsorption impair bone metabolism.

Additionally, in general, bisphosphonates are indicated. Guidelines on indications and choices for specific drugs differ somewhat between countries.

Oral GC treatment with >5 mg prednisone daily can lead to a reduction in BMD and a rapid dose-dependent increase in the risk of fracture.[106 107] However, in many studies on GC-induced osteoporosis, it is ignored that GCs are usually prescribed for inflammatory diseases which themselves have a negative impact on BMD. For instance, in RA, it has been shown that BMD loss may develop in absence of GC therapy, especially in the first months of disease.[108 109] Correlations of loss of BMD with parameters of inflammation have also been found in other studies.[110–113] Therefore, the independent contribution of GCs to this problem may be lower than estimated. Several algorithms have been developed to refine the estimate of the risk of fractures for individual patients, such as the FIGS (fracture risk in GC-induced osteoporosis score) which includes the GC dosage taken, and FRAX (Fracture Risk Assessment),[88 114 115] for which also adjustments have been suggested for GC dosages >7.5 mg prednisone equivalent daily.[116 117]

Patients and the patients' treatment teams should receive appropriate, practical advice on how to manage with GC-induced hypothalamic-pituitary-adrenal axis suppression

Risk of adrenal insufficiency is considered to be present if GC therapy is stopped suddenly in chronic users, and in acute situations such as acute illnesses and surgical interventions. We found two systematic reviews on the value of additional GC supplementation in the perioperative setting.[118 119] One review, mainly on patients with organ transplants, concluded that patients on GCs do not require perioperative stress doses if they

Recommendation

Table 3 Risks of GC-related AEs based on placebo-controlled studies and studies without control group*

Placebo-controlled studies

AE	Dose range and application	Events/100 patient-years for GC users	Events/100 patient-years for GC-naive patients
Osteoporosis	chronic medium dose	16	3
	intramuscular	2	0
Cardiovascular disease (ie, myocardial infarction)	chronic medium dose	0–1	0–1
	step-down	1	0
	intramuscular	0–1	0–1
Diabetes	chronic medium dose	0–3	0–1
	intramuscular	1	0
Weight gain	intramuscular	0	1
Renal dysfunction	chronic medium dose	1–6	0
	step-down	0–17	0–1
Peptic ulcer disease	chronic medium dose	1–4	0–2
Hypertension	chronic medium dose	3–28	0–19
	step-down	0	0
	intramuscular	4	1

Studies without control group

AE	Dose range and application	Events/100 patient-years for GC users
Osteoporosis	chronic medium dose	1–3
	chronic high	2
	step-down	0–23
Cardiovascular disease (ie, myocardial infarction)	chronic medium dose	0–1
	chronic high	0
Diabetes	chronic medium dose	0–13
	chronic high	1
	step-down	0–18
Weight gain	chronic medium dose	0–63
	step-down	3–21
Renal dysfunction	chronic medium dose	9–13
	step-down	5–40
Peptic ulcer disease	chronic medium dose	0–1
	step-down	0
Hypertension	chronic medium dose	0–63
	chronic high	2
	step-down	0–38

*AEs that concern patients and rheumatologists most.[63] These AEs should be discussed with patients when GC therapy is initiated.
Events per 100 patient years, based on information gained with the general literature search on medium/high-dose GC treatment, are given in this table (detailed information on all AEs reported is given in the tables of online supplementary appendix 2).
AE, adverse event; GC, glucocorticoid.

continue their daily dose between 5 and 16 mg prednisone[118]; the other concluded that data was too limited to support or refute perioperative stress doses.[119]

Circumstantial evidence: Although hypothalamic–pituitary–adrenal axis suppression may vary greatly from person to person, it should be anticipated in any patient receiving more than 7.5 mg of prednisolone equivalent daily for more than 3 weeks.[120] The risk cannot be excluded by alternate day GC therapy, and remains difficult to predict.[121] [122] On the basis of these data, to be cautious, adequate GC replacement is recommended by the task force in acute situations for patients on chronic medium/high-dose GC treatment; GC therapy should not be stopped without tapering. Evidence supporting superiority of a specific replacement or stress scheme is not available. Pragmatically, one could choose to increase the dosage for 3 days, or, depending on the clinical situation, switch to intravenous hydrocortisone (eg, starting two times 25 mg daily for patients on 10 mg prednisone daily, or three times 50 mg daily for patients on high-dose GC therapy). The need for stress schemes with higher dosages has not been proven, although in some situations they might be considered. Patients and their treatment teams, including the general practitioner, should be informed on the risk of adrenal insufficiency, and should know how to prevent it.

