

# 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.<sup>1–7</sup> 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.<sup>8</sup> General recommendations on the management of GC therapy have been developed by

the EULAR task force on GC therapy,<sup>9</sup> 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

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## Recommendation

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).<sup>10</sup>

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.<sup>9 11</sup>

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.<sup>2 3 7 12–61</sup> 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-naïve 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.<sup>62 63</sup> 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).<sup>62</sup> A study on patients' views on GC therapy indicated that information should be given in a structured manner in small steps over time.<sup>63</sup>

Circumstantial evidence: RCTs in asthma and chronic obstructive pulmonary disease often showed better adherence to (inhaled) GC treatment after patient education,<sup>64–71</sup> and fewer exacerbations and reduced hospitalisation in some but not all studies.<sup>72–74</sup> 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.<sup>75</sup> This is in line with other studies showing that patients' knowledge about GCs is best served by written information combined with verbal instructions.<sup>75–78</sup> 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.<sup>62 79–82</sup>

To guide education on AEs of GCs, those that concern patients and rheumatologists most are shown in table 3.<sup>63</sup>

### 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.<sup>83</sup> 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).<sup>84</sup>

**Table 1** The level of evidence based on study design<sup>10</sup>

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
<b>Education and prevention</b>			
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
<b>Dosing/risk-benefit</b>			
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		
<b>Monitoring</b>			
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,<sup>85–87</sup> and is recommended in recent guidelines on prevention of GC-induced osteoporosis.<sup>88</sup> Benefits of exercise training regarding the risk of GC-induced osteoporosis have also been found in organ transplants and pulmonary disease patients.<sup>89–93</sup> Other lifestyle advices for the prevention of osteoporosis include stopping of smoking,<sup>94</sup> limiting alcohol intake,<sup>94</sup> maintaining an adequate dietary calcium intake,<sup>95</sup> training muscles for strength,<sup>97</sup> and performing weight-bearing exercises on a daily basis.<sup>88</sup>

Although recommendations on diet and physical activity are broadly endorsed for the general population to prevent cardiovascular disease<sup>85</sup> which occurs in a higher frequency in patients with inflammatory rheumatic diseases compared with the general population,<sup>98</sup> 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.<sup>100</sup>

**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.<sup>96</sup> 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.<sup>106</sup> 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.<sup>108</sup> Correlations of loss of BMD with parameters of inflammation have also been found in other studies.<sup>110–113</sup> 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),<sup>88</sup> for which also adjustments have been suggested for GC dosages >7.5 mg prednisone equivalent daily.<sup>116</sup>

**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.<sup>118</sup> One review, mainly on patients with organ transplants, concluded that patients on GCs do not require perioperative stress doses if they

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

<i>Placebo-controlled studies</i>			
<i>AE</i>	<i>Dose range and application</i>	<i>Events/100 patient-years for GC users</i>	<i>Events/100 patient-years for GC-naive patients</i>
Osteoporosis	chronic medium dose	16	3
	intramuscular	2	0
Cardiovascular disease (ie, myocardial infarction)	chronic medium dose	0–1	0–1
	step-down intramuscular	1 0–1	0 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 intramuscular	0 4	0 1
<i>Studies without control group</i>			
<i>AE</i>	<i>Dose range and application</i>	<i>Events/100 patient-years for GC users</i>	
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.<sup>63</sup> 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<sup>118</sup>; the other concluded that data was too limited to support or refute perioperative stress doses.<sup>119</sup>

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.<sup>120</sup> The risk cannot be excluded by alternate day GC therapy, and remains difficult to predict.<sup>121 122</sup> 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,<sup>123</sup> 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.<sup>124</sup> 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,<sup>9 125</sup> 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.<sup>100 126 127</sup> 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.<sup>128 129</sup> A recent study showed that a 1-week exposure to high-dose GCs did not deteriorate the metabolic state in active RA.<sup>130</sup> Chronic treatment with 10 mg prednisone daily did not lead to higher glucose levels or increased incidence of diabetes.<sup>7</sup> However, worsening of pre-existent diabetes has been described in RA,<sup>131</sup> 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.<sup>132</sup> 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.<sup>99</sup> 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.<sup>61 133–136</sup> GC therapy has been related to decreases in total and high-density lipoprotein cholesterol, but net results on the atherogenic index are conflicting.<sup>61 133 136</sup> The effect on blood pressure is also uncertain.<sup>134 135</sup> Therefore, assessment of cardiovascular risk factors is not only important for patients starting GCs, but for all patients with inflammatory diseases.<sup>137</sup> 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).<sup>126 138 139</sup> However, GC use can lead to reduced NSAID use.<sup>140</sup> 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,<sup>2 3 7 28 36</sup> GC therapy was associated with increased infection risk in patients with RA in cohort and case-control studies.<sup>101 141–143</sup> 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,<sup>144</sup> and that recommendations for vaccination in patients with inflammatory rheumatic diseases have been developed.<sup>145</sup>

**Glaucoma:** GCs can increase intraocular pressure or worsen pre-existing glaucoma.<sup>146</sup> The risk of glaucoma is dose dependent.<sup>147</sup> 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.<sup>148</sup>

**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.<sup>149</sup> 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,<sup>59</sup> but not in another RCT.<sup>23</sup> 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.<sup>150</sup>

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.<sup>151</sup>

**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,<sup>6</sup> and a maximum of 2 years.<sup>1 4–7</sup> Rapid tapering of GC therapy has been associated with higher rates of relapse in polymyalgia and more frequent unsuccessful cessation of therapy.<sup>149</sup> 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.<sup>149 152</sup> These papers were on GC-sparing effect solely in polymyalgia and GCA.

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

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,<sup>100 126 127</sup> 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.<sup>148</sup> 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.<sup>158 159</sup> 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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## APPENDIX 1

### General systematic literature search to create an overview for the task force

Database:	Search string:	Number of studies:
Pubmed	<p>((("asthma"(MeSH Major Topic) NOT ("asthma, aspirin-induced"(MeSH Terms) OR aspirin induced asthma(Title/Abstract) OR NSAID-induced asthma(Title/Abstract) OR aspirin-induced asthma syndrome(Title/Abstract))) OR "rheumatic diseases"(MeSH Major Topic) OR "rheumatic disease"(Title/Abstract) OR "rheumatic diseases"(Title/Abstract) OR "rheumatoid arthritis"(Title/Abstract) OR "arthritis, rheumatoid"(MeSH Major Topic) OR "polymyalgia rheumatica"(MeSH Terms) OR "lupus erythematosus, systemic"(MeSH Terms) OR "polymyositis"(MeSH Terms) OR "dermatomyositis"(MeSH Terms) OR "giant cell arteritis"(MeSH Terms) OR "takayasu arteritis"(MeSH Terms) OR "polyarteritis nodosa"(MeSH Terms) OR "wegener granulomatosis"(MeSH Terms) OR "microscopic polyangiitis"(MeSH Terms) OR "churg-strauss syndrome"(MeSH Terms) OR "behcet syndrome"(MeSH Terms) OR "sarcoidosis"(MeSH Major Topic) OR "polychondritis, relapsing"(MeSH Terms) OR "shock, septic"(MeSH Terms) OR "inflammatory bowel diseases"(MeSH Major Topic) OR "inflammatory bowel disease"(Title/Abstract) OR "inflammatory bowel diseases"(Title/Abstract) OR "pulmonary disease, chronic obstructive"(MeSH Major Topic) OR "chronic obstructive pulmonary disease"(Title/Abstract) OR COPD(Title/Abstract) OR "scleroderma, systemic"(MeSH Terms))</p> <p>AND</p> <p>((("Glucocorticoids/therapeutic use"(Mesh) OR glucocorticoids(MeSH Terms) OR prednisolone(MeSH Terms) OR prednisone(MeSH Terms) OR predniso*(Title/Abstract) OR dexamethasone(MeSH Terms) OR methylprednisolone(MeSH Terms) OR budesonide(MeSH Terms) OR triamcinolone(MeSH Terms) OR deflazacort(Title/Abstract) OR hydrocortisone(MeSH Terms) OR cortisone(MeSH Terms) OR solumedrol(Title/Abstract) OR "solu medrol"(Title/Abstract) OR depomedrol(Title/Abstract) OR "depo medrol"(Title/Abstract))</p> <p>AND</p> <p>("7.5 mg"(Title/Abstract) OR "7,5 mg"(Title/Abstract) OR "10 mg"(Title/Abstract) OR "15 mg"(Title/Abstract) OR "20 mg"(Title/Abstract) OR "25 mg"(Title/Abstract) OR "30 mg"(Title/Abstract) OR "40 mg"(Title/Abstract) OR "60 mg"(Title/Abstract) OR "80 mg"(Title/Abstract) OR "100 mg"(Title/Abstract) OR "120 mg"(Title/Abstract) OR "200 mg"(Title/Abstract) OR "1000 mg"(Title/Abstract) OR "high dose"(Title/Abstract) OR "high dose glucocorticoid"(Title/Abstract) OR "high dose glucocorticoids"(Title/Abstract) OR "medium dose"(Title/Abstract) OR "high dosages"(Title/Abstract) OR "moderate dose"(Title/Abstract) OR "medium dosages"(Title/Abstract) OR "moderate dosages"(Title/Abstract))</p> <p>AND</p> <p>((Oral(Title/Abstract) OR intramuscular(Title/Abstract) OR intravenous(Title/Abstract) OR "pulse treatment"(Title/Abstract) OR "pulse therapy"(Title/Abstract)) NOT (topical(Title/Abstract) OR transdermal(Title/Abstract) OR nasal(Title/Abstract) OR intranasal(Title/Abstract) OR rectal(Title/Abstract)))</p> <p>AND</p> <p>("adverse effect"(Title/Abstract) OR "adverse effects"(Title/Abstract) OR "adverse event"(Title/Abstract) OR "adverse events"(Title/Abstract) OR "side effect"(Title/Abstract) OR "side effects"(Title/Abstract) OR</p>	461

	<p>"side-effect"(Title/Abstract) OR "side-effects"(Title/Abstract) OR "unwanted effect"(Title/Abstract) OR "unwanted effects"(Title/Abstract) OR "osteoporosis"(MeSH Terms) OR "osteonecrosis"(MeSH Terms) OR "muscle weakness"(MeSH Terms) OR "glucose intolerance"(MeSH Terms) OR "diabetes mellitus"(MeSH Terms) OR "weight gain"(MeSH Terms) OR "hyperglycemia"(MeSH Terms) OR "menstruation disturbances"(MeSH Terms) OR "dyslipidemias"(MeSH Terms) OR "atherosclerosis"(MeSH Terms) OR "hypertension"(MeSH Terms) OR "edema"(MeSH Terms) OR "heart failure"(MeSH Terms) OR "water-electrolyte imbalance"(MeSH Terms) OR "myocardial infarction"(MeSH Terms) OR "coronary artery disease"(MeSH Terms) OR "tachycardia, sinus"(MeSH Terms) OR "hypokalemia"(MeSH Terms) OR "hypocalcemia"(MeSH Terms) OR "hirsutism"(MeSH Terms) OR "alopecia"(MeSH Terms) OR "hypertrichosis"(MeSH Terms) OR "cushing syndrome"(MeSH Terms) OR "purpura"(MeSH Terms) OR "cataract"(MeSH Terms) OR "glaucoma"(MeSH Terms) OR "peptic ulcer"(MeSH Terms) OR "pancreatitis"(MeSH Terms) OR "candidiasis"(MeSH Terms) OR "depression"(MeSH Terms) OR "anxiety"(MeSH Terms) OR "irritable mood"(MeSH Terms) OR "dizziness"(MeSH Terms) OR "tinnitus"(MeSH Terms) OR "carcinoma"(MeSH Terms) OR "thrombocytopenia"(MeSH Terms) OR "leukopenia"(MeSH Terms) OR "leukocytosis"(MeSH Terms) OR "proteinuria"(MeSH Terms) OR "arrhythmias, cardiac"(MeSH Terms) OR "hyponatremia"(MeSH Terms) OR "bone loss"(Title/Abstract) OR "Vertebral deformity"(Title/Abstract) OR "Vertebral deformities"(Title/Abstract) OR "fracture"(Title/Abstract) OR "fractures"(Title/Abstract) OR "bone mineral density"(Title/Abstract) OR "bone density"(Title/Abstract) OR myopathy(Title/Abstract) OR "blood glucose"(Title/Abstract) OR "fasting glucose"(Title/Abstract) OR "urine glucose"(Title/Abstract) OR "glycosuria"(Title/Abstract) OR "adipositas"(Title/Abstract) OR "buffalo hump"(Title/Abstract) OR "hyperlipidemia"(Title/Abstract) OR hyperlipidaemia(Title/Abstract) OR hypercholesterolaemia(Title/Abstract) OR "angina pectoris"(Title/Abstract) OR "blood pressure"(Title/Abstract) OR oedema(Title/Abstract) OR "cardiac insufficiency"(Title/Abstract) OR "fluid retention"(Title/Abstract) OR "facial fullness"(Title/Abstract) OR "facial swelling"(Title/Abstract) OR "moon face"(Title/Abstract) OR "cutaneous atrophy"(Title/Abstract) OR "skin atrophy"(Title/Abstract) OR "skin hemorrhage"(Title/Abstract) OR "skin bleeding"(Title/Abstract) OR striae(Title/Abstract) OR "easy bruisability"(Title/Abstract) OR "easy bruising"(Title/Abstract) OR "wound healing"(Title/Abstract) OR "hair loss"(Title/Abstract) OR "gastric ulcer"(Title/Abstract) OR "gastroduodenal ulcer"(Title/Abstract) OR dyspepsia(Title/Abstract) OR dysphagia(Title/Abstract) OR "gastric hemorrhage"(Title/Abstract) OR "stomach hemorrhage"(Title/Abstract) OR "gastroduodenal hemorrhage"(Title/Abstract) OR "viral infection"(Title/Abstract) OR "fungal infection"(Title/Abstract) OR "bacterial infection"(Title/Abstract) OR "skin infection"(Title/Abstract) OR "urinary infection"(Title/Abstract) OR "respiratory infection"(Title/Abstract) OR infection(Title/Abstract) OR libido(Title/Abstract) OR infertility(Title/Abstract) OR palpitation(Title/Abstract) OR psychosis(Title/Abstract) OR euphoria(Title/Abstract) OR seizures(Title/Abstract) OR tremor(Title/Abstract) OR "mood disturbance"(Title/Abstract) OR "mood lability"(Title/Abstract)</p>	
Embase	<p>(('asthma'/exp NOT ('asthma, aspirin-induced'/exp OR 'aspirin induced asthma'/exp OR 'nsaid-induced asthma'/exp OR 'aspirin-induced asthma'/exp) OR 'rheumatic disease'/exp OR 'rheumatic diseases'/exp OR 'rheumatoid arthritis'/exp OR 'arthritis, rheumatoid'/exp OR 'polymyalgia rheumatica'/exp OR 'lupus erythematosus, systemic'/exp</p>	427

OR 'polymyositis'/exp OR 'dermatomyositis'/exp OR 'giant cell arteritis'/exp OR 'takayasu arteritis'/exp OR 'polyarteritis nodosa'/exp OR 'wegener granulomatosis'/exp OR 'microscopic polyangiitis'/exp OR 'churg-strauss syndrome'/exp OR 'behcet syndrome'/exp OR 'sarcoidosis'/exp OR 'polychondritis, relapsing'/exp OR 'shock, septic'/exp OR 'inflammatory bowel disease'/exp OR 'inflammatory bowel diseases'/exp OR 'pulmonary disease, chronic obstructive'/exp OR 'chronic obstructive pulmonary disease'/exp OR 'copd'/exp OR 'scleroderma, systemic'/exp) AND ((article)/lim OR (article in press)/lim OR (conference abstract)/lim OR (conference paper)/lim OR (conference review)/lim OR (review)/lim OR (short survey)/lim) AND ((adult)/lim OR (aged)/lim) AND (humans)/lim)

AND

(('glucocorticoids'/exp OR 'glucocorticoid'/exp OR 'prednisolone'/exp OR 'prednisone'/exp OR predniso\* OR 'dexamethasone'/exp OR 'methylprednisolone'/exp OR 'budesonide'/exp OR 'triamcinolone'/exp OR 'deflazacort'/exp OR 'hydrocortisone'/exp OR 'cortisone'/exp OR 'solumedrol'/exp OR 'solu medrol'/exp OR 'depomedrol'/exp OR 'depo medrol'/exp) AND ('7.5 mg' OR '10 mg' OR '15 mg' OR '20 mg' OR '25 mg' OR '30 mg' OR '40 mg' OR '60 mg' OR '80 mg' OR '100 mg' OR '120 mg' OR '200 mg' OR '1000 mg' OR 'high dose'/exp OR 'drug megadose'/exp) AND (('oral'/exp OR 'intravenous'/exp OR 'drug pulse therapy'/exp OR 'short course therapy'/exp OR 'intramuscular'/exp) NOT ('rectal'/exp OR 'transdermal'/exp OR 'topical'/exp OR 'intranasal drug administration'/exp)) AND ((article)/lim OR (article in press)/lim OR (conference abstract)/lim OR (conference paper)/lim OR (conference review)/lim OR (review)/lim OR (short survey)/lim) AND ((adult)/lim OR (aged)/lim) AND (humans)/lim)

