Aan oma Kramer
Voor Joëlle

AN INCOMPATIBLE TRIANGLE?

OPTIMISING GLUCOCORTICOID THERAPY IN RHEUMATIC DISEASES

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OPTIMISING GLUCOCORTICOID THERAPY IN RHEUMATIC DISEASES: AN INCOMPATIBLE TRIANGLE?

Optimaliseren van glucocorticoid therapie in reumatische ziekten:
Een incoherente driehoek? (met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 11 mei 2011 des middags te 4.15 uur

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TABLE OF CONTENTS

Z-AXIS: SAFETY

CHAPTER 1

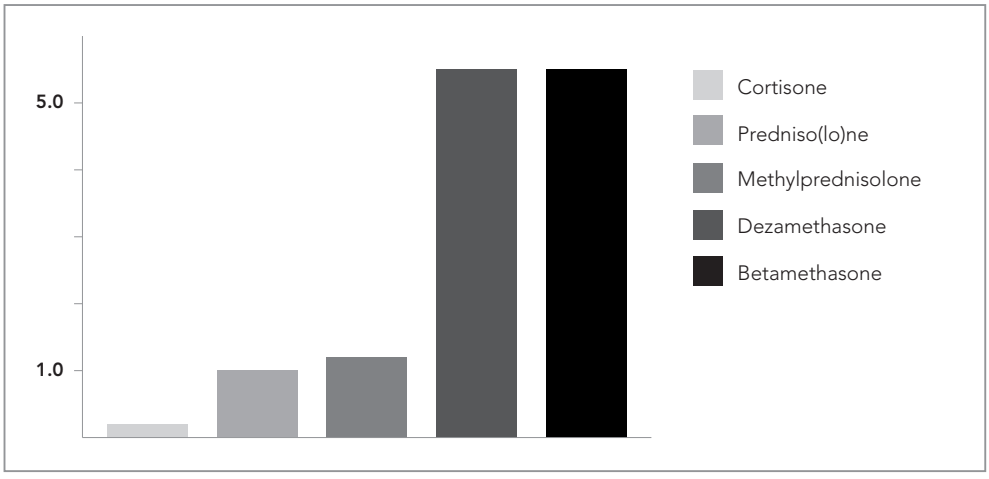
INTRODUCTION

Since their discovery in 1948,[1] glucocorticoids (GCs) have been among the most frequently used anti-inflammatory and immunosuppressive drugs for rheumatic diseases. Rheumatoid arthritis (RA) patients with active disease often use systemic low dose GCs concomitantly with disease modifying anti-rheumatic drugs (DMARDs);[2] also local administration and temporary high dosed parenteral treatment are frequently used. Research in the past two decades has shown that treatment with GCs delays both onset and progression of radiographic joint damage.[3] This long-term efficacy of GCs has resulted in a revival of their position for the treatment of RA, although caution is still warranted because of the adverse effects (AEs) spectrum that encompasses high cumulative doses of GC treatment. First, a short general introduction on the three dimensions of the effects of GCs, i.e. efficacy, toxicity and safety will be given, followed by the outline of this thesis.

X-axis: efficacy

The anti-inflammatory effects of GCs are based on classic or genomic effects, which are mediated by GC-receptors in the cytosol of cells. When glucocorticoids form a complex with the GC-receptor, inflammation can be suppressed through transrepression after this complex has moved into the nucleus of the cell.[4] Transrepression implies inhibition of transcription of DNA and is the key mechanism of the anti-inflammatory mechanism of glucocorticoids.[4] The size of classic or genomic effects of GC-subtypes defines their dose equivalents. Dose is related to saturation of the GC-receptor; dexamethasone and betamethasone are considered most potent, followed by methylprednisolone, predniso(lo)ne and cortisone (figure 1).[5] Dosages of the specific GC-regimens are expressed in relation to the potency of the most

Figure 1 / Different glucocorticoid regimen potencies
Different glucocorticoid regimens and their relative potency; all potencies are relative to predniso(lo)ne.



frequently used regimen, i.e. prednisone or prednisolone equivalent. A daily dose ≤ 7.5mg prednisone equivalent is defined as low dose, >7.5mg - 30mg = medium dose, >30 - 100mg = high dose, >100mg = very high dose, and >250mg = pulsed therapy.[5]

RA is treated with DMARDs; mostly starting with the anchor drugs methotrexate or sulphasalazine,[6] and in case of insufficient response often followed by biological DMARDs such as TNF-alpha inhibitors.[7] These treatments offer disease control with a good benefit-risk ratio and are aimed at remission of disease. The ever further increasing capability of DMARDs to control the disease, has lead to more aggressive treatment strategies that are to be started early after diagnosis. Such strategies are based on the facts that (1) RA is most responsive to treatment in the early phase after diagnosis; i.e. the so called 'window of opportunity', and (2) continuous low disease activity hampers long-term disability, ultimately leading to joint replacement surgery. These strategies resulted in the treatment paradigm of 'tight control', in which treatment is tailored to the individual patient to achieve a low level of disease activity within a limited period of time.[8] This 'treatment tailoring' comprises control through both steering and combination strategies,[9] which means a good response to treatment is achieved

through frequent evaluation of the treatment outcome,[10] and through the use of combinations of multiple DMARDs instead of DMARD mono-therapy.[11]

Glucocorticoids are primarily being used for rapid symptomatic relief, due to their anti-inflammatory effects. Because of these strong anti-inflammatory effects, GCs also are part of the above mentioned combinational treatment strategies and thus form an attractive co-therapy for RA together with other DMARDs. As such, GCs can thus be used for achieving remission and preventing long-term joint damage.

Y-axis: Toxicity

Although the anti-inflammatory effects are clear and are very well explained by the above-mentioned molecular mechanisms, GCs also have other genomic effects, through so called transactivation. In transactivation, glucocorticoids again form a complex with the GC-receptor leading to transcription of DNA, which is the key mechanism of metabolic and endocrine AEs of glucocorticoids. In the early days of the use of GCs, when the molecular background was unknown, these AEs arose shortly after increasing dosages of GCs being used based on their impressive anti-inflammatory effects.

A notorious GC-associated AE is osteoporosis. The deleterious effects of GCs on bone start rapidly after the commencement of treatment,[12] comprising a reduction in number and function of osteoblasts and decreased intestinal calcium absorption on the one hand,[13,14] and an increase in osteoclast function and renal calcium excretion on the other hand.[15,16] The resulting osteoporosis is defined as low bone mineral density (BMD) 2.5 or more standard deviations below the young adult female reference mean,[17] which leads to an increase in vertebral and hip fractures.[17] Anti-osteoporosis therapies in this context include calcium and vitamin D supplementation, and bisphosphonates.[18] These therapies act against osteoporosis through enhancement of calcium absorption from the gut, decrease of parathyroid production, a direct stimulation of osteoblasts (calcium and vitamin D),[19] and inhibition of osteoclasts (bisphosphonates).[20] Since GCs are mostly administered in inflammatory diseases, the effects of GCs on bone are not as straightforward as suggested above. RA as such is an inflammatory

disease and is associated with increased bone loss due to persistent inflammation,[21] which is believed to have crosstalk and shared mechanisms with bone metabolism.[22] The inflammatory state of RA induces bone resorption through an imbalance of the Receptor Activator for Nuclear Factor κ B Ligand (RANK-Ligand) and osteoprotegerin (OPG), which is modulated by pro-inflammatory cytokines, such as interleukin-1, tumour necrosis factor alpha, interleukin-12, and interleukin-17.[23] Of special interest in this respect is the cytokine MIF, which could influence bone metabolism in its own right and through inhibition of deleterious effects of GCs. MIF has been shown to be a regulator of bone metabolism in mice,[24] and to protect against bone resorption in situations of injured bone. This implies a function for MIF in bone metabolism, particularly in an environment of GCs, because MIF is regarded as an endogenous antagonist of GCs.[25]

Another notorious GC-associated AE is glucose intolerance, which is based on disturbance of the intracellular mechanisms of peripheral glucose uptake or insulin sensitivity and insulin secretion or pancreatic beta-cell function.[26,27] Nevertheless, the exact mechanisms through which glucose intolerance occurs remain incompletely known, and the theoretical working mechanisms are mainly based on in vitro or animal studies. In human studies the effects of GCs needs further evaluation, since on the one hand prolonged exposure with GCs induces hyperinsulinaemia due to compensation for GC-induced insulin resistance, while on the other hand chronic exposure likely results in a loss of beta-cell function in susceptible individuals. Most studies so far were limited by the fact that GC exposure was only up to 14 days and beta-cell function was assessed by intravenous glucose tolerance tests.[26] The latter represents a less physiological condition compared to tests using orally administered insulin secretagogues (e.g. glucose). Recently new methods have been validated to determine various aspects of beta-cell function from frequently-sampled oral glucose tolerance tests (OGTT) and from standardised mixed-meal tests, by using modelling analysis.[28,29] Nonetheless, no studies evaluated the effects of GCs on glucose metabolism with modelling analysis in inflammatory states, whereas in daily practice GCs are administered mainly in patients with inflammatory conditions, such as RA.

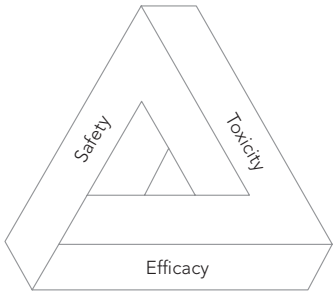
Z-axis: safety

The opportunities of effective DMARDs and the association of AEs with GCs soon pushed GCs from the list of primary treatment options for RA and made them into a short-lived option used only for treating exacerbations of the disease. However, with the development of aggressive DMARD-combination treatment, the risk of AEs also increased. Since GCs are often part of such treatment combinations, both their association with the above-described AEs and the general AE-risk of aggressive treatment,[30] require adequate focus on safety issues like dosing, co-morbidities, and heightened AE-risk during usage of GCs.

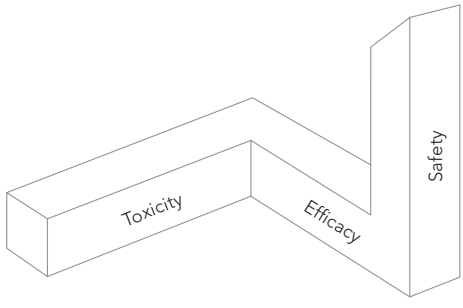
Incompatible triangle

The above-mentioned dimensions are involved in the use of GCs, i.e. (1) efficacy, (2) toxicity, and (3) safety. All three are connected to one of the other (figure 2), but they form an incompatible triangle. In non-inflammatory states or in case of high cumulative doses of GCs, toxicity predominates over efficacy. In inflammatory states such as RA, when GC therapy is applied with sufficient safety, however, the benefit-risk ratio would be optimal, closing the circuit of the three dimensions (figure 2) and thus creating a compatible triangle.

Figure 2 / the (in)compatible triangle of glucocorticoid therapy in rheumatic diseases / x, efficacy; y, toxicity; z, safety



Situation A: short-term and lowest dose GC-treatment; used with safety precautions.



Situation B: long-term treatment and high dose GC-treatment; used without safety precautions.

This thesis focuses on the position of low dose GCs in RA and aims on solving the 'incompatible triangle' by connecting dimensions for (1) efficacy and (2) toxicity with (3) safety. By doing so, a good benefit-risk ratio is guaranteed which improves adequate use of GCs.

OUTLINE OF THIS THESIS

This thesis elaborates on the various effects of GCs, and through this intends to optimise the balance between efficacy and toxicity. In order to achieve this, several clinical reviews and studies in both RA and other inflammatory rheumatic disease patients were performed.

This thesis aims to explain the incompatible triangle by answering the following questions:

With regards to efficacy (X-axis):

- How are GCs used as co-therapy with DMARDs in RA?
- Can GCs be regarded as DMARD in their own right?

With regards to toxicity (Y-axis):

- What is the pattern of vertebral fractures in long-term GC-using RA patients? What influences the occurrence of these vertebral fractures?
- What is the relation between MIF and bone metabolism in long-term GC-using patients with inflammatory rheumatic diseases?
- How does RA influence glucose metabolism? And how does chronic GC-use affect this relation?

With regards to safety (Y-axis):

- What is the adverse event rate in GC-using RA and polymyalgia rheumatica patients? And how does this rate differ from glucocorticoid-using inflammatory bowel disease patients?
- What safety measures should a treating rheumatologist adhere to during systemic low-to-medium dose GC-treatment of a patient?

Chapters of the theme 'X-axis: efficacy' focus on how the disease-modifying properties of GCs are currently used, in conjunction with other DMARDs, to achieve optimal disease control. **Chapter 2** discusses the full range of GC co-therapies with regards to their position in treatment strategies. Different usages of GCs in treatment strategies are summarized, including both the use of systemic and intra-articular GCs as part of combination regimens. Also the use of high dose GCs for bridging therapies is described. The importance of good disease control is further emphasized by **Appendix A;** although this article didn't focus on GCs, it describes the effect of early DMARD therapy (as compared to a delayed start) and the predictive value of good response to treatment on the occurrence of joint replacement surgery in the long run.

The next theme of this thesis "Y-axis: toxicity" discusses the inevitable dimension of dealing with GCs: toxicity. The chapters of this theme discuss two of the most notorious adverse events that are associated with GCs: osteoporosis and glucose intolerance. **Chapter 3** describes the occurrence and type of vertebral fractures in inflammatory rheumatic patients after long-term GC use, and the factors associated with them, such as cumulative GC dose. This chapter discusses the pattern of vertebral deformities and whether former treatment with alfacalcidol or alendronate had an impact on these. **Chapter 4** also deals with GC related osteoporosis, more specifically with osteo-immunity. In this sub-analysis of a previously performed trial,[20] associations of cytokine profiles and bone metabolism are described. Particularly the relation between MIF and BMD is elaborated on. After having discussed the effects of long-term GCs on bone metabolism, **Chapter 5** discusses another toxic effect that is often associated with GCs: glucose intolerance. This chapter describes associations between inflammatory parameters and cumulative GC dose with measures of glucose intolerance, insulin sensitivity and pancreatic beta-cell function, by comparing frequently-sampled oral glucose tolerance tests in both a GC naive and a long-term GC using group of RA patients with healthy controls.

The final theme "Z-axis: safety" discusses safety during GC treatment, i.e. how to find the balance between the previous themes of beneficial and harmful effects of GCs.

In order to give adequate safety advice on GC therapy, the scope of the problem of GC-associated adverse events will first be assessed. **Chapter 6** discusses a meta-analysis on the occurrence and profile of adverse events in rheumatic diseases and inflammatory bowel disease. This study served to inform the EULAR taskforce on GCs on the type of adverse events that were shown in GC studies, and to focus on what advice was still needed for safer use of GCs. This resulted in the formulation of recommendations on the safe use of GCs by this EULAR taskforce, which are discussed in **Chapter 7**. Ten recommendations were generated using a combination of systematically retrieved research evidence and expert consensus, discussing patient education, risk factors, adverse effects, concomitant therapy (i.e. gastroprotection and anti-osteoporotic measures) and special safety advice (i.e. adrenal insufficiency, pregnancy, and growth impairment). Furthermore, areas of importance where further research is warranted were identified as part of this chapter.

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x

CHAPTER 2

CURRENT VIEW OF GLUCOCORTICOID CO-THERAPY WITH DMARDS IN RHEUMATOID ARTHRITIS

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GCs are widely used anti-inflammatory and immunosuppressive drugs for rheumatoid arthritis (RA). The disease-modifying potential of low to medium doses of GCs has been reconfirmed in the past decade, and co-administration of DMARDs and GCs has become standard in many treatment protocols, especially those for early disease stages but also for long-standing RA. The glucocorticoid regimens used range from low continuous doses to intermittent high doses. Studies of the rationale for and clinical use of GCs as co-therapy with DMARDs in RA have shown that this approach has a place in modern (tight control) treatment strategies, and that glucocorticoid co-therapy has disease-modifying effects during the first 2 years of treatment in patients with early RA. Furthermore, medium and high doses of GCs are useful for bridging the interval between initiation of DMARDs and onset of their therapeutic effect. Intra-articular GCs give good local control and have been used in tight control strategies. New glucocorticoid compounds are becoming available for clinical use that might have an enhanced risk:benefit ratio. Better monitoring of glucocorticoid use will also improve this ratio, and help to allay both patient and rheumatologist concerns about treatment-related adverse effects.

Key points

- GCs have a place in modern (tight control) treatment strategies in rheumatoid arthritis
- GCs have disease-modifying effects during the first 2 years of treatment in early rheumatoid arthritis
- Medium and high doses of GCs are useful for bridging the interval between initiation of DMARDs and onset of their therapeutic effect
- Safe use of GCs is enabled by adherence to newly developed guidelines, including those for monitoring of adverse effects
- New glucocorticoid formulations, some in development, offer delayed release, increased local concentrations and reduced adverse metabolic effects, which should improve their risk:benefit ratio

Since their discovery in 1948,[1] glucocorticoids (GCs) have been among the most frequently used anti-inflammatory and immunosuppressive drugs for rheumatoid arthritis (RA). Patients with active RA often use GCs concomitantly with DMARDs. In Germany, up to 55% of patients with RA use glucocorticoids[2] (versus 38% in the USA).[3] In developing countries, GCs probably are being used more frequently than in Germany in the treatment of RA because they are cheap and widely available, often without prescription.[4] The initial rationale for GC-use in the treatment of active RA was simply the fast symptomatic relief the drugs gave through inhibition of inflammation. However, research in the past decade has shown that treatment with GCs delays both onset and progression of radiographic joint damage, such that GCs are now also considered to be DMARDs in their own right (Figure 1).

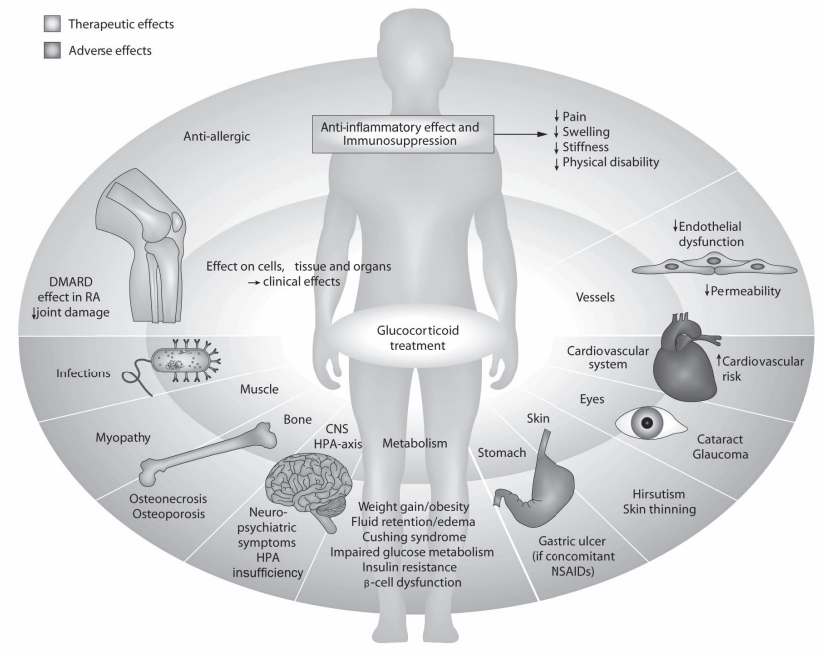

Figure 1/ Clinical effects spectrum of glucocorticoids.

Glucocorticoid therapy is associated with both beneficial effects (upper part of figure)—especially relief of symptoms and long-term benefit on radiological progression in RA—and adverse effects (lower part of figure), the incidence and severity of which are dependent on the dose and duration of the glucocorticoid therapy. Abbreviations: CNS, central nervous system; HPA, hypothalamic pituitary adrenal. Adapted from The Lancet 365, Buttgereit F. *et al*. 801–803 (2005) with permission from Elsevier Ltd.[70]

Combinations of drugs are often needed to treat patients with RA according to the new paradigm of 'tight control'. Strategies for tight control are tailored to the individual patient to achieve a predefined, low level of disease activity (or remission) within a limited period of time after the onset of disease. With the modest adverse effect profile of low to medium doses of glucocorticoids,[5-7] the diversity of agents and regimens available, and their low cost, these drugs are an attractive co-therapy for RA in conjunction with other DMARDs. Nevertheless, persistent misconceptions of the risk:benefit ratio of GC-therapy can unnecessarily restrict their use.