Provide an accessible resource to promote best practice in the management of patients using medium/high-dose GCs to general practitioners

General practitioners frequently prescribe GC therapy, for example, to treat polymyalgia,[123] and are likely to be consulted for problems with GCs. A cross-sectional study among general practitioners showed insufficient guidance on GC use for patients with exacerbations of chronic obstructive pulmonary disease, and insufficient knowledge on how to take comorbidity into account.[124] Thus, although our search yielded no data on an accessible resource to inform general practitioners on the management of medium/high-dose GC therapy, such a source makes sense. This could be a website on the benefits and risks of GC treatment, advising how to manage intercurrent illnesses and acute situations. Ultimately these recommendations could be included in general practitioner guidelines. We do not suggest that general practitioners should manage all patients on medium/high-dose GC

treatment, but they should be able to adequately respond when consulted with questions regarding this therapy.

Before starting medium/high-dose GC treatment, consider comorbidities predisposing to AEs. These include diabetes, glucose intolerance, cardiovascular disease, peptic ulcer disease, recurrent infections, immunosuppression, (risk factors of) glaucoma and osteoporosis. Patients with these comorbidities require tight control to manage the risk/benefit ratio

All patients with inflammatory rheumatic diseases require monitoring of comorbidities as part of good clinical practice. There are no studies evaluating the benefits of screening for comorbidities especially before starting GC therapy. However, as several individual comorbidities are also known as (risk factors for) AEs of GC therapy, identification and (preventive) treatment can be expected to diminish the frequency and severity of AEs. The reporting of GC-related AEs in the literature has been studied,[9] [125] but these reviews mostly excluded long-term high-dose treatment. Some studies showed that the frequency of occurrence of specific AEs increased with higher doses of GC therapy.[100] [126] [127] These are arguments to pay specific attention to comorbidities predisposing to AEs before starting medium/high-dose GC treatment. In case comorbidities are present, tight control (ie, more intensive monitoring and adjusting medication, if needed) is recommended.

Diabetes and glucose intolerance: In RA, impaired insulin sensitivity has been reported and associated with increased disease activity.[128] [129] A recent study showed that a 1-week exposure to high-dose GCs did not deteriorate the metabolic state in active RA.[130] Chronic treatment with 10 mg prednisone daily did not lead to higher glucose levels or increased incidence of diabetes.[7] However, worsening of pre-existent diabetes has been described in RA,[131] and an incidence of 12.6% of GC-induced diabetes has been found among lupus patients after a mean of 34 days after starting high-dose GC therapy.[132] So, although GC therapy could be a safe treatment option in this regard for most patients, especially for those with very active disease on low/medium dosages, glucose monitoring before start of therapy and during therapy is advised, due to individual differences in glucose tolerance and response to GCs.

Cardiovascular disease: Retrospective analyses, not corrected for disease severity, showed an increased occurrence of cardiovascular disease in rheumatoid factor-positive RA patients.[99] Cardiovascular parameters (eg, blood pressure, lipids) can be negatively influenced by inflammatory diseases, and intensive treatment with GCs might mitigate or even reverse this negative influence rather than worsen it.[61] [133–136] GC therapy has been related to decreases in total and high-density lipoprotein cholesterol, but net results on the atherogenic index are conflicting.[61] [133] [136] The effect on blood pressure is also uncertain.[134] [135] Therefore, assessment of cardiovascular risk factors is not only important for patients starting GCs, but for all patients with inflammatory diseases.[137] Pretreatment screening may reveal the need for preventive interventions, and will provide baseline values to which the follow-up measurements can be related.

Peptic ulcer disease: GC use is associated with an increased risk for peptic ulcer disease, especially when combined with non-steroidal anti-inflammatory drugs (NSAIDs).[126] [138] [139] However, GC use can lead to reduced NSAID use.[140] Patients should be informed and appropriate preventive measures (eg, prescriptions of proton pump inhibitors) should be taken if patients have risk factors for peptic ulcer disease, such as concomitant NSAID use, an inflammatory disease and high age.