AND

'adverse effect'/exp OR 'side effect'/exp OR 'side-effect'/exp OR 'osteoporosis'/exp OR 'osteonecrosis'/exp OR 'muscle weakness'/exp OR 'glucose intolerance'/exp OR 'diabetes mellitus'/exp OR 'weight gain'/exp OR 'hyperglycemia'/exp OR 'menstruation disturbances'/exp OR 'dyslipidemias'/exp OR 'atherosclerosis'/exp OR 'hypertension'/exp OR 'edema'/exp OR 'heart failure'/exp OR 'water-electrolyte imbalance'/exp OR 'myocardial infarction'/exp OR 'coronary artery disease'/exp OR 'tachycardia, sinus'/exp OR 'hypokalemia'/exp OR 'hypocalcemia'/exp OR 'hirsutism'/exp OR 'alopecia'/exp OR 'hypertrichosis'/exp OR 'cushing syndrome'/exp OR 'purpura'/exp OR 'cataract'/exp OR 'glaucoma'/exp OR 'peptic ulcer'/exp OR 'pancreatitis'/exp OR 'candidiasis'/exp OR 'depression'/exp OR 'anxiety'/exp OR 'irritable mood'/exp OR 'dizziness'/exp OR 'tinnitus'/exp OR 'carcinoma'/exp OR 'thrombocytopenia'/exp OR 'leukopenia'/exp OR 'leukocytosis'/exp OR 'proteinuria'/exp OR 'arrhythmias, cardiac'/exp OR 'hypernatremia'/exp OR 'bone loss'/exp OR 'vertebral deformity'/exp OR 'fracture'/exp OR 'fractures'/exp OR 'bone mineral density'/exp OR 'bone density'/exp OR 'myopathy'/exp OR 'blood glucose'/exp OR 'urine glucose'/exp OR 'glycosuria'/exp OR 'adipositas'/exp OR 'hyperlipidemia'/exp OR 'hyperlipidaemia'/exp OR 'hypercholesterolaemia'/exp OR 'angina pectoris'/exp OR 'blood pressure'/exp OR 'oedema'/exp OR 'cardiac insufficiency'/exp OR 'fluid retention'/exp OR 'face edema'/exp OR 'moon face'/exp OR 'cutaneous atrophy'/exp OR 'skin atrophy'/exp OR 'skin hemorrhage'/exp OR 'skin bleeding'/exp OR 'striae'/exp OR 'easy bruisability'/exp OR 'restlessness'/exp OR 'wound healing'/exp OR 'hair loss'/exp OR 'gastric ulcer'/exp OR 'gastroduodenal ulcer'/exp OR 'dyspepsia'/exp OR 'dysphagia'/exp OR 'gastric hemorrhage'/exp OR 'stomach hemorrhage'/exp OR 'gastroduodenal hemorrhage'/exp OR 'viral infection'/exp OR 'fungal infection'/exp OR 'bacterial infection'/exp OR 'skin infection'/exp OR 'urinary infection'/exp OR 'respiratory

	infection'/exp OR 'infection'/exp OR 'libido'/exp OR 'infertility'/exp OR 'palpitation'/exp OR 'psychosis'/exp OR 'euphoria'/exp OR 'seizures'/exp OR 'tremor'/exp OR 'mood disturbance'/exp OR 'mood lability'/exp) AND ((article)/lim OR (article in press)/lim OR (conference abstract)/lim OR (conference paper)/lim OR (conference review)/lim OR (review)/lim OR (short survey)/lim) AND ((adult)/lim OR (aged)/lim) AND (humans)/lim	
Cochrane	<p>asthma NOT ("asthma, aspirin-induced" OR "aspirin induced asthma" OR "NSAID-induced asthma" OR "aspirin-induced asthma syndrome") OR "rheumatic diseases" OR "rheumatic disease" OR "rheumatic diseases" OR "rheumatoid arthritis" OR "arthritis, rheumatoid" OR "polymyalgia rheumatica" OR "lupus erythematosus, systemic" OR polymyositis OR dermatomyositis OR "giant cell arteritis" OR "takayasu arteritis" OR "polyarteritis nodosa" OR "wegener granulomatosis" OR "microscopic polyangiitis" OR "churg-strauss syndrome" OR "behcet syndrome" OR sarcoidosis OR "polychondritis, relapsing" OR "shock, septic" OR "inflammatory bowel diseases" OR "inflammatory bowel disease" OR "inflammatory bowel diseases" OR "pulmonary disease, chronic obstructive" OR "chronic obstructive pulmonary disease" OR COPD OR "scleroderma, systemic"</p> <p>AND</p> <p>glucocorticoids OR prednisolone OR prednisone OR predniso* OR dexamethasone OR methylprednisolone OR budesonide OR triamcinolone OR deflazacort OR hydrocortisone OR cortisone OR solumedrol OR "solu medrol" OR depomedrol OR "depo medrol":ti,ab,kw</p> <p>AND</p> <p>"7,5 mg" OR "7.5 mg" OR "10 mg" OR "15 mg" OR "20 mg" OR "25 mg" OR "30 mg" OR "40 mg" OR "60 mg" OR "80 mg" OR "100 mg" OR "120 mg" OR "200 mg" OR "1000 mg" OR "high dose" OR "high dose glucocorticoid" OR "high dose glucocorticoids" OR "medium dose" OR "high dosages" OR "moderate dose" OR "medium dosages" OR "moderate dosages":ti,ab,kw</p> <p>AND</p> <p>oral OR intravenous OR "pulse treatment" OR "pulse therapy" OR intramuscular):ti,ab,kw NOT (topical OR transdermal OR nasal OR intranasal OR rectal):ti,ab,kw</p> <p>AND</p> <p>("adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR "side effect" OR "side effects" OR "side-effect" OR "side-effects" OR "unwanted effect" OR "unwanted effects" OR osteoporosis OR osteonecrosis OR "muscle weakness" OR "glucose intolerance" OR "diabetes mellitus" OR "weight gain" OR hyperglycemia OR "menstruation disturbances" OR dyslipidemias OR atherosclerosis OR hypertension OR edema OR "heart failure" OR "water-electrolyte imbalance" OR "myocardial infarction" OR "coronary artery disease" OR "tachycardia, sinus" OR hypokalemia OR hypocalcemia OR hirsutism OR alopecia OR hypertrichosis OR "cushing syndrome" OR "purpura" OR "cataract" OR "glaucoma" OR "peptic ulcer" OR pancreatitis OR candidiasis OR depression OR anxiety OR "irritable mood" OR dizziness OR tinnitus OR carcinoma OR thrombocytopenia OR leukopenia OR leukocytosis OR proteinuria OR "arrhythmias, cardiac" OR hypernatremia OR hypernatraemia OR "bone loss" OR "Vertebral deformity" OR "Vertebral deformities" OR "fracture" OR "fractures" OR "bone mineral density" OR "bone density" OR myopathy OR "blood glucose" OR "fasting glucose" OR "urine glucose" OR glycosuria OR adipositas OR "buffalo hump" OR hyperlipidemia OR hyperlipidaemia OR hypercholesterolaemia OR "angina pectoris" OR "blood pressure" OR oedema OR "cardiac insufficiency" OR "fluid retention" OR "facial fullness" OR "facial</p>	216

	swelling" OR "moon face" OR "cutaneous atrophy" OR "skin atrophy" OR "skin hemorrhage" OR "skin bleeding" OR striae OR "easy bruisability" OR "easy bruising" OR "wound healing" OR "hair loss" OR "gastric ulcer" OR "gastroduodenal ulcer" OR dyspepsia OR dysphagia OR "gastric hemorrhage" OR "stomach hemorrhage" OR "gastroduodenal hemorrhage" OR "viral infection" OR "fungal infection" OR "bacterial infection" OR "skin infection" OR "urinary infection" OR "respiratory infection" OR infection OR libido OR infertility OR palpitation OR psychosis OR euphoria OR seizures OR tremor OR "mood disturbance" OR "mood lability"):ti,ab,kw	
<i>Total number of studies (excluding duplicates):</i>		916

Inclusion criteria:

- Patients with rheumatic disease, inflammatory bowel disease, inflammatory respiratory disease, or septic shock
- Prospective study including treatment with systemic medium to high dose GC therapy (i.e. medium dose, high dose, pulse therapy, intramuscular therapy or step down scheme) and information on GC dose and duration of treatment provided (to calculate cumulative dosages and mean daily dosages)
- Reporting of at least one GC-related adverse effect

Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Retrospective studies
- Language other than English, German or Dutch
- Topical, inhalation or intra-articular GC use
- Insufficient data given to calculate the cumulative GC dose during the study period
- Case series or case reports
- Letters, editorials
- Congress abstracts
- Reviews

## APPENDIX 2

### Results of the general systematic literature search: individual adverse effects

#### Abbreviations:

AE	Adverse event
AZA	Azathioprine
BMD	Bone mineral density
Ca	Calcium
CD	Crohn's disease
CI	Confidence interval
CYC	Cyclophosphamide
Cyclo	Cyclosporin
Different	Predefined rheumatic and immune diseases (these could include inflammatory respiratory diseases such as COPD, asthma, sarcoidosis)
DMARD	Disease-modifying antirheumatic drug
GC	Glucocorticoid
GC+	Patients on GC therapy
GC-	Patients not on GC therapy
GCA	Giant cell arteritis
HCQ	Hydroxychloroquine
IBD	Inflammatory bowel disease
IM	Intramuscular
IP	Inflammatory polyarthritis
IV	Intravenous
LEF	Leflunomide
MFP	Monofluorophosphate
MMF	Mycophenolate mofetil
MP	Methylprednisolone
MP induction	3 gram methylprednisolone
MPA	Microscopic polyangiitis
MTX	Methotrexate
n	Number
N/A	Not applicable
NSAID	Non-steroidal anti-inflammatory drug
PAN	Polyarteritis nodosa
PMR	Polymyalgia rheumatica
PR	Predniso(lo)ne
RA	Rheumatoid arthritis
rh IL11	Recombinant human interleukin-11
SLE	Systemic lupus erythematosus
SSZ	Sulphasalazine
UC	Ulcerative colitis
Vit D	Vitamin D

#### Note:

- Events/patient year are calculated over the complete follow up time.
- The mean daily dose is calculated by dividing the cumulative dose during the study by the duration of treatment according to the study protocol.

Adverse event: Moon face											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Messina, O.D. 1992(A)	1b	RA	8	x	PR/NSAID for 1 year	0.63 (5/8)			3650	
Chronic medium	Messina, O.D. 1992(B)	1b	RA	8	x	Deflazacort/NSAID for 1 year	0.00 (0/8)			3650	
Chronic medium	van Schaardenburg, D. 1995	1b	RA	28	28	PR vs HCQ for 2 years	0.05 (3/28)	0.00 (0/28)	7.8 (0.4-159)	5840	
Chronic medium	Joint Committee Report, 1959*	1b	RA	41	36	PR vs Aspirin for 2 years	0.33 (27/41)	0.00 (0/36)	138 (7.9-2423)	9928	
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.06 (3/30)			3266	
Chronic medium	Rhodes, J.M. 2007(A)*	1b	UC	59	x	Predocol 40 mg/Mesalazine/AZA for 0.5 year	0.17 (5/59)			4500	
Chronic high	Rhodes, J.M. 2007(B)*	1b	UC	61	x	Predocol 60 mg/Mesalazine/AZA for 0.5 year	0.23 (7/61)			6840	
Stepdown	Rhodes, J.M. 2007(C)*	1b	UC	61	x	PR/Mesalazine/AZA for 0.5 year	0.49 (15/61)			1365	
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	1.38 (20/58)			3605	
Stepdown	Rutgeerts, P. 1994	1b	CD	88	x	PR vs Budesonide (low dose) for 0.2 year	1.70 (30/88)			1680	
Stepdown	Bar-Meir, S. 1998	1b	CD	101	x	PR 40 mg vs Budesonide (low dose) for 0.16 year	2.04 (33/101)			1295	
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.07 (3/21)			5490	
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.14 (6/21)			5490	
Stepdown	Chevalet, P. 2000(A)	1b	GCA	61	x	once MP 240 mg IV/0.7 mg/kg PR/Ca-Vit D for 1 year	0.11 (7/61)			5777	
Stepdown	Chevalet, P. 2000(B)	1b	GCA	53	x	0.7 mg/kg PR/Ca-Vit D for 1 year	0.11 (6/53)			5578	
Stepdown	Chevalet, P. 2000(C)	1b	GCA	50	x	once MP 240 mg IV/0.5 mg/kg PR/Ca-Vit D for 1 year	0.10 (5/50)			5168	
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.17 (3/9)			5908	
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.13 (3/12)			6469	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.79 (11/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.77 (10/13)			3100	
Stepdown	Bootsma, H. 1995(A)	1b	SLE	22	x	PR±CYC/Ca (early treatment) for 3 years	0.11 (7/22)			8052	
Stepdown	Bootsma, H. 1995(B)	1b	SLE	24	x	PR±CYC/Ca (conventional treatment) for 3 years	0.03 (2/24)			4515	
IM	Choy, E.H. 2005	1b	RA	48	43	120 mg MP IM monthly/DMARD vs DMARD for 2 years	0.03 (3/48)	0.00 (0/43)	6.7 (0.3-133)	3600	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year			GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value		
Chronic medium		174	11.9	0.00-0.63			2 studies. 69 vs 64	35 (4.5-282)	3.4		
Chronic high		61	37.5	0.23							
Stepdown		608	14.3	0.03-2.04							
IM		48	4.9	0.03			1 study. 48 vs 43	6.7 (0.3-133)	1.2		

\* the AE could be recorded more than one time in one patient



Adverse event: Buffalo hump										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	Messina, O.D. 1992(A)	1b	RA	8	x	PR/NSAID for 1 year	0.63 (5/8)			3650
Chronic medium	Messina, O.D. 1992(B)	1b	RA	8	x	Deflazacort/NSAID for 1 year	0.00 (0/8)			3650
Stepdown	Rutgeerts, P. 1994	1b	CD	88	x	PR vs Budesonide (low dose) for 0.2 year	0.17 (3/88)			1680
Stepdown	Bar-Meir, S. 1998	1b	CD	101	x	PR 40 mg vs Budesonide (low dose) for 0.16 year	0.62 (10/101)			1295
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	0.14 (2/58)			3605
Summary		All studies								
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year						
Chronic medium		16	10.0	0.00-0.63						
Stepdown		247	29.8	0.14-0.62						

Adverse event: Hirsutism										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	Messina, O.D. 1992(A)	1b	RA	8	x	PR/NSAID for 1 year	0.63 (5/8)			3650
Chronic medium	Messina, O.D. 1992(B)	1b	RA	8	x	Deflazacort/NSAID for 1 year	0.00 (0/8)			3650
Chronic medium	Joint Committee Report, 1959*	1b	RA	41	36	PR vs Aspirin for 2 years	0.14 (12/41)	0.08 (6/36)	2.1 (0.7-6.2)	9928
Chronic medium	Rhodes, J.M. 2007(A)*	1b	UC	59	x	Predocol 40 mg/Mesalazine/AZA for 0.5 year	0.10 (3/59)			4500
Chronic high	Rhodes, J.M. 2007(B)*	1b	UC	61	x	Predocol 60 mg/Mesalazine/AZA for 0.5 year	0.07 (2/61)			6840
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	0.21 (3/58)			3605
Stepdown	Bar-Meir, S. 1998	1b	CD	101	x	PR 40 mg vs Budesonide (low dose) for 0.16 year	0.50 (8/101)			1295
Stepdown	Rutgeerts, P. 1994	1b	CD	88	x	PR vs Budesonide (low dose) for 0.2 year	0.11 (2/88)			1680
Stepdown	Rhodes, J.M. 2007(C)*	1b	UC	61	x	PR/Mesalazine/AZA for 0.5 year	0.33 (11/67)			1365
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.06 (1/9)			5908
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.04 (1/12)			6469
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value		
Chronic medium		116	14.6	0.00-0.63		1 study. 41 vs 36	2.1 (0.7-6.2)	1.3		
Chronic high		61	37.5	0.07						
Stepdown		329	19	0.04-0.50						

\* the AE could be recorded more than one time in one patient

Adverse event: Alopecia										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	van der Veen, M.J. 1996(A) <sup>§</sup>	1b	PMR/GCA	40	x	PR/Ca for 1 year (follow up 2 years)	0.00 (0/40)			2947
Chronic medium	van der Veen, M.J. 1996(B) <sup>§</sup>	1b	PMR/GCA	40	x	PR/Ca/MTX for 1 year (follow up 2 years)	0.01 (1/40)			2400
Chronic medium	Bakker, M.F. 2012 <sup>§</sup>	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.04 (10/117)	0.07 (17/119)	0.6 (0.2-1.3)	7300
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.00 (0/36)			2600
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.02 (1/36)			2600
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.06 (1/9)			5908
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.04 (1/12)			6469
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.02 (1/21)			5490
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.05 (2/21)			5490
Stepdown	de Groot, K. 2009	1b	Vasculitis	149	x	PR/CYC IV or CYC oral for 1.5 years	0.01 (2/149)			7587
Stepdown	Wang, H.Y. 2003(A)	2a	SLE	70	x	PR/LEF for 0.5 year	0.31 (11/70)			5894
Stepdown	Wang, H.Y. 2003(B)	2a	SLE	40	x	PR/CYC for 0.5 year	0.20 (7/70)			5894
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value	
Chronic medium		269	10.6	0.00-0.04		1 study. 117 vs 119		0.6 (0.2-1.3)	1.4	
Stepdown		322	15.8	0.01-0.31						

<sup>§</sup> hair loss

Adverse event: Skin hemorrhage										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.07 (4/30)			3266
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.01 (1/40)	0.01 (1/41)	1.0 (0.1-17)	7300
Chronic medium	Joint Committee Report, 1959	1b	RA	41	36	PR vs Aspirin for 2 years	0.04 (3/41)	0.01 (1/36)	2.8 (0.3-28)	9928
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.06 (1/9)			5908
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.17 (4/12)			6469
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	0.48 (7/58)			3605
IM	Dasgupta, B. 1998(B)	1b	PMR	30	x	MP IM every 3 weeks for 1.8 years	0.19 (10/30)			1825
IM	Choy, E.H. 2005	1b	RA	48	43	120 mg MP IM monthly/DMARD vs DMARD for 2 years	0.03 (3/48)	0.00 (0/43)	6.7 (0.3-133)	3600
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value	
Chronic medium		111	9.5	0.01-0.07		2 studies. 81 vs 77		1.9 (0.3-11)	0.7	
Stepdown		79	18.8	0.06-0.48						
IM		78	3.9	0.03-0.19		1 study. 48 vs 43		6.7 (0.3-133)	1.2	

Adverse event: Striae										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	0.00 (0/58)			3605
Stepdown	Rutgeerts, P. 1994	1b	CD	88	x	PR vs Budesonide (low dose) for 0.2 year	0.11 (2/88)			1680
Stepdown	Bar-Meir, S. 1998	1b	CD	101	x	PR 40 mg vs Budesonide (low dose) for 0.16 year	0.12 (2/101)			1295
Summary		All studies								
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year						
Stepdown		247	29.8	0.00-0.12						