This Review details how the disease-modifying properties of GCs are currently used, in conjunction with other DMARDs, to achieve optimal disease control. First, we discuss the rapid effect of GCs on clinical outcome and their long-term effects on radiographic damage, followed by the different administration routes of GCs and their use as bridging therapies. The next topics—of glucocorticoid-related adverse effect profiles, monitoring of adverse events, and perceptions of risk, —are all crucial for dealing with drugs that are subject to controversy and feared for adverse effects. Finally, we describe new developments that might improve the risk:benefit ratio of GC-therapy.

REVIEW CRITERIA

PubMed was searched for original articles and reviews published in the past two decades of GC-co-therapy in rheumatoid arthritis, using many variants of the search terms "glucocorticoids", "DMARDs" and "RA". Further relevant papers were identified from the reference lists of these articles, evidence-based recommendations and meta-analyses. The primary focus of the search was on the rationale for and efficacy of GC-co-therapy, with a secondary focus on administration routes and monitoring of toxic effects.

CLINICAL APPLICATION OF GLUCOCORTICOIDS IN RA

The rationale for co-therapy with DMARDs

Both monotherapy and co-therapy using low to medium GC-doses (low dose ≤7.5 mg; medium dose 7.5–30.0 mg)[5] inhibit radiographic damage in patients with early RA after 1–2 years of treatment (Table 1). Long-lasting benefits demonstrated after withdrawal of GC-therapy, have granted GCs a position in combination treatment and tight-control strategies for RA [8-10]. A further argument for including systemic GCs in DMARD combination strategies is that these agents reduce the need for NSAIDs and intra-articular GC-injections;[11] moreover, GCs reduce DMARD-related adverse events,[12] and improve the tolerability of infusions of biologic agents.[13,14]

Several trials have compared the effects of GC-co-therapies, either added to conventional DMARD monotherapy or to a combination of conventional DMARDs (Table 1). Most used GC-doses equivalent to ≤10 mg of prednisone. These studies showed that co-therapy with DMARDs and GCs performed better than treatment regimes without glucocorticoids, not only in terms of short-term clinical outcomes (that is, relief of symptoms and improved function) but also in long-term reduction of radiographic damage.

Disease-modifying effects of glucocorticoids

The long-term benefits of GC-co-therapies are explained by the influence of these agents on bone metabolism in inflamed joints. GCs inhibit release and effects of proinflammatory cytokines, such as interleukin (IL) 1 and tumor necrosis factor, which stimulate production of the ligand for Receptor Activator for Nuclear Factor κ B, (RANKL; tumor necrosis factor ligand superfamily member 11) by osteoblasts and T cells. RANKL binds to its receptor on osteoclast precursor cells and on mature osteoblasts, leading to activation of osteoclasts, which are responsible for bone resorption, periarticular osteopenia and formation of bone erosions in patients with RA.[15] The inhibition of GCs of this mechanism

Table 1 / Effects of low to medium doses of glucocorticoids during randomized controlled trials, and follow-up thereafter, in rheumatoid arthritis

Study name and details	Protocol in glucocorticoid-treatment group	Outcome for glucocorticoid treatment group compared with control group*		
		Clinical effects	*Radiographic damage*	*Follow-up‡*
Kirwan et al. (1995)[24] 2 year study, n = 128 (glucocorticoid, 61; control, 67)	7.5 mg predniso(lo)ne, with any DMARD	9 months: improvements in pain, disability and articular index	Reduced erosions	1 year after trial: Joint destruction resumed after GCs stopped.[71]
COBRA Boers et al. (1997)[23] 80 week study, n = 155 (glucocorticoid, 76; control, 79)	60 mg predniso(lo)ne tapered to 0 mg over 28 weeks, with methotrexate, sulfasalazine	28 weeks: improved well-being, grip strength, ESR, articular index	Reduced SHS	4-5 years,[9] and 11 years after trial[10]: Better DAS28,[9] less radiographic progression in former glucocorticoid-group.[9 10]
BeSt Goekoop-Ruiterman et al. (2007)[30] 2 year study, n = 508 (glucocorticoid, 133; control, 375)	60 mg predniso(lo)ne tapered to 0 mg over 28 weeks, with methotrexate, sulfasalazine	2 years: improved DAS and HAQ score	Reduced SHS	2 years after trial: Less radiographic progression in former combination therapy groups [72]
Hansen et al. (1999)[19] 1 year study, n = 102 (glucocorticoid, 51; control, 51)	Median 6 mg predniso(lo)ne, with any DMARD	2 weeks: improved articular index, HAQ score, CRP 6 months: no different to control group	No significant difference in Larsen score	N/A
FIN-RaCo Mottonen et al. (1999)[73] 2 year study, n = 195 (glucocorticoid, 97; control, 98)	Median 5 mg predniso(lo)ne for ≥9 months, with sulfasalazine, methotrexate, hydroxychloroquine	2 years: improved ACR50 response	Reduced erosions and Larsen score	N/A
van Everdingen et al. (2002)[25] 2 year study, n = 81 (glucocorticoid, 41 control, 40)	10 mg predniso(lo)ne, no DMARD (sulfasalazine rescue after 6 months)	6 months: improved well-being and morning pain, reduced NSAID and/or analgesic use	Reduced SHS	3 years after trial: Less radiographic progression in former glucocorticoid-group (figure 3).[8]
TICORA Grigor et al. (2004)[35] 1.5 year study, n = 110 (glucocorticoid, 55; control, 55)	Intra-articular glucocorticoids given to each swollen joint at start of each new DMARD, oral glucocorticoids as part of step-up protocol, with sulfasalazine, methotrexate, hydroxychloroquine, ciclosporin	18 months: improved DAS	Reduced SHS	N/A
WOSERACT Capell et al. (2004)[18] 2 year study, n = 128 (glucocorticoid, 61; control, 67)	7 mg predniso(lo)ne, with sulfasalazine	No significant difference in pain score, articular index, HAQ, ESR or CRP	No significant difference in SHS	N/A
LDPT Wassenberg et al. (2005)[26] 2 year study, n = 76 (glucocorticoid, 34; control, 42)	5 mg predniso(lo)ne, with intramuscular gold or methotrexate	6 months: improved Thompson joint score	Reduced SHS	N/A
BARFOT Svensson et al. (2005)[80] 2 year study, n = 258 (glucocorticoid, 119; control, 139)	7.5 mg predniso(lo)ne, with any DMARD	2 years: improved DAS28, HAQ, functional impairment	Reduced SHS	N/A
CARDERA Choy et al. (2008)[29] 2 year study, n = 376 (glucocorticoid, 131; control, 236)	60 mg predniso(lo)ne tapered to 0 mg over 34 weeks, with methotrexate or methotrexate and ciclosporin	2 years: improved quality of life, DAS28, reduced disability	Reduced Larsen score; greatest effect from triple glucocorticoid, ciclosporin and methotrexate therapy	N/A

*Control groups received traditional DMARDs, except where no DMARD was administered in the glucocorticoid-treatment group. ‡During follow-up, medication use for the former glucocorticoid or combination treatment groups was not restricted by a protocol. Abbreviations: ACR50, American College of Rheumatology criteria for 50% improvement; CRP, C-reactive protein; DAS, disease activity score; DAS28, disease activity score using 28 joint counts; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; NA, not applicable; SHS, modified Sharp–van der Heijde score.

explains why they particularly reduce the formation of new erosions, whereas they have little or no effect on joint space narrowing.[16] Although not every study has replicated the joint-sparing effect of GC-treatment (Table 1), a meta-analysis showed a definite effect (Figure 2).[17] This analysis comprised 15 studies and 1,414 patients, and included all studies that have compared GCs with placebo or with another active treatment for RA with radiographic results as the outcome measure. All study results were expressed as a percentage of the maximum possible score for the radiographic scoring method used.[17] Glucocorticoid therapy was associated with reduced progression in radiographically visible erosions compared with that seen in control groups (standardized mean difference in progression 0.39; 95% CI 0.26–0.52).[17] This value was considered a conservative estimate, since in each individual study the most conservative estimate of the difference in radiographic parameters was chosen.

Within the meta-analysis, two studies on oral GCs included patients with established RA; these trials did not show inhibition of erosions.[18,19] One of these 2 trials was the only one with a negative (albeit not statistically significant) effect (Figure 2). However, the method used to read the radiographs in this particular study has been questioned.[18,20] The durations of the studies in this meta-analysis, and thus also the duration of the GC-administration protocols, were maximally 2 years, and most studies included patients with early RA (disease duration <2 years). The results, therefore, are only applicable to this patient population and these study durations. Furthermore — except for the 1 year data from the BeST trial—the studies included did not apply tight control strategies.

Future trials should investigate GC-co-therapy in strategies with biologic DMARDs, looking at additional effects in terms of reduction of disease activity and delay of joint damage as well as adverse effects, such as infections. In such future trials it seems feasible, however, to keep the dose of GCs low. Data showing glucocorticoid-sparing effects of biologic DMARDs are still limited,[21] but a study showed that the required dose of GCs for RA decreased after the addition of a biologic DMARD.[22]

Figure 2 / Fewer erosions after glucocorticoid therapy in patients with early RA who also received DMARDs. The forest plot depicts the standard mean difference between the means (SD) of percentages of maximal scores for joint erosions observed in the glucocorticoid co-treated groups versus DMARD-only groups after 1 year. Results of studies after 2 years are similar. Adapted from Kirwan *et al*. *Cochrane Database Syst. Rev*. Issue 1. Art. No.:CD006356 (2007), copyright Cochrane Collaboration, with permission.[17]

Figure 2 /	Glucocorticoids		Comparator		Standard mean difference	
Study or subgroup	*n*	*Mean (SD)*	*n*	*Mean (SD)*	*IV, random, 95% CI*	*IV, random, 95% CI*
Boers et al. (1997)[23]	70	1.57 (2.36)	65	2.93 (3.04)		–0.50 (–0.84, –0.16)
Capell et al. (2004)[18]	59	15.1 (15.08)	55	12.6 (1.47)		0.23 (–0.14, 0.60)
Choy et al. (2005)[29]	32	–0.42 (5.28)	30	1.97 (5.48)		–0.44 (–0.94, 0.07)
Empire (1957)[74]	35	6 (8.28)	31	10 (11.69)		–0.39 (–0.88, 0.09)
Goekoop et al. (2005)[75]	121	0.32 (0.68)	115	1.25 (2.93)		–0.44 (–0.70, –0.18)
Hansen et al. (1999)[19]	42	1.29 (3.85)	34	2.43 (7.28)		–0.20 (–0.65, 0.25)
Harris et al. (1983)[76]	18	1.85 (7.86)	16	8.33 (14.91)		–0.54 (–1.23, 0.15)
Joint Committee Report (1960)[77]	41	4.88 (10.03)	35	14.29 (16.37)		–0.70 (–1.16, –0.23)
Kirwan (1995)[24]	49	0.93 (18.15)	54	8.84 (22.34)		–0.38 (–0.77, 0.01)
an Schaardenburg et al. (1995)[78]	26	1.5 (2.27)	24	1.92 (2.63)		–0.17 (–0.72, 0.39)
Suponitskaia et al. (2004)[79]	20	3.43 (10.29)	20	4.93 (12)		–0.13 (–0.75, 0.49)
Svensson et al. (2005)[80]	101	0.29 (0.57)	112	0.86 (1.43)		–0.51 (–0.79, –0.24)
van Everdingen et al. (2002)[25]	39	2.14 (3.48)	35	3.93 (3.92)		–0.48 (–0.94, –0.02)
van Gestel et al. (1995)[81]	1	0 (0)	1	0 (0)		0.0 (0.0, 0.0)
Wassenberg et al. (2005)[26]	68	0.42 (1.37)	72	1.68 (2.42)		–0.63 (–0.97, –0.29)
Total (95% CI)	**722**		**699**			**–0.39 (–0.52, –0.26)**
Heterogeneity: Tau² = 0.02; Chi² = 18.03, df = 13 (P = 0.16); I² = 28% Test for overall effect: z=5.96 (P<0.00001)					-1 -0.5 00 0.5 1 Favors treatment Favors control	

Long-term outcomes and established RA

Long-term follow-up results of GC-monotherapy and co-therapy administered for ≤2 years to patients with early RA indicate that the initial beneficial effect on joint damage persists in the long run (Figure 3).[8-10] However, the joint-sparing and symptom-relieving effects of GC-co-therapy on established RA, and the effect of GC-use for >2 years on early RA, remain subjects for future studies.

A further issue is the possible development of GC-resistance, which might influence the efficacy of long-term GC-co-therapy. In clinical practice, fading of symptom relief is frequently reported by patients after 6 to 9 months months of GC-therapy.[23-26] However, fading of the apparent effects of GCs should not be mistaken for the loss of a clinical difference between glucocorticoid-treated groups and control groups caused by the increasing effects

of other therapies.[11] In a randomized study of patients with RA on long-term GC-treatment, withdrawal of GCs was difficult in a large proportion of the cohort,[27] indicating a sustained benefit of glucocorticoids. Various mechanisms leading to GC-resistance have been described (Table 2);[28] nevertheless, the evidence for the existence of GC-resistance is as yet rather circumstantial.

Bridging therapy

In clinical practice, systemic GCs are often used to treat exacerbations of RA and, in patients who initiate DMARD treatment or need to be switched to another such drug, to bridge the period until treatment with the new agent has become effective (so-called bridging therapy). For this purpose, low to medium oral doses of glucocorticoids, high-dose intramuscular glucocorticoids, intravenous pulse glucocorticoids, and subcutaneous synacthen (a synthetic form of adrenocorticotropic hormone depots are used. The step-down COBRA regime, comprising temporary high-dose oral glucocorticoids, was used by three of the trials mentioned above and is also a type of bridging therapy (Table 1).[23,29,30]

Figure 3 / Evidence for long-term preventive effects of glucocorticoids on radiographic damage. **a |** Radiographic damage (measured using modified Sharp–van der Heijde score) during the 2 year trial period and at follow up at 5 years for patients initially randomized to receive either prednisone or placebo. **b |** Cumulative probability of mean yearly modified Sharp–van der Heijde erosion change score for individual patients from the former prednisone or placebo groups during the follow up period (2–5 years). Both panels show a beneficial effect on joint damage in the former glucocorticoid group, compared with the former placebo group, which persists at 5 years. Adapted from *Arthritis Rheum*. 54, Jacobs, J. W. *et al* 1422–1428 (2006) with permission from Elsevier Ltd.[8]

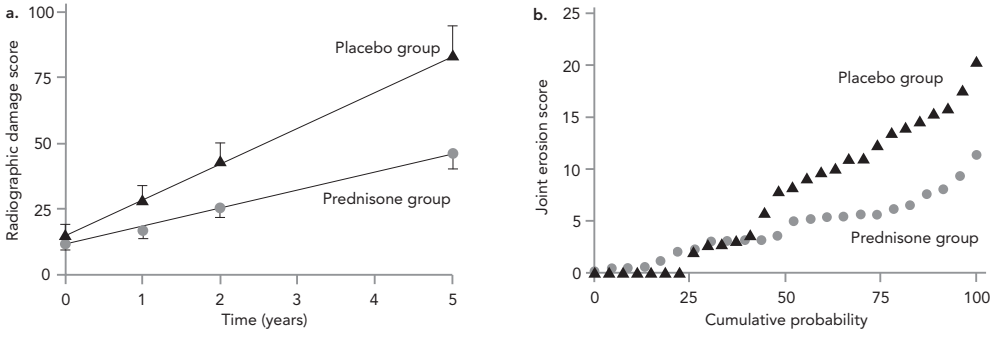

Table 2 / Proposed mechanisms of glucocorticoid resistance

	Familial glucocorticoid resistance
	Glucocorticoid receptor modification: Phosphorylation, Nitrosylation, Ubiquitination
	Increased glucocorticoid receptor β expression
	Increased levels of proinflammatory transcription factors (AP1, JNK, STAT5, JAK3)
	Defective histone acetylation: Reduced acetylation of lysine 5 on histone 4: Reduced activity of histone deacetylase 2 (owing to increased oxidative stress or increased phosphoinositide-3-kinase-δ activation)
	Increased levels of P-glycoprotein
	Increased efflux of steroids

Abbreviations: AP1, activator protein 1; ERK,extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; MAP, mitogen-activated protein; MIF, macrophage migration inhibitory factor; STAT, signal transduction-activated transcription factor. Adapted from Barnes *et al*.[28]

Glucocorticoid pulse treatment is frequently used. In one study, 66 patients with active, established RA received three intravenous administrations of 200 mg open-label dexamethasone given on alternate days. This GC-pulse treatment produced significant ($p < 0.05$) improvements from baseline in disease activity, physical functioning and psychological wellbeing. These short-term clinical and functional benefits were similar to the long-term effects of conventional DMARD treatment in patients with early RA.[31] Psychological disorders were uncommon short-term AEs of the GC-pulse treatment in this trial.[31]

In a trial that included 30 patients with established active RA (mean disease duration 12 years) who started methotrexate therapy, the effect of two different GC-pulse regimes (three administrations of 1,000 mg intravenous methylprednisolone on alternate days or three administrations of 100 mg oral prednisolone) was compared with that of no additional GC-therapy. A better effect on disease activity parameters (tender and swollen joint counts, erythrocyte sedimentation rate, C-reactive protein levels) was seen when methotrexate was combined with pulsed GCs than with methotrexate alone.[32] The initial effects in the oral GC-group were not as strong as and were of shorter duration than those in the intravenous GC-group.

Another study compared the effects of monthly intramuscular GCs (120 mg depomedrone) with those of placebo in a 2 year randomized controlled trial. The participants were 91 patients with established RA who used DMARD therapy but nevertheless had active disease.[33] The patients continued their DMARDs. Disease activity scores (DAS28) initially improved more rapidly in the glucocorticoid-treated patients than in those on placebo, but at 6 months this difference had disappeared. A small reduction in erosive damage was found in the GC-group compared with the placebo group after 2 years. Adverse effects occurred more frequently in the GC-treated group than in the placebo group, particularly conditions –discussed below– that are traditionally associated with GCs. The authors concluded that high-dose, long-term, intramuscular depomedrone improved disease activity for a limited period only, and produced a small reduction in bone erosions at the cost of an increase in adverse events. Consequently, they advised that patients with RA who experienced a suboptimal effect of DMARD treatment should not be given long-term glucocorticoids, but should instead be given additional DMARDs or switched to an alternative DMARD.

Synacthen as adrenocorticotropic hormone stimulates the secretion of endogenous glucocorticoids; subcutaneous depots of this drug can be used in clinical practice for short-term bridging treatment. Theoretically**,** this treatment carries a lower risk of adrenal atrophy than GC-bridging therapies. In a double-blind, randomized, controlled trial, 31 hospitalized patients with active RA were given either subcutaneous synacthen depot (0.5 mg) or saline in two injections on alternate days. A minor and only short-lived improvement in clinical outcome was shown in synacthen-treated patients.[34]

Collectively, these studies show that short-term administration of medium-dose to high-dose GCs serve well as DMARD bridging therapy because of their rapid clinical benefits.