Recurrent infections and immunosuppression: Although RCTs with GCs are often reporting no significant difference in occurrence of infections,[2] [3] [7] [28] [36] GC therapy was associated with increased infection risk in patients with RA in cohort and case-control studies.[101] [141–143] Moreover, other immunosuppressive treatments simultaneously given can further elevate the risk. These data suggest that awareness of the risk of infections before and during GC treatment is needed. One should realise that GC treatment may affect the performance of screening tests for infections, such as the QuantiFERON gold in-tube test and the tuberculin skin test,[144] and that recommendations for vaccination in patients with inflammatory rheumatic diseases have been developed.[145]

Glaucoma: GCs can increase intraocular pressure or worsen pre-existing glaucoma.[146] The risk of glaucoma is dose dependent.[147] Patients should be asked for high myopia, presence of diabetes, or a family history of glaucoma. In case any of these factors is present, screening should be performed by an ophthalmologist.[148]

Osteoporosis: see recommendation 2 and 3.

Select the appropriate starting dose to achieve therapeutic response, taking into account the risk of undertreatment

The search revealed one systematic review on the treatment of polymyalgia looking into starting dosages up to 100 mg prednisone equivalent daily, in which the scarcity of RCTs and the heterogeneity of studies were emphasised.[149] However, the conclusion was that remission can be achieved with a starting dose of 15 mg prednisone daily in most patients.

In giant cell arteritis (GCA), higher initial doses are often used (mostly 40–60 mg prednisone daily). Compared with these doses, the benefits of pulse treatment ($\geq$250 mg prednisone equivalent) were significant in one RCT,[59] but not in another RCT.[23] The different study designs applied, the limited number of patients included, the different patient selection criteria, the different doses and routes of GC administration used and the varying follow up measurements performed, preclude to recommend a specific GC regimen for GCA.[150]

For no other rheumatic diseases have specific starting dosages been tested in RCTs. In general, the appropriate starting dose will depend on (the severity of) the disease, the goals of treatment and characteristics of the individual patient, including age, comorbidities and body weight, all influencing pharmacokinetics, pharmacodynamics and sensitivity for GCs.[151]

Keep the requirement for continuing GC treatment under constant review, and titrate the dose against therapeutic response, risk of undertreatment and development of AEs

There is no literature on how to weigh doses, benefits and risks of GC therapy. This again will depend on the disease, indication and goals of treatment, initial response to treatment, development of AEs, and individual patient characteristics. It is not possible, with the evidence currently available, to provide clear guidance on this important and difficult task. Nevertheless, it has face validity to keep the dose as low as needed to achieve therapeutic effect in each individual patient. Specific treatment goals may require different GC regimes or different periods of treatment. For example, for achieving joint protective effects in early RA, evidence only exists for a GC treatment duration of at least 6 months,[6] and a maximum of 2 years.[1] [4–7] Rapid tapering of GC therapy has been associated with higher rates of relapse in polymyalgia and more frequent unsuccesfull cessation of therapy.[149] Regular checks of the requirement for GC therapy are needed for appropriate decisions on continuing, increasing or tapering dosages, because patient and disease conditions will change over time.

Rejected: If long-term medium/high-dose GC therapy is anticipated to be necessary, actively consider GC-sparing therapy

Other immunomodulatory drugs, including biologicals, are often added to GC therapy to improve efficacy; if these drugs enable decreasing the dose or duration of GC therapy, they can be seen as GC-sparing agents. Among all studies, 2 level 1A articles on 'GC-sparing properties of other medication', that is, use of other agents to decrease the cumulative GC dose, were retrieved by the literature search.[149 152] These papers were on GC-sparing effect solely in polymyalgia and GCA.

A systematic review on GC-sparing agents in polymyalgia[149] included five RCTs investigating the possibility of substituting partially or totally the GC by methotrexate,[22 43 153] azathioprine,[154] or infliximab.[49] Two RCTs of this review showed that GCs doses could be reduced,[22 153] two showed no sparing properties,[43 49] and one RCT showed GC dose reduction with azathioprine, but at the cost of high rates of withdrawal due to AEs.[154] A meta-analysis in GCA concluded that adjunctive treatment with methotrexate lowers the risk of relapse and reduces exposure to GCs,[152] while the results of the individual RCTs were conflicting.[29 45 60] Other RCTs with infliximab and cyclosporine in GCA did not show GC-sparing effects of these drugs,[155 156] while etanercept was effective as GC-sparing agent in a small group of patients.[157]

Because these results on GC-sparing effects in polymyalgia and GCA are conflicting, the task force decided to reject this recommendation.