Adverse event: Skin changes										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	van Everdingen, A.A. 2002#	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.04 (3/40)	0.02 (2/41)	1.6 (0.3-10)	7300
Chronic medium	Bakker, M.F. 2012□	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.04 (10/117)	0.05 (11/119)	0.9 (0.4-2.3)	7300
Chronic medium	Empire, 1957‡	1b	RA	49	50	Cortisone vs Aspirin for 3 years	0.01 (1/49)	0.00 (0/50)	3.1 (0.1-79)	14782
Stepdown	Boers, M. 1997	1b	RA	76	79	PR/SSZ/MTX vs SSZ for >1 year	0.07 (5/76)	0.08 (6/79)	0.9 (0.3-2.9)	2345
Stepdown	Pagnoux, C. 2008(A)¥	1b	Vasculitis	63	x	induction MP/CYC IV. then PR/AZA for 2.2 years	0.01 (1/63)			10760
Stepdown	Pagnoux, C. 2008(B)¥	1b	Vasculitis	63	x	induction MP/CYC IV. then PR/MTX for 2.2 years	0.01 (1/63)			10760
IM	Corkill, M.M. 1990□	1b	RA	35	24	MP 120 mg 3x/NSAID/GOLD vs Placebo/NSAID/GOLD for 0.5 year	0.11 (2/35)	0.00 (0/24)	3.7 (0.2-80)	450
Summary		All studies								
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		Placebo-controlled studies				
						GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value		
Chronic medium		206	11.2	0.01-0.04		3 studies. 206 vs 210		1.0 (0.5-2.2) 0.05		
Stepdown		202	11.1	0.01-0.07		1 study. 76 vs 79		0.9 (0.3-2.9) -0.2		
IM		35	2.5	0.11		1 study. 35 vs 24		3.7 (0.2-80) 0.8		

# ulcer cruris, exanthema, petechiae; ‡ dermatitis; ¥ cutaneous eruption; □ pruritus

Adverse event: Weight gain (numerical)											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	van der Veen, M.J. 1996(A)‡	1b	PMR/GCA	40	x	PR/Ca for 1 year (follow up 2 years)	0.06 (5/40)			2947	
Chronic medium	van der Veen, M.J. 1996(B)‡	1b	PMR/GCA	40	x	PR/Ca/MTX for 1 year (follow up 2 years)	0.14 (11/40)			2400	
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.04 (2/36)			2600	
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.08 (4/36)			2600	
Chronic medium	Tait, T.J. 1994	3	RA	15	x	PR/NSAID±DMARDs for 0.9 year	0.07 (1/15)			1680	
Chronic medium	Messina, O.D. 1992(A)	1b	RA	8	x	PR/NSAID for 1 year	0.63 (5/8)			3650	
Chronic medium	Messina, O.D. 1992(B)	1b	RA	8	x	Deflazacort/NSAID for 1 year	0.00 (0/8)			3650	
Stepdown	Jover, J.A. 2001(A)*	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.17 (7/21)			5490	
Stepdown	Jover, J.A. 2001(B)*	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.21 (9/21)			5490	
Stepdown	Bootsma, H. 1995(A)	1b	SLE	22	x	PR±CYC/Ca (early treatment) for 3 years	0.05 (3/22)			8052	
Stepdown	Bootsma, H. 1995(B)	1b	SLE	24	x	PR±CYC/Ca (conventional treatment) for 3 years	0.03 (2/24)			4515	
IM	Choy, E.H. 2005	1b	RA	48	43	120 mg MP IM monthly/DMARD vs DMARD for 2 years	0.00 (0/48)	0.01 (1/43)	0.3 (0.0-7.4)	3600	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value		
Chronic medium		183	9.8	0.00-0.63							
Stepdown		88	6.6	0.03-0.21							
IM		48	4.9	0.00		1 study. 48 vs 43		0.3 (0.0-7.4)	-0.7		

‡ ≥ 1kg, \* > 5% increase in body weight

Adverse event: Diabetes mellitus											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Salvarani, C. 2007(A)	1b	PMR	28	x	PR for 0.33 year	0.00 (0/28)			910	
Chronic medium	Salvarani, C. 2007(B)	1b	PMR	23	x	PR/Infliximab for 0.33 year	0.13 (1/23)			910	
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.04 (2/36)			2600	
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.00 (0/36)			2600	
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.00 (1/117)	0.00 (1/119)	1.0 (0.1-16)	7300	
Chronic medium	van Everdingen, A.A. 2002*	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.03 (2/40)	0.01 (1/41)	2.1 (0.2-24)	7300	
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.01 (9/124)			>7900	
Stepdown	Chevalet, P. 2000(A)	1b	GCA	61	x	once MP 240 mg IV/0.7 mg/kg PR/Ca-Vit D for 1 year	0.03 (2/61)			5777	
Stepdown	Chevalet, P. 2000(B)	1b	GCA	53	x	0.7 mg/kg PR/Ca-Vit D for 1 year	0.06 (3/53)			5578	
Stepdown	Chevalet, P. 2000(C)	1b	GCA	50	x	once MP 240 mg IV/0.5 mg/kg PR/Ca-Vit D for 1 year	0.04 (2/50)			5168	
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.07 (3/21)			5490	
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.17 (7/21)			5490	
Stepdown	Hernandes-Garcia C, 1994	2b	GCA	11	x	PR/MTX for 2.5 years	0.18 (5/11)			3400	
Stepdown	Bootsma, H. 1995(A)	1b	SLE	22	x	PR±CYC/Ca (early treatment) for 3 years	0.00 (0/22)			8052	
Stepdown	Bootsma, H. 1995(B)	1b	SLE	24	x	PR±CYC/Ca (conventional treatment) for 3 years	0.01 (1/24)			4515	
Stepdown	de Groot, K. 2009	1b	Vasculitis	149	x	PR/CYC IV or CYC oral for 1.5 years	0.05 (12/149)			7587	
IM	Choy, E.H. 2005	1b	RA	48	43	120 mg MP IM monthly/DMARD vs DMARD for 2 years	0.01 (1/48)	0.00 (0/43)	2.7 (0.1-69)	3600	
IM	Verstappen, S.M. 2010	1b	IP	133	132	MP IM 3x vs Placebo (±DMARD) (follow up 1 year)	0.01 (1/132)	0.00 (0/132)	3.0 (0.1-75)	300	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value		
Chronic medium		280	10.6	0.00-0.13		2 study. 157 vs 160		1.5 (0.3-9.3)	0.5		
Chronic high		124	43.3	0.01							
Stepdown		412	9.9	0.00-0.18							
IM		181	2.9	0.01		2 studies. 181 vs 175		2.9 (0.3-28)	0.9		

\*from 5.1±0.6 SD to 5.9 SD 1.9 mmol/l

Adverse event: Hyperglycaemia											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Messina, O.D. 1992 (A)	1b	RA	8	x	PR/NSAID for 1 year	0.25 (2/8)			3650	
Chronic medium	Messina, O.D. 1992 (B)	1b	RA	8	x	Deflazacort/NSAID for 1 year	0.00 (0/8)			3650	
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.06 (13/117)	0.04 (9/119)	1.5 (0.6-3.7)	7300	
Chronic medium	van der Veen, M.J. 1996(A)	1b	PMR/GCA	40	x	PR/Ca for 1 year (follow up 2 years)	0.09 (7/40)			2947	
Chronic medium	van der Veen, M.J. 1996(B)	1b	PMR/GCA	40	x	PR/Ca/MTX for 1 year (follow up 2 years)	0.06 (5/40)			2400	
Chronic medium	Ferraccioli, G.1996 (A)	1b	PMR	12	x	PR for 1 year	0.17 (2/12)			3200	
Chronic medium	Ferraccioli, G.1996 (B)	1b	PMR	12	x	PR/MTX for 1 year	0.00 (0/12)			1840	
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.06 (1/9)			5908	
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.04 (1/12)			6469	
Summary		All studies						Placebo-controlled studies			
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		237	8.4	0.00-0.25		1 study. 117 vs 119	1.5 (0.6-3.7)	0.9			
Stepdown		21	8.5	0.04-0.06							

Adverse event: Glucose intolerance											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Joint Committee Report, 1959*	1b	RA	41	36	PR vs Aspirin for 2 years	0.01 (1/41)	0.00 (0/36)	2.7 (0.1-68)	9928	
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.05 (2/21)			5490	
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.05 (2/21)			5490	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.07 (1/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.08 (1/13)			3100	
Summary		All studies						Placebo-controlled studies			
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		41	13.6	0.01		1 study. 41 vs 36	2.7 (0.1-68)	0.6			
Stepdown		69	10.6	0.05-0.08							

\* glucosuria

Adverse event: Dyslipidemia											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Messina, O.D. 1992 (A)	1b	RA	8	x	PR/NSAID for 1 year	0.13 (1/8)			3650	
Chronic medium	Messina, O.D. 1992 (B)	1b	RA	8	x	Deflazacort/NSAID for 1 year	0.00 (0/8)			3650	
Stepdown	Boers, M. 2003	1b	RA	76	79	PR/SSZ/MTX vs SSZ for >1 year	*minus 4.5	*minus 4.5		2345	
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.00 (0/21)			5490	
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.05 (2/21)			5490	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.21 (3/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.23 (3/13)			3100	
IM	Choy, E.H. 2005	1b	RA	48	43	120 mg MP IM monthly/DMARD vs DMARD for 2 years	0.01 (1/48)	0.00 (0/43)	2.7 (0.1-69)	3600	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)		Mean daily PR equivalent dose (mg)		Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI) Z-Value	
Chronic medium		16		10.0		0.00-0.13					
Stepdown		145		9.8		0.00-0.23		1 study. 76 vs 79		N/A N/A	
IM		48		4.9		0.01		1 study. 48 vs 43		2.7 (0.1-69) 0.6	

\* arthrogenic index ( $\Delta$  cholesterol/ HDL) after 28 weeks minus 5.1 in GC+ vs minus 1.4 in GC-

Adverse event: Myocardial infarction											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Verschueren, P. 2008(A)	2a	RA	19	x	PR/SSZ/MTX for 2 years	0.00 (0/19)			2603	
Chronic medium	Verschueren, P. 2008(B)	2a	RA	52	x	PR/step up DMARD for 2 years	0.01 (1/52)			997	
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.00 (1/117)	0.00 (0/119)	3.1 (0.1-76)	7300	
Chronic medium	Joint Committee Report, 1959	1b	RA	41	36	PR vs Aspirin for 2 years	0.01 (1/41)	0.00 (0/36)	2.7 (0.1-68)	9928	
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.01 (1/40)	0.00 (0/41)	3.2 (0.1-80)	7300	
Chronic medium	Empire, 1957	1b	RA	49	50	Cortisone vs Aspirin for 3 years	0.00 (0/49)	0.01 (1/50)	0.3 (0.0-8.4)	14782	
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.00 (0/124)			>7900	
Stepdown	Boers, M. 1997	1b	RA	76	79	PR/SSZ/MTX vs SSZ for >1 year	0.01 (1/76)	0.00 (0/79)	3.2 (0.1-79)	2345	
IM	Choy, E.H. 2005	1b	RA	48	43	120 mg MP IM monthly/DMARD vs DMARD for 2 years	0.01 (1/48)	0.00 (0/43)	2.7 (0.1-69)	3600	
IM	Verstappen, S.M. 2010	1b	IP	133	132	MP IM 3x monthly vs Placebo ( $\pm$ DMARD) (follow up 1 year)	0.00 (0/133)	0.01 (1/132)	0.3 (0.0-8.1)	300	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)		Mean daily PR equivalent dose (mg)		Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI) Z-Value	
Chronic medium		318		8.7		0.00-0.01		4 studies. 247 vs 246		3.0 (0.3-29) 1.0	
Chronic high		124		43.3		0.00					
Stepdown		76		6.4		0.01		1 study. 76 vs 79		3.2 (0.1-79) 0.7	
IM		181		2.9		0.00-0.01		2 studies. 181 vs 175		0.9 (0.1-9.2) -0.0	

Adverse event: Hypertension										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	Messina, O.D. 1992 (A)	1b	RA	8	x	PR/NSAID for 1 year	0.63 (5/8)			3650
Chronic medium	Messina, O.D. 1992 (B)	1b	RA	8	x	Deflazacort/NSAID for 1 year	0.13 (1/8)			3650
Chronic medium	Joint Committee Report, 1959	1b	RA	41	36	PR vs Aspirin for 2 years	0.28 (23/41)	0.19 (14/36)	2.0 (0.8-5.0)	9928
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.09 (7/40)	0.07 (6/41)	1.2 (0.4-4.1)	7300
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.05 (11/117)	0.08 (18/119)	0.6 (0.3-1.3)	7300
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.04 (2/30)			3266
Chronic medium	Salvarani, C. 2007(A)	1b	PMR	28	x	PR for 0.33 year	0.54 (5/28)			910
Chronic medium	Salvarani, C. 2007(B)	1b	PMR	23	x	PR/Infliximab for 0.33 year	0.00 (0/23)			910
Chronic medium	Ferraccioli, G.1996 (A)	1b	PMR	12	x	PR for 1 year	0.17 (2/12)			3200
Chronic medium	Ferraccioli, G.1996 (B)	1b	PMR	12	x	PR/MTX for 1 year	0.00 (0/12)			1840
Chronic medium	van der Veen, M.J. 1996(A)	1b	PMR/GCA	40	x	PR/Ca for 1 year (follow up 2 years)	0.06 (5/40)			2947
Chronic medium	van der Veen, M.J. 1996(B)	1b	PMR/GCA	40	x	PR/Ca/MTX for 1 year (follow up 2 years)	0.11 (9/40)			2400
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.06 (3/36)			2600
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.10 (5/36)			2600
Chronic medium	Empire, 1957	1b	RA	49	50	Cortisone vs Aspirin for 3 years	0.03 (4/49)	0.00 (0/50)	10 (0.5-191)	14782
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.02 (11/124)			>7900
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.29 (12/21)			5490
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.38 (16/21)			5490
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.21 (3/14)			6947
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.31 (4/13)			3100
Stepdown	Hernandes-Garcia, C. 1994	2b	GCA	11	x	PR/MTX for 2.5 years	0.07 (2/11)			3400
Stepdown	Bootsma, H. 1995(A)	1b	SLE	22	x	PR±CYC/Ca (early treatment) for 3 years	0.06 (4/22)			8052
Stepdown	Bootsma, H. 1995(B)	1b	SLE	24	x	PR±CYC/Ca (conventional treatment) for 3 years	0.01 (1/24)			4515
Stepdown	Wang, H.Y. 2003(A)	2a	SLE	70	x	PR/LEF for 0.5 year	0.20 (7/70)			5894
Stepdown	Wang, H.Y. 2003(B)	2a	SLE	40	x	PR/CYC for 0.5 year	0.05 (1/40)			5894
Stepdown	Boers, M. 1997	1b	RA	76	79	PR/SSZ/MTX vs SSZ for >1 year	0.00 (0/76)	0.00 (0/79)	N/A	2345
Stepdown	Choy, E.H. 2008(A)	1b	RA	115	x	PR/MTX for 0.75 year	0.09 (8/115)			>1135
Stepdown	Choy, E.H. 2008(B)	1b	RA	116	x	PR/MTX/cyclo for 0.75 year	0.20 (17/116)			>1135
Stepdown	de Groot, K. 2009	1b	Vasculitis	149	x	PR/CYC IV or CYC oral for 1.5 years	0.01 (2/149)			7587
Stepdown	Silva, F. 2010	2b	MPA	17	x	PR/MP IV induction/MMF/Cotrimoxazol for 0.5 year (follow up 1.5 y)	0.00 (0/17)			8200
IM	Choy, E.H. 2005	1b	RA	48	43	120 mg MP IM monthly/DMARD vs DMARD for 2 years	0.04 (4/48)	0.01 (1/43)	3.8 (0.4-36)	3600
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value		
Chronic medium		520	9.6	0.00-0.63		4 studies. 247 vs 246		1.2 (0.8-2.0) 0.8		
Chronic high		124	43.3	0.02						
Stepdown		709	14.1	0.00-0.38		1 study. 76 vs 79		N/A		
IM		48	4.9	0.04		1 study. 48 vs 43		3.8 (0.4-36) 1.2		



Adverse event: Heart rhythm disorder										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	Rhodes, J.M. 2007(A)*	1b	UC	59	x	Predocol 40 mg/Mesalazine/AZA for 0.5 year	0.10 (3/59)			4500
Chronic medium	Caporali, R. 2004(A)‡	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.04 (2/36)			2600
Chronic medium	Caporali, R. 2004(B)‡	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.00 (0/36)			2600
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.01 (1/40)	0.02 (2/41)	0.5 (0.0-5.7)	7300
Chronic high	Rhodes, J.M. 2007(B)*	1b	UC	61	x	Predocol 60 mg/Mesalazine/AZA for 0.5 year	0.13 (4/61)			6840
Chronic high	Ribi, C. 2010*	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.00 (1/124)			>7900
Stepdown	Rhodes, J.M. 2007(C)*	1b	UC	61	x	PR/Mesalazine/AZA for 0.5 year	0.26 (8/61)			1365
Stepdown	Wang, H.Y. 2003(A)	2a	SLE	70	x	PR/LEF for 0.5 year	0.11 (4/70)			5894
Stepdown	Wang, H.Y. 2003(B)	2a	SLE	40	x	PR/CYC for 0.5 year	0.05 (1/40)			5894
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.00 (0/14)			6947
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.15 (2/13)			3100
IV	Walters, M.T. 1988	1b	RA	17	x	MP IV vs MP IV/GOLD vs MP IV/CYC vs MP IV/GOLD/CYC for 0.5 year	0.12 (1/17)			2625
IV	Hansen, T.M. 1990‡	1b	RA	50	47	MP IV/Penicillamine or AZA vs Penicillamine or AZA for 0.5 year#	0.60 (15/50)	0.26 (6/47)	2.9 (1.0-8.4)	7875
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value	
Chronic medium		171	15.8	0.00-0.10		1 study, 40 vs 41		0.5 (0.0-5.7)	-0.6	
Chronic high		185	40.4	0.00-0.13						
Stepdown		198	19.9	0.00-0.26						
IV		67	28.8	0.12-0.60		1 study, 50 vs 47		2.9 (1.0-8.4)	2.0	