Intra-articular glucocorticoids

Intra-articular GCs can be useful for local control of arthritis and tenosynovitis and they could be used in this way as part of a modern tight control strategy of RA, such as has been done in the TICORA trial.[35] An anti-inflammatory effect is produced within one to

several days, with improvement of joint tenderness, swelling, effusion, and range of motion. Immediate pain relief is also provided by a local anesthetic added to the glucocorticoid and by synovial fluid removal, which reduces distension of the joint capsule.[36] Three days of bed rest are recommended to improve the outcome of intra-articular GC-treatment of the knee and to avoid leakage of the glucocorticoid from the joint, which can result from the increased intra-articular pressure generated by movement.[37] Nevertheless, a proportion of the injected compound will inevitably be absorbed systemically, resulting in measurable serum levels over days to weeks following the injection, depending on the type and dose of the glucocorticoid and the number of injected joints.[38] Not surprisingly, systemic effects of intra-articular GC-administration have been described, both in terms of efficacy and of adverse events. A review of mostly case reports of intra-articular GCs administered to the knee reported beneficial effects in joints that had not been injected, which is probably due to systemic effects, since suppression of cortisol and adrenocorticotropic hormone for up to 48 h after intra-articular application was measured.[39] Metabolic adverse events, such as elevated glucose levels and impaired bone turnover, were also reported.[39]

In patients with active RA, the clinical effect of intra-articular GC-injections is temporary, but treatment regimens using intra-articular GCs alongside DMARDs have successfully been used and resulted in long-term benefits. In the CIMESTRA trial, 160 patients with early RA (disease duration <6 months) were randomly allocated to receive intra-articular betamethasone (up to 28 mg) in any swollen joint, in combination with step-up treatment comprising methotrexate plus either placebo or ciclosporin for 76 weeks of the total trial duration of 104 weeks. Methotrexate and intra-articular GC-treatment gave good disease control over 2 years, with minimal erosive progression of joints.[40] Addition of ciclosporine did not have any additional effect on remission rate and radiographic outcome.[40] The TICORA trial also used intra-articular GCs as part of an intensive treatment strategy.[38] The results showed a better clinical outcome and inhibition of radiographic damage in the intensive-treatment group than was observed among participants who received a less-intensive strategy involving lower usage of intra-articular glucocorticoids.[35]

In conclusion, intra-articular GCs as part of intensive treatment strategies can be used with good results to treat RA. However, the independent effects of intra-articular GCs on radiographic progression have not been studied. Furthermore, their clinical application is limited to local control in a limited number of joints in patients with otherwise inactive RA; active RA should be treated (also) with systemic treatment.

TOXIC EFFECTS

Incidence and monitoring

Soon after the introduction of glucocorticoids, the impressive clinical effects associated with high doses proved to be accompanied by a variety of adverse events (Figure 1), awareness of which brought about more-reserved prescription. Both the profile and severity of glucocorticoid-related adverse events depend on the cumulative and daily dose; low-dose GCs have a modest toxicity profile.[6,7] However, prescribing physicians are often unaware that the adverse-effect spectrum of high-dose GCs differs from that of low dose GCs.

Safe use of these agents is especially an issue in the context of intensive (tight control) treatment strategies that involve GC-co-therapy with DMARDs, which might increase the risk of adverse events. On the basis of experts' and patients' opinions, recommendations have been formulated to monitor patients receiving low-dose GC-therapy. The conclusion of these recommendations was that in daily practice, standard monitoring, as part of good clinical care in all rheumatic patients, needs not be extended for patients on low-dose GC-therapy, with exception of screening for osteoporosis, and pretreatment assessments of fasting blood glucose levels, risk factors for glaucoma, and a check for ankle edema.[41]

Of course, for patients receiving medium or high doses of GCs monitoring should be intensified; however, for these dosages no guidelines yet exist. In future clinical trials of glucocorticoid-based therapies for RA, comprehensive monitoring and reporting of treatment-related adverse events is advised, to obtain further data on the spectrum, incidence and severity of adverse effects in this setting.[41]

Osteoporosis and peptic ulcers

Glucocorticoid-induced osteoporosis is one of the most well-known adverse effects of GC-treatment; however, with adequate monitoring and therapeutic measures, the risk of osteoporosis needs not be a barrier to the use of GCs. The use of bisphoshonates has proven superior for increasing bone mineral density compared with calcium alone and/or biologically active forms of vitamin D,[42,43] and for decreasing the risk of vertebral fractures compared with active vitamin D_3 analogues.[44]

Concomitant NSAID use is a well-known and preventable risk factor for peptic ulcer disease in glucocorticoid-treated patients with RA.[45] NSAIDs are frequently prescribed, and many patients also purchase them over the counter.[46] Concomitant proton pump inhibitors or misoprostol, or a switch to from non-selective NSAIDs to a selective cyclo-oxygenase 2 inhibitor reduce the risk of gastric and duodenal ulcers and bleeds in patients taking GCs as well as NSAIDs.[47,48]

Cardiovascular risks

The incidence rate of cardiovascular events (coronary disease, cerebral artery disease, and sudden death) is twice as high in patients with RA as it is in the general population, and is similar to that in patients with type 2 diabetes mellitus.[49] This increased risk is probably caused by several aspects of RA and its treatment, including the negative effects of inflammation on conventional risk factors, such as dyslipidemia, negative effects of RA therapies on conventional risk factors—such as hypertension due to use of NSAIDs, ciclosporin and leflunomide—and by specific and unknown RA-related mechanisms.

The negative influence of RA on cardiovascular risk is only partly reflected by the presence of conventional risk factors. Consequently, guidelines published in 2010 recommend that a multiplication factor of 1.5 should be applied to cardiovascular risk scores based on such factors for patients with RA who have the following characteristics: disease duration >10 years; positive serology for rheumatoid factor or antibodies to cyclic citrullinated peptides; or extra-articular manifestations (e.g. vasculitis, pericarditis, pleuritis,

and/or Felty's syndrome).[50] The magnitude of this multiplication factor is mostly based on consensus, as precise evidence is lacking.

GCs might enhance cardiovascular risk via their potentially deleterious effects on lipid profiles, glucose tolerance, insulin production and resistance, blood pressure and obesity.[50] However, these adverse effects seem not to be associated with low doses of glucocorticoids. Atherosclerosis is an inflammatory disease of arterial walls that might be aggravated by the inflammation of RA, and for which GC-therapy may be beneficial; GCs inhibit macrophage accumulation in injured arterial walls *in vitro*, possibly resulting in attenuation of the local inflammatory response.[51] Low-dose GCs might also improve dyslipidemia associated with inflammatory disease.[52-54] However, the effects of low-dose GCs on lipids and other cardiovascular risk factors in inflammatory diseases probably differ from those of medium and high doses of GCs, or those of GC-therapy in noninflammatory states.

Infection risk

GCs increase the risk of systemic infection,[3,55] and this association is considered to be dose-dependent. In a large cohort study of patients with RA, GC-use was associated with an increased rate of serious bacterial infections, compared with methotrexate use.[56] A clear dose–response relationship was seen: The relative risk of serious bacterial infection increased from 1.3 to 5.5 as prednisone-equivalent GC-dosages increased from ≤ 5 mg to ≥ 20 mg daily. Nevertheless, because of the retrospective study design bias by indication - i.e. patients with higher disease activity and thus higher risk of disease related complications and adverse effects got higher dosages of GCs - cannot be excluded. Among GC-treated patients with RA undergoing major surgery under GC-replacement schemes, the risk of wound infection or disturbed wound healing seems not to be increased.[57]

In summary, GCs seem to heighten infection risk in a dose-dependent way.

Patient and rheumatologist perspectives

Perceptions of the occurrence and severity of glucocorticoid-related adverse effects are in

part similar for patients and doctors (both groups are concerned about osteoporosis, diabetes and cardiovascular disease) but do show some important differences. For instance, patients are most worried about fatigue, palpitations and dyspnea, whereas rheumatologists show most concern about diabetes, osteoporosis, hypertension and infections.[58]

Due to the historical association of GCs with a wide range of serious adverse events, these drugs engender strong feelings in patients and doctors alike, with probable consequences for their use. These concerns are important to address when GC-treatment is discussed, since diminishing both patients' and physicians' unfounded worries is likely to increase adherence to this treatment. The prescribing behavior of doctors might be influenced by incorrectly attributing similar levels of risk to high-dose and/or long-term GC-therapy, and to short-term and/or low-dose use.[59] Patients' prejudices against glucocorticoids, however, also have a clear role in resistance to their use. In a survey on the BeSt-trial, more patients disliked oral GC-therapy than intravenous Tumor Necrosis Factor alpha inhibitor treatment in the hospital.[60]

New strategies to reduce toxic effects

The modes of action of GCs have been described in this journal,[61] and knowledge about these mechanisms creates opportunities for new developments to optimize the effects of these agents. For example, modified-release dosing can be employed to combat the circadian flare in disease symptoms caused by the nocturnal increase in release of proinflammatory cytokines.[62] A modified-release oral prednisone tablet is now on the market, and has shown a clinically relevant reduction of morning stiffness compared to conventional prednisone.[63] GCs bound to liposomes, which accumulate at sites of inflammation, are also being studied.[64,65] The potency, duration and selective biodistribution of liposome-bound GCs may ultimately enable less-frequent dosing, which in turn could result in an improved adverse-effect profile. The safety of liposomal prednisolone has recently been evaluated in a small group of patients with RA, and the results seem promising.[66]

Other compounds under development are GCs coupled to nitric oxide, which augments their anti-inflammatory effects.[67] Combining GCs with agents that selectively

amplify the anti-inflammatory activity of GCs could improve the risk:benefit ratio by reducing the effective dose. The platelet-activation blocker dipyridamole may be such an agent.[68] Nitro-GCs and dipyridamole combined with GCs have so far only been studied *in vitro* and in animal models; studies in humans are needed to confirm whether these drugs are more beneficial than conventional GCs in clinical use. Other novel drugs under development are selective GC-receptor agonists. These drugs cause less DNA transactivation than conventional GCs do, and thus are associated with fewer metabolic and endocrine adverse effects. Again, these agents have shown good results in animal studies but clinical data are needed.[69]

CONCLUSIONS

GCs are frequently used in the treatment of RA because they enable fast relief of symptoms and retardation of radiologically visible joint damage. Systemic GCs are used as combination therapy with DMARDs and as such have additional value in both the short term and long term. Furthermore, due to their rapid anti-inflammatory effects, GCs are very frequently used as bridging therapy in patients with established RA. Intra-articular GCs are used mostly for local control, but can also be part of a treatment strategy in combination with other DMARDs.

New products, such as the modified-release glucocorticoids, have been developed with the aim of targeted administration, delayed dosing and improved risk:benefit ratios. To improve the use of both old and new GC-compounds in the future, it is necessary to monitor future GC-trials in a comprehensive manner. Otherwise, patients' and doctors' perceptions of the risk:benefit ratio will continue to suffer from the fear of adverse events, and the use of GCs will remain a point of discussion.

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CHAPTER 3

HIGH INCIDENCE RATE OF VERTEBRAL FRACTURES DURING CHRONIC PREDNISONE TREATMENT, IN SPITE OF BISPHOSPHONATE OR ALFACALCIDOL USE. EXTENSION OF THE "ALENDRONATE OR ALFACALCIDOL IN GLUCOCORTICOID-INDUCED OSTEOPOROSIS" - TRIAL.

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Objective

In the 18 month 'alendronate or alfacalcidol in glucocorticoid-induced osteoporosis"-trial (STOP-trial) patients with rheumatic diseases who started glucocorticoids were randomized to anti-osteoporosis therapy with either daily alendronate (10 mg) or alfacalcidol (1 µg). In the present observational open follow-up study of the STOP-trial, we report the long-term effects of risk factors on the incidence and pattern of vertebral fractures, assessed using the Genant method.

Results

Of the 201 included patients in the STOP-trial, 163 completed the trial and of those 116 underwent a follow-up radiography of the spine. Twenty-eight patients had developed one or more new vertebral fractures since the end of the STOP-trial. The majority of fractures was wedge shaped and the deformities were intermediate to severe in both the former alendronate and alfacalcidol group. Multivariate logistic regression analysis showed that STOP-trial medication and presence of pre-existing fractures did not predict development of new fractures, whereas age and cumulative glucocorticoid-dose did.

Conclusion

During the follow-up 2.7 years after the STOP-trial both in the former alendronate and alfacalcidol group 24% of the patients underwent at least one new vertebral fracture. This underlines that prevention of vertebral fractures remains a clinical challenge, even when anti-osteoporosis drugs are prescribed.

Key message

- 1) During the follow-up 2.7 years after the "Alendronate or alfacalcidol in glucocorticoid-induced osteoporosis" (STOP-trial), in 24% of the patients at least one new vertebral fracture occurred.
- 2) Prevention of vertebral fractures remains a clinical challenge, even when anti-osteoporosis drugs are prescribed.

Key words

- Glucocorticoid induced osteoporosis; bisphosphonate; vitamin D; alendronate; alfacalcidol; rheumatic disease; vertebral fracture; STOP-trial.

Rapidly after starting glucocorticoid (GC) therapy bone loss occurs,[1] especially due to a reduction in number and function of osteoblasts leading to less bone formation on the one hand but also to an increase in osteoclast function and decreased intestinal calcium absorption, and renal calcium excretion, leading to increased bone resorption on the other hand.[2-5] The consequence is osteoporosis, a disease which clearly has clinical relevance,[6] also in male patients.[7] Anti-osteoporosis therapy typically consists of calcium and vitamin D supplementation and bisphosphonates.[8,9] However, anabolic drugs, such as parathyroid hormone (PTH) and active vitamin D, increasing bone formation and improving micro-architecture, [10-12] fit the pathogenesis of glucocorticoid-induced osteoporosis (GIOP) better than bisphosphonates. Indeed PTH has been shown to be more effective compared to alendronate to reduce vertebral fracture risk in GIOP.[13] Furthermore, bisphosphonates have been associated with osteonecrosis of the jaw.[14]

In the 18 month '*alendronate or alfacalcidol in glucocorticoid-induced osteoporosis'-trial* (STOP-trial), the active vitamin D metabolite alfacalcidol prevented glucocorticoid-induced bone loss in patients with rheumatic diseases starting GC therapy less effectively compared to alendronate.[15] The primary outcome of the STOP-trial was bone mineral density (BMD) as a surrogate marker of fracture outcome.[10] However,theoretically, active vitamin D could decrease the risk of osteoporotic fractures also by improving micro-architecture of bone and strength and coordination of muscles, reducing the risk of falling.[16] These effects would not be assessable by measuring BMD. Although the STOP-trial had not been powered nor designed to detect differences in fractures, during both the trial and follow-up period the incidence and pattern of vertebral fractures has been accurately documented.

The primary aim of this study was to analyze the incidence, pattern and risk factors of vertebral fractures during and after the STOP-trial as a planned extension of the STOP-trial. The secondary aim of this study was to investigate whether base-line patient characteristics, risks factors and randomized STOP-trial medication were predictive of new vertebral fractures, to provide directions for the long-term use of anabolic and anti-resorptive treatment.

METHODS

Patients

Patients with an inflammatory rheumatic disease, in whom GCs were initiated (or had been started within the previous 12 weeks) in a daily dose of at least 7.5 mg prednisolone or equivalent for an expected period of 6 months or longer had been included in the STOP-trial, a multi-centre randomized, double-blind, double-placebo clinical trial of 18 months' duration. Approval for the trial and its follow-up had been given by the local Human Research Review Committees. Patients (n=201) had been randomized either for treatment with alendronate 10 mg and placebo-alfacalcidol daily or alfacalcidol 1 µg and placebo-alendronate daily. Participating centers, patient demographics and other study-details have been described elsewhere.[15] At the end of the trial, blinding was removed and treatment of osteoporosis was left to the judgment of each physician. Radiograph assessment of the thoracic and lumbar spine was performed between 2 and 4 years after the trial; at that point treatment with glucocorticoids and anti-osteoporosis therapy were evaluated. This long-term evaluation had been pre-defined at the start of the STOP-trial.

Of the 201 patients included, 163 completed the STOP-trial, and 116 patients underwent a follow-up X-ray of the thoracic and lumbar spine. Eighty-eight patients filled out a questionnaire on previous GC use and anti-osteoporosis treatment during the follow-up visit.

Methods

For scoring of vertebral deformities, lateral radiographs of vertebrae T4 to L5 were evaluated qualitatively, semi-quantitatively and quantitatively. Only fractures of previously normal vertebral bodies were counted as new fractures. The anterior (a), medial (m), and posterior (p) heights of each vertebra were measured. Because radiographs of the different centers had not been calibrated, absolute heights could not be calculated and heights ratios were used: the anterior/posterior ratio (a/p), medial/posterior ratio (m/p), and two posterior ratios (p/pu and p/pl). For the posterior ratios

the posterior height of a given vertebra (p) was divided by the posterior height of the vertebra above (pu) to get the ratio p/pu and it was divided by the posterior height of the vertebra below (pl) to get the ratio p/pl. If one of the ratios (a/p, m/p, p/pu, p/pl) was ≤ 0.80, the vertebra was considered as wedge (a/p), biconcave (m/p), or crush (p/pu, p/pl) shaped deformed, respectively. Since this 20% threshold for definition of a fracture might be rather sensitive but less specific, semi-quantitative scoring was also applied using other thresholds: The shape and severity of deformed vertebrae were defined according to the proportions of ratios as described by Genant et al.[17] This method defines mild, intermediate and severe deformation using 20%, 25%, and 40%, thresholds respectively.

In addition, for every vertebra scored as deformed, a naked eye inspection was performed to try to distinguish between osteoporotic, degenerative, traumatic and other causes of the deformation. Two researchers (JH and HH) from two different hospitals blindly and independent of each other analyzed all X-rays. The level of agreement between the two researchers scoring at the 20% cut-off was 92% (standard error 0.045); differences in score classifications were resolved by discussion. If no consensus was achieved, the vertebra was excluded from analysis.

Statistical analyses

Differences between dichotomous data of patients with or without fractures were evaluated by Chi-square tests; differences between continuous data of these groups were evaluated by T-tests or Mann-Whitney-U tests, where appropriate. Multiple logistic regression analyses were used to study the effect of patient characteristics and risk factors (age, diagnosis, gender, allocated STOP-trial medication, pre-existing fractures, cumulative GC-dose, vitamin D level at baseline and anti-osteoporosis medication used after the STOP-trial) on the incidence of new vertebral fractures.

RESULTS

In 116 patients a follow-up X-ray of the vertebral spine was taken on average 2.7 (standard deviation (SD) 0.8) years after the blinded STOP-trial. Withdrawal reasons of the other patients were (1) non-response to invitation (2) death (3) unwillingness to participate. The 116 patients who were studied during follow-up did not differ in demographic (age, diagnosis, or gender) or study characteristics (change in BMD and serum vitamin D levels) compared to the 201 patients who were included in the STOP-trial, or compared to the group withdrawn during the STOP-trial, or the group lost to follow-up (data not shown). This suggests that the results of this study are generalizable to the whole trial population. Patients who used GCs during follow-up

Table 1 / Characteristics of patients studied during follow-up*.

Vertebral x-ray taken during follow-up after STOP-trial - n.	**116 (100%)**
Duration of follow-up after STOP-trial - months	33±10
Age at follow-up after STOP-trial - years	65±12
Diagnosis - n. Rheumatoid arthritis Polymyalgia rheumatica Other, e.g. SLE, Myositis	 33 (37%) 33 (37%) 30 (26%)
Female sex - n.	71 (61%)
Change in bone mineral density (BMD) during the STOP-trial — percentage At lumbar spine At femoral neck At total hip	 0.4±5.9 -0.18±5.4 0.07±4.8
Level of 25-OH-vitamin D at baseline — nmol/L Vitamin D level <30nmol/L — no.	50±22 25 (22%)
Patients who used predniso(lo)ne during STOP-trial — no. Daily dose — mg Cumulative dose — mg	116 (100%) 10.1±6.1 6075±3596
Patients who used bisphosphonates during STOP-trial (e.g. alendronate) — no. Duration of bisphosphonate-use — months	58 (50%) 18
Data in questionnaire filled out at follow-up after STOP-trial — no.	**88 (100%)**
Patients who used predniso(lo)ne during follow-up after STOP-trial — no. Daily dose — mg Cumulative dose — mg	59 (67%) 7.5±6.08 6439±6596
Patients who used bisphosphonates during follow-up after STOP-trial — no. Duration of bisphosphonate-use — months	37 (42%) 28±9
Patients who used both predniso(lo)ne and bisphosphonates — no.	32 (36%)
* Plus-minus values are means ±SD.	

only used predniso(lo)ne as preparations and almost all used alendronate as bisphosphonate.

In 28 patients one or more new vertebral fractures since the end of the trial were seen. On the naked eye inspection, all fractures were deemed to be osteoporotic, except for one probable malignant fracture; this patient has not been included in the analyses. Most fractures were located at thoracic vertebra 9 to lumbar vertebra 1; the location of fractures did not differ between the two former allocated treatment groups (Data not shown). Many patients developed multiple, mostly wedge-type, and mostly intermediate type-type vertebral fractures during the STOP-trial and follow-up period (Table 2). Table 3 shows characteristics of patients who had developed a vertebral fracture during follow-up, compared to data of patients who had not. Multiple logistic regression analyses (independent variables: age, diagnosis, gender, STOP-trial medication, pre-existing fractures, cumulative GC-dose, vitamin D level at baseline and anti-osteoporosis medication used after the STOP-trial), showed that allocated STOP-trial medication, and pre-existing fractures did not predict new vertebral fractures (dependent variable), whereas age and cumulative GC-dose did (Table 4).