All patients should have appropriate monitoring for clinically significant AEs. The treating physician should be aware of the possible occurrence of diabetes, hypertension, weight gain, infections, osteoporotic fractures, osteonecrosis, myopathy, eye problems, skin problems and neuropsychological AEs

Since we found no evidence showing the effectiveness of monitoring, this recommendation is based on expert opinion only. For several AEs it has been proven that the occurrence depends on dose and duration of GC treatment,[100 126 127] so these factors should dictate what to monitor and how often. Monitoring is useful for preventable and treatable AEs especially if the AE is common (ie, low number needed to screen), the AE is severe or has a significant impact on quality of life, the cost of monitoring is low, and monitoring is feasible in clinical practice.[148] Monitoring and prevention of (extra-articular) complications should—as part of good clinical practice—be performed in all patients with inflammatory diseases, whether using GCs or not.

DISCUSSION

These recommendations as guidance for daily practice are an attempt to promote safer use of medium/high-dose GCs in rheumatic diseases. The order of recommendations in this paper does not reflect importance or the level of evidence, but reflects the logical order in patient management.

Strengths of this paper are the broad participation of experts and patients, the use of research data however limited, and the use of an evidence-based format. Many text books and review articles provide recommendations on the use of GCs based on traditional practice and widely held beliefs that developed before adequate attention was paid to the quality of the evidence base. Here, as far as possible, we have avoided their automatic reiteration or the expression of our own beliefs, but have concentrated on what can be concluded from published studies.

Sound evidence is scarce. To some readers this will have produced less clear-cut and less comprehensive recommendations than they would have liked to get. This reflects changes in the approach to evidence-based medical practice. This paper also has limitations. First, the literature searches may have been too specific, thus missing relevant studies. Second, systematic reviews and RCTs are considered as highest quality evidence, but these studies are often focused on treatment efficacy.[158 159] They have not been powered or designed to assess toxicity or long-term efficacy, and therefore, uncertainty of the true incidence and relevance of several AEs remains. Had these studies been graded for study quality based on their analyses of AEs, study quality probably would have been graded much lower. In all observational (ie, not randomised) studies, the problem of channeling bias/confounding by indication severely impairs or precludes the possibility of drawing conclusions. In other words: in general, the more severe the inflammatory status of patients, the higher the chance of starting GCs; however, due to the design, no conclusion on causality between therapy and negative effects or events can be drawn. Third, rather heterogeneous studies (eg, different diseases, ages, GC schemes and cotreatment) have been pooled to get at least an overall impression of AE occurrence (see online supplementary appendix 2). In these studies, almost all patients with inflammatory rheumatic diseases (except those with polymyalgia or GCA) have been treated with multiple agents, which obviously impairs studying the risk-benefit ratio of GCs separately. Finally, these recommendations address issues on GC therapy from a general perspective, that is, not disease specific or patient specific. However, appropriate management varies considerably for different indications for such treatment, as discussed for starting doses with recommendation 7. Next, individual patient characteristics may warrant dose adaptations or more frequent monitoring for AEs.

Research agenda

The paucity of data we found illustrates that crucial knowledge on cellular mechanisms of GC and on wanted and unwanted clinical effects of medium/high-dose GCs is missing. A robust database on the AE profile of medium/high-dose GCs is urgently needed to inform patients and their doctors with precise definitions of AEs, and standardised reporting both on the group level (eg, in means) and on the patients' level (eg, percentages). All future studies evaluating medium/high-dose GC therapy should systematically check for and register all AEs in this way, indexed to the type of GC, its regimen, duration of treatment and cumulative dose. This would enable the investigation of the influence of patient-related factors, such as gender, age, weight, comorbidity and co-medication. Also, research on timing of GC administration and perceptions and misconceptions of patients and healthcare providers is needed. Alternative therapies to GCs and GC-sparing therapies, including biologicals, need to be evaluated in well-designed trials.

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