‡ tachycardia, \* atrial fibrillation, # per month 1050 mg IV MP for 6 months

\* the AE could be recorded more than one time in one patient

Adverse event: Edema											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Dasgupta, B. 1998 (A)	1b	PMR	30	x	PR for 1.8 years	0.06 (3/30)			3266	
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.01 (1/40)	0.00 (0/41)	3.2 (0.1-80)	7300	
Chronic medium	Joint Committee Report, 1959	1b	RA	41	36	PR vs Aspirin for 2 years	0.05 (4/41)	0.07 (5/36)	0.7 (0.2-2.7)	9928	
Chronic medium	Empire, 1957	1b	RA	49	50	Cortisone vs Aspirin for 3 years	0.01 (2/49)	0.00 (0/50)	5.3 (0.2-114)	14782	
Chronic medium	Rhodes, J.M. 2007(A)*	1b	UC	59	x	Predocol 40 mg/Mesalazine/AZA for 0.5 year	0.07 (2/59)			4500	
Chronic high	Rhodes, J.M. 2007(B)*	1b	UC	61	x	Predocol 60 mg/Mesalazine/AZA for 0.5 year	0.13 (4/61)			6840	
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	0.21 (3/58)			3605	
Stepdown	Rutgeerts, P. 1994	1b	CD	88	x	PR vs Budesonide (low dose) for 0.2 year	0.60 (10/88)			1680	
Stepdown	Bar-Meir, S. 1998	1b	CD	101	x	PR 40 mg vs Budesonide (low dose) for 0.16 year	0.57 (9/101)			1295	
Stepdown	Herrlinger, K.R. 2006	1b	CD	24	27	PR 60 mg/AZA vs rh IL11/AZA for 0.25 year	0.17 (1/24)	0.00 (0/27)	3.5 (0.1-90)	1890	
Stepdown	Rhodes, J.M. 2007(C)*	1b	UC	61	x	PR/Mesalazine/AZA for 0.5 year	0.30 (9/61)			1365	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.07 (1/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.00 (0/13)			3100	
IM	Dasgupta, B. 1998 (B)	1b	PMR	30	x	MP IM every 3 weeks for 1.8 years	0.06 (3/30)			1825	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		219	13.3	0.01-0.07		3 studies. 130 vs 127		1.1 (0.3-3.7) 0.2			
Chronic high		61	37.5	0.13							
Stepdown		359	20.7	0.00-0.60		1 study. 24 vs 27		3.5 (0.1-90) 0.8			
IM		30	2.8	0.06							

\* the AE could be recorded more than one time in one patient

Adverse event: Renal disturbances											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	van der Veen, M.J. 1996(A)*	1b	PMR/GCA	40	x	PR/Ca for 1 year (follow up 2 years)	0.13 (10/40)			2947	
Chronic medium	van der Veen, M.J. 1996(B)*	1b	PMR/GCA	40	x	PR/Ca/MTX for 1 year (follow up 2 years)	0.09 (7/40)			2400	
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.01 (2/117)	0.00 (1/119)	2.1 (0.2-23)	7300	
Chronic medium	van Gestel, A.M. 1995^	1b	RA	20	20	PR/NSAID/GOLD vs Placebo/NSAID/GOLD for 0.8 years	0.06 (1/20)	0.00 (0/20)	3.2 (0.1-82)	1078	
Stepdown	Choy, E.H. 2008 (A)*	1b	RA	115	x	PR/MTX for 0.75 year	0.05 (4/115)			>1135	
Stepdown	Choy, E.H. 2008 (B)*	1b	RA	116	x	PR/MTX/cyclo for 0.75 year	0.40 (35/116)			>1135	
Stepdown	Boers, M. 1997‡	1b	RA	76	79	PR/SSZ/MTX vs SSZ for >1 year	0.00 (0/76)	0.01 (1/79)	0.3 (0.0-8.5)	2345	
Stepdown	Herrlinger, K.R. 2006 #	1b	CD	24	27	PR 60 mg/AZA vs rh IL11/AZA for 0.25 year	0.17 (1/24)	0.00 (0/27)	3.5 (0.1-90)	1890	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		217	7.1	0.01-0.13		2 study. 137 vs 139		3.1 (0.3-30) 1.0			
Stepdown		331	8.9	0.00-0.40		2 studies. 100 vs 106		1.1 (0.1-11) 0.1			

\* increased creatinine, ^ renal failure, ‡ proteinuria, # kidney infarction

Adverse event: Osteonecrosis										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic high	Sakamoto, M. 1997	2b	Different	48	x	PR/MP IV for > 0.5 year (follow up 2.6 years)	0.14 (17/48)			5876
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.00 (1/124)			>7900
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	0.00 (0/58)			3605
Stepdown	Silva, F. 2010	2b	MPA	17	x	PR/MP IV induction/MMF/Cotrimoxazol for 0.5 year (follow up 1.5 y)	0.04 (1/17)			8200
IV	Shipley, M.E. 1988	1b	RA	71	x	1 g MP IV 1x (follow up 0.5 years)	0.09 (1/23)			1250
Summary		All studies								
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year						
Chronic high		172	37.7	0.00-0.14						
Stepdown		75	42.2	0.00-0.04						
IV		71	?	0.09						

Adverse event: Myopathy										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.13 (86/124)			>7900
Stepdown	Bar-Meir, S. 1998	1b	CD	101	x	PR 40 mg vs Budesonide 9 mg for 0.16 year	1.61 (26/101)			1295
Stepdown	Chevalet, P. 2000(A)	1b	GCA	61	x	once MP 240 mg IV/0.7 mg/kg PR/Ca-Vit D for 1 year	0.02 (1/61)			5777
Stepdown	Chevalet, P. 2000(B)	1b	GCA	53	x	0.7 mg/kg PR/Ca-Vit D for 1 year	0.00 (0/53)			5578
Stepdown	Chevalet, P. 2000(C)	1b	GCA	50	x	once MP 240 mg IV/0.5 mg/kg PR/Ca-Vit D for 1 year	0.02 (1/50)			5168
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.05 (2/21)			5490
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.02 (1/21)			5490
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.44 (8/9)			5908
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.50 (12/12)			6469
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.00 (0/14)			6947
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.00 (0/13)			3100
Summary		All studies								
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year						
Chronic high		124	43.3	0.13						
Stepdown		355	12.7	0.00-1.61						

Adverse event: Vertebral fracture											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Ferraccioli, G.1996(A)	1b	PMR	12	x	PR for 1 year	0.08 (1/12)			3200	
Chronic medium	Ferraccioli, G.1996(B)	1b	PMR	12	x	PR/MTX for 1 year	0.00 (0/12)			1840	
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.17 (9/30)			3266	
Chronic medium	Reid, D.M. 2000(A)	1b	Different	96	x	PR/Ca-Vit D for 5.5 years	0.01 (3/96)			30240	
Chronic medium	Reid, D.M. 2000(B)	1b	Different	100	x	PR/Ca-Vit D/Risedronate for 5.5 years	0.02 (9/100)			30240	
Chronic medium	Boutsen, Y. 1997(A)	1b	Different	14	x	PR/Ca/Pamidronate for 1 year	0.00 (0/14)			5726	
Chronic medium	Boutsen, Y. 1997(B)	1b	Different	13	x	PR/CA for 1 year	0.08 (1/13)			4027	
Chronic medium	Guaydier-Souquieres, G. 1996(A)	1b	Different	17	x	PR/Ca/MFP for 2 years	0.06 (2/17)			10600	
Chronic medium	Guaydier-Souquieres, G. 1996(B)	1b	Different	18	x	PR/Ca for 2 years	0.00 (0/18)			14200	
Chronic medium	van Schaardenburg, D. 1995	1b	RA	28	28	PR vs HCQ for 2 years	0.02 (1/28)	0.00 (0/28)	3.1 (0.1-80)	5840	
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.00 (1/117)	0.00 (0/119)	3.1 (0.1-76)	7300	
Chronic medium	van Everdingen, A.A. 2002*	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.10 (8/40)	0.05 (4/41)	2.3 (0.6-8.4)	7300	
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.00 (1/124)			>7900	
Stepdown	Spiers, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.17 (3/9)			5908	
Stepdown	Spiers, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.04 (1/12)			6469	
Stepdown	Hernandes-Garcia, C. 1994*	2b	GCA	11	x	PR/MTX for 2.5 years	0.18 (5/11)			3400	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.00 (0/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.00 (0/13)			3100	
Stepdown	Hoffman, G.S. 2002(A)	1b	GCA	47	x	PR/Ca-VitD for 1 year	0.00 (0/47)			5275	
Stepdown	Hoffman, G.S. 2002(B)	1b	GCA	47	x	PR/Ca-Vit D/MTX for 1 year	0.04 (2/47)			5375	
IM	Dasgupta, B. 1998(B)	1b	PMR	30	x	MP IM every 3 weeks for 1.8 years	0.02 (1/30)			1825	
Summary		All studies				Placebo-controlled studies					
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		497	11.5	0.00-0.17		3 studies. 185 vs 188	2.6 (0.8-8.5)	1.6			
Chronic high		124	43.3	0							
Stepdown		153	11.1	0.00-0.18							
IM		30	2.8	0.02							

\* the AE could be recorded more than one time in one patient

Adverse event: Non-vertebral fracture										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	van Schaardenburg, D. 1995	1b	RA	28	28	PR vs HCQ for 2 years	0.02 (1/28)	0.02 (1/28)	1.0 (0.1-17)	5840
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.00 (1/117)	0.00 (0/119)	3.1 (0.1-76)	7300
Chronic medium	Reid, D.M. 2000(A)	1b	Different	96	x	PR/Ca-Vit D for 5.5 years	0.01 (6/96)			30240
Chronic medium	Reid, D.M. 2000(B)	1b	Different	100	x	PR/Ca-Vit D/Risedronate for 5.5 years	0.01 (8/100)			30240
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.17 (9/30)			3266
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.02 (1/36)			2600
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.04 (2/36)			2600
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.00 (1/124)			>7900
Stepdown	Hoffman, G.S. 2002(A)	1b	GCA	47	x	PR/Ca-VitD for 1 year	0.02 (1/47)			5275
Stepdown	Hoffman, G.S. 2002(B)	1b	GCA	47	x	PR/Ca-Vit D/MTX for 1 year	0.00 (0/47)			5375
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.10 (4/21)			5490
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.05 (2/21)			5490
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.00 (0/14)			6947
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.08 (1/13)			3100
Stepdown	Pagnoux, C. 2008(A)	1b	Vasculitis	63	x	induction MP/CYC IV. then PR/AZA for 2.2 years	0.01 (1/63)			10760
Stepdown	Pagnoux, C. 2008(B)	1b	Vasculitis	63	x	induction MP/CYC IV. then PR/MTX for 2.2 years	0.02 (3/63)			10760
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	0.07 (1/58)			3605
IM	Dasgupta, B. 1998(B)	1b	PMR	30	x	MP IM every 3 weeks for 1.8 years	0.02 (1/30)			1825
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value	
Chronic medium		443	11.7	0.00-0.17		2 study, 245 vs 247		2.0 (0.2-22)	0.6	
Chronic high		124	43.3	0,00						
Stepdown		347	15.3	0.00-0.10						
IM		30	2.8	0.02						

fracture localisation: 7 pelvis, 1 wrist, 1 tibia, 1 rib, 1 femoral head, 1 elbow

Adverse event: Osteoporosis (numerical)										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	van der Veen, M.J. 1996(A)*	1b	PMR/GCA	40	x	PR/Ca for 1 year (follow up 2 years)	0.03 (2/40)			2947
Chronic medium	van der Veen, M.J. 1996(B)*	1b	PMR/GCA	40	x	PR/Ca/MTX for 1 year (follow up 2 years)	0.01 (1/40)			2400
Chronic medium	Joint Committee Report, 1959*	1b	RA	41	36	PR vs Aspirin for 2 years	0.16 (13/41)	0.03 (2/36)	7.9 (1.6-38)	9928
Chronic high	Ribi, C. 2010#	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.02 (13/124)			>7900
Stepdown	Bootsma, H. 1995(A)	1b	SLE	22	x	PR±CYC/Ca (early treatment) for 3 years	0.00 (0/22)			8052
Stepdown	Bootsma, H. 1995(B)	1b	SLE	24	x	PR±CYC/Ca (conventional treatment) for 3 years	0.00 (0/24)			4515
Stepdown	de Groot, K. 2009	1b	Vasculitis	149	x	PR/CYC IV or CYC oral for 1.5 years	0.01 (2/149)			7587
Stepdown	Mazlumzadeh, M. 2006(A)‡	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.21 (3/14)			6947
Stepdown	Mazlumzadeh, M. 2006(B)‡	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.23 (3/13)			3100
IM	Choy, E.H. 2005‡	1b	RA	48	43	120 mg MP IM monthly/DMARD vs DMARD for 2 years	0.02 (2/48)	0.00 (0/43)	4.7 (0.2-100)	3600
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value	
Chronic medium		121	9.4	0.01-0.16		1 study, 41 vs 36		7.9 (1.6-38)	2.6	
Chronic high		124	43.3	0.02						
Stepdown		222	11.0	0.00-0.23						
IM		48	4.9	0.02		1 study, 48 vs 43		4.7 (0.2-100)	1.0	

\* routinely spinal X-ray; ‡ routinely DXA performed; # not routinely DXA performed

Adverse event: Non-specified infections										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	van der Veen, M.J. 1996(A)	1b	PMR/GCA	40	x	PR/Ca for 1 year (follow up 2 years)	0.03 (2/40)			2947
Chronic medium	van der Veen, M.J. 1996(B)	1b	PMR/GCA	40	x	PR/Ca/MTX for 1 year (follow up 2 years)	0.06 (5/40)			2400
Chronic medium	Salvarani, C. 2007(A)	1b	PMR	28	x	PR for 0.33 year	0.00 (0/28)			910
Chronic medium	Salvarani, C. 2007(B)	1b	PMR	23	x	PR/Infliximab for 0.33 year	0.13 (1/23)			910
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.00 (1/117)	0/00 (0/119)	3.1 (0.1-76)	7300
Chronic medium	Joint Committee Report, 1959	1b	RA	41	36	PR vs Aspirin for 2 years	0.05 (4/41)	0.04 (3/36)	1.2 (0.2-5.7)	9928
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.01 (1/40)	0.02 (2/41)	0.5 (0.0-5.7)	7300
Chronic medium	Empire, 1957	1b	RA	49	50	Cortisone vs Aspirin for 3 years	0.03 (4/49)	0.02 (3/50)	1.4 (0.3-6.6)	14782
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.19 (8/21)			5490
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.24 (10/21)			5490
Stepdown	Chevalet, P. 2000(A)	1b	GCA	61	x	once MP 240 mg IV/0.7 mg/kg PR/Ca-Vit D for 1 year	0.25 (15/61)			5777
Stepdown	Chevalet, P. 2000(B)	1b	GCA	53	x	0.7 mg/kg PR/Ca-Vit D for 1 year	0.11 (6/53)			5578
Stepdown	Chevalet, P. 2000(C)	1b	GCA	50	x	once MP 240 mg IV/0.5 mg/kg PR/Ca-Vit D for 1 year	0.20 (10/50)			5168
Stepdown	Boers, M. 1997	1b	RA	76	79	PR/SSZ/MTX vs SSZ for >1 year	0.16 (12/76)	0.08 (6/79)	2.3 (0.8-6.4)	2345
Stepdown	Choy, E.H. 2008(A)	1b	RA	115	x	PR/MTX for 0.75 year	0.05 (4/115)			>1135
Stepdown	Choy, E.H. 2008(B)	1b	RA	116	x	PR/MTX/cyclo for 0.75 year	0.02 (2/116)			>1135
Stepdown	de Groot, K. 2009	1b	Vasculitis	149	x	PR/CYC IV or CYC oral for 1.5 years	0.23 (51/149)			7587
Stepdown	Pagnoux, C. 2008(A)	1b	Vasculitis	63	x	induction MP/CYC IV. then PR/AZA for 2.2 years	0.14 (19/63)			10760
Stepdown	Pagnoux, C. 2008(B)	1b	Vasculitis	63	x	induction MP/CYC IV. then PR/MTX for 2.2 years	0.18 (25/63)			10760
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value		
Chronic medium		378	9.6	0.00-0.13		4 studies. 247 vs 246	1.3 (0.5-3.2)	0.5		
Stepdown		788	10.5	0.02-0.25		1 study. 76 vs 79	2.3 (0.8-6.4)	1.6		

Adverse event: Upper respiratory tract infections											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Verschuereen, P. 2008(A)	2a	RA	19	x	PR/SSZ/MTX for 2 years	0.03 (1/19)			2603	
Chronic medium	Verschuereen, P. 2008(B)	2a	RA	52	x	PR/step up DMARD for 2 years	0.00 (0/52)			997	
Stepdown	Herrlinger, K.R. 2006	1b	CD	24	27	PR 60 mg/AZA vs rh IL11/AZA for 0.25 year	0.33 (2/24)			1890	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.21 (3/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.15 (2/13)			3100	
Stepdown	Wang, H.Y. 2003(A)*	2a	SLE	70	x	PR/LEF for 0.5 year	0.06 (2/70)			5894	
Stepdown	Wang, H.Y. 2003(B)*	2a	SLE	40	x	PR/CYC for 0.5 year	0.05 (1/40)			5894	
IM	Verstappen, S.M. 2010	1b	IP	133	132	MP IM 3x monthly vs Placebo (±DMARD) (follow up 1 year)	0.01 (1/133)	0.00 (0/132)	3.0 (0.1-74)	300	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		71	2.5	0.00-0.03							
Stepdown		161	22.6	0.05-0.33		1 study, 24 vs 27					
IM		133	0.8	0.01		1 study, 133 vs 132			3.0 (0.1-74)	0.7	