DISCUSSION

Over 4 years after the start of the STOP-trial, a considerable proportion of the patients, i.e. 28%, had new morphometric vertebral fractures. The majority of these deformities was intermediate to severe, and located at the lower thoracic/upper lumbar vertebrae. The high incidence of radiological vertebral fractures has significant clinical relevance, since they increase limited-activity days and bed-disability,[18] and are a risk factor for new vertebral and hip fractures.[19] The severity of vertebral deformations could indicate that our population had ongoing deterioration of bone micro-architecture.

Although the incidence of vertebral fractures during the STOP-trial period did not differ from that reported in other trials on anti-osteoporotic treatment,[20] our study is the first analyzing the pattern of vertebral fracturing at the start, during and after randomized treatment of GIOP with an anti-resorptive compared to an anabolic agent. Similar to studies

in rheumatoid arthritis (RA) patients treated with GCs,[21,22] the number of vertebral fractures may have been influenced by disease activity of the included patients, since inflammatory diseases like RA are known for their harmful effects on bone.[23,24] Age and cumulative GC-dose of the patients were predictors of new vertebral fractures. This finding reflects the well known pathology of glucocorticoid induced bone loss, and both risk factors have been widely included in guidelines on GIOP.[25] Our study further underlines the vulnerability for osteoporosis of elderly who use long-term GCs.

Table 2 / Fracture characteristics of patients studied both during STOP-trial and follow-up (n=116).

N patients with new fractures (n fractures)	
At baseline	8 (9)
During STOP-trial[1]	5 (9)
During follow-up[1]	28 (46)
Type of new fractures (n patients (n fractures))	
At baseline	
Wedge	7 (8)
Biconcave	1 (1)
Crush	-
During STOP-trial	
Wedge	5 (9)
Biconcave	-
Crush	-
During follow-up	
Wedge	16 (34)
Biconcave	3 (3)
Crush	9 (9)
Severity of new fractures (n patients (n fractures))[2]	
At baseline	
Mild (~20% - 25%)	1 (1)[3]
Intermediate (~25% - 40%)	7 (7)[3]
Severe (~40%)	1 (1)
During STOP-trial	
Mild (~20% - 25%)	-
Intermediate (~25% - 40%)	3 (7)
Severe (~40%)	2 (2)
During follow-up	
Mild (~20% - 25%)	12 (19)
Intermediate (~25% - 40%)	12 (23)
Severe (~40%)	4 (4)

Only patient characteristics of patients studied during both the STOP-trial and follow-up thereafter are shown here; therefore the data are different from the STOP-trial data.15 No statistical differences were found between former treatment groups (Alendronate vs. alfacalcidol).

[1] During STOP-trial: between 0 and 18 months; During follow-up: between 18 and 50.7 months.

[2] Definition of fracture severity according to the Genant method.[17]

[3] One patient had both an intermediate and a mild fracture.

Table 3 / Characteristics of patients with and without new fractures at follow-up (n=116).*

	New fractures during follow-up (n=28; 46 fractures)	*No new fractures during follow-up (n=88)*
Vertebral X-ray taken during follow-up after STOP-trial - no.	**28 (100%)**	**88 (100%)**
Duration of follow-up after STOP-trial - months	32±10	33±10
Age at follow-up after STOP-trial - years	70±9	63±12
Diagnosis - no. Rheumatoid Arthritis PolyMyalgia Rheumatica Other, e.g. SLE, Myositis	 9 (32%) 11 (39%) 8 (29%)	 34 (39%) 32 (36%) 22 (25%)
Female sex - no.	17 (61%)	54 (61%)
Change in bone mineral density (BMD) during the STOP-trial - percentage At lumbar spine At femoral neck At total hip	 0.7±4.5 -1.3±5.4 -0.5±4.6	 0.3±6.4 0.2±5.3 0.3±4.9
Level of 25-OH-vitamin D at baseline - nmol/L Vitamin D level <30nmol/L no.	47±26 10 (36%)	51±21 15 (17%)
Patients with fractures at baseline - no. Total fractures at baseline - no.	2 (7%) 2	6 (7%) 7
Patients with new fractures during the STOP-trial - no. Total fractures during the STOP-trial - no.	1 (4) 2	4 (5) 7
Patients who used predniso(lo)ne during STOP-trial - no. Mean daily predniso(lo)ne-dose - mg Cumulative predniso(lo)ne-dose - mg	28 (100%) 9.8±4.5 6024±2724	88 (100%) 10.2±6.6 6091±3846
Patients who used bisphosphonates during STOP-trial (e.g. alendronate group) - no. Duration of bisphosphonate-use - months	14 (50%) 18	44 (50%) 18
Questionnaire filled in during follow-up after STOP-trial - no.	**20 (100%)**	**68 (100%)**
Patients who used predniso(lo)ne during follow-up after STOP-trial - no. Mean daily predniso(lo)ne-dose - mg Cumulative predniso(lo)ne-dose - mg	16 (80%) 6.0±3.5 5336±4551	43 (63%) 7.3±5.1 5783±4993
Patients who used bisphosphonates during follow-up after STOP-trial - no. Duration of bisphosphonate-use - months	10 (50%) 28±12	27 (40%) 26±8
Patients who used both predniso(lo)ne and bisphosphonates during follow-up after STOP-trial - no.	10 (50%)	22 (32%)

* Plus-minus values are means ±SD. There were no significant differences between the two groups.

The early effects of alendronate on BMD after 18 months were not reflected in a significantly decreased vertebral fracture rate at follow-up. However, the 18 month STOP-trial had been designed to study BMD as primary outcome and possibly the follow-up was underpowered to study the long-term effects (i.e. vertebral fractures) because of the

Table 4 / Multiple logistic regression analysis of prognostic factors for new vertebral fractures (≥1) during follow-up.

Patient characteristic	*Odds ratio*	*95% confidence interval*	*Coefficient (beta)*	*Standard error*
Age	1.14	1.05;1.23	0.13	0.04
Cumulative GC-dose (in mg) during both STOP-trial and follow-up	1.00016	1.00003;1.00029	0.00016	0.00007
Diagnosis (PMR, RA, or other)	1.41	0.31;6.40	0.34	0.77
Sex	1.96	0.47;7.98	0.67	0.72
STOP-trial treatment (alendronate vs. alfacalcidol)	1.90	0.51;7.07	0.64	0.67
Pre-existent fractures	0.38	0.04;3.30	-0.97	1.11
Bisphosphonate use after STOP-trial	0.52	0.11;2.49	-0.65	0.80
Calcium and vitamin D use after STOP-trial	0.49	0.08;3.00	-0.71	0.92
Baseline level of 25OH-vitamin D	0.99	0.96;1.03	-0.0075	0.016

substantial withdrawal that was encountered during this period.

We did not include change in BMD during the STOP-trial as independent variable in the logistic regression for two reasons. First, because alendronate acts via increase of BMD and alfacalcidol also via other mechanisms, this would have had an unbalanced influence on the included independent variable allocated STOP-trial medication. Second, patients of both former treatment groups were roughly equally treated for GIOP during follow-up after the STOP-trial, which could mean there was a 'catch-up' effect in BMD in the former alfacalcidol group, diluting the differences in BMD between the two former groups.

A possible role of vitamin D throughout the trial and follow-up thereafter cannot be ignored. Although not significantly, the prevalence of hypovitaminosis D at baseline was twice as high in patients who suffered from fractures during follow-up (table 3) compared to that of those who did not. Although supplemented adequately during the trial, the bone in these former patients could nevertheless have suffered from residual effects of osteomalacia. Furthermore, it should be noted that patients had a higher risk of developing hypovitaminosis D during the follow-up period after the trial due to the frequent switch from alfacalcidol to bisphosphonate therapy and to the stopping of the vitamin D supplementation (given during the trial per protocol in case of hypovitaminosis D at baseline).

An important result of our study is that 1 out of 3 to 4 patients treated with GCs develops vertebral fractures within approximately 4 years. This high incidence of fractures is mainly related to GCs, disease activity and age, as described above. Although the physicians participating in our study were all member of the Osteoporosis Working Group of the Dutch Society for Rheumatology, and thus osteoporosis-minded, there might have been suboptimal treatment of GIOP during the follow-up after the STOP-trial. In the Netherlands, national guidelines for treating GIOP only got published in 2004 [25], advising more uniform and intensive treatment strategies than those probably applied during follow-up. Furthermore, patient compliance is known to be often suboptimal;[26] In order to achieve a better long-term effect it is necessary to maintain intensive treatment. Specific attention with regards to anti-osteoporosis treatment should be payed to GC-using patients of older age and/or with a high cumulative GC-dose.

Future research should focus on combination strategies to prevent GIOP, e.g. with active vitamin D added to anti-osteoporosis regimes with an anti-resorptive drug or *sequential* therapy with PTH and bisphosphonates, as *concomitant* therapy with PTH and bisphosphonate was not beneficial in postmenopausal women.[27] PTH was more effective than alendronate in preventing morphometric vertebral fractures in GIOP,[13] but duration of this treatment is limited. An additional important item for future studies and clinical practice is how to increase adherence to treatment and treatment guidelines in patients and physicians, respectively. The latter should particularly focus on high-risk patients, such as high cumulative dose GC-users and older patients, as our study has confirmed their precarious position.

In conclusion, our study indicates that during current treatment strategies for GIOP vertebral fractures still occur on a large scale, with age and cumulative GC-use as important predictors of new vertebral fractures.

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CHAPTER 4

INCREASES IN MACROPHAGE INHIBITORY FACTOR CORRELATE WITH INCREASES IN BONE MINERAL DENSITY IN GLUCOCORTICOID-TREATED PATIENTS WITH RHEUMATOID ARTHRITIS.

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Objective

To investigate whether changes in bone density and turnover are associated with changes in inflammatory mediators in RA patients, treated with glucocorticoids upon vitamin D treatment in comparison with alendronate treatment.

Methods

RA patients (n=40) on long-term oral glucocorticoid treatment received either active vitamin D treatment (alfacalcidol) or the bisphosphonate alendronate in a double-blind double placebo-controlled manner. At baseline and after 18 months, we measured cytokines capable of antagonizing glucocorticoids (macrophage migration inhibitory factor - MIF, interleukin -IL- 13 and IL7), cytokines causing T cell differentiation (IL6, IL7, IL12, IL10 and IL23), and cytokines produced by effector T cells (interferon γ (IFNγ), IL4, IL17, IL22). Associations of cytokine profiles with bone markers and bone mineral density changes of the lumbar spine were explored using multiple regression analyses that corrected for study medication and risk factors of osteoporosis.

Results

Alendronate unlike alfacalcidol increased bone mineral density changes of the lumbar spine. Neither alfacalcidol nor alendronate significantly influenced serum concentrations of cytokines. Interestingly, we show that increases in MIF were associated with increased bone mineral density changes of the lumbar spine in multivariate analysis (Beta = 0.02, 95% confidence interval 0.004 to 0.04).

Conclusion

During glucocorticoid treatment increases in the glucocorticoid-antagonist MIF were associated with increased bone mineral density, which could mean MIF has bone-protecting capacities in patients that suffer from GC-induced bone destruction.

Key messages

- Active vitamin D did not influence serum cytokine levels including IL23 or MIF.
- In RA patients using glucocorticoids, increase in MIF is associated with an increase in BMD.

Inflammation and bone metabolism are characterized by crosstalk and shared mechanisms,[1] both of which can be influenced by glucocorticoids (GCs) and vitamin D. GCs are used frequently in rheumatic diseases because they have powerful anti-inflammatory effects. The use of GCs in the treatment of rheumatoid arthritis (RA) has received much attention in the last two decades, because low dose GCs in addition to disease modifying anti-rheumatic drugs (DMARDs) have been shown to prevent radiographic joint damage.[2] This has granted GCs a position in the latest treatment recommendations by EULAR.[3] However, their use has been hampered considerably because of associated adverse effects (AEs); osteoporosis being a notorious AE, with bone loss starting promptly after GC therapy.[4] In order to prevent GC-related AEs, dose-lowering strategies are now sought; for example, concomitant administration with dipyridamole was shown to amplify the anti-inflammatory effects of GCs.[5] Another such strategy could be concomitant administration with vitamin D, which is part of the steroid family.

The biologically active form of vitamin D (1.25-dihydroxyvitamin D) has anti-osteoporotic effects through enhancement of calcium absorption from the gut, decrease PTH production, and a direct stimulating effect on osteoblasts is suggested.[6] Although on the long run the deleterious effects of GCs on bone certainly outweigh their positive anti-inflammatory effects, vitamin D could certainly add to the long-term beneficial effects of GCs both by positive effects on bone metabolism and inflammation. In vitro vitamin D was described to have anti-inflammatory effects through an effect on T-cell cytokine production,[7,8] in particular IL-17 that has been shown to mediate strong inflammatory and destructive capacities.[9,10] Although there are indications that vitamin D therapy might influence bone metabolism by modulating inflammatory pathways in GC-users there is little and only in vitro evidence.[9]

In the present study in GC-treated RA patients we investigated the effect of 1.25-vitamin D (as compared to alendronate) on systemic cytokine levels that are indicative of inflammatory pathways that could influence bone metabolism. Cytokines capable of antagonizing GCs (MIF, IL13 and IL7), cytokines causing T cell differentiation (IL6, IL7, IL12, IL10 and IL23), and cytokines produced by effector T cells (IFNγ, IL4, IL17, IL22) were studied.

METHODS

Patients

Forty RA patients, in whom GCs were initiated within the previous 12 weeks in a daily dose of at least 7.5 mg prednisolone or equivalent for an expected period of 6 months or longer, had been randomised either to treatment with 18 months of alendronate 10 mg and placebo-alfacalcidol daily or alfacalcidol 1 µg and placebo-alendronate daily.[11] This patient subgroup was a subgroup of the patients that were included in the STOP-trial.[11]

Methods

At the start and at the end of the trial, after 18 months of treatment, MIF, IL4, IL6, IL7, IL10, IL12, IL13, IL17, IL22, IL23, and IFNγ were measured in serum using a multiplex cytokine assay, as has been described elsewhere.[12] Next to this several measures of bone metabolism were measured at these time points: (1) bone turnover markers were measured as described elsewhere,[11,13] i.e. in serum, bone formation/protection markers: procollagen type I C-propeptide (P1CP), osteocalcin, and osteoprotegerin (OPG), and urinary bone resorption markers: deoxypyridinoline (dPyr), and cross-linked N-telopeptides (Ntx); (2) Lumbar spine bone mineral density (lBMD) was measured with dual-energy x-ray absorptiometry; as described elsewhere.[11,13]

Statistical analyses

Differences between the two treatment groups were tested with Mann-whitney-U tests (because of non-normality) and chi-square test in case of dichotomous data. Associations between bone markers and lBMD with difference in MIF and other cytokine levels were studied using multivariate regression analyses that corrected for patient characteristics and risk factors for osteoporosis (age, gender, cumulative GC-dose, allocated study medication).

RESULTS

The RA patients that were studied consisted of 20 patients randomised to alendronate and 20 to alfacalcidol; participating centers, patient demographics and other study-details have been described elsewhere.[11,13] Patients were comparable with regards to age (mean±SD 63±13, 59±10, respectively), gender (70% vs. 75% female, respectively) and cumulative GC-dose (mean±SD 4.9g±2.3g, 4.9g±1.4g, respectively).

Like in the larger STOP cohort, alendronate significantly increased BMD compared to a decrease in the alfacalcidol group,[11] whereas alfacalcidol increased bone formation markers P1CP and osteocalcin.[13] Several cytokines were undetectable in all samples (IL4, IL10, IL12, IL13, IL17, IL22, and IFNγ). In addition, a number of cytokines were only measured in a limited number of patients (IL-6 (40%), IL-7 (8%)). Neither treatment significantly altered the concentrations of these cytokines. Because of the low number of patients with detectable levels, correlation analyses of these cytokines with parameters of bone metabolism were considered not reliable and thus were not performed. MIF and IL-23 were measured in the majority of samples. Baseline median plus interquartile range values of MIF and IL-23 were 50 (26 to 88)pg/ml vs. 67 (44 to 117)pg/ml, p=0.3, and 122 (29 to 1649)pg/ml vs. 84 (43 to 359)pg/ml, p=0.5, in the alfacalcidol and alendronate groups, respectively; however, alfacalcidol nor alendronate treatment did not significantly influence levels of MIF or IL-23 (alfacalcidol vs. alendronate group: median plus interquartile range of cytokine levels at 18 months minus baseline: MIF: -8 (-35 to 6) pg/ml vs. -5 (-69 to 26) pg/ml, p=1.0; IL-23: -4 (-536 to 57)pg/ml vs. -3 (-47 to 111)pg/ml, p=0.5).

Changes in levels of IL23 did not correlate with BMD of bone markers (beta = $-2x10^4$ (95% CI $-6x10^4$ to $8x10^{4)}$). Interestingly, increases in MIF as compared to baseline were significantly associated with increased BMD (figure 1), which remained significantly associated in multivariate regression (p=0.018, table 1). Each bone marker was separately tested in the multivariate model: none correlated with patient characteristics or MIF, except

for the correlation of alfacalcidol-treatment with bone formation markers (data not shown), as has also been described elsewhere.[13]

DISCUSSION

We here demonstrate that neither alfacalcidol nor alendronate significantly affect concentrations of circulating proinflammatory mediators. However, we observed a significant correlation of increases in MIF levels and increases in bone mineral density.

In the present study systemic cytokine profiles were measured in RA patients that

Table 1 / Multivariate regression analysis of prognostic factors of bone metabolism

Patient characteristic	***Coefficient (beta (95% CI))***	***p-value***
Independent variable: ΔBMD (% difference from baseline at 18 months)		
Vitamin D (vs. alendronate)	-4 (-7, -1)	0.004
Age	0.2 (0.04, 0.3)	0.010
ΔMIF	0.02 (0.004, 0.04)	0.018
Gender	-1 (-4, 3)	n.s.

Abbreviations: CI, confidence interval; MIF, macrophage migration inhibitory factor; ΔMIF, change from baseline at 18 months; ΔBMD, % difference in bone mineral density from baseline at 18 months; n.s., not significant ($p<0.05$).

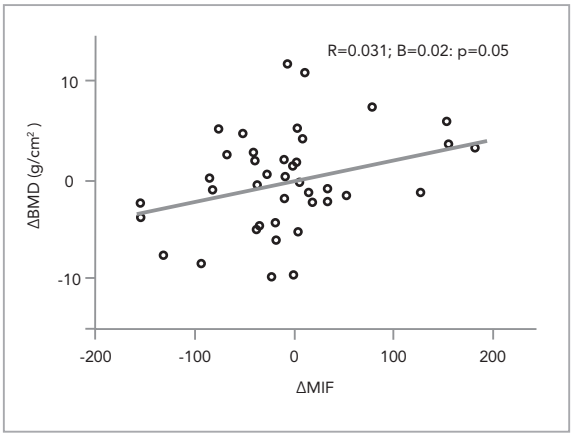

Figure 1 / Changes in MIF significantly correlate with changes in lBMD
Abbreviations: ΔMIF, change in levels of macrophage migration inhibitory factor (values at 18 monts minus values at baseline); ΔBMD, change in lumbar spine bone mineral density (grams per square centimeter; valuesafter 18 months minus baseline); pg/ml, picogram/milliliter.

were using GCs before the start of the study medication. This offered us the opportunity to study the effect of alfacalcidol (compared to alendronate) and the regulation of bone metabolism in individuals whose bone was influenced/affected by GCs. The downside of this approach is that many cytokines may be affected by GC treatment. Indeed many cytokines were undetectable, which made it impossible to draw conclusions concerning the involvement of several inflammatory mediators in bone metabolism. MIF levels, however, were detectable and increases in MIF levels correlated to increases in BMD.

MIF has been identified as a component of the GC counter-regulatory system and is viewed as an endogenous antagonist of the effects of GCs on the immune system.[14] The effects of MIF on the immune system have been extensively described;[15] MIF has been described to be induced by GCs.[16] In the present study we did not observe a significant correlation between increases in GC dose and MIF. This however may be related to the fact that patients were already using GCs at the start of our study medication.