Adverse event: Lower respiratory tract infections											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.07 (4/30)			3266	
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.00 (0/117)	0.00 (1/119)	0.3 (0.0-8.3)	7300	
Chronic medium	van Everdingen, A.A. 2002*	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.16 (13/40)	0.16 (13/41)	1.0 (0.4-2.6)	7300	
Chronic high	Ritbi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.01 (4/124)			>7900	
Stepdown	Boers, M. 1997	1b	RA	76	79	PR/SSZ/MTX vs SSZ for >1 year	0.01 (1/76)	0.00 (0/79)	3.2 (0.1-79)	2345	
Stepdown	Spiers, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.06 (1/9)			5908	
Stepdown	Spiers, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.00 (0/9)			6469	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.07 (1/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)*	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.15 (2/13)			3100	
Stepdown	Choy, E.H. 2008 (A)	1b	RA	115	x	PR/MTX for 0.75 year	0.57 (49/115)			>1135	
Stepdown	Choy, E.H. 2008 (B)	1b	RA	116	x	PR/MTX/cyclo for 0.75 year	0.63 (55/116)			>1135	
Stepdown	Wang, H.Y. 2003(A)*	2a	SLE	70	x	PR/LEF for 0.5 year	0.03 (1/70)			5894	
Stepdown	Wang, H.Y. 2003(B)*	2a	SLE	40	x	PR/CYC for 0.5 year	0.05 (1/40)			5894	
Stepdown	Silva, F. 2010	2b	MPA	17	x	PR/MP IV induction/MMF/Cotrimoxazol for 0.5 year (follow up 1.5 y)	0.04 (1/17)			8200	
Stepdown	Wanchu, A. 2009	2b	SSc	36	x	PR/ CYC for 0.5 years	0.01 (1/36)			8260	
IM	Dasgupta, B. 1998(B)	1b	PMR	30	x	MP IM every 3 weeks for 1.8 years	0.06 (3/30)			1825	
IM	Verstappen, S.M. 2010	1b	IP	133	132	MP IM 3x monthly vs Placebo (±DMARD) (follow up 1 year)	0.03 (4/133)	0.01 (1/132)	4.1 (0.5-37)	300	
IV	Sharada, B. 1994	1b	SSC	17	18	100 mg IV dexamethasone per month vs placebo for 0.5 year	1.06 (9/17)	0.33 (3/18)	5.6 (1.2-27)	3996	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		287	8.3	0.00-0.16		2 study, 157 vs 160			0.9 (0.4-2.1)	0.2	
Chronic high		124	43.3	0.01							
Stepdown		518	19.5	0.00-0.63		1 study, 76 vs 79			3.2 (0.1-79)	0.7	
IM		163	1.8	0.03-0.06		1 study, 133 vs 132			4.1 (0.5-37)	1.2	
IV		17	21.9	1.06		1 study, 17 vs 18			5.6 (1.2-27)	2.2	

\* the AE could be recorded more than one time in one patient



Adverse event: Skin infections											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	van Everdingen, A.A. 2002*	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.00 (0/40)	0.06 (5/41)	0.1 (0.0-1.5)	7300	
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.06 (1/9)			5908	
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.04 (1/12)			6469	
Stepdown	Chevalet, P. 2000(A)	1b	GCA	61	x	once MP 240 mg IV/0.7 mg/kg PR/Ca-Vit D for 1 year	0.02 (1/61)			5777	
Stepdown	Chevalet, P. 2000(B)	1b	GCA	53	x	0.7 mg/kg PR/Ca-Vit D for 1 year	0.00 (0/53)			5578	
Stepdown	Chevalet, P. 2000(C)	1b	GCA	50	x	once MP 240 mg IV/0.5 mg/kg PR/Ca-Vit D for 1 year	0.08 (4/50)			5168	
IV	Sharada, B. 1994	1b	SSC	17	18	100 mg IV dexamethasone per month vs placebo for 0.5 year	0.24 (2/17)	0.22 (2/18)	1.1 (0.1-8.6)	3996	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		40	10	0,00		1 study. 40 vs 41	0.1 (0.0-1.5)	-1.7			
Stepdown		185	12.4	0.00-0.08							
IV		17	21.9	0.24		1 study. 17 vs 18	1.1 (0.1-8.6)	0.1			

\* the AE could be recorded more than one time in one patient

Adverse event: Urinary tract infections											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.02 (1/30)			3266	
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.12 (6/36)			2600	
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.14 (7/36)			2600	
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.04 (3/40)	0.02 (2/41)	1.6 (0.3-10)	7300	
Chronic medium	Tait, T.J. 1994	3	RA	15	x	PR/NSAID±DMARDs for 0.9 year	0.07 (1/15)			1680	
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.00 (3/124)			>7900	
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.06 (1/9)			5908	
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.04 (1/12)			6469	
Stepdown	Mazlumzadeh, M. 2006(A)*	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.21 (3/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)*	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.15 (2/13)			3100	
Stepdown	Wang, H.Y. 2003(A)* *	2a	SLE	70	x	PR/LEF for 0.5 year	0.00 (0/70)			5894	
Stepdown	Wang, H.Y. 2003(B)* *	2a	SLE	40	x	PR/CYC for 0.5 year	0.05 (1/40)			5894	
IM	Choy, E.H. 1993	1b	RA	21	x	120 mg MP IM/GOLD for 0.2 year	0.48 (2/21)			450	
IM	Corkill, M.M. 1990	1b	RA	35	24	MP 120 mg 3x/NSAID/GOLD vs Placebo/NSAID/GOLD for 0.5 year	0.06 (1/35)	0.00 (0/24)	2.1 (0.1-55)	450	
IM	Verstappen, S.M. 2010	1b	IP	133	132	MP IM 3x monthly vs Placebo (±DMARD) (follow up 1 year)	0.01 (1/133)	0.00 (0/132)	3.0 (0.1-74)	300	
Summary		All studies					Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		157	9.7	0.02-0.14		1 study. 40 vs 41	1.6 (0.3-10)	0.5			
Chronic high		124	43.3	0,00							
Stepdown		158	18.2	0.00-0.21							
IM		189	3.2	0.01-0.48		2 studies. 168 vs 156	2.5 (0.3-25)	0.8			

\* pyelonephritis

\* the AE could be recorded more than one time in one patient

Adverse event: Dyspepsia											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.06 (3/30)			3266	
Chronic medium	Salvarani, C. 2007(A)	1b	PMR	28	x	PR for 0.33 year	0.11 (1/28)			910	
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.04 (2/36)			2600	
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.12 (6/36)			2600	
Chronic medium	Tait, T.J. 1994	3	RA	15	x	PR/NSAID±DMARDs for 0.9 year	0.07 (1/15)			1680	
Chronic medium	Joint Committee Report, 1959*	1b	RA	41	36	PR vs Aspirin for 2 years	0.29 (24/41)	0.76 (55/36)	N/A	9928	
Chronic medium	Empire, 1957	1b	RA	49	50	Cortisone vs Aspirin for 3 years	0.01 (1/49)	0.02 (3/50)	0.3 (0.0-3.3)	14782	
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.09 (7/40)	0.04 (3/41)	2.7 (0.6-11)	7300	
Chronic medium	Reid, D.M. 2000(A)	1b	Different	96	x	PR/Ca-Vit D for 5.5 years	0.02 (9/96)			30240	
Chronic medium	Reid, D.M. 2000(B)	1b	Different	100	x	PR/Ca-Vit D/Risedronate for 5.5 years	0.02 (13/100)			30240	
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.33 (6/9)			5908	
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.42 (10/12)			6469	
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.02 (1/21)			5490	
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.07 (3/21)			5490	
Stepdown	Bar-Meir, S. 1998	1b	CD	101	x	PR 40 mg vs Budesonide (low dose) for 0.16 year	1.86 (30/101)			1295	
IM	Dasgupta, B. 1998(B)	1b	PMR	30	x	MP IM every 3 weeks for 1.8 years	0.09 (5/30)			1825	
Summary		All studies				Placebo-controlled studies					
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year	GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value			
Chronic medium		471	11.3	0.01-0.29	2 studies. 89 vs 91		1.5 (0.4-5.0)	0.6			
Stepdown		164	10.8	0.02-1.86							
IM		30	2.8	0.09							

\* the AE could be recorded more than one time in one patient

Adverse event: Gastroduodenal ulcer										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.01 (1/40)	0.02 (2/41)	0.5 (0.0-5.7)	7300
Chronic medium	Joint Committee Report, 1959	1b	RA	41	36	PR vs Aspirin for 2 years	0.04 (3/41)	0.00 (0/36)	6.6 (0.3-133)	9928
Chronic medium	Empire, 1957	1b	RA	49	50	Cortisone vs Aspirin for 3 years	0.01 (1/49)	0.00( 0/50)	3.1 (0.1-79)	14782
Chronic medium	Verschueren, P. 2008(A)	2a	RA	19	x	PR/SSZ/MTX for 2 years	0.00 (0/19)			2603
Chronic medium	Verschueren, P. 2008(B)	2a	RA	52	x	PR/step up DMARD for 2 years	0.01 (1/52)			997
Chronic medium	Reid, D.M. 2000(A)	1b	Different	96	x	PR/Ca-Vit D for 5.5 years	0.00 (1/96)			30240
Chronic medium	Reid, D.M. 2000(B)	1b	Different	100	x	PR/Ca-Vit D/Risedronate for 5.5 years	0.00 (0/100)			30240
Chronic medium	Guaydier-Souquieres G, 1996(A)	1b	Different	17	x	PR/Ca/MFP for 2 years	0.00 (0/17)			10600
Chronic medium	Guaydier-Souquieres G, 1996(B)	1b	Different	18	x	PR/Ca for 2 years	0.00 (0/18)			14200
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.00 (0/14)			6947
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.00 (0/13)			3100
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)		Odds ratio (95% CI)	Z-Value	
Chronic medium		432	11.8	0.00-0.04		3 studies. 130 vs 127		1.7 (0.3-8.8)	0.7	
Stepdown		27	13.8	0.00						

Adverse event: Cataract											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.02 (1/30)			3266	
Chronic medium	Salvarani, C. 2007(A)	1b	PMR	28	x	PR for 0.33 year	0.22 (2/28)			910	
Chronic medium	Ferraccioli, G.1996(A)	1b	PMR	12	x	PR for 1 year	0.00 (0/12)			3200	
Chronic medium	Ferraccioli, G.1996(B)	1b	PMR	12	x	PR/MTX for 1 year	0.33 (4/12)			1840	
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.04 (2/36)			2600	
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.00 (0/36)			2600	
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.00 (1/117)	0.00 (0/119)	3.1 (0.1-76)	7300	
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.01 (1/40)	0.01 (1/41)	1.0 (0.1-17)	7300	
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.02 (12/124)			>7900	
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.05 (2/21)			5490	
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.02 (1/21)			5490	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.07 (1/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.00 (0/13)			3100	
Stepdown	de Groot, K. 2009	1b	Vasculitis	149	x	PR/CYC IV or CYC oral for 1.5 years	0.01 (3/149)			7587	
Summary		All studies				Placebo-controlled studies					
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		311	9.3	0.00-0.33		2 study. 157 vs 160	2.1 (0.2-23)	0.6			
Chronic high		124	43.3	0.02							
IM		218	11.3	0.00-0.07							

Adverse event: Glaucoma											
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg	
				GC+	GC-		GC+	GC-			
Chronic medium	Dasgupta, B. 1998(A)	1b	PMR	30	x	PR for 1.8 years	0.04 (2/30)			3266	
Chronic medium	Bakker, M.F. 2012	1b	RA	117	119	PR 10mg/MTX/Bisphos./CaVit D vs MTX /Bisphos./CaVit D for 2 years	0.00 (0/117)	0.00 (1/119)	0.3 (0.0-8.3)	7300	
Chronic medium	van Everdingen, A.A. 2002	1b	RA	40	41	PR/NSAID vs Placebo/NSAID for 2 years	0.01 (1/40)	0.00 (0/41)	3.2 (0.1-80)	7300	
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.01 (4/124)			>7900	
Stepdown	Mazlumzadeh, M. 2006(A)	1b	GCA	14	x	PR/3 g MP IV/Ca-Vit D for 1 year	0.07 (1/14)			6947	
Stepdown	Mazlumzadeh, M. 2006(B)	1b	GCA	13	x	PR/Placebo/Ca-Vit D for 1 year	0.00 (0/13)			3100	
IM	Dasgupta, B. 1998 (B)	1b	PMR	30	x	MP IM every 3 weeks for 1.8 years	0.02 (1/30)			1825	
IV	Williams, I.A. 1982	1b	RA	10	10	once 1 g MP IV vs Placebo IV (follow up 0.1 year)	1.00 (1/10)	0.00 (0/10)	3.3 (0.1-92)	1250	
Summary		All studies				Placebo-controlled studies					
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value			
Chronic medium		187	8.3	0.00-0.04		2 study. 157 vs 160	1.0 (0.1-16)	0.01			
Chronic high		124	43.3	0,00							
Stepdown		27	13.8	0.00-0.07							
IM		30	2.8	0.02							
IV		10	34.2	1,00		1 study. 10 vs 10	3.3 (0.1-92)	0.7			

Adverse event: Mood disturbance										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	Joint Committee Report, 1959* <sup>x</sup>	1b	RA	41	36	PR vs Aspirin for 2 years	0.04 (3/41)	0.01 (1/36)	2.8 (0.3-28)	9928
Chronic medium	Rhodes, J.M. 2007(A)*	1b	UC	59	x	Predocol 40 mg/Mesalazine/AZA for 0.5 year	0.34 (10/59)			4500
Chronic high	Rhodes, J.M. 2007(B)*	1b	UC	61	x	Predocol 60 mg/Mesalazine/AZA for 0.5 year	0.30 (9/61)			6840
Stepdown	Rhodes, J.M. 2007(C)*	1b	UC	61	x	PR/Mesalazine/AZA for 0.5 year	0.72 (22/61)			1365
Stepdown	Campieri, M. 1997	1b	CD	58	x	PR/AZA/Metronidazole vs low dose budesonide for 0.25 year	0.48 (7/58)			3605
Stepdown	Rutgeerts, P. 1994	1b	CD	88	x	PR vs Budesonide (low dose) for 0.2 year	0.34 (6/88)			1680
Stepdown	Spiera, R.F. 2001(A)	1b	GCA	9	x	PR/Ca-Vit D for 2 years	0.50 (9/9)			5908
Stepdown	Spiera, R.F. 2001(B)	1b	GCA	12	x	PR/MTX/Ca-Vit D for 2 years	0.50 (12/12)			6469
IM	Verstappen, S.M. 2010	1b	IP	133	132	MP IM 3x monthly vs Placebo (±DMARD) (follow up 1 year)	0.01 (1/133)	0.00 (0/132)	3.0 (0.1-74)	300
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value		
Chronic medium		100	19.1	0.04-0.34		1 study, 41 vs 36		2.8 (0.3-28)		0.9
Chronic high		61	37.5	0.3						
Stepdown		228	18.3	0.34-0.72						
IM		133	0.8	0.01		1 study, 133 vs 132		3.0 (0.1-74)		0.7

\* euphoria

<sup>x</sup> the AE could be recorded more than one time in one patient

Adverse event: Psychological or psychiatric disorders										
GC dose and pattern	Study	Design	Disease	Patients (n)		Intervention	Events/patient year		Odds ratio (95% CI)	Cumulative dose in mg
				GC+	GC-		GC+	GC-		
Chronic medium	Caporali, R. 2004(A)	1b	PMR	36	x	PR for 0.5 year (follow up 1.4 years)	0.10 (5/36)			2600
Chronic medium	Caporali, R. 2004(B)	1b	PMR	36	x	PR/MTX for 0.5 year (follow up 1.4 years)	0.06 (3/36)			2600
Chronic medium	Verschueren, P. 2008(B)	2a	RA	52	x	PR/step up DMARD for 2 years	0.01 (1/52)			997
Chronic medium	Joint Committee Report, 1959*	1b	RA	41	36	PR vs Aspirin for 2 years	0.02 (2/41)	0.00 (0/36)	4.6 (0.2-99)	9928
Chronic high	Ribi, C. 2010	1b	MPA/PAN	124	x	PR/MP IV with AZA or CYC IV for 0.5 years (follow up 5.2 years)	0.00 (2/124)			>7900
Stepdown	Chevalet, P. 2000(A)	1b	GCA	61	x	once MP 240 mg IV/0.7 mg/kg PR/Ca-Vit D for 1 year	0.10 (6/61)			5777
Stepdown	Chevalet, P. 2000(B)	1b	GCA	53	x	0.7 mg/kg PR/Ca-Vit D for 1 year	0.04 (2/53)			5578
Stepdown	Chevalet, P. 2000(C)	1b	GCA	50	x	once MP 240 mg IV/0.5 mg/kg PR/Ca-Vit D for 1 year	0.10 (5/50)			5168
Stepdown	Jover, J.A. 2001(A)	1b	GCA	21	x	PR/Ca-Vit D for 2 years	0.24 (10/21)			5490
Stepdown	Jover, J.A. 2001(B)	1b	GCA	21	x	PR/MTX/Ca-Vit D for 2 years	0.19 (8/21)			5490
Stepdown	Pagnoux, C. 2008(A)	1b	Vasculitis	63	x	induction MP/CYC IV. then PR/AZA for 2.2 years	0.01 (1/63)			10760
Stepdown	Pagnoux, C. 2008(B)	1b	Vasculitis	63	x	induction MP/CYC IV. then PR/MTX for 2.2 years	0.01 (2/63)			10760
Stepdown	Bootsma, H. 1995(A)	1b	SLE	22	x	PR±CYC/Ca (early treatment) for 3 years	0.00 (0/22)			8052
Stepdown	Bootsma, H. 1995(B)	1b	SLE	24	x	PR±CYC/Ca (conventional treatment) for 3 years	0.00 (0/24)			4515
Summary		All studies				Placebo-controlled studies				
		GC+ patients (n)	Mean daily PR equivalent dose (mg)	Range of AE-rate per patient year		GC+ patients vs GC- patients (n)	Odds ratio (95% CI)	Z-Value		
Chronic medium		165	10.9	0.01-0.10		1 study, 41 vs 36		4.6 (0.2-99)		1.0
Chronic high		124	43.3	0.00						
Stepdown		378	11.2	0.00-0.24						