Although it has been reported that MIF in human osteoblastic cells upregulates the expression of mediators involved in bone tissue remodelling,[17] data on the capacity of MIF to regulate bone metabolism in humans are largely lacking. So far the role of MIF in bone remodelling has mainly been investigated in rodents, demonstrating inconsistent outcomes on bone with both pro- and anti-resorptive properties. Pro-resorption effects were demonstrated in vitro and in vivo, where MIF upregulated bone-destructive enzymes MMP-9 and MMP-13 expression by osteoblasts, associated with osteoporosis induction in mice;[18,19] induction of these enzymes by MIF was nevertheless also beneficial for fracture healing in rats.[20] The latter implies positive or anti-osteoporotic effects. These anti-osteoporotic effects were also shown in MIF-deficient mice that had an increased capacity to form osteoclasts in vitro and these mice had significantly decreased trabecular bone volume.[21] Another study showed delayed fracture healing in MIF knock out mice, which was mainly attributable to a delay in osteoid mineralization.[22] Our data, demonstrating the correlation of increases in MIF with increases in BMD, are in line with these latter murine studies demonstrating bone formation or anti-resorption effects of MIF.

All of the studies mentioned above show that MIF is involved in regulating bone turnover and could be an important regulator for creating healthy bone through effects on both bone resorption and formation; dependent on stimuli and presence of an injured environment. Nevertheless, all of these studies are murine studies and none of them study the influence of MIF in a GC environment. Our study now demonstrates increased MIF to correlate with increased BMD, suggesting that in vivo MIF might contribute to increases in bone turnover in GC-using RA patients, with BMD as clinically relevant outcome.

Our findings indicate that MIF could be an important regulator for bone metabolism in GC-induced osteoporosis in patients with RA. The exact mechanisms by which MIF induces these effects remain to be addressed, i.e. does MIF independent of GCs affect bone or does it antagonize the direct effects of GCs on bone and what mediators are involved? Therefore, further research needs to focus on the manner how MIF orchestrates bone formation in GC-induced osteoporosis.

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CHAPTER 5

EFFECTS OF CHRONIC LOW-TO-MEDIUM DOSE GLUCOCORTICOIDS ON GLUCOSE TOLERANCE, INSULIN SENSITIVITY AND BETA-CELL FUNCTION IN CHRONIC RHEUMATOID ARTHRITIS PATIENTS

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Submitted for publication

Objective

To compare glucose tolerance and parameters of insulin sensitivity and beta-cell function between chronic glucocorticoid-using and glucocorticoid-naive RA patients.

Methods

Frequently-sampled 75-g oral glucose tolerance tests were performed in 58 chronic glucocorticoid-using and 82 glucocorticoid-naive RA patients with established disease, known type 2 diabetes mellitus (T2DM) precluded participation, and fifty control subjects of comparable age with normal glucose tolerance. The associations between cumulative glucocorticoid dose and disease characteristics and glucose tolerance state, insulin sensitivity and beta-cell function were tested using multivariate linear and logistic regression models, correcting for patient characteristics.

Results

Glucose tolerance state, insulin sensitivity and beta-cell function did not differ between both RA populations; we detected de novo T2DM in 11% and impaired glucose metabolism in 35% of RA patients. Within RA patients, cumulative glucocorticoid dose was associated with T2DM, which seemed mostly driven by the effects of cumulative glucocorticoid dose on insulin resistance; however, the association decreased when corrected for current disease activity. RA patients had decreased insulin sensitivity and impaired beta-cell dysfunction compared to controls, and multivariate regression analyses showed a negative association between the presence of RA and insulin sensitivity.

Conclusions

Glucocorticoid-using and glucocorticoid-naive RA patients had comparable metabolic parameters, and had decreased insulin sensitivity and beta-cell function as compared to healthy controls. Although cumulative glucocorticoid dose was shown to have a negative impact on glucose tolerance state and insulin sensitivity, confounding by indication remains the main challenge in this cross-sectional analysis.

Rheumatoid arthritis (RA) patients are at increased risk to develop cardiovascular disease, comparable to the risks observed in subjects with type 2 diabetes mellitus (T2DM).[1] Additional impairment in glucose metabolism may contribute significantly to the accelerated atherogenesis in RA patients.[2] Two main determinants of glucose metabolism are insulin sensitivity (glucose uptake) and beta-cell function (insulin production). Previously, RA patients were shown to have impaired fasting insulin sensitivity (homeostatic model assessment (HOMA)-IR) and fasting beta-cell function (HOMA-B), which correlated with disease activity and markers of inflammation.[3-5] Consequently, prevalent diabetes was estimated to be up to 15-19% in RA patients,[6,7] an increased number as compared to the estimated T2DM prevalence of 4-8% in middle-aged men and women in the general population.[8]

The role of glucocorticoids (GCs) in glucose intolerance in RA patients has been one of paradox. On the one hand, in animal models and in short-term clinical trials in healthy subjects, GCs were shown to deteriorate glucose metabolism by impairing hepatic and peripheral insulin sensitivity and by inducing beta-cell dysfunction.[9] In retrospective, population-based studies, GC therapy was associated with incident diabetes,[10] and the need for blood-glucose lowering treatment in a cumulative dose-dependent way.[11] In retrospective studies in RA patients, GC exposure was shown to correlate with insulin resistance,[12] and to predict diabetes.[13] On the other hand, the use of GCs in chronic inflammatory states may improve glucose tolerance by their anti-inflammatory effects, as was demonstrated in a number of short-term studies using GC-treatment;[14,15] this was also shown in a study using methotrexate.[16] In addition, confounding by indication should be kept in mind when evaluating the relation between GC use and glucose tolerance in RA patients in observational studies. This is the possibility that patients with higher cumulative inflammation (i.e. higher disease activity), resulting in a priori increased insulin resistance, were more likely to be given high-dose GCs than those with less inflammation (disease) activity. Thus, the impact of GC-treatment on glucose metabolism in RA patients requires further clarification.

Previous studies that have addressed the effects of GCs on glucose tolerance, insulin sensitivity and beta-cell function in RA patients included a small number of patients,[14] or

relied solely on fasting parameters, i.e. HOMA-IR and HOMA-B.[12] As mentioned above, in as much as insulin sensitivity and insulin secretion are interrelated, the use of the HOMA formulas, both of which utilize the same fasting variables, i.e. fasting plasma insulin and glucose, may not be appropriate to discern changes in insulin sensitivity from those in insulin secretion.[17] Although these model-derived indices are well-validated, they provide no information about the stimulated, postload state.[17] From dynamic tests, such as the frequently-sampled oral glucose tolerance test (OGTT), indices of postload insulin sensitivity and glucose-stimulated beta-cell function may be calculated, in order to provide more detailed information on glucose metabolism.[18]

Therefore, in the present study, we compared glucose tolerance and (fasting and dynamic) parameters of insulin sensitivity and beta-cell function from frequently-sampled OGTTs in a large group of chronic GC-using RA patients versus GC-naive RA patients. Furthermore, we included a control group of comparable age to create a perspective of our OGTT findings in RA patients, and to assess the association of RA *per se* on measures of insulin sensitivity and beta-cell function in subjects with normal glucose tolerance. Finally, we assessed the association between cumulative GC-dose and disease characteristics with these metabolic parameters.

METHODS

Population

RA patients with established disease, i.e. defined as having a disease duration of more than 2 years, were recruited in 5 rheumatology clinics in the region of Utrecht, the Netherlands. Patients were either current and chronic GC-users (RA+GC), which indicated GC-treatment for at least 3 months, or they were GC usage naïve (RA-GC). Known T2DM was an exclusion criterion. We included a control group (controls) with normal glucose tolerance and without first-degree relatives with T2DM, consisting of individuals who had undergone an OGTT for screening purposes for other studies at the Diabetes Centre of the VU University

Medical Centre in Amsterdam. Accordingly, this group consisted of relatively overweight predominantly male individuals. An independent ethics committee approved the study and all subjects provided written informed consent before participation; the protocol was according to the 'Declaration of Helsinki'.

Protocol

Participants visited the clinic following an overnight fast of minimally 10 hours. A physical examination, including recording of length, weight and waist circumference was performed and fasting blood tests were acquired in all patients. In the RA patients, in addition, the disease activity score (DAS28 and DAS28-CRP)[19,20] was calculated; in addition, DMARD-history taking, anti-citrullinated protein antibodies (ACPA) laboratory measurement, and X-rays of hands and feet (to detect erosive damage) were performed. Finally, all participants underwent a 2-hr 75 g OGTT. Blood samples for determination of glucose, insulin and C-peptide were collected at times 0, 10, 20, 30, 60, 90, and 120 minutes, starting immediately after the ingestion of the 75 g glucose solution. Since insulin clearance may vary considerably between subjects,[21] plasma C-peptide levels may provide additional information on beta-cell function.

Analytical Determinations

Plasma glucose was measured using a chemical technique on a DXC-800 analyser (Beckman Coulter, Los Angeles, USA). Plasma insulin was measured using an immunometric technique on an IMMULITE 1000 Analyzer (Siemens Medical Solutions Diagnostics, Los Angeles, USA). Plasma C-peptide was measured using an electrochemiluminescence immunoassay on the Modular E170 (Roche Diagnostics GmbH, D-68298 Mannheim, Germany).

Data analysis

Glucose tolerance state was assessed by the OGTT. Normal glucose tolerance was defined as fasting plasma glucose (FPG) < 6.1 and a 2-hour glucose value < 7.8 mM; impaired glucose metabolism (IGM) as FPG between 6.1 and 7.1 mM or a 2-hour glucose value between 7.8 mM

and 11.1 mM; T2DM as FPG > 7.1 mM or a 2-hour glucose value > 11.1 mM. Area under the 2-hour glucose (AUC_{gluc}), insulin (AUC_{ins}), and C-peptide ($AUC_{c\text{-}pep}$) curves were determined by using the trapezoidal rule. Insulin sensitivity in the fasted state was computed by HOMA-IR.[22] Estimated metabolic clearance rate (MCR_{est}/Stumpvoll Index) and oral glucose insulin sensitivity (OGIS) were used to estimate postload insulin sensitivity.[23] Various measures of beta-cell function were calculated: HOMA-B was derived from fasting measures.[22] Dynamic measures of beta-cell function were derived from OGTT data and included: $AUC_{c\text{-}pep}$/AUC_{gluc} ratio over the 2-hour period and the insulinogenic index (IGI): $insulin_{t=30}$-$insulin_{t=0}$)/($gluc_{t=30}$-$gluc_{t=0}$), as measure for early insulin secretion.[24] The oral disposition index (DI) was calculated by multiplying IGI and OGIS, to adjust insulin secretion for insulin sensitivity. Insulin clearance was calculated by dividing $AUC_{c\text{-}pep}$ and AUC_{ins}.[21]

Statistical analysis

Comparison of parameters of glucose tolerance state, insulin sensitivity and beta-cell function of RA+-GC groups and controls

Data were presented as mean values ±S.D. and as median (interquartile range) in case of non-normal distribution. Intergroup differences in continuous outcomes were tested by ANOVA, and with the Kruskal-Wallis tests in case of non-normal distribution. Differences between groups in dichotomous outcomes were tested with the chi-square test. Post-hoc Bonferroni correction was applied in case of multiple testing by multiplying the p-value times 2 (3 groups minus 1).

Associations between patient and disease characteristics and parameters of glucose tolerance state, insulin sensitivity and beta-cell function

Associations between known determinants of insulin sensitivity and beta-cell function (age, waist circumference, BMI, and insulin clearance) and gender, and, within the RA populations, cumulative GC-dose and disease activity (DAS28 and its components, DMARD-use, hand or feet erosions on X-ray, ACPA) and parameters of insulin sensitivity and beta-cell function

were investigated with linear regression analysis; associations of the above factors with IGM and T2DM were investigated with logistic regression analyses. If cumulative GC-dose was replaced by daily GC-dose (cumulative dose divided by duration of use) in the regression models similar associations were shown; therefore only cumulative GC-dose is depicted. Non-normally distributed variables were log-transformed when used in multivariate linear regression analysis. In the multivariate analyses with OGTT-outcomes as dependent variable where the RA populations were compared with the controls, RA patients with previously unknown T2DM, IGM or with 1st degree relatives with T2DM were excluded (i.e. fitting the exclusion criteria of CO). SPSS for Mac version 16.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses. A p-value <0.05 was considered statistically significant.

Effect modification

As compared to RA patients, controls had a higher percentage of male gender, and had a higher body mass index (BMI) and waist circumference; in addition, RA+GC had higher disease activity as compared to RA-GC patients (Table 1). These factors were studied for effect modification using interaction-terms in the below-mentioned regression models, and were shown not to modify the effects of patient and disease characteristics on glucose metabolism outcomes in the multivariate models (data not shown).

RESULTS

Baseline characteristics

After screening 167 RA patients, a total of 140 middle-aged established RA patients were included; 82 were GC naïve (RA-GC) and 58 were current GC users (RA+GC). Sixteen of the 27 excluded RA patients were known T2DM patients (11 RA-GC and 5 RA+GC). In addition, 50 controls with comparable age were recruited. Subject characteristics are provided in Table 1. As compared to RA patients, controls had a higher percentage of male gender, and had a higher body mass index (BMI) and waist circumference; these factors were

Table 1 / Baseline characteristics

	Controls	RA-GCs	RA+GCs	P-value Controls*	
				vs. RA-GCs	vs. RA+GCs
N	50	82	58	-	
Age (years)	56 ± 8	57 ± 12	59 ± 12	1.0	0.4
Female (%)	38	71	71	<0.001	<0.001
BMI (kg m^{-2})	29 ± 4	25 ± 4	26 ± 6	<0.001	0.008
Waist circumference male (cm) Waist circumference female (cm)	104 ± 10 100 ± 12	95 ± 8 82 ± 11	94 ± 10 91 ± 16	0.002 <0.001	0.005 0.03
Increased waist* (%)	62	24	35	<0.001	0.003
SBP (mmHg)	125 ± 10	124 ± 18	125 ± 17	1.0	1.0
DBP (mmHg)	80 ± 7	73 ± 10	73 ± 10	0.001	0.002
Hypertension* (%)	10	23	26	0.6	0.3
Anti-hypertensive drugs (%)	-	24	29	-	-
Fasting plasma glucose (mM)	5.4 ± 0.5	5.5 ± 0.7	5.3 ± 0.7	0.6	1.0
Triglycerides (mM)	1.2 ± 0.4	1.0 ± 0.5	1.2 ± 0.7	0.2	1.0
LDL (mM)	3.3 ± 0.9	3.4 ± 0.9	3.4 ± 1	1.0	1.0
HDL male (mM) HDL female (mM)	1.4 ± 0.3 1.6 ± 0.5	1.1 ± 0.3 1.5 ± 0.4	1.4 ± 0.4 1.6 ± 0.4	0.02 0.4	1.0 1.0
Total Cholesterol (mM)	5.3 ± 0.9	5.2 ± 1.0	5.4 ± 1.2	1.0	1.0
Dyslipidaemia*** (%)	50	82	62	<0.001	0.3
Hypercholesterolaemia***(%)	78	76	76	0.6	0.7
Statin use (%)	-	12	7	-	-

RA-characteristics			P-value
Duration of RA (years)	13 ± 8	13 ± 8	0.6
Diabetes** (%) IGM** (%)	9 37	14 33	0.3 0.6
Current DMARD use Synthetic (% / n) Biologic (%)	 89 / 1.2 21	 78 / 1.2 55	 0.07 <0.001
Historic DMARD use Synthetic (% / n) Biologic (% / n)	 71 / 1.9 7 / 1.3	 71 / 2.8 24 / 1.9	 1.0 0.005
DAS28 (no dimension)	2.8 ± 1.3	3.5 ± 1.2	0.002
Tender joint count	0 (0-3)	2 (0-5)	0.004
Swollen joint count	0 (0-1)	1 (0-2)	0.09
General well being (VAS 0 (good) to 100)	26 ± 21	38 ± 25	0.002
ESR (mm/hr)	11 (8-21)	14 (9-28)	0.1
Anti-CCP positive (%)	71	71	0.9
Any erosive damage at X-ray of hands or feet (%)	72	81	0.2 / only hand-erosions P=0.06
Cumulative dose GCs (g. prednisone equivalent)	0	13 (7-27)	-
Daily dose (mg)	0	6.3 (5-10)	-
Dexamethasone pulse (% ever used pulse / mean n pulses)	0	19 / 2	-

Data represent means ± standard deviation or median (interquartile range) when data was not normally distributed. Intergroup differences in continuous outcomes were tested by ANOVA, and with both the Kruskal-Wallace and Mann-Whitney tests in case of non-normal distribution. Differences between groups in dichotomous outcomes were tested with the chi-square test. Post-hoc Bonferroni correction was applied in case of multiple testing (p-value times 2).
* P-value controls is the intergroup difference tested by ANOVA, Mann-Whitney or chi-square test with the Bonferroni post-hoc test. P-values of the RA-GC RA+GC difference was not depicted; the only significant/trend differences were male HDL P=0.07; dyslipidaemia P=0.009.
* Increased waist circumference was defined as > 102 cm in male and > 88 cm in female. Hypertension was defined as ≥ 140 mmHg systolic or 90 mmHg diastolic pressure. ** Diabetes was defined as either fasting plasma glucose ≥ 7.1, or ≥ 11 at 120 min of OGTT; Impaired glucose metabolism was defined as either fasting plasma glucose (< 7.1 and > 6.1), or impaired glucose tolerance (<11 and >7.8 at 120 min of OGTT). *** Dyslipidaemia was defined as Triglycerides > 1,7 mmol/l and/or HDL-cholesterol < 0,9 mmol/l (male) and < 1 mmol/l (female). Hypercholesterolemia was defined as Total cholesterol > 5 mmol/l and/or LDL-cholesterol > 3 mmol/l.

Abbreviations: RA–GCs, rheumatoid arthritis patients, glucocorticoid naive; RA+GCs, rheumatoid arthritis patients, currently using glucocorticoids; Controls, control subjects; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; IGM, impaired glucose metabolism; LDL, low density lipoprotein ; HDL, high density lipoprote in, DAS28, Disease activation score using 28 joints; ESR, erythrocyte sedimentation rate; GC, glucocorticoids; VAS, visual analogue scale.

corrected for in the multivariate models. The RA groups had similar anthropometrics, but RA+GC had higher disease activity as compared to RA-GC (Table 1).

Glucose tolerance state

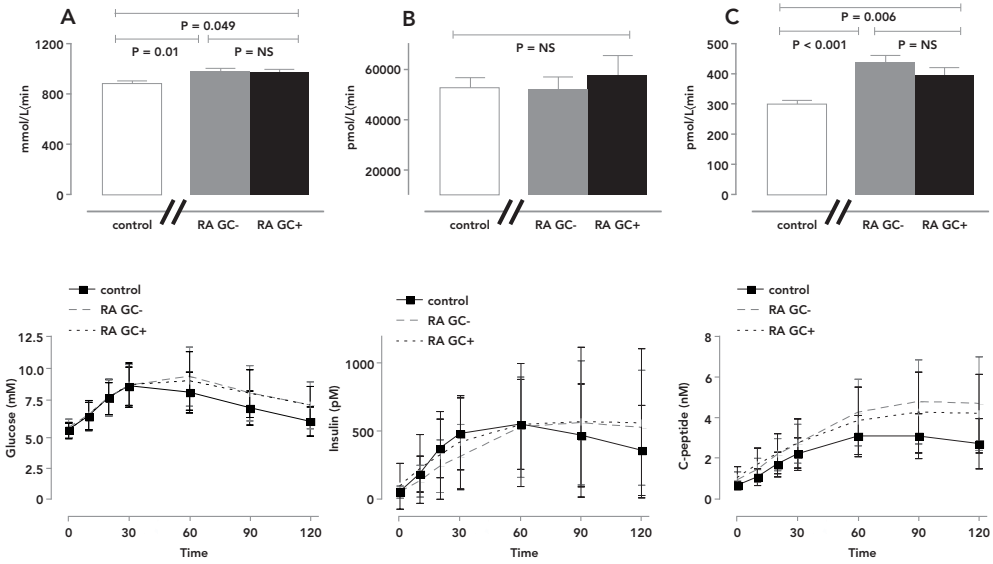
The prevalence of previously unknown T2DM was comparable between the two RA groups (Table 1). If those RA-patients who were excluded because of known T2DM (n=27) were included, then the prevalence of T2DM would be 19% (RA-GC 18% vs. RA+GC 21%, p=0.9). Within the RA groups, cumulative prednisolone dose was associated with incident T2DM in univariate analyses (odds ratio: 1.04; P=0.002). This association sustained after adjusting for disease activity and patient characteristics (DAS28, ACPA, erosions, DMARD history, disease duration, age, BMI, waist circumference, and gender; odds ratio: 1.04; P= 0.03), whereas it was decreased and less significant (a trend) after adjustment for current disease activity alone and patient characteristics (DAS28, age, BMI, waist circumference, and gender; odds ratio: 1.02; P= 0.08).

Metabolic responses during OGTT

Glucose levels during the OGTT were not different between the RA groups, whereas AUC_{gluc} was higher in RA patients as compared to controls, which was mostly driven by higher glucose levels during the final 90 minutes of the test (Figure 1A). Insulin levels were comparable

Figure 1 / glucose and insulin levels during OGTT

Figure 1 shows the mean (±SD) of glucose and c-peptide levels respectively, during the oral glucose tolerance test for control subjects (control), glucocorticoid naive RA patients (RA and GC-using RA patients). Intergroup differences were tested by ANOVA, and with the Kruskal-Wallis test in case of non-normal distribution. Post-hoc Bonferroni correction was applied in case of multiple testing (p-value times 2).



between all groups (Figure 1B); however, C-peptide secretion was higher in the RA groups as compared to controls (Figure 1C), with no difference between the RA groups, indicating increased insulin clearance in RA patients as compared to controls (data not shown). Insulin clearance was decreased in RA+GC as compared to RA-GC (data not shown).

Parameters of insulin sensitivity

Parameters of both fasting (Figure 2A) and postload insulin sensitivity (Figure 2 B+C) were comparable between the RA groups. In multivariate linear regression analyses (correcting for age, gender, BMI, waist circumference, and disease activity) the presence of RA, waist circumference and cumulative GC dose were independent predictors of HOMA-IR (Table 2). MCRest was negatively associated with DAS28, ESR, age, BMI and waist circumference (Table 2); a similar pattern was observed for OGIS (data not shown). The healthy control group was more insulin sensitive in the fasted state, but had similar postload insulin sensitivity as compared to the RA groups.

Figure 2 / insulin sensitivity indices

Figure 2 shows the mean (±SD) of insulin sensitivity indices HOMA-IR (fasting index), and of the dynamic parameters MCRest index and OGIS (representing glucose clearance during a 2hour oral glucose tolerance test. Intergroup differences were tested by ANOVA, and with the Kruskal-Wallis test in case of non-normal distribution. Post-hoc Bonferroni correction was applied in case of multiple testing (p-value times 2).

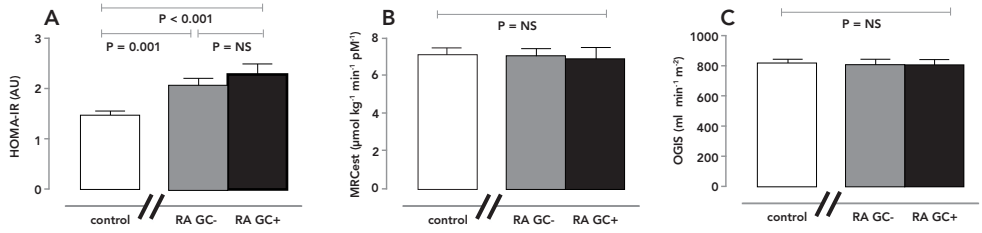
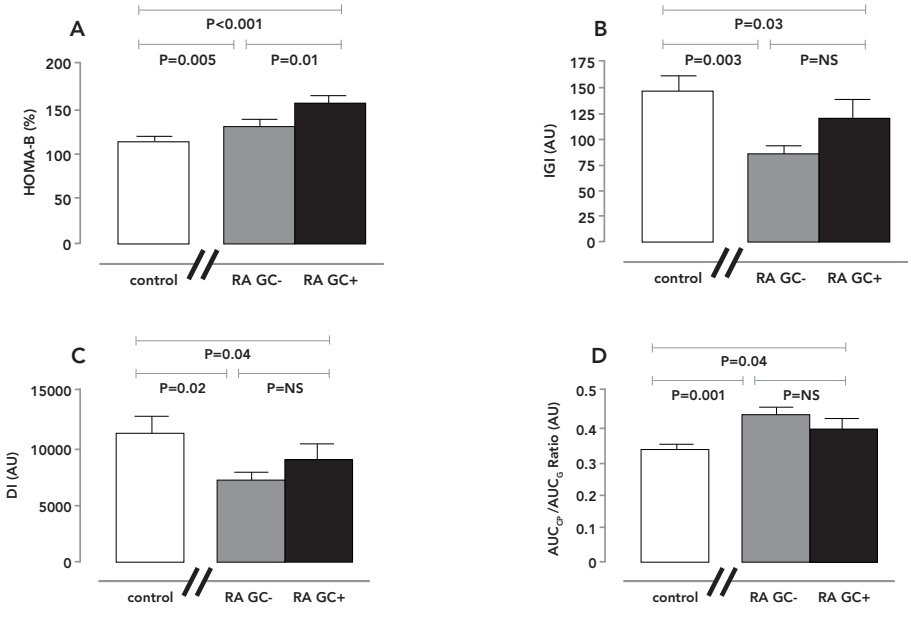


Figure 3 / parameters of beta cell function

Figure 3 shows the mean (±SD) of beta cell indices HOMA-B (fasting index), and of the dynamic parameters insulinogenic index (IGI) and disposition index (DI), and of the AUCc-pep/AUCgluc ratio. Intergroup differences were tested by ANOVA, and with the Kruskal-Wallis and Mann-Whitney tests in case of non-normal distribution. Post-hoc Bonferroni correction was applied in case of multiple testing (p-value times 2).



Parameters of beta-cell function

HOMA-B was higher in RA+GC as compared to RA-GC (Figure 3A), while all dynamic measures of beta-cell function were comparable between the RA groups (Figure 3B-3D).

Table 2 / Association of risk factors and disease characteristics with HOMA-IR and MCRest

Table 2a : *4 multivariate regression analysis models with HOMA-IR as dependent variable.*

Patient characteristic	Beta (95% CI) (RA-patients, controls)	Beta (95% CI) (RA-patient only)	Beta (95% CI) (RA-patient only)
RA-GC*	0.6 (0.08, 1.0)		
RA+GC*	1.0 (0.6, 1.5)		
Waist circumference	0.02 (-0.01, 0.04)	0.02 (-0.003, 0.05)	0.03 (0.0002, 0.06)
Age	0.002 (-0.02, 0.02)	0.008 (-0.007, 0.02)	0.006 (-0.01, 0.02)
BMI	0.03 (-0.05, 0.1)	0.05 (-0.2, 0.1)	0.03 (-0.04, 0.1)
Female gender	0.2 (-0.2, 0.6)	-0.1 (-0.5, 0.3)	-0.06 (-0.5, 0.4)
Cumulative GC-dose (g)**		0.01 (0.003, 0.02)	0.01 (0.003, 0.02)
DAS28***			0.1 (-0.04, 0.3)
Any erosions of the hands or feet			-0.3 (-0.7, 0.2)
Past DMARDs (n)****			-0.06 (-0.2, 0.05)
ACPA			0.2 (-0.7, 0.2)
Disease duration (years)			0.02 (-0.008, 0.04)

Table 2b : *4 multivariate regression analysis models with MCRest as dependent variable.*

RA-GC*	0.4 (-0.5, 1.3)		
RA+GC*	0.4 (-0.5, 1.2)		
Waist	-0.02 (-0.07, 0.03)	-0.06 (-0.1, 0.01)	-0.09 (-0.2, -0.02)
Age	-0.03 (-0.06, 0.005)	-0.07 (-0.1, -0.03)	-0.07 (-0.1, -0.03)
BMI	-0.3 (-0.4, -0.1)	-0.2 (-0.4, -0.06)	-0.1 (-0.3, -0.06)
Female gender	-0.8 (-1.6, 0.08)	-0.08 (-1.3, 1.1)	-0.5 (-1.7, 0.7)
Cumulative GC-dose (g)**		0.002 (-0.01, 0.04)	0.01 (-0.01, 0.04)
DAS28***			-0.5 (-0.9, -0.1)
Any erosions of the hands or feet			0.8 (-0.3, 2.0)
Past DMARDs (n)****			0.2 (-0.06, 0.5)
ACPA			-0.7 (-1.8, 0.4)
Disease duration (years)			0.03 (-0.04, 0.1)

* RA-GC and RA+GC populations are tested with the healthy control group used as the reference population; only RA patients with normal glucose tolerance during OGTT and without 1st degree relatives with type 2 diabetes mellitus were included in the model for the comparison with healthy controls.
** Cumulative GC-dose and current disease parameters (DAS28, DAS28CRP, CRP, ESR) were separately tested in models of only the RA population.
*** Only DAS28 is depicted, whereas ESR was also significantly associated with MCRest in this model.
**** Number of DMARDs (both synthetic and biological; not glucocorticoids) that were used by a patient in the past.

Abbreviations: CI, confidence interval; BMI, body mass index; RA, rheumatoid arthritis; GC, glucocorticoid; HOMA-IR, homeostatic model assessment of insulin resistance; MCRest, insulin sensitivity index by Stumvoll; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activation score measured by questioning general health, physical examination of 28 joints and ESR or CRP; ACPA, anti-citrullinated protein antibodies.

Table 3 / Association of risk factors and disease characteristics with the disposition index.

4 multivariate regression analysis models with disposition index as dependent variable.

Independent variable	Beta (95% CI) (RA-patients, controls)	Beta (95% CI) (RA-patient only)	Beta (95% CI) (RA-patient only)
RA-GC*	-42489 (-96745, 11767)		
RA+GC*	-23040 (-75891, 29810)		
Waist circumference	-1778 (-4895, 1338)	315 (-1831, 2462)	274 (-2009, 2557)
Age	-3295 (-5219, -1370)	-1280 (-2502, -57)	-1100 (-2385, 186)
BMI	6205 (-1930, 14340)	-2771 (-8193, 2650)	-3070 (-8893, 2752)
Female gender	-8287 (-52574, 36000)	25773 (-10358, 61904)	31014 (-6984, 69013)
Cumulative GC-dose (g)**		-482 (-1307, 343)	-284 (-1150, 582)
DAS28***			-4759 (-16525, 7007)
Any erosions of the hands or feet			-14480 (-50730, 21770)
Past DMARDs (n) ****			662 (-7572, 8896)
ACPA			24336 (-9300, 57973)
Disease duration (years)			-1392 (-3447, 664)

* RA-GC and RA+GC populations are tested against the control subject population; only RA patients with normal glucose tolerance during OGTT and without 1st degree relatives with type 2 diabetes mellitus were included for the comparison with control subjects. RA+GC was significantly associated with DI when these analyses were performed with log-transformed DI.
** Cumulative glucocorticoid dose was tested in a model of only the RA population.
*** Disease parameters (DAS28, DAS28CRP, CRP, ESR, ACPA, erosions of hands or feet, disease duration) were separately tested in the model of only the RA population; only DAS28 and significant correlations are depicted.
**** Number of DMARDs (both synthetic and biological; not glucocorticoids) that were used by a patient in the past.

Abbreviations: CI, confidence interval; RA–GCs, glucocorticoid naive rheumatoid arthritis patients; RA+GCs, rheumatoid arthritis patients currently using glucocorticoids; BMI, body mass index; RA, rheumatoid arthritis; GC, glucocorticoid; HOMA-B, homeostatic model assessment of beta cell function; IGI, insulinogenic index; DI, disposition index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activation score measured by questioning general health, physical examination of 28 joints and ESR or CRP.

Positive associations between the presence of RA and cumulative GC-use with HOMA-B were found (corrected for age, gender, BMI, waist circumference, and disease activity; data not shown). Age and both RA-GC and RA+GC were negatively associated with IGI (corrected for age, gender, BMI, waist circumference; data not shown). As compared to healthy controls, RA patients had higher basal C-peptide secretion (higher HOMA-B), but impaired early insulin secretion, also when corrected for insulin sensitivity (Figure 3B+C). The total amount of C-peptide secreted during the entire OGTT relative to glucose levels, was higher in RA patients than healthy controls (Figure 3D).

DISCUSSION

In this study of RA patients with established disease, chronic GC-users and GC-naive patients had similar insulin sensitivity and beta-cell function parameters; however high cumulative GC-dose was associated with T2DM. In addition, in all RA patients IGM and T2DM were frequently diagnosed, suggesting that glucose intolerance remains an underestimated problem in RA. As compared to a healthy control group, RA patients had impaired insulin sensitivity and beta-cell dysfunction, explaining their impaired metabolic state.

To our knowledge, this is the first study that has examined glucose metabolism in a relatively large sample of RA patients with established disease in such detail. Few studies investigated glucose tolerance state in RA: One study showed an increased prevalence of T2DM when compared to age-matched controls;[25] another study reported 19% diabetes prevalence as part of a longitudinal medical record cohort on cardiovascular risk.[6] Both studies relied on self-reported T2DM and did not perform glucose measurements. Because of the OGTT measurements of glucose at 0 and 120 minutes we were now able to register 11% T2DM prevalence in RA patients with established disease without known T2DM, and in addition, identify high-risk patients, by detecting 35% prevalence of IGM. This shows that glucose intolerance is a considerable and underestimated problem in RA patients with established disease, and might (partially) explain their increased cardiovascular risk.[1]

The subject of insulin resistance in RA has been addressed in recent years, but was only evaluated by fasting measure HOMA-IR.[2-4] Unlike these studies, we were able to show a negative association of DAS28 with insulin sensitivity after correcting for potential confounders and other risk factors, which could have been due to the fact that we also used stimulated measures of insulin sensitivity and because our sample size was larger.

Another important finding of our study was impaired beta-cell function in RA patients as compared to controls, as was shown by decreased dynamic parameters IGI and DI, also when correcting for age, BMI and waist circumference (in case of IGI). This indicates impaired insulin secretion during the early phase after glucose stimulation. So far, a limited

number of other studies have reflected upon beta-cell function in RA, and only used the fasting state measure HOMA-B. In one retrospective study HOMA-B was decreased in RA patients with a higher level of inflammation when compared to RA patients with lower level of inflammation,[4] which seems in line with our findings of impaired beta-cell function in RA patients when compared to the control population. In our current analysis, HOMA-B was higher in RA patients, which indicates increased basal C-peptide secretion. This seems contradictory next to the decrease in beta-cell function parameters obtained in the stimulated state. However, HOMA-B should always be interpreted in the context of prevailing insulin resistance.[17] Since HOMA-IR was increased, HOMA-B merely reflects fasting insulin resistance and has little value predicting beta-cell function.

In addition, we addressed the specific role of cumulative GC-dose and disease characteristics within RA patients and found strong indications that RA+GC patients were less glucose tolerant in a dose-dependent manner: Although no relation was shown between cumulative GC-dose and dynamic tests of insulin sensitivity and beta-cell function, cumulative GC-dose was associated with previously unknown T2DM and negatively affected fasting insulin sensitivity (HOMA-IR); independent of age, gender, BMI, waist circumference, and disease activity. Our results are in line with one other retrospective study of non-diabetic RA patients;[12] this study analysed a successive group of RA patients and showed that ever having taken oral prednisone and/or high doses of pulsed GCs were independently associated with decreased insulin sensitivity independent of BMI.

We acknowledge some limitations in our study design; one is the difference with regards to anthropometrics between controls (with normal glucose tolerance) and RA patients, i.e. controls were primarily recruited for other studies at the VUMC Diabetes Centre and therefore consisted of more males and had a relatively high BMI, and lower insulin clearance. Compared to these control subjects RA patients were more insulin resistant and had more beta-cell dysfunction. Although the use of this controls population, as compared to more lean, insulin sensitive controls, may be suboptimal, it is very likely that the impact of RA and the associated pro-inflammatory state on glucose metabolism as described here, may even

be underestimated. Besides, in multivariate analyses we corrected for these anthropometrics, and furthermore the control subjects served mainly to create a perspective for the insulin resistance and beta-cell parameters of RA patients. Another point is confounding by indication that could have caused the effects of GCs on glucose metabolism, since cumulative GC-use could be a proxy for long-term disease activity, which itself influences glucose metabolism. This was shown also in our study by a decrease of the regression coefficient (beta) for the association between cumulative GC-dose and T2DM when disease activity (DAS28) was added to the multivariate regression model.

Concluding, because of (1) the stimulated state measurement of glucose metabolism parameters, (2) the size of our population, and (3) the contrast with control subjects, we were able to draw firm conclusions on the prevalence of glucose tolerance abnormalities in RA patients with established disease and to confirm the relation between RA (activity) and insulin resistance and beta-cell dysfunction. Chronic GC-use was associated with metabolic toxicity in a dose dependent way, but this association was difficult to assess due to confounding by indication.

Until more clarity is given on the issue of glucose intolerance in GC-using RA patients, it remains important to keep the use of GCs of short duration and lowest possible dose, as is advised by the EULAR recommendations on RA treatment,[26] and on systemic GC-use.[27] The question how harmful long-term GCs are with regards to diabetogenic effects in established RA patients needs further assessment in longitudinal (randomised) trials. These trials should measure glucose metabolism with stimulated state measures, and study whether GCs exert direct metabolic toxicity or secondary to other GC-related phenomena, such as abdominal fat and adipocytokines, which are known mediators of metabolic toxicity in RA.[28]

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CHAPTER 6

ADVERSE EVENTS OF LOW-TO-MEDIUM-DOSE ORAL GLUCOCORTICOIDS IN INFLAMMATORY DISEASES: A META-ANALYSIS

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Objectives

To systematically analyze the literature on reported adverse events of low to medium dose glucocorticoids during ≥ 1 month for inflammatory diseases.

Methods

Data were systematically retrieved and selected from PUBMED, EMBASE, and CINAHL databases (6097 hits).

Results

In total, 28 studies (2,382 patients) met the inclusion criteria. The risk of adverse events over all studies together was 150 per 100 patient year (95% confidence interval (CI) 132;169). Psychological & behavioural adverse events (e.g. minor mood disturbances) were most frequently reported, followed by gastro-intestinal (e.g. dyspepsia, dysfagia).

In 14 studies comprising 796 patients with rheumatoid arthritis the risk of adverse events was 43/100 patient years (CI 30 ; 55), in 4 studies with 167 patients with polymyalgia rheumatica the risk of adverse events was 80/100 (CI 15;146), and in 10 studies, 1,419 patients, with inflammatory bowel disease the risk of adverse events was 555/100 (CI 391;718). High adverse events rates were reported in high quality studies with short follow-up, notably in inflammatory bowel patient studies.

Conclusions

The risk of adverse events depends on study design and disease. Studies on inflammatory bowel disease were often clinical trials of short duration with frequent documentation of adverse events which resulted in higher adverse events rates, whereas in rheumatoid arthritis studies, the rather long follow-up may have resulted in lower adverse events rates. In most studies, aimed at efficacy of glucocorticoids or other drugs, adverse events were not systematically assessed. Clear guidelines on assessment of adverse events are lacking.

Glucocorticoids (GCs) are a widely prescribed medication group, as immunosuppressants after organ transplant and in chemotherapy in oncology. They are also used as mainstay treatment of vasculitides and several chronic autoimmune and inflammatory diseases, notably rheumatoid arthritis (RA), polymyalgia rheumatica or temporal arthritis (PMR), and systemic lupus erythematosus (SLE), obstructive lung diseases (asthma and chronic obstructive pulmonary disease), and inflammatory bowel diseases (IBD: ulcerative colitis and Crohn's disease). Different routes of GC-administration are used, e.g. intravenous, inhalation, intra-muscular, intra-articular and oral, while regimens vary from high pulse dose to low dose long-term treatments. Daily oral GCs are prescribed for long-term treatment in more severe cases of chronic pulmonary and inflammatory bowel diseases, and in inflammatory rheumatic diseases. Prednisolone and prednisone are the most frequently used GCs for oral treatment; other oral GCs are dexametasone, budesonide, beclometasone, fluticasone, and deflazacort. In general, long-term dosage is medium to low (defined as ≤30 mg prednisolone equivalent per day)[1] to control the inflammation. In patients with early RA, several trials have also shown that low dose GCs also modify the course of the disease and are joint sparing.[2-6]

In RA, PMR and IBD low-to-medium dose GC-treatment is common in daily treatment, but, it is feared for its adverse events (AE), although AE most often occur during high GC-dosages; their frequency with lower dosages is uncertain. Golder *et al.* reported that there is no systematic and comprehensive overview of studies quantifying the risk of AE of GC.[7] A previous review discussed GC-related AE in RA patients (Table 1),[8] but did not quantify their occurrence. So, more data on AE of low to medium dose GCs are needed.