\* psychosis

Adverse event: Osteoporosis BMD total (means)												
Study	Design	Disease	GC dose and pattern	Patients (n)		Intervention	Cumulative dose in mg	Timepoint assessment	Change in BMD (g/cm <sup>2</sup> ) with baseline (%)		Value	
				GC+	GC-				GC +	GC-	Baseline	End
Nordborg, E. 1999(A)	1b	GCA	Chronic medium	14	x	PR/Clodronate/Ca for 1 year	3700	1 year	minus 1.0	x	1.06	1.07
Nordborg, E. 1999(B)	1b	GCA	Chronic medium	13	x	PR/Ca for 1 year	3900	1 year	minus 2.0	x	1.02	1.04
Frediani, B. 2003(A)	1b	RA	Chronic medium	31	x	MP oral/MTX/SSZ for 1 year	3060	1 year	minus 7.8	x	1.06	0.98
Mok, C.C. 2008	2b	SLE	Stepdown	29	x	PR/Ca-Vit D for 0.5 year	>7900	0.5 year	minus 0.7	x	1.06	1.05
Frediani, B. 2003(B)	1b	RA	IV	31	x	MP IV/MTX/SSZ for 1 year	18750	1 year	minus 7.1	x	1.05	0.98
Summary		All studies										
Range of change in BMD compared with baseline (%)		GC+ patients (n)		Mean daily PR equivalent dose (mg)								
Chronic medium	minus 7.8 - minus 1.0	58	9.7									
Stepdown	minus 0.7	29	43.3									
IV	minus 7.1	31	51.4									

Adverse event: Osteoporosis BMD lumbar spine (means)												
Study	Design	Disease	GC dose and pattern	Patients (n)		Intervention	Cumulative dose in mg	Timepoint assessment	Change in BMD (g/cm <sup>2</sup> ) with baseline (%)		Value	
				GC+	GC-				GC +	GC-	Baseline	End
Guaydier-Souquieres, G. 1996(A)	1b	Different	Chronic medium	17	x	PR/Ca/MFP for 2 years	10600	2 years	11.0	x	0.91	0.99
Guaydier-Souquieres, G. 1996(B)	1b	Different	Chronic medium	18	x	PR/Ca for 2 years	14200	2 years	1.2	x	0.93	0.93
Reid, D.M. 2000(A)	1b	Different	Chronic medium	96	x	PR/Ca-Vit D for 5.5 years	30240	1 year	0.4	x	x	x
Reid, D.M. 2000(B)	1b	Different	Chronic medium	100	x	PR/Ca-Vit D/Risedronate for 5.5 years	30240	1 year	2.9	x	x	x
Bernstein, C.N. 1996(A)	1b	IBD	Chronic medium	9	x	PR/Ca-Vit D	>5071	1 year	3.3	x	x	x
Bernstein, C.N. 1996(B)	1b	IBD	Chronic medium	8	x	PR	>4514	1 year	0.6	x	x	x
Boutsen, Y. 1997(A)	1b	Different	Chronic medium	14	x	PR/Ca/Pamidronate for 1 year	5726	1 year	3.6	x	0.86	x
Boutsen, Y. 1997(B)	1b	Different	Chronic medium	13	x	PR/CA for 1 year	4027	1 year	minus 5.3	x	0.96	x
Frediani, B. 2003(A)	1b	RA	Chronic medium	31	x	MP oral/MTX/SSZ for 1 year	3060	1 year	minus 9.0	x	1.00	0.9
Verhoeven, A.C. 2001(A)	1b	RA	Stepdown	76	79	PR/SSZ/MTX for 1 year	2345	1 year	minus 1.4	minus 0.4	1.13	x
Verhoeven, A.C. 2001(B)	1b	RA	Stepdown	76	79	SSZ for 1 year	0	1 year	minus 1.4	minus 0.4	1.11	x
Mok, C.C. 2008	2b	SLE	Stepdown	29	x	PR/Ca-Vit D for 0.5 year	>7900	0.5 year	minus 0.5	x	0.96	0.95
Choy, E.H. 2005(A)*	1b	RA	IM	48	43	DMARD/120 mg MP monthly for 2 years	3600	0.5 year	minus 18.0*	minus 1*	minus 0.39*	minus 0.46*
Choy, E.H. 2005(B)*	1b	RA	IM	48	43	DMARD for 2 years	0	0.5 year	minus 18.0*	minus 1*	minus 0.60*	minus 0.61*
Frediani, B. 2003(B)	1b	RA	IV	31	x	MP IV/MTX/SSZ for 1 year	18750	1 year	minus 5.2	x	1.00	x
Summary		All studies										
Range of change in BMD compared with baseline (%)		GC+ patients (n)		Mean daily PR equivalent dose (mg)								
Chronic medium	minus 9.0 - 11.0	306	13.9									
Stepdown	minus 1.4 - minus 0.5	105	24.9									
IM	minus 18.0	48	4.9									
IV	minus 5.2	31	51.4									

\* T-score instead of BMD

Adverse event: Osteoporosis BMD femoral trochanter (means)												
Study	Design	Disease	GC dose and pattern	Patients (n)		Intervention	Cumulative dose in mg	Timepoint assessment	Change in BMD (g/cm <sup>2</sup> ) with baseline (%)		Value	
				GC+	GC-				GC +	GC-	Baseline	End
Reid. D.M. 2000(A)	1b	Different	Chronic medium	96	x	PR/Ca-Vit D for 5.5 years	30240	1 year	1.0	x	x	x
Reid. D.M. 2000(B)	1b	Different	Chronic medium	100	x	PR/Ca-Vit D/Risedronate for 5.5 years	30240	1 year	2.4	x	x	x
Boutsen. Y. 1997(A)	1b	Different	Chronic medium	14	x	PR/Ca/Pamidronate for 1 year	5726	1 year	3.3	x	x	x
Boutsen. Y. 1997(B)	1b	Different	Chronic medium	13	x	PR/CA for 1 year	4027	1 year	minus 3.1	x	x	x
Summary		All studies										
Range of change in BMD compared with baseline (%)		GC+ patients (n)		Mean daily PR equivalent dose (mg)								
Chronic medium		minus 3.1 - 3.3		223		14.2						

Adverse event: Osteoporosis BMD femoral neck (means)												
Study	Design	Disease	GC dose and pattern	Patients (n)		Intervention	Cumulative dose in mg	Timepoint assessment	Change in BMD (g/cm <sup>2</sup> ) with baseline (%)		Value	
				GC+	GC-				GC +	GC-	Baseline	End
Reid. D.M. 2000(A)	1b	Different	Chronic medium	96	x	PR/Ca-Vit D for 5.5 years	30240	1 year	minus 0.3	x	x	x
Reid. D.M. 2000(B)	1b	Different	Chronic medium	100	x	PR/Ca-Vit D/Risedronate for 5.5 years	30240	1 year	1.8	x	x	x
Boutsen. Y. 1997(A)	1b	Different	Chronic medium	14	x	PR/Ca/Pamidronate for 1 year	5726	1 year	2.2	x	0.72	x
Boutsen. Y. 1997(B)	1b	Different	Chronic medium	13	x	PR/CA for 1 year	4027	1 year	minus 5.3	x	0.71	x
Frediani. B. 2003(A)	1b	RA	Chronic medium	31	x	MP oral/MTX/SSZ for 1 year	3060	1 year	minus 10.0	x	0.87	0.78
Verhoeven. A.C. 2001(A)	1b	RA	Stepdown	76	79	PR/SSZ/MTX for 1 year	2345	1 year	minus 1.4	minus 1.3	0.93	x
Verhoeven. A.C. 2001(B)	1b	RA	Stepdown	76	79	SSZ for 1 year	0	1 year	minus 1.4	minus 1.3	0.92	x
Frediani. B. 2003(B)	1b	RA	IV	31	x	MP IV/MTX/SSZ for 1 year	18750	1 year	minus 5.2	x	0.87	0.83
Summary		All studies										
Range of change in BMD compared with baseline (%)		GC+ patients (n)		Mean daily PR equivalent dose (mg)								
Chronic medium		minus 10.0 - 2.2		254		13.0						
Stepdown		minus 1.4		76		6.4						
IV		minus 5.2		31		51.4						

Adverse event: Osteoporosis BMD total hip (means)													
Study	Design	Disease	GC dose and pattern	Patients (n)		Intervention	Cumulative dose in mg	Timepoint assessment	Change in BMD with baseline (%)		Value		
				GC+	GC-				GC +	GC-	Baseline	End	
Bernstein, C.N. 1996(A)	1b	IBD	Chronic medium	9	x	PR/Ca-Vit D	>5071	1 year	3.3	x	x	x	
Bernstein, C.N. 1996(B)	1b	IBD	Chronic medium	8	x	PR	>4514	1 year	0.6	x	x	x	
van Schaardenburg, D. 1995	1b	RA	Chronic medium	28	28	PR vs HCQ for 2 years	5840	2 years	minus 6.8	minus 4.8	x	x	
Boutsen, Y. 1997(A)	1b	Different	Chronic medium	14	x	PR/Ca/Pamidronate for 1 year	5726	1 year	1.9	x	x	x	
Boutsen, Y. 1997(B)	1b	Different	Chronic medium	13	x	PR/CA for 1 year	4027	1 year	minus 3.4	x	x	x	
Mok, C.C. 2008	2b	SLE	Stepdown	29	x	PR/Ca-Vit D for 0.5 year	>7900	0.5 year	minus 1.7	x	0.85	0.83	
Choy, E.H. 2005(A)*	1b	RA	IM	48	43	DMARD/120 mg MP monthly for 2 years	3600	0.5 year	minus 15.0*	minus 6*	minus 0.84*	minus 0.97*	
Choy, E.H. 2005(B)*	1b	RA	IM	48	43	DMARD for 2 years	0	0.5 year	minus 15.0*	minus 6*	minus 1.35*	minus 1.44*	
Summary		All studies											
Range of change in BMD compared with baseline (%)		GC+ patients (n)		Mean daily PR equivalent dose (mg)									
Chronic medium		minus 6.8 - 3.3		72		12.2							
Stepdown		minus 1.7		29		43.3							
IM		minus 15.0*		48		4.9							

\*T-score instead of BMD

Adverse event: Weight gain (means)										
Study	Design	Disease	Patients (n)		GC dose pattern	Intervention	Cumulative dose in mg	GC+ (mean)	GC- (mean)	
			GC+	GC-						
Frediani, B. 2003(A)	1b	RA	31	x	Chronic medium	MP oral/MTX/SSZ for 1 year	3060	1.8 kg	?	
Bakker, M.F. 2012	1b	RA	117	119	Chronic medium	PR/MTX/Bisphos./Ca-Vit D vs MTX/Bisphos./Ca-Vit D for 2 years	7300	2.9kg	1.3kg	
van Everdingen, A.A. 2002	1b	RA	40	41	Chronic medium	PR/NSAID vs Placebo/NSAID for 2 years	7300	1 kg	?	
Boers, M. 1997*	1b	RA	76	79	Stepdown	PR/SSZ/MTX vs SSZ for 1 year	2345	3 kg	1.5 kg	
Mok, C.C. 2008	2b	SLE	29	x	Stepdown	PR/Ca-Vit D for 0.5 year	2700	2.5 kg	?	
Frediani, B. 2003(B)	1b	RA	31	x	IV	MP IV/MTX/SSZ for 1 year	18750	1.2 kg	?	
Summary		All studies								
Range of change in BMD compared with baseline (%)		GC+ patients (n)		Mean daily PR equivalent dose (mg)						
Chronic medium		188		9.5						
Stepdown		105		10.6						
IV		31		51.4						



## APPENDIX 3

### Proposition-specific searches

Literature searches for evidence supporting the 10 recommendations.  
Date of search: 16-05-2012.

#### Recommendation 1

##### Pubmed, 1666 hits

((“adrenal cortex hormone”[Tiab] OR “adrenal cortical hormone”[Tiab] OR “adrenal cortex steroid”[Tiab] OR “adrenal cortical steroid”[Tiab] OR “adrenal steroid hormone”[Tiab] OR “adrenocortical hormone”[Tiab] OR “adrenocortical steroid”[Tiab] OR corticosteroid\*[Tiab] OR corticoid\*[Tiab] OR cortison\*[Tiab] OR cortisol\*[Tiab] OR hydrocortison\*[Tiab] OR dexamethason\*[Tiab] OR methylpredniso\*[Tiab] OR deflazacort\*[Tiab] OR glucocort\*[Tiab] OR predniso\*[Tiab] OR “Glucocorticoids”[MESH]) AND (“drug information”[Tiab] OR “patient information”[Tiab] OR “counseling”[Tiab] OR “counselling”[Tiab] OR “information session”[Tiab] OR “information leaflet”[Tiab] OR “information booklet”[Tiab] OR “information brochure”[Tiab] OR “information folder”[Tiab] OR “information pamphlet”[Tiab] OR “written information”[Tiab] OR “spoken information”[Tiab] OR “oral information”[Tiab] OR educat\*[Tiab] OR “patient education”[Tiab] OR “patient instruction”[Tiab] OR “patient perspective”[Tiab] OR “patient perspectives”[Tiab] OR “patients perspective”[Tiab] OR “patients perspectives”[Tiab] OR “rheumatologist perspective”[Tiab] OR “rheumatologist perspectives”[Tiab] OR “rheumatologists perspective”[Tiab] OR “rheumatologists perspectives”[Tiab] OR “doctor perspective”[Tiab] OR “doctor perspectives”[Tiab] OR “doctors perspective”[Tiab] OR “doctors perspectives”[Tiab] OR “physician perspective”[Tiab] OR “physician perspectives”[Tiab] OR “physicians perspective”[Tiab] OR “physicians perspectives”[Tiab] OR “patient viewpoint”[Tiab] OR “patient viewpoints”[Tiab] OR “patients viewpoint”[Tiab] OR “patients viewpoints”[Tiab]))

##### Embase, 1988 hits

((‘adrenal cortex hormone’ OR ‘adrenal cortical hormone’ OR ‘adrenal cortex steroid’ OR ‘adrenal cortical steroid’ OR ‘adrenal steroid hormone’ OR ‘adrenocortical hormone’ OR ‘adrenocortical steroid’ OR corticosteroid\* OR corticoid\* OR cortison\* OR cortisol\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\*) AND (‘drug information’ OR ‘patient information’ OR ‘counseling’ OR ‘counselling’ OR ‘information session’ OR ‘information leaflet’ OR ‘information booklet’ OR ‘information brochure’ OR ‘information folder’ OR ‘information pamphlet’ OR ‘written information’ OR ‘spoken information’ OR ‘oral information’ OR educat\* OR ‘patient education’ OR ‘patient instruction’ OR ‘patient perspective’ OR ‘patient perspectives’ OR ‘patients perspective’ OR ‘patients perspectives’ OR ‘rheumatologist perspective’ OR ‘rheumatologist perspectives’ OR ‘rheumatologists perspective’ OR ‘rheumatologists perspectives’ OR ‘doctor perspective’ OR ‘doctor perspectives’ OR ‘doctors perspective’ OR ‘doctors perspectives’ OR ‘physician perspective’ OR ‘physician perspectives’ OR ‘physicians perspective’ OR ‘physicians perspectives’ OR ‘patient viewpoint’ OR ‘patient viewpoints’ OR ‘patients viewpoint’ OR ‘patients viewpoints’)):ti:ab

##### Cochrane Library, 290 hits

((“adrenal cortex hormone” OR “adrenal cortical hormone” OR “adrenal cortex steroid” OR “adrenal cortical steroid” OR “adrenal steroid hormone” OR “adrenocortical hormone” OR “adrenocortical steroid” OR corticosteroid\* OR corticoid\* OR cortison\* OR cortisol\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR “Glucocorticoids”[MESH]) AND (“drug information” OR “patient information” OR “counseling” OR “counselling” OR “information session” OR “information leaflet” OR “information booklet” OR “information brochure” OR “information folder” OR “information

pamphlet" OR "written information" OR "spoken information" OR "oral information" OR educat\* OR "patient education" OR "patient instruction" OR "patient perspective" OR "patient perspectives" OR "patients perspective" OR "patients perspectives" OR "rheumatologist perspective" OR "rheumatologist perspectives" OR "rheumatologists perspective" OR "rheumatologists perspectives" OR "doctor perspective" OR "doctor perspectives" OR "doctors perspective" OR "doctors perspectives" OR "physician perspective" OR "physician perspectives" OR "physicians perspective" OR "physicians perspectives" OR "patient viewpoint" OR "patient viewpoints" OR "patients viewpoint" OR "patients viewpoints")):ti,ab,kw

Inclusion criteria:

- Patients (or family/carers/physicians) on/starting GC therapy
- Informing on GC therapy

Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports
- Letters, editorials
- Congress abstracts
- Reviews

Search result: 2549 articles retrieved (duplicates excluded)

Best level of evidence supporting the recommendation in asthma or COPD: I-B

Best level of evidence supporting the recommendation in rheumatic diseases: 3

Van der Goes: patients underline their wish for more information regarding GC therapy; information about GC therapy should be given over time, in small steps

Helliwell: lack of effective communication could be a reason for termination of DMARD therapy (among which GCs) in South Asian people in UK

## Recommendation 2

### Pubmed, 2767 hits

((“adrenal cortex hormone”[Tiab] OR “adrenal cortical hormone”[Tiab] OR “adrenal cortex steroid”[Tiab] OR “adrenal cortical steroid”[Tiab] OR “adrenal steroid hormone”[Tiab] OR “adrenocortical hormone”[Tiab] OR “adrenocortical steroid”[Tiab] OR corticosteroid\*[Tiab] OR corticoid\*[Tiab] OR cortison\*[Tiab] OR hydrocortison\*[Tiab] OR dexamethason\*[Tiab] OR methylpredniso\*[Tiab] OR deflazacort\*[Tiab] OR glucocort\*[Tiab] OR predniso\*[Tiab] OR “Glucocorticoids”[MESH]) AND (nutrition[Tiab] OR diet[Tiab] OR food\*[Tiab] OR weight[Tiab] OR appetite[Tiab] OR sport\*[Tiab] OR training\*[Tiab] OR exercise\*[Tiab] OR “physical activity”[Tiab] OR “weight bearing activity”[Tiab] OR “weight-bearing activity”[Tiab] OR osteoporosis[Tiab] OR wound\*[Tiab]) AND (prevent\*[Tiab] OR mitigat\*[Tiab] OR counterbalance\*[Tiab] OR “risk reduction”[Tiab] OR “risk decrease”[Tiab]))

### Embase, 3028 hits

((‘adrenal cortex hormone’ OR ‘adrenal cortical hormone’ OR ‘adrenal cortex steroid’ OR ‘adrenal cortical steroid’ OR ‘adrenal steroid hormone’ OR ‘adrenocortical hormone’ OR ‘adrenocortical steroid’ OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\*) AND (nutrition OR diet OR food\* OR weight OR appetite OR sport\* OR training\* OR exercise\* OR ‘physical activity’ OR ‘weight bearing activity’ OR ‘weight-bearing activity’ OR osteoporosis OR wound\*) AND (prevent\* OR mitigat\* OR counterbalance\* OR ‘risk reduction’ OR ‘risk decrease’)):ti:ab

### Cochrane Library, 434 hits

((“adrenal cortex hormone” OR “adrenal cortical hormone” OR “adrenal cortex steroid” OR “adrenal cortical steroid” OR “adrenal steroid hormone” OR “adrenocortical hormone” OR “adrenocortical steroid” OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR “Glucocorticoids”[MESH]) AND (nutrition OR diet OR food\* OR weight OR appetite OR sport\* OR training\* OR exercise\* OR “physical activity” OR “weight bearing activity” OR “weight-bearing activity” OR osteoporosis OR wound\*) AND (prevent\* OR mitigat\* OR counterbalance\* OR “risk reduction” OR “risk decrease”)):ti,ab,kw

### Inclusion criteria:

- Patients on/starting GC therapy
- Studies focused on diet, exercise or wound care (as preventive or therapeutic measure for GC induced adverse effects)

### Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports
- Letters, editorials
- Congress abstracts
- Reviews
- Studies on topical, intranasal, inhaled or enema GCs

Search result: 3906 articles retrieved (duplicates excluded)

Best level of evidence supporting the recommendation in transplants and chronic obstructive pulmonary disease patients: I-B

Beneficial effects of exercise on muscle strength and BMD.