Our aim is to provide a systematic and comprehensive overview of studies quantifying the risk of AE of low-to-medium dose GCs (i.e. ≤30 mg prednisolone equivalent) during ≥1 month in chronic inflammatory diseases.

METHODS

Study retrieval

Studies were sought in Pubmed, Embase, and CINAHL by JNH and SMMV. A list of relevant keywords for disease (RA, SLE, PMR, COPD, asthma, and IBD) and treatment (low-to-medium-dose GCs) was compiled and checked by experts (JWGJ and JWJB). Keywords, including words of title, abstract and Mesh were combined using Boolean operators (AND, OR) search filter (Appendix 1).

Study selection

Selection of potentially relevant retrieved publications by JNH and SMMV was based on applying the following criteria to the title, abstract, full-text or all:

1) Study population. Adults with inflammatory diseases, notably RA, SLE, PMR, COPD, asthma, and IBD, who were treated with GCs. Studies involving patients who received GCs for another disease were excluded.

2) GC-dose. The dose of GCs had to be low to medium (≤ 30 mg prednisolone equivalent during the study, except of the first month, when a high dose (≤ 60 mg) was allowed like in the COBRA trial)[2]. Studies were excluded if patients had previously used long-term (≥ 3 months) GCs or if any GCs had been used within 3 months before study onset. If only a group of the whole study population used a suitable dose, then only this part of the population was used for analysis, if stratified data were reported for this group.

3) Type of publication. Only full papers on original patient data reporting on AE of GC-treatment were considered for further appraisal.

4) Type of study. (Randomized) trials and follow-up studies were considered for further appraisal if follow up had been clearly assessed and the duration of the study was ≥ 1 month. See Figure 2 for the description of the several designs of included studies.

5) Type of AE-reporting. Only studies who were reporting dichotomous AE outcomes were included.

Disagreements in selection were resolved by discussion; selection was based on full consensus.

Quality-appraisal

The following criteria were used for quality-appraisal of the selected studies:

a) Standardized AE scoring protocol; did the study use an AE protocol? How many AE were monitored during the study? How often were AE scored?

b) Predefined AE, e.g. did the study predefine AE? How many AE were predefined?

c) Description of missing data, e.g. did the study detail the number of missing data and the reason of missing?

Each study could score 1 point per criterion, up to a maximum of 3 points.

The quality of the articles was critically appraised and AE data were summarized by two assessors (JNH and SMMV) independently of each other. Disagreements regarding study quality were resolved by discussion; results are based on full consensus.

Data extraction

Data from studies were found useful for meta-analysis, when the following could be extracted by JNH and SMMV:

- The type and number of AE; AE that did not fit one of the predefined AE-list (Table 1) were listed as 'other'.
- The number of patient years (py) (= duration of follow-up (years) x number of patients)
- Gender, age.
- Type of GC, mean dosage of GC; low GC-dose was defined as dosages of 0 – 7.5mg and medium dose as > 7.5 – 30mg prednisolone equivalent; short follow-up was defined as ≥ 1 – 6 months and long follow-up as > 6 months.
- The number of missing data, i.e. patients dropping out from each study, was noted.

Table 1 / Glucocorticoid-related AE.[8]

Type of AE:
Musculoskeletal
• Osteoporosis, osteonecrosis, myopathy
Endocrine and metabolic
• Glucose intolerance and diabetes, fat redistribution and body weight, suppression of sex hormones secretion
Cardiovascular
• Dyslipidemia, atherosclerosis, cardiovascular disease, water and electrolyte balance, edema, renal and heart function, hypertension
Dermatological
• Cutaneous atrophy, acne, hirsutism, alopecia
Ophthalmologic
• Cataract, glaucoma
Gastrointestinal
• Peptic ulcer disease, pancreatitis
Infectious
• Viral, bacterial, skin infections
Psychological and behavioral disturbances
• Steroid psychosis, minor mood disturbances
Neurologicala
• Headache, vertigo, dizziness, tinnitus

[a] Unlike other AE-subgroups, neurological AE were not described as a subgroup by da Silva et al.8 added these because they were relatively frequently reported.

Data- analyses

The AE-rate of GC-users, defined as AE per patient year, was calculated by pooling the data of all retrieved follow-up studies using the software 'Comprehensive Meta-Analysis'.[9] We explored differences in the pooled AE-rates by disease, study quality and dosage for which we used a Mantel-Haenszel approach to control for confounding.

RESULTS

Search and selection

With our search strategy we retrieved 6,097 studies (appendix 1), which we loaded into an electronic bibliographic management system (Reference Manager).

Figure 1 and Appendix 2 display the results of retrieval and selection of studies. From the 6,097 studies, 28 met the inclusion criteria and from these 28 studies, AE-data were extracted. No study on obstructive pulmonary diseases (asthma, COPD)

fitted the selection criteria, so studies on RA, PMR and IBD were evaluated in this review.

For some studies the entire population did not fit our inclusion criteria. For instance, certain studies evaluated the anti-osteoporosis effect of bisphosphonates against placebo in a population that used GCs. We then looked at AE of the placebo or control groups on GC therapy of these studies, but we did not include the group on bisphosphonates.

Quality of the studies

Figure 2 shows the studies categorized according to their quality. The mean (SD) quality of the studies was 2.2 out of 3, and this did not differ much between the different subpopulations, i.e. disease (RA, PMR, and IBD), low to medium dose GCs (up to 7.5 mg or from 7.5 up to 30 mg), or short/long term follow-up (up to 6 months or longer than 6 months) (Figure 3).

Study characteristics

Table 2 describes the quality and characteristics of all studies and of the different subgroups. The included 28 studies reported on AE-data of 2,382 patients using GCs,

Figure 1 / Results of retrieval and selection of studies.
At the search, several double hits were found.

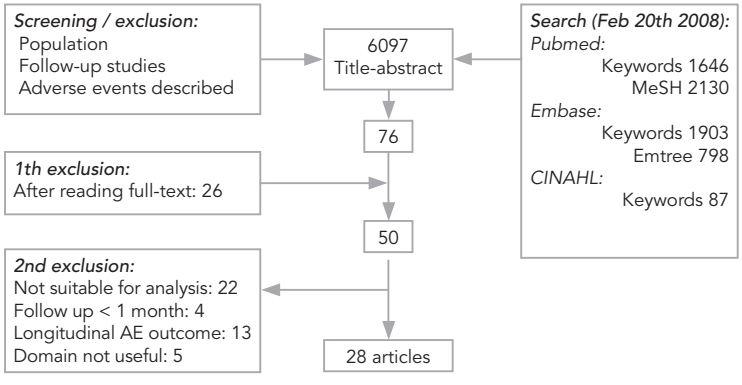


Table 2 / Study characteristics.[a]

	All patients	*RA*	*PMR*	*IBD*	*Low dose*	Medium dose	Short follow-up	Short follow-up
N studies	28; 3780	14; 1708	4; 167	10; 1905	17[b]; 2184	13[b]; 1596	14; 1762	14; 2018
N GC-using populations	39; 2382	17; 796	6; 167	16; 1419	23; 1398	16; 984	21; 1362	18; 1020
Age (yrs)	46	54	72	37	47	44	39	52
Gender (% female)	63	70	69	55	64	61	56	68
Mean dose prednisone equivalent (mg(SD))	11.5(14.5)	7.5(5.9)	8.6(3.2)	13.9(13)	6.7(4.8)	18.0(20)	14.6(17.4)	7.2(4.8)
Quality analysis of the (sub)populations of the included studies.								
AE-scoring per protocol (N)	22; 2960	10; 1047	3; 142	9; 1771	15; 1817	9; 1143	11; 1470	11; 1490
Mean time AE-scoring (months)	1.7	3.4	1.4	0.9	2.2	1.0	0.5	3
Predefined AE (N)	15; 1976	9; 1072	3; 142	3; 762	10; 1438	5; 538	5; 578	10; 1398
Number of predefined AE	7.9	8.8	5.8	7.0	8.3	6.8	6.2	8.6
Missing data (N) [c]	24; 3471	11; 1424	3; 142	10; 1905	14; 1900	12; 1571	12; 1702	12; 1769
% missing data [d]	21.3	19.8	23.9	21.7	22.1	20.1	22	19.7

[a] N = the number of studies/populations; number of patients. = Inflammatory Bowel Disease; PMR = Polymyalgia Rheumatica; RA = Rheumatoid Arthritis. Low dose = lower or equal to 7.5 mg prednisolone equivalent. Medium dose = Higher than 7.5 mg and lower or equal to 30 mg prednisolone equivalent. follow-up = Study duration of less than or equal to 6 months. Long follow-up = Study duration of more than 6 months.
[b] Two studies (Sandborn 1998 and Rutgeers 1994) were split in two sub-populations, since these studies included both a low as a medium dose population.
[c] Missing data: Number of studies, which noted patients that dropped out of the study.
[d] Percentage of patients of the study population that dropped out of the study.

representing 39 subgroups. The mean number of predefined AE and the percentage of drop-outs did not differ across studies.

Characteristics of patients included in studies among IBD patients, generally with short term follow-up were different from those in studies among RA/PMR patients, generally with long term follow-up (Table 2). The majority of studies were randomized trials, most of which compared the effect of GCs with that of placebo or other medication,

e.g. Disease Modifying Drugs (DMARDs) in addition to standard therapy. Typically, studies on RA used low dose GCs and had long term follow-up, while most studies on IBD applied both low and medium GC-doses and had a short term follow-up. Compared to long-term studies on RA and PMR, AE in short-term IBD studies were scored more frequently (e.g. every 0.5-1 month, see Table 2), which will automatically result in higher AE-rates.

Adverse Event rates

The reported AE rates for GC-users over all studies together was 150 events per 100 py (95% confidence interval (CI): 132 ; 169). The rates of the various AE were comparable, but psychological and behavioral AE were the highest (table 3). Comparison of low and medium dosages did not show dose-dependency of any of the AE.

Figure 3 shows the data per diagnosis subgroup; In RA-patients using GCs (14 studies, 796 patients), the AE-rate was 43/100 py (CI 30; 55). Shorter term follow-up and higher study quality or design resulted in higher reported AE-rates.

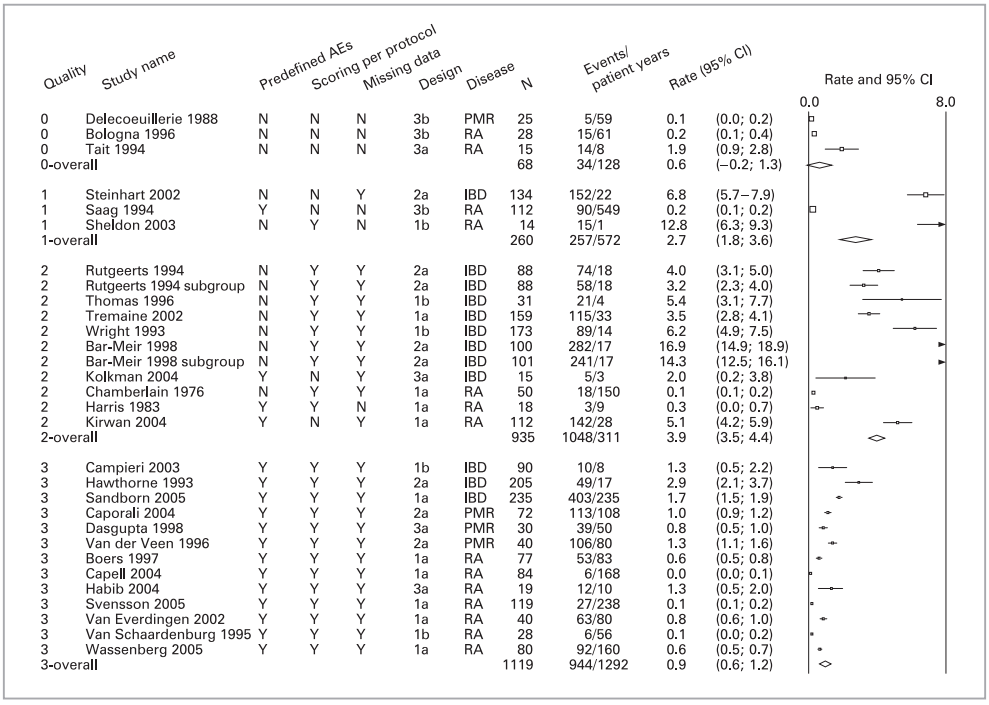
In PMR-patients using GCs (4 studies, 167 patients), the AE-rate was 80/100 py (CI 15 ; 146). PMR-patients most often reported gastro-intestinal, endocrine and metabolic, cardiovascular, and infectious AE. Higher dosages of GCs resulted in higher AE-rates in PMR-studies of comparable quality.

Among IBD-patients on GCs (10 studies, 1,419 patients), the AE-rate was 555/100 py (CI 391 ; 718). IBD-patients most often reported gastro-intestinal and neurological AE. Studies with short term follow-up, most of which concerned randomised trials in IBD-patients, reported higher AE-rates than those with long term follow-up.

DISCUSSION

To our knowledge this is the first study presenting a pooled analysis of AE of only low to medium dose GCs (up to 30 mg of prednisone equivalent) in patients with inflammatory

Figure 2 / Quality of studies. The following criteria were used for quality appraisal of the selected studies: (a) Did the study predefine adverse events (AE)? (b) Standardised AE scoring protocol? (c) Did the study detail the number of missing data and the reason of missing? Each study could score 1 point per criterion (Y, yes; N, no) up to a maximum of 3 points. Design of included studies: (1) randomised trials comparing glucocorticoids (GCs) with placebo or non-GCs: (1a) all patients use identical co-medication (disease-modifying antirheumatic drug (DMARD), inhalation GC); (1b) different patients use different co-medication (DMARD). (2) Randomised trial comparing two medication groups (DMARDs vs placebo, GC vs another type of GC, antibiotic vs other antibiotic, bisphosphonate vs placebo or calcium): (2a) all patients received GCs; (2b) a subgroup of patients received GCs. (3) Longitudinal cohorts (prospective/inception/retrospective including follow-up): (3a) all patients received GCs; (3b) a subgroup of patients received GCs. IBD, inflammatory bowel disease; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; N, number of patients using GCs.



diseases (i.e. RA, PMR and IBD) using longer term (1 month) GCs. Although dosages up to 30 mg may seem high, the actual dosages as used by the included studies in this review were much lower (table 2).

Overall, 150 AE occur per 100 py with GC-use. The AE rate largely depends on the study quality but most of all on the population: 43/100 py in RA, 80/100 py in PMR, and 555/100 py in IBD. Psychological, behavioral and gastro-intestinal AE were most often reported. Studies of IBD patients were often clinical trials of short duration with accurate and frequent documentation of all types of AE. In RA patient studies scoring AE also in an accurate and pre-defined manner, the generally longer follow-up may have resulted

in the lower AE rates. A limited number of relatively high quality studies was found on AE in patients with PMR using GC. As a substantial part of included studies did not report on the frequency of scoring AE, it was not possible to compute AE rates adjusted for frequency of scoring.

Our results show that design of studies hampers direct comparison of GC-related AE-rates in patients with different diseases. Especially when looking at figure 2, the frequency of side effects seems to be not higher in patients enrolled in high quality trials, suggesting that the difference between the diseases was the most important factor (and not the quality of the study). The differences between AE rates of the different diseases studied could be related to patients' and study characteristics. E.g. IBD studies were often short studies, using higher GC-dosage next to other medications, and most importantly AE were measured very frequently (Table 2), resulting in a high reporting of AE. In PMR, doses also were high, but study duration was longer, co-medication more limited and disease symptoms possibly are less prone to be interpreted as AE. So, the large differences in AE occurrence

Table 3 / Rate of adverse event (AE) groups per 100 patient-years (py)[a]

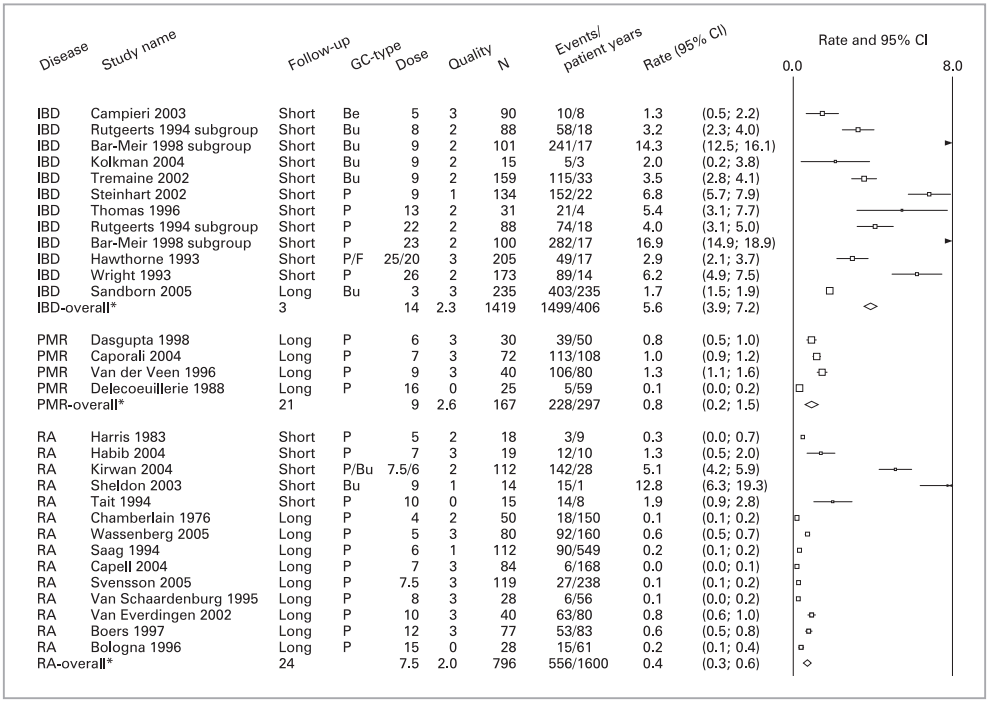
	All patients		*RA*		*PMR*		IBD	
	AE-Rate (AE/ 100 py (95 CI))	*Percentage of total all AE rate (%)*	*AE-Rate (AE/ 100 py (95 CI))*	*Percentage of total all AE rate*	*AE-Rate (AE/ 100 py (95 CI))*	*Percentage of total all AE rate*	*AE-Rate (AE/ 100 py (95 CI))*	*Percentage of total all AE rate*
Psychological and behavioural disturbances	25 (15-34)	20	19 (4-34)	31	4 (-1 - 10)	6	65 (37 - 93)	8
Gastrointestinal	19 (14-24)	15	5 (3-8)	9	14 (5 - 22)	18	169 (118 - 220)	21
Dermatological	15 (10-20)	12	6 (2-11)	11	2 (0 - 5)	3	107 (65 - 148)	13
Neurological	12 (6-19)	10	1 (0-1)	1	x		140 (73 - 207)	17
Musculoskeletal	12 (7-17)	9	4 (2-7)	7	6 (2 - 11)	8	113 (61 - 166)	14
Infectious	12 (8-16)	9	4 (2-7)	8	11 (7 - 15)	14	58 (21 - 95)	7
Endocrine	11 (7-14)	8	4 (2-6)	6	12 (2 - 23)	16	120 (74 - 166)	15
Cardiovascular	8 (5-11)	7	6 (2-11)	11	12 (4 21)	16	13 (2 - 25)	2
Other[b]	8 (5-11)	7	6 (2-10)	10	12 (-2 - 26)	15	16 (3 - 28)	2
Ophthalmological	3 (2-4)	3	4 (2-5)	6	3 (-1 - 6)	4	x	

[a]AE groups as defined in box 1, ranked.
[b]Microhaematuria, proteinuria, dysuria, episodes of salivary gland enlargement, pain, tremor, leucopenia, thrombocytopenia, other haematological AE, elevated liver enzymes, taste
disturbance, ''serious adverse events'', cervix carcinoma, carcinoma, death by cancer.
IBD, inflammatory bowel disease; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis.

between the study populations, RA, PMR, and IBD, are most likely due to the fact that the study characteristics of these populations varied substantially. Our review didn't provide us with other clues or alternative explanations that disease-specific influences caused the large difference in AE occurrence between RA, PMR, and IBD.

Previous studies [8,10,11] showed a dose and time relation for more serious long term GC-related AE, like osteoporotic fractures. In this systematic review we report on commonly reported GC-related AE, of which most may interfere with compliance of GC-use. The low AE-rate in patients with RA using long-term low doses of GCs confirms the

Figure 3 / Figure 3 Disease: IBD, inflammatory bowel disease; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis. Follow-up: short, study duration of >1 month and (6 months; long, study duration .6 months. The number for ''follow-up'' of the overall groups represents the mean follow-up (months) corrected for the number of patients per individual study. Glucocorticoid (GC) type: 1502 patients used prednisone (P), 685 budesonide (B), 90 beclometasone (B), 105 fluticasone (F). Dose: dose of glucocorticoid in mg. The number for ''dose'' of the overall groups represents the mean dose of prednisone equivalent (mg) corrected for the number of patients per individual study. The relative potency of budesonide is 0.83.12 No relative potency was known to the authors for beclometasone and fluticasone, which are mainly used topically (enema or aerosol) but, since these drugs were not more efficacious in the included studies,[13 14] it was assumed that the dosages of these compounds were of equal or less potency than equal dosages of prednisone. Quality: as described in fig 2. Design of included studies: as described in fig 2. N, number of patients using GCs.



modest toxicity profiles previously described.[8] Nevertheless, it is contra intuitive that medium dosage and longer term GC-use seem to cause as frequent AE as low dosage and short term GC-use. However, the dose and duration of GC therapy were related to the different disease populations with different base-line risks for AE, different study designs and different comedication and comorbidities. So it is difficult to unravel the direct relation of GC-therapy and AE.

Although included in our search strategy, we found no studies on patients with obstructive pulmonary diseases (asthma, COPD) that fit our selection criteria. This probably reflects clinical practice, where these patients do not use oral GCs on a long term but only for short periods (< 1 month) to overcome disease exacerbations.

It should be noted that the main goal of this meta-analysis was to extract rates for GC-related AE. Since we did not want to make etiologic or casual inferences, i.e. extract relative risks or odds ratio on AE from the reported data, we could do without a reference population. The primary aim of most studies included in this review was to demonstrate the beneficial effects of GCs, not to measure harm.

In conclusion, the occurrence of GC-use related AE largely depends from the disease in the population. With an overall mean of 150 AE per 100 py with GC-use, the AE rate varies from 43/100 py in RA and 80/100 py in PMR to 555/100 py in IBD.

Recommendations on the use of long-term GCs have recently been published for the rheumatic diseases.[12] Adherence to these recommendations will most likely help to reduce the occurrence of GC-related AE in any disease. Still, more thorough research on the safety of long-term GC-use is needed to establish a more exact risk-harm ratio of GCs. The risk-benefit ratio of GCs is an important issue for future studies on GCs, and could help to create new targets for drug-development, e.g. selective glucocorticoid receptor agonists. For this aim, the development of a core set of AE-assessment tools for GC-related AE is needed, with directives on systematic and accurate scoring of predefined AE. In the development of these tools, we consider patient involvement as crucial.

APPENDIX 1

Result of search performed 28 February 2008

(n = number of titles of possible publications of use for analysis).

Database	Search string	n
Pubmed	*Keywords:* ("rheumatoid arthritis" [Title/Abstract] OR "arthritis, rheumatoid" [MeSH Terms] OR "polymyalgia rheumatica" [Title/Abstract] OR "polymyalgia rheumatica"[MeSH Terms] OR vasculit*[Title/Abstract] OR "vasculitis"[MeSH Terms] OR "systemic lupus erythematosus"[Title/Abstract] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[Title/Abstract] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[Title/Abstract] OR "rheumatic disease" [Title/Abstract] OR "Rheumatic Diseases" [MeSH] OR "chronic obstructive pulmonary disease" [Title/Abstract] OR "pulmonary disease, chronic obstructive" [MeSH Terms] OR COPD[Title/Abstract] OR "asthma"[MeSH Terms] OR asthma[Title/Abstract] OR "inflammatory bowel diseases" [Title/Abstract] OR "inflammatory bowel diseases"[MeSH Terms]) AND (("adrenal cortex hormones"[Title/Abstract]) OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR *cortisone* [Title/Abstract] OR ("Glucocorticoids/adverse effects"[MESH] AND "Glucocorticoids/therapeutic use"[MESH])) AND ("low dose" [Title/Abstract] OR ("2.5 mg" OR "5 mg" OR "7.5 mg" OR "10 mg" OR "12.5 mg" OR "15 mg" OR "17.5 mg" OR "20 mg" OR "22.5 mg" OR "25 mg" OR "27.5 mg" OR "30 mg")) *MeSH-database search:* "Glucocorticoids/adverse effects" [MAJR] AND "Glucocorticoids/adverse effects" [MESH] AND "Glucocorticoids/therapeutic use" [MESH]	1646 2130
Embase	*Keywords:* ((‘rheumatoid arthritis’/exp) OR (‘polymyalgia rheumatica’/exp) OR ‘vasculitis’/exp OR (‘systemic lupus erythematosus’/exp) OR ‘polymyositis’/exp OR ‘dermatomyositis’/exp OR (‘rheumatic diseases’/exp) OR (‘chronic obstructive pulmonary disease’/exp) OR ‘copd’/exp OR ‘asthma’/exp OR (‘inflammatory bowel diseases’/exp)) AND ((‘adrenal cortex hormones’/exp) OR glucocort* OR predniso* OR *cortisone*) AND ((‘low dose’/exp) OR ((‘2.5 mg’) OR (‘5 mg’) OR (‘7.5 mg’) OR (‘10 mg’) OR (‘12.5 mg’) OR (‘15 mg’) OR (‘17.5 mg’) OR (‘20 mg’) OR (‘22.5 mg’) OR (‘25 mg’) OR (‘27.5 mg’) OR (‘30 mg’))) AND [english]/lim AND [humans]/lim AND [embase]/lim *Emtree-database search:* (‘glucocorticoid’/exp/dd_ae,dd_to/mj AND [english]/lim AND [humans]/lim AND [embase]/lim) AND (‘glucocorticoid’/exp/dd_po/mj AND [english]/lim AND [humans]/lim AND [embase]/lim)	1903 798
CINAHL	*Keywords:* ((rheumatoid arthritis) OR vasculit* OR (systemic lupus erythematosus) OR polymyositis OR dermatomyositis) AND ((adrenal cortex hormones) OR glucocorticoids OR prednisone OR prednison OR prednisolone OR prednisolon OR cortisone OR cortison OR hydrocortisone OR hydrocortison) AND (Low-dose OR ((2.5 mg) OR (5 mg) OR (7.5 mg) OR (10 mg) OR (12.5 mg) OR (15 mg) OR (17.5 mg) OR (20 mg) OR (22.5 mg) OR (25 mg) OR (27.5 mg) OR (30 mg)))	87
Total of possible relevant hits (minus duplicates):		6097

APPENDIX 2

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* Of the 76 references that were possibly suitable for inclusion, references 1-28 were finally included. References 29-54 were excluded after reading the full-text articles, since they did not fulfill the inclusion criteria, and references 55-76 were excluded since they were not suitable for analysis, e.g. only longitudinal AE expression

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CHAPTER 7

EULAR EVIDENCE BASED RECOMMENDATIONS ON THE MANAGEMENT OF SYSTEMIC GLUCOCORTICOID THERAPY IN RHEUMATIC DISEASES.

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Objectives

To develop evidence based recommendations for the management of systemic glucocorticoid (GC) therapy in rheumatic diseases.

Methods

The multidisciplinary guideline development group from 11 European countries, Canada and the USA consisted of 15 rheumatologists, 1 internist, 1 rheumatologist-epidemiologist, 1 health professional, 1 patient and 1 research fellow. Each participant contributed up to 10 propositions describing key clinical points concerning the use of GCs. The final recommendations were agreed using a Delphi consensus approach. A systematic literature search of PUBMED, EMBASE, CINAHL, and Cochrane Library was used to identify the best available research evidence to support each of the propositions. The strength of recommendation was given according to research evidence, clinical expertise and perceived patient preference.

Results

The 10 propositions were generated through three Delphi rounds and included patient education, risk factors, adverse effects (AEs), concomitant therapy (i.e. non-steroidal anti-inflammatory drugs (NSAIDs), gastroprotection and cyclo-oxygenase-2 selective inhibitors (coxibs), calcium and vitamin D, bisphosphonates), and special safety advice (i.e. adrenal insufficiency, pregnancy, growth impairment). Of the 10 propositions, only 3 propositions were fully supported and 2 were partially supported by research evidence. The remaining propositions were supported by circumstantial evidence and/or by expert opinion alone. The strength of each recommendation differed according to level of evidence and clinical expertise.

Conclusions

Ten key recommendations for the management of systemic GC-therapy were formulated using a combination of systematically retrieved research evidence and expert consensus. For all propositions the evidence was evaluated and the strength of recommendation was provided. There are areas of importance that have little evidence (i.e. dosing and tapering strategies, timing, risk factors and AE-monitoring, perioperative GC-replacement) and need further research; therefore also a research agenda was formulated.

Since 1948, glucocorticoids (GCs) have been widely used in medicine.[1] Although GCs soon became associated with the occurrence of adverse effects (AEs), they are still the most frequently used anti-inflammatory and immune-suppressive drugs in rheumatic diseases. Arguments against the use of GCs are often based on fear for toxicity, which originated in observations of AEs seen in patients using high doses of GCs. High dose is defined as higher than 30 mg prednisolone or equivalent, medium dose is defined as higher than 7.5 mg up to (and including) 30 mg, and low dose is defined as doses up to 7.5 mg.[2] Prednisolone and prednisone are the most commonly used GCs, but not the most potent one, i.e. methylprednisolone is 1.25 times as potent as prednisolone, and betamethasone and dexamethasone are about 6 times as potent.[2] Recent studies demonstrated the disease modifying potential of low dose GCs in rheumatoid arthritis (RA) and this has renewed the debate on the risk-benefit ratio of this treatment.[3] Current literature on the risk-benefit ratio of GCs is nevertheless inconsistent, and inappropriate use of GCs could lead to increased toxicity;[4] this emphasizes the need for clear statements on proper use of GCs. In addition, patients' perspective on toxicity might differ from physicians' perspective. Hence, a EULAR task force on GCs, including a patient, was formed to develop evidence based recommendations, to provide a tool for the better use and management of GC-therapy in rheumatic diseases.

METHODS

Participants

The Taskforce on GCs is a multidisciplinary guideline development committee, which was endorsed by EULAR-ESCISIT. Twenty experts in the field of GCs (15 Rheumatologists, 1 Internist, 1 Rheumatologist-Epidemiologist, 1 Health Professional, 1 patient and 1 research fellow) from 11 European countries, Canada and the USA, participated in the process. The objectives were 1) to agree on 10 key propositions related to the safe use of GCs; 2) to identify and critically appraise research evidence for the risk-benefit ratio of GC-treatment; 3) to generate recommendations based on the best available evidence.

Experts' consensus and Delphi rounds

As a first step, a general systematic search was performed aimed at identifying the current available follow-up studies in rheumatic disease populations which used low-to-medium dose GCs (up to 30 mg prednisolone or equivalent[2]) and reported AEs (appendix 1). This general systematic search was done of the literature published between 1966 and early 2006 using the Pubmed, Embase, and CINAHL databases. The results of this search were raw data, not corrected for disease activity or co-morbidity, and were reported at the first group meeting of the committee to facilitate the group discussion. Thereafter, each participant independently contributed up to 10 propositions related to key clinical aspects in the use of GCs in rheumatic diseases. The Delphi technique was used to reach consensus on the propositions, as follows. The initial propositions were assembled into a list and overlapping propositions were combined. The list was returned to the experts and they were asked to select the 10 most important propositions from the list. A proposition was accepted for the final list if over half the participants selected it in any round and removed if it received less than four votes. If a proposition received less than 50% of the votes but more than three votes, then it entered a second Delphi round. After two rounds, 10 propositions were agreed upon.

Systematic literature search of the propositions

After agreement on the 10 propositions, proposition-specific searches were performed. Contrary to the general search, performed before the Delphi-procedure to facilitate group discussion, these searches were not limited to studies on low-to-medium dose GCs. They were done of the literature published between 1966 and mid 2006 using the Pubmed, Embase, and Cochrane databases. The CINAHL database was not used for the proposition specific search, since it did not produce additional search results in the general literature search. The search strategy consisted of a search string per proposition, which was based on a translation of the proposition into specific terms. Each search string consisted of

terms for GCs and any possible term for the specific component of each proposition. For example, "osteoporosis", "bone loss", "vertebral deformity", "vertebral deformities", "fracture", "fractures", "bone mineral density", and "bone density", were used for searching osteoporosis related literature. Components were combined in a structured manner: terms related to Patient/domain, or Intervention/determinant, or Comparison, or Outcome (PICO)[5], were combined to create a search string, which was sensitive enough to yield all available evidence (appendix 2). The search in the Cochrane library included the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and The Cochrane Central Register of Controlled Trials. Reference lists within reviews and systematic reviews were examined and any additional study meeting the inclusion criteria was included. The results of the proposition specific searches of the different databases were then combined and duplications excluded.

Inclusion / exclusion criteria

Studies that described clinical aspects of GCs or clinical outcomes which were directly or indirectly relevant to a proposition were included. The main focus was on systematic reviews/meta-analyses, randomized controlled trials (RCTs)/controlled trials, uncontrolled trials (for example, one group intervention, quasi-experimental study), cohort studies, case–control studies, and cross sectional studies. Review articles were sometimes used to describe expert opinion, whereas case reports, editorials, and commentaries were excluded. Studies on healthy subjects or animals and studies in a non-European language were also excluded. Where evidence related to GC-use in non-rheumatic diseases was found, it was extrapolated to rheumatic diseases if assumed valid.

Categorizing evidence

Categorization of evidence was according to the quality of study design (Table 1 shows the hierarchy of importance). Questions were answered using the best available evidence and adverse effects were evaluated irrespective of medical condition.

Table 1 / Level of evidence	
I-A	Meta-analysis of randomised controlled trials
I-B	Randomised controlled trial
II-A	Controlled study without randomization
II-B	Quasi-experimental study
III	Descriptive studies (comparative, correlation, case-control)
IV	Expert committee reports/opinions and/or clinical opinion of respected authorities

Approval of propositions and strength of recommendations

After the literature search on each proposition, a first draft of the manuscript was written and the Task Force met to discuss each proposition. During this meeting the wording of a proposition could be adjusted by majority agreement only in order to clarify a specific proposition or to reduce any ambiguity. The 10 final propositions and the final adjusted manuscript were approved by all task force 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 0–100 mm visual analogue scale (VAS). Task force members were asked to consider both the quality of research evidence presented and their own clinical expertise while grading. For each proposition, the mean VAS and 95% confidence interval (CI), and the percentage of strongly to fully recommended (A–B) propositions were calculated. This grading method has not been fully evaluated but it has been considered advantageous in giving SOR for procedures which cannot be assessed in RCTs; SOR has been used too in other EULAR recommendations.[6] For propositions with more than one statement or aspect, SOR was scored both for the whole proposition as well as for the individual parts. Throughout the paper, where prednisolone is mentioned, prednisone also applies, and vice versa.

Future research agenda

Each Task force member proposed up to10 topics for future research on the management of systemic GC-therapy in rheumatic diseases, based on current evidence and clinical experience. The Delphi method, including the same criteria as those for selecting the propositions, was used to reach consensus on the most important research topics.

RESULTS

Study populations and types of research evidence

The general search on AEs in patients on GCs yielded 4645 hits (MEDLINE 3176, EMBASE 2491, CINAHL 87), and 4140 hits minus duplications. Of these, only 40 studies met the inclusion criteria. Figure 1 and Table 2 show the different study populations and the estimated incidence of different types of AEs as derived from the studies reporting on dichotomous AE outcomes.

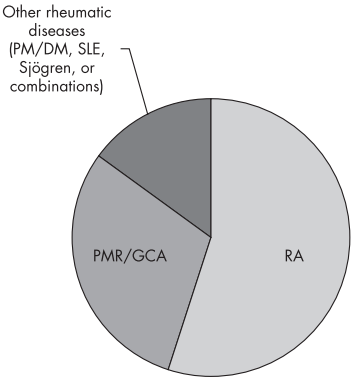


Figure 1:
Different study populations of the included studies from the general search.

Table 2 / Reported AEs in GC-treated patients with rheumatic diseases. (Results of the general search)

Type of AE:	*Median: (25th -75th percentiles) (AEs per 100 patient years)*
Cardiovascular (dyslipidemia, water and electrolyte imbalance, oedema, renal and heart dysfunction, hypertension)	15 (3-28)
Infectious (viral, bacterial, skin infections)	15 (3-15)
Gastro-intestinal (peptic ulcer disease, pancreatitis)	10 (4-20)
Psychological and behavioral (minor mood disturbances, steroid psychosis)	9 (2-236)
Endocrine & metabolic (glucose intolerance and diabetes, fat redistribution, interference with hormone secretion)	7 (3-34)
Dermatological (Cutaneous atrophy, acne, hirsutism, alopecia)	5 (2-80)
Musculoskeletal (osteoporosis, osteonecrosis, myopathy)	4 (3-9)
Ophtalmological (Glaucoma, cataract)	4 (0-5)

This table summarizes reported AEs in studies (n = 18) of the general search of patients using GCs (n= 963) for a rheumatic disease. Only those studies of patients who were using GCs up to 30 mg prednisolone or equivalent and reporting dichotomous AE outcomes were included in the data of the table, which was used as introductory information for the taskforce. Raw data, not corrected for disease activity, co-morbidity and the frequency of AEs in the contrast group, if present, were used. So not all AEs can be specifically attributed to the use of GCs; common events may be overestimated and less common ones underestimated. For instance, cardiovascular events are poorly correlated with GC-use. Types of AEs were divided into different groups (as has been published before55) and per group AEs per 100 patient years were derived by dividing the number of AEs by the duration of follow up in years, times 100. Mean daily GC-dose was 8 mg and the average duration of studies was 19.6 months.

Table 3 / Experts' propositions developed throughout 3 Delphi rounds including the strength of recommendation.

Proposition		SOR		Evidence level of data
		VAS 100 (95% CI)	A+B %	
1a	The adverse effects of glucocorticoid therapy should be considered and discussed with the patient before glucocorticoid therapy is started.	92 (85-100)	93	IV
1b	This advice should be reinforced by giving information regarding glucocorticoid management.	88 (80-96)	93	IV
1c	If glucocorticoids are to be used for a more prolonged period of time, a "glucocorticoid card" is to be issued to every patient, with the date of commencement of treatment, the initial dosage and the subsequent reductions and maintenance regimens.	78 (67-89)	79	IV
1	Full proposition (1A + 1B + 1C)	91 (86-96)	92	
2a	Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, disease activity, risk factors and individual responsiveness of the patient.	92 (83-100)	86	IA-III
2b	Timing may be important, with respect to the circadian rhythm of both the disease and the natural secretion of glucocorticoids.	74 (59-89)	57	-
2	Full proposition (2A + 2B)	83 (70-97)	85	
3	When it is decided to start glucocorticoid treatment, comorbidities and risk factors for adverse effects should be evaluated and treated where indicated. These include hypertension, diabetes, peptic ulcer, recent fractures, presence of cataract or glaucoma, presence of (chronic) infections, dyslipidemia and co-medication with non-steroidal anti-inflammatory drugs.	92 (87-96)	100	IV
4	For prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity. The reasons to continue glucocorticoid therapy should be regularly checked.	81 (68-94)	86	IV
5	During treatment, patients should be monitored for body weight, blood pressure, peripheral oedema, cardiac insufficiency, serum lipids, blood and/or urine glucose and ocular pressure depending on individual patient's risk, glucocorticoid dose and duration.	89 (81-97)	93	IV
6a	If a patient is started on prednisone > 7.5 mg daily and continues on prednisone for more than 3 months, calcium and vitamin D supplementation should be prescribed.	95 (91-99)	100	IA
6b	Antiresorptive therapy with bisphosphonates to reduce