Best level of evidence supporting the recommendation in rheumatic diseases: III-IV  
Tourinho (72% of patients on GCs, mean 7.3 mg): moderate physical activity reduced the risk of osteopenia by 50%; sedentarism and low weight are the main factors associated with bone loss.

Madsen (most patients are/were on GCs): quadriceps strenght is associated with BMD.

NB: No evidence on diet and wound care available to support the recommendation.

### Recommendation 3

#### Pubmed, 927 hits

((“steroid induced osteoporosis”[Tiab] OR “steroid-induced osteoporosis”[Tiab] OR “corticosteroid induced osteoporosis”[Tiab] OR “corticosteroid-induced osteoporosis”[Tiab] OR “glucocorticosteroid induced osteoporosis”[Tiab] OR “glucocorticosteroid-induced osteoporosis”[Tiab] OR “glucocorticoid induced osteoporosis”[Tiab] OR “glucocorticoid-induced osteoporosis”[Tiab] OR “steroid induced bone loss”[Tiab] OR “steroid-induced bone loss”[Tiab] OR “corticosteroid induced bone loss”[Tiab] OR “corticosteroid-induced bone loss”[Tiab] OR “glucocorticosteroid induced bone loss”[Tiab] OR “glucocorticosteroid-induced bone loss”[Tiab] OR “glucocorticoid induced bone loss”[Tiab] OR “glucocorticoid-induced bone loss”[Tiab] OR GIOP[Tiab] OR (Glucocorticoids[Mesh] AND osteoporosis[Mesh])) AND (prophylaxis[Tiab] OR prevention[Tiab] OR preventive[Tiab] OR bisphosphonate\*[Tiab] OR alendronate[Tiab] OR zoledron\*[Tiab] OR ibandronate[Tiab] OR neridronate[Tiab] OR etidronate[Tiab] OR risedronate[Tiab] OR teriparatide[Tiab] OR PTH[Tiab] OR raloxi\*[Tiab] OR calcitonin\*[Tiab] OR calcium[Tiab] OR “vitamin D”[Tiab] OR “vitamin D3”[Tiab] OR hydroxycholecalciferol[Tiab] OR alphacalcidol[Tiab]))

#### Embase, 827 hits

((‘steroid induced osteoporosis’ OR ‘steroid-induced osteoporosis’ OR ‘corticosteroid induced osteoporosis’ OR ‘corticosteroid-induced osteoporosis’ OR ‘glucocorticosteroid induced osteoporosis’ OR ‘glucocorticosteroid-induced osteoporosis’ OR ‘glucocorticoid induced osteoporosis’ OR ‘glucocorticoid-induced osteoporosis’ OR ‘steroid induced bone loss’ OR ‘steroid-induced bone loss’ OR ‘corticosteroid induced bone loss’ OR ‘corticosteroid-induced bone loss’ OR ‘glucocorticosteroid induced bone loss’ OR ‘glucocorticosteroid-induced bone loss’ OR ‘glucocorticoid induced bone loss’ OR ‘glucocorticoid-induced bone loss’ OR GIOP) AND (prophylaxis OR prevention OR preventive OR bisphosphonate\* OR alendronate OR zoledron\* OR ibandronate OR neridronate OR etidronate OR risedronate OR teriparatide OR PTH OR raloxi\* OR calcitonin\* OR calcium OR ‘vitamin D’ OR ‘vitamin D3’ OR hydroxycholecalciferol OR alphacalcidol)):ti:ab

#### Cochrane Library, 186 hits

((“steroid induced osteoporosis” OR “steroid-induced osteoporosis” OR “corticosteroid induced osteoporosis” OR “corticosteroid-induced osteoporosis” OR “glucocorticosteroid induced osteoporosis” OR “glucocorticosteroid-induced osteoporosis” OR “glucocorticoid induced osteoporosis” OR “glucocorticoid-induced osteoporosis” OR “steroid induced bone loss” OR “steroid-induced bone loss” OR “corticosteroid induced bone loss” OR “corticosteroid-induced bone loss” OR “glucocorticosteroid induced bone loss” OR “glucocorticosteroid-induced bone loss” OR “glucocorticoid induced bone loss” OR “glucocorticoid-induced bone loss” OR GIOP OR (Glucocorticoids[Mesh] AND osteoporosis[Mesh])) AND (prophylaxis OR prevention OR preventive OR bisphosphonate\* OR alendronate OR zoledron\* OR ibandronate OR neridronate OR etidronate OR risedronate OR teriparatide OR PTH OR raloxi\* OR calcitonin\* OR calcium OR “vitamin D” OR “vitamin D3” OR hydroxycholecalciferol OR alphacalcidol)):ti,ab,kw

#### Inclusion criteria:

- Patients on/starting oral GC therapy
- Studies focused on prevention or therapy of osteoporosis with medication, reporting BMD measurements

#### Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports

- Letters, editorials, comments, erratum
- Congress abstracts
- Reviews
- Studies on inhaled GCs or very short treatment duration (i.e. less than 1 month)

Search result: 1248 articles retrieved (duplicates excluded)

Best level of evidence supporting the recommendation: I-A

Homik: bisphosphonates are effective in preventing and treating GC-induced osteoporosis.

Amin: bisphosphonates most effective, efficacy enhanced by combination with vitamin D.

De Nijs: active vitamin D analogues are more effective in preserving bone compared to plain vitamin D and/or calcium; bisphosphonates are more effective.

Richy: vitamin D analogues seem to prevent spinal fractures to a greater extent than do native vitamin D.

Homik (calcium and vitamin D): prevention of bone loss with vitamin D and calcium

## Recommendation 4

### Pubmed, 2005 hits

((“adrenal cortex hormone”[Tiab] OR “adrenal cortical hormone”[Tiab] OR “adrenal cortex steroid”[Tiab] OR “adrenal cortical steroid”[Tiab] OR “adrenal steroid hormone”[Tiab] OR “adrenocortical hormone”[Tiab] OR “adrenocortical steroid”[Tiab] OR corticosteroid\*[Tiab] OR corticoid\*[Tiab] OR cortison\*[Tiab] OR hydrocortison\*[Tiab] OR dexamethason\*[Tiab] OR methylpredniso\*[Tiab] OR deflazacort\*[Tiab] OR glucocort\*[Tiab] OR predniso\*[Tiab] OR “Glucocorticoids”[MESH]) AND (“hypothalamic-pituitary-adrenal axis”[Tiab] OR “pituitary-adrenal system”[Tiab] OR “pituitary-adrenal response”[Tiab] OR “adrenal insufficiency”[Tiab] OR “adrenal deficiency”[Tiab] OR “adrenal crisis”[Tiab] OR “adrenocortical insufficiency”[Tiab] OR “adrenocortical deficiency”[Tiab]) AND (advice\*[Tiab] OR recommendation\*[Tiab] OR inform\*[Tiab] OR educat\*[Tiab] OR scheme[Tiab] OR substitute\*[Tiab] OR supplem\*[Tiab] OR supplet\*[Tiab] OR replace\*[Tiab] OR “stress dose”[Tiab] OR “stress doses”[Tiab] OR surgery[Tiab] OR surgical[Tiab] OR safe\*[Tiab] OR regulat\*[Tiab] OR perioperative[Tiab] OR preoperative[Tiab] OR postoperative[Tiab] OR peri-operative[Tiab] OR pre-operative[Tiab] OR post-operative[Tiab] OR “peri operative”[Tiab] OR “pre operative”[Tiab] OR “post operative”[Tiab] OR measure\*[Tiab] OR prevent\*[Tiab] OR mitigat\*[Tiab]))

### Embase, 2098 hits

((‘adrenal cortex hormone’ OR ‘adrenal cortical hormone’ OR ‘adrenal cortex steroid’ OR ‘adrenal cortical steroid’ OR ‘adrenal steroid hormone’ OR ‘adrenocortical hormone’ OR ‘adrenocortical steroid’ OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\*) AND (‘hypothalamic-pituitary-adrenal axis’ OR ‘pituitary-adrenal system’ OR ‘pituitary-adrenal response’ OR ‘adrenal insufficiency’ OR ‘adrenal deficiency’ OR ‘adrenal crisis’ OR ‘adrenocortical insufficiency’ OR ‘adrenocortical deficiency’) AND (advice\* OR recommendation\* OR inform\* OR educat\* OR scheme OR substitute\* OR supplem\* OR supplet\* OR replace\* OR ‘stress dose’ OR ‘stress doses’ OR surgery OR surgical OR safe\* OR regulat\* OR perioperative OR preoperative OR postoperative OR peri-operative OR pre-operative OR post-operative OR ‘peri operative’ OR ‘pre operative’ OR ‘post operative’ OR measure\* OR prevent\* OR mitigat\*)):ti:ab

### Cochrane Library, 240 hits

((“adrenal cortex hormone” OR “adrenal cortical hormone” OR “adrenal cortex steroid” OR “adrenal cortical steroid” OR “adrenal steroid hormone” OR “adrenocortical hormone” OR “adrenocortical steroid” OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR “Glucocorticoids”[MESH]) AND (“hypothalamic-pituitary-adrenal axis” OR “pituitary-adrenal system” OR “pituitary-adrenal response” OR “adrenal insufficiency” OR “adrenal deficiency” OR “adrenal crisis” OR “adrenocortical insufficiency” OR “adrenocortical deficiency”) AND (advice\* OR recommendation\* OR inform\* OR educat\* OR scheme OR substitute\* OR supplem\* OR supplet\* OR replace\* OR “stress dose” OR “stress doses” OR surgery OR surgical OR safe\* OR regulat\* OR perioperative OR preoperative OR postoperative OR peri-operative OR pre-operative OR post-operative OR “peri operative” OR “pre operative” OR “post operative” OR measure\* OR prevent\* OR mitigat\*)):ti,ab,kw

#### Inclusion criteria:

- Patients on/starting oral GC therapy (or their general practitioners, family or carers involved in this treatment)
- Studies focused on informing on HPA effects of GC therapy or applying preventive schemes

#### Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports
- Letters, editorials, comments, erratum
- Congress abstracts
- Reviews
- Studies on topical, nasal or inhaled GCs

Search result: 2592 articles retrieved (duplicates excluded)

Best level of evidence supporting the recommendation: IV

Yong (Cochrane review): limited data, unable to support or refute use of supplemental perioperative GCs for patients with risk of adrenal insufficiency

Marik: patients on GC do not require perioperative stress doses if they continue their daily dose (disagreement with recommendation)



## Recommendation 5

### Pubmed, 146 hits

((“adrenal cortex hormone”[Tiab] OR “adrenal cortical hormone”[Tiab] OR “adrenal cortex steroid”[Tiab] OR “adrenal cortical steroid”[Tiab] OR “adrenal steroid hormone”[Tiab] OR “adrenocortical hormone”[Tiab] OR “adrenocortical steroid”[Tiab] OR corticosteroid\*[Tiab] OR corticoid\*[Tiab] OR cortison\*[Tiab] OR hydrocortison\*[Tiab] OR dexamethason\*[Tiab] OR methylpredniso\*[Tiab] OR deflazacort\*[Tiab] OR glucocort\*[Tiab] OR predniso\*[Tiab] OR “Glucocorticoids”[MESH]) AND (GP[Tiab] OR “general practitioner”[Tiab] OR doctor\*[Tiab] OR prescriber\*[Tiab] OR “prescribing doctor” [Tiab] OR “prescribing physician”[Tiab]) AND (resource[Tiab] OR forum[Tiab] OR website[Tiab] OR webpage[Tiab] OR online[Tiab] OR internet[Tiab] OR “information page”[Tiab] OR “best practice”[Tiab] OR guideline\*[Tiab] OR “health service”[Tiab] OR “health services”[Tiab] OR NIH[Tiab] OR NHG[Tiab]))

### Embase, 197 hits

((‘adrenal cortex hormone’ OR ‘adrenal cortical hormone’ OR ‘adrenal cortex steroid’ OR ‘adrenal cortical steroid’ OR ‘adrenal steroid hormone’ OR ‘adrenocortical hormone’ OR ‘adrenocortical steroid’ OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\*) AND (GP OR ‘general practitioner’ OR doctor\* OR prescriber\* OR ‘prescribing doctor’ OR ‘prescribing physician’) AND (resource OR forum OR website OR webpage OR online OR internet OR ‘information page’ OR ‘best practice’ OR guideline\* OR ‘health service’ OR ‘health services’ OR NIH OR NHG)):ti:ab

### Cochrane Library, 26 hits

((“adrenal cortex hormone” OR “adrenal cortical hormone” OR “adrenal cortex steroid” OR “adrenal cortical steroid” OR “adrenal steroid hormone” OR “adrenocortical hormone” OR “adrenocortical steroid” OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR “Glucocorticoids”[MESH]) AND (GP OR “general practitioner” OR doctor\* OR prescriber\* OR “prescribing doctor” OR “prescribing physician”) AND (resource OR forum OR website OR webpage OR online OR internet OR “information page” OR “best practice” OR guideline\* OR “health service” OR “health services” OR NIH OR NHG)):ti,ab,kw

#### Inclusion criteria:

- articles about information resources for GPs about GC therapy and management

#### Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports
- Letters, editorials, comments, erratum
- Congress abstracts
- Reviews
- Studies on inhaled GCs or very short treatment duration (<1 month)

Search result: 235 articles retrieved (duplicates excluded)

Best level of evidence supporting the recommendation: IV

## Recommendation 6

### Pubmed, 432 hits

((“adrenal cortex hormone”(Tiab) OR “adrenal cortical hormone”(Tiab) OR “adrenal cortex steroid”(Tiab) OR “adrenal cortical steroid”(Tiab) OR “adrenal steroid hormone”(Tiab) OR “adrenocortical hormone”(Tiab) OR “adrenocortical steroid”(Tiab) OR corticosteroid\*(Tiab) OR corticoid\*(Tiab) OR cortison\*(Tiab) OR hydrocortison\*(Tiab) OR dexamethason\*(Tiab) OR methylpredniso\*(Tiab) OR deflazacort\*(Tiab) OR glucocort\*(Tiab) OR predniso\*(Tiab) OR “Glucocorticoids”(MESH)) AND (“rheumatoid arthritis”(Tiab) OR “arthritis, rheumatoid”(MESH) OR “polymyalgia”(Tiab) OR “polymyalgia rheumatica”(MESH) OR “giant cell arteritis”(Tiab) OR “giant cell arteritis”(MESH) OR vasculit\*(Tiab) OR “vasculitis”(MESH) OR lupus(Tiab) OR “lupus erythematosus, systemic”(MESH) OR “polymyositis”(Tiab) OR “polymyositis”(MESH) OR “dermatomyositis”(Tiab) OR “dermatomyositis”(MESH) OR “rheumatic diseases”(Tiab) OR “Rheumatic Diseases”(MESH)) AND (“co morbidity”(Tiab) OR comorbidity(Tiab) OR “co morbidity”(Tiab) OR “risk factor”(Tiab) OR “risk factors”(Tiab) OR “contra indication”(Tiab) OR “contra-indication”(Tiab) OR contraindication(Tiab) OR diabetes(Tiab) OR glucose(Tiab) OR glycosuria(Tiab) OR hyperglycaemia(Tiab) OR lipids(Tiab) OR dyslipid\*(Tiab) OR hyperlipid\*(Tiab) OR hypercholest\*(Tiab) OR atherosclerosis(Tiab) OR “coronary artery disease”(Tiab) OR “coronary heart disease”(Tiab) OR “myocardial infarction”(Tiab) OR “heart infarction”(Tiab) OR hypertension(Tiab) OR “blood pressure”(Tiab) OR “cardiac insufficiency”(Tiab) OR “heart failure”(Tiab) OR infection\*(Tiab) OR immunosuppr\*(Tiab) OR glaucoma(Tiab) OR “ocular pressure”(Tiab) OR “intraocular pressure”(Tiab) OR osteoporosis(Tiab) OR “bone loss”(Tiab) OR fracture\*(Tiab) OR “bone mineral density”(Tiab) OR “bone density”(Tiab)) AND (before(Tiab) OR begin(Tiab) OR start(Tiab) OR baseline(Tiab) OR “prior to”(Tiab)) AND (treatment(Tiab) OR therapy(Tiab)))

### Embase, 1033 hits

((‘adrenal cortex hormone’ OR ‘adrenal cortical hormone’ OR ‘adrenal cortex steroid’ OR ‘adrenal cortical steroid’ OR ‘adrenal steroid hormone’ OR ‘adrenocortical hormone’ OR ‘adrenocortical steroid’ OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\*) AND (‘rheumatoid arthritis’ OR ‘polymyalgia’ OR ‘giant cell arteritis’ OR vasculit\* OR lupus OR ‘polymyositis’ OR ‘dermatomyositis’ OR ‘rheumatic diseases’) AND (‘co morbidity’ OR comorbidity OR ‘co morbidity’ OR ‘risk factor’ OR ‘risk factors’ OR ‘contra indication’ OR ‘contra-indication’ OR contraindication OR diabetes OR glucose OR glycosuria OR hyperglycaemia OR lipids OR dyslipid\* OR hyperlipid\* OR hypercholest\* OR atherosclerosis OR ‘coronary artery disease’ OR ‘coronary heart disease’ OR ‘myocardial infarction’ OR ‘heart infarction’ OR hypertension OR ‘blood pressure’ OR ‘cardiac insufficiency’ OR ‘heart failure’ OR infection\* OR immunosuppr\* OR glaucoma OR ‘ocular pressure’ OR ‘intraocular pressure’ OR osteoporosis OR ‘bone loss’ OR fracture\* OR ‘bone mineral density’ OR ‘bone density’) AND ((before OR begin OR start OR baseline OR ‘prior to’) AND (treatment OR therapy OR glucocorticoid\*)):ti:ab

### Cochrane Library, 138 hits

((“adrenal cortex hormone” OR “adrenal cortical hormone” OR “adrenal cortex steroid” OR “adrenal cortical steroid” OR “adrenal steroid hormone” OR “adrenocortical hormone” OR “adrenocortical steroid” OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR “Glucocorticoids”(MESH)) AND (“rheumatoid arthritis” OR “arthritis, rheumatoid”(MESH) OR “polymyalgia” OR “polymyalgia rheumatica”(MESH) OR “giant cell arteritis” OR “giant cell arteritis”(MESH) OR vasculit\* OR “vasculitis”(MESH) OR lupus OR “lupus erythematosus, systemic”(MESH) OR “polymyositis” OR “polymyositis”(MESH) OR “dermatomyositis” OR “dermatomyositis”(MESH) OR “rheumatic diseases” OR “Rheumatic Diseases”(MESH)) AND (“co morbidity” OR comorbidity OR “co morbidity” OR “risk factor” OR “risk factors” OR

“contra indication” OR “contra-indication” OR contraindication OR diabetes OR glucose OR glycosuria OR hyperglycaemia OR lipids OR dyslipid\* OR hyperlipid\* OR hypercholest\* OR atherosclerosis OR “coronary artery disease” OR “coronary heart disease” OR “myocardial infarction” OR “heart infarction” OR hypertension OR “blood pressure” OR “cardiac insufficiency” OR “heart failure” OR infection\* OR immunosuppr\* OR glaucoma OR “ocular pressure” OR “intraocular pressure” OR osteoporosis OR “bone loss” OR fracture\* OR “bone mineral density” OR “bone density”) AND (before OR begin OR start OR baseline OR “prior to”) AND (treatment OR therapy OR glucocorticoid\*):ti,ab,kw

Inclusion criteria:

- Patients with rheumatic disease starting oral GC therapy
- Reporting on effect of screening for co morbidity/AEs before start of therapy

Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports
- Letters, editorials, comments, erratum
- Congress abstracts
- Reviews
- Studies on topical, nasal or inhaled GCs

Search result: 1603 articles retrieved (duplicates excluded)

Best level of evidence supporting the recommendation: IV  
No evidence retrieved.

## Recommendation 7

### Pubmed, 1380 hits

((“adrenal cortex hormone”[Tiab] OR “adrenal cortical hormone”[Tiab] OR “adrenal cortex steroid”[Tiab] OR “adrenal cortical steroid”[Tiab] OR “adrenal steroid hormone”[Tiab] OR “adrenocortical hormone”[Tiab] OR “adrenocortical steroid”[Tiab] OR corticosteroid\*[Tiab] OR corticoid\*[Tiab] OR cortison\*[Tiab] OR hydrocortison\*[Tiab] OR dexamethason\*[Tiab] OR methylpredniso\*[Tiab] OR deflazacort\*[Tiab] OR glucocort\*[Tiab] OR predniso\*[Tiab] OR “Glucocorticoids”[MESH]) AND (“polymyalgia”[Tiab] OR “polymyalgia rheumatica”[MESH] OR “giant cell arteritis”[Tiab] OR “giant cell arteritis”[MESH]))

### Embase, 1148 hits

((‘adrenal cortex hormone’ OR ‘adrenal cortical hormone’ OR ‘adrenal cortex steroid’ OR ‘adrenal cortical steroid’ OR ‘adrenal steroid hormone’ OR ‘adrenocortical hormone’ OR ‘adrenocortical steroid’ OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR ‘Glucocorticoids’) AND (‘polymyalgia’ OR ‘polymyalgia rheumatica’ OR ‘giant cell arteritis’ OR ‘giant cell arteritis’)):ti:ab

### Cochrane Library, 73 hits

((“adrenal cortex hormone” OR “adrenal cortical hormone” OR “adrenal cortex steroid” OR “adrenal cortical steroid” OR “adrenal steroid hormone” OR “adrenocortical hormone” OR “adrenocortical steroid” OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR “Glucocorticoids”[MESH]) AND (“polymyalgia” OR “polymyalgia rheumatica”[MESH] OR “giant cell arteritis” OR “giant cell arteritis”[MESH])):ti,ab,kw

#### Inclusion criteria:

- Patients on/starting oral GC therapy for giant cell arteritis or polymyalgia rheumatica
- Studies comparing different starting dosages

#### Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports
- Letters, editorials, comments, erratum
- Congress abstracts
- Reviews

Search result: 1688 articles retrieved (duplicates excluded)

Best level of evidence supporting the recommendation: I-A

Hernandez-Rodriguez: scarcity of RCTs and heterogeneity of studies on PMR therapy do not allow firm conclusions. PMR remission seems to be achieved with prednisone treatment at a dose of 15 mg/d in most patients.

## Recommendation 8

### Pubmed, 137 hits

((“adrenal cortex hormone”[Tiab] OR “adrenal cortical hormone”[Tiab] OR “adrenal cortex steroid”[Tiab] OR “adrenal cortical steroid”[Tiab] OR “adrenal steroid hormone”[Tiab] OR “adrenocortical hormone”[Tiab] OR “adrenocortical steroid”[Tiab] OR corticosteroid\*[Tiab] OR corticoid\*[Tiab] OR cortison\*[Tiab] OR hydrocortison\*[Tiab] OR dexamethason\*[Tiab] OR methylpredniso\*[Tiab] OR deflazacort\*[Tiab] OR glucocort\*[Tiab] OR predniso\*[Tiab] OR “Glucocorticoids”[MESH]) AND (“rheumatoid arthritis”[Tiab] OR “arthritis, rheumatoid”[MESH] OR “polymyalgia”[Tiab] OR “polymyalgia rheumatica”[MESH] OR “giant cell arteritis”[Tiab] OR “giant cell arteritis”[MESH] OR vasculit\*[Tiab] OR “vasculitis”[MESH] OR lupus[Tiab] OR “lupus erythematosus, systemic”[MESH] OR “polymyositis”[Tiab] OR “polymyositis”[MESH] OR “dermatomyositis”[Tiab] OR “dermatomyositis”[MESH] OR “rheumatic diseases”[Tiab] OR “Rheumatic Diseases”[MESH]) AND (“therapeutic dose” [Tiab] OR “maintenance dose”[Tiab] OR “dose adaptation”[Tiab] OR “dose adjustment”[Tiab] OR “dose reduction”[Tiab] OR “dose-ranging”[Tiab] OR “dose ranging”[Tiab] OR “dose-finding”[Tiab] OR “dose finding”[Tiab] OR “dose-titration”[Tiab] OR “dose titration”[Tiab] OR “initial dosage”[Tiab] OR “starting dosage”[Tiab] OR “expected dosage”[Tiab] OR “maintenance dosage”[Tiab] OR “dosage adaptation”[Tiab] OR “dosage adjustment”[Tiab] OR “dosage reduction”[Tiab] OR “dosage-ranging”[Tiab] OR “dosage ranging”[Tiab] OR “dosage-finding”[Tiab] OR “dosage finding”[Tiab] OR “dosage-titration”[Tiab] OR “dosage titration”[Tiab] OR “dosage titration”[Tiab]) AND (“adverse events”[Tiab] OR “adverse effects”[Tiab] OR “side events”[Tiab] OR “side effects”[Tiab] OR “unwanted events”[Tiab] OR “unwanted effects”[Tiab] OR toxicity[Tiab] OR risk[Tiab] OR “risk-benefit”[Tiab] OR benefit[Tiab] OR efficacy[Tiab] OR outcome\*[Tiab] OR effect\*[Tiab]))

### Embase, 144 hits

((‘adrenal cortex hormone’ OR ‘adrenal cortical hormone’ OR ‘adrenal cortex steroid’ OR ‘adrenal cortical steroid’ OR ‘adrenal steroid hormone’ OR ‘adrenocortical hormone’ OR ‘adrenocortical steroid’ OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\*) AND (‘rheumatoid arthritis’ OR ‘polymyalgia’ OR ‘giant cell arteritis’ OR vasculit\* OR lupus OR ‘polymyositis’ OR ‘dermatomyositis’ OR ‘rheumatic diseases’) AND (‘therapeutic dose’ OR ‘maintenance dose’ OR ‘dose adaptation’ OR ‘dose adjustment’ OR ‘dose reduction’ OR ‘dose-ranging’ OR ‘dose ranging’ OR ‘dose-finding’ OR ‘dose finding’ OR ‘dose-titration’ OR ‘dose titration’ OR ‘initial dosage’ OR ‘starting dosage’ OR ‘expected dosage’ OR ‘maintenance dosage’ OR ‘dosage adaptation’ OR ‘dosage adjustment’ OR ‘dosage reduction’ OR ‘dosage-ranging’ OR ‘dosage ranging’ OR ‘dosage-finding’ OR ‘dosage finding’ OR ‘dosage-titration’ OR ‘dosage titration’) AND (‘adverse events’ OR ‘adverse effects’ OR ‘side events’ OR ‘side effects’ OR ‘unwanted events’ OR ‘unwanted effects’ OR toxicity OR risk OR ‘risk-benefit’ OR benefit OR efficacy OR outcome\* OR effect\*)):ti:ab

### Cochrane Library, 34 hits

((“adrenal cortex hormone” OR “adrenal cortical hormone” OR “adrenal cortex steroid” OR “adrenal cortical steroid” OR “adrenal steroid hormone” OR “adrenocortical hormone” OR “adrenocortical steroid” OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR “Glucocorticoids”[MESH]) AND (“rheumatoid arthritis” OR “arthritis, rheumatoid”[MESH] OR “polymyalgia” OR “polymyalgia rheumatica”[MESH] OR “giant cell arteritis” OR “giant cell arteritis”[MESH] OR vasculit\* OR “vasculitis”[MESH] OR lupus OR “lupus erythematosus, systemic”[MESH] OR “polymyositis” OR “polymyositis”[MESH] OR “dermatomyositis” OR “dermatomyositis”[MESH] OR “rheumatic diseases” OR “Rheumatic Diseases”[MESH]) AND (“therapeutic dose” OR “maintenance dose” OR “dose adaptation” OR “dose adjustment” OR “dose reduction” OR “dose-ranging” OR “dose ranging” OR “dose-finding” OR “dose finding” OR “dose-titration” OR “dose titration” OR “initial dosage” OR “starting dosage” OR

“expected dosage” OR “maintenance dosage” OR “dosage adaptation” OR “dosage adjustment” OR “dosage reduction” OR “dosage-ranging” OR “dosage ranging” OR “dosage-finding” OR “dosage finding” OR “dosage-titration” OR “dosage titration”) AND (“adverse events” OR “adverse effects” OR “side events” OR “side effects” OR “unwanted events” OR “unwanted effects” OR toxicity OR risk OR “risk-benefit” OR benefit OR efficacy OR outcome\* OR effect\*):ti,ab,kw

Inclusion criteria:

- Patients with rheumatic disease starting/on oral GC therapy
- Information on dose titration

Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports
- Letters, editorials, comments, erratum
- Congress abstracts
- Reviews
- Studies on topical, nasal or inhaled GCs

Search result: 162 articles retrieved (duplicates excluded)

Best level of evidence supporting the recommendation: IV  
No evidence retrieved.

## Recommendation 9

### Pubmed, 277 hits

((“adrenal cortex hormone”[Tiab] OR “adrenal cortical hormone”[Tiab] OR “adrenal cortex steroid”[Tiab] OR “adrenal cortical steroid”[Tiab] OR “adrenal steroid hormone”[Tiab] OR “adrenocortical hormone”[Tiab] OR “adrenocortical steroid”[Tiab] OR corticosteroid\*[Tiab] OR corticoid\*[Tiab] OR cortison\*[Tiab] OR hydrocortison\*[Tiab] OR dexamethason\*[Tiab] OR methylpredniso\*[Tiab] OR deflazacort\*[Tiab] OR glucocort\*[Tiab] OR predniso\*[Tiab] OR “Glucocorticoids”[MESH]) AND (“rheumatoid arthritis”[Tiab] OR “arthritis, rheumatoid”[MESH] OR “polymyalgia”[Tiab] OR “polymyalgia rheumatica”[MESH] OR “giant cell arteritis”[Tiab] OR “giant cell arteritis”[MESH] OR vasculit\*[Tiab] OR “vasculitis”[MESH] OR lupus[Tiab] OR “lupus erythematosus, systemic”[MESH] OR “polymyositis”[Tiab] OR “polymyositis”[MESH] OR “dermatomyositis”[Tiab] OR “dermatomyositis”[MESH] OR “rheumatic diseases”[Tiab] OR “Rheumatic Diseases”[MESH]) AND (“steroid sparing”[Tiab] OR “steroid-sparing”[Tiab] OR “glucocorticoid sparing”[Tiab] OR “glucocorticoid-sparing”[Tiab] OR “corticosteroid sparing”[Tiab] OR “corticosteroid-sparing”[Tiab] OR “prednisone sparing”[Tiab] OR “prednisone-sparing”[Tiab] OR “prednisolone sparing”[Tiab] OR “prednisolone-sparing”[Tiab] OR sparing[Tiab]))

### Embase, 305 hits

((‘adrenal cortex hormone’ OR ‘adrenal cortical hormone’ OR ‘adrenal cortex steroid’ OR ‘adrenal cortical steroid’ OR ‘adrenal steroid hormone’ OR ‘adrenocortical hormone’ OR ‘adrenocortical steroid’ OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\*) AND (‘rheumatoid arthritis’ OR ‘polymyalgia’ OR ‘giant cell arteritis’ OR vasculit\* OR lupus OR ‘polymyositis’ OR ‘dermatomyositis’ OR ‘rheumatic diseases’) AND (‘steroid sparing’ OR ‘steroid-sparing’ OR ‘glucocorticoid sparing’ OR ‘glucocorticoid-sparing’ OR ‘corticosteroid sparing’ OR ‘corticosteroid-sparing’ OR ‘prednisone sparing’ OR ‘prednisone-sparing’ OR ‘prednisolone sparing’ OR ‘prednisolone-sparing’ OR sparing)):ti:ab

### Cochrane Library, 36 hits

((“adrenal cortex hormone” OR “adrenal cortical hormone” OR “adrenal cortex steroid” OR “adrenal cortical steroid” OR “adrenal steroid hormone” OR “adrenocortical hormone” OR “adrenocortical steroid” OR corticosteroid\* OR corticoid\* OR cortison\* OR hydrocortison\* OR dexamethason\* OR methylpredniso\* OR deflazacort\* OR glucocort\* OR predniso\* OR “Glucocorticoids”[MESH]) AND (“rheumatoid arthritis” OR “arthritis, rheumatoid”[MESH] OR “polymyalgia” OR “polymyalgia rheumatica”[MESH] OR “giant cell arteritis” OR “giant cell arteritis”[MESH] OR vasculit\* OR “vasculitis”[MESH] OR lupus OR “lupus erythematosus, systemic”[MESH] OR “polymyositis” OR “polymyositis”[MESH] OR “dermatomyositis” OR “dermatomyositis”[MESH] OR “rheumatic diseases” OR “Rheumatic Diseases”[MESH]) AND (“steroid sparing” OR “steroid-sparing” OR “glucocorticoid sparing” OR “glucocorticoid-sparing” OR “corticosteroid sparing” OR “corticosteroid-sparing” OR “prednisone sparing” OR “prednisone-sparing” OR “prednisolone sparing” OR “prednisolone sparing” OR “prednisolone-sparing” OR sparing)):ti,ab,kw

#### Inclusion criteria:

- Patients on/starting oral GC therapy for rheumatic disease
- Studies assessing the efficacy of sparing regimens

#### Exclusion criteria:

- Animal studies
- Studies in children (<18 years)
- Language other than English, German or Dutch
- Case series or case reports
- Letters, editorials, comments, erratum

- Congress abstracts
- Reviews

Search result: 382 articles retrieved (duplicates excluded)

Recommendation rejected: IV

Hernandez-Rodriguez (level I-A): uncertainty about sparing effects of methotrexate, azathioprine and etanercept.

Mahr (level I-A): methotrexate lowers the risk of relapse and reduces exposure to GCs in giant cell arteritis in the meta-analysis, but individual studies are conflicting.

## **Recommendation 10**

See appendix 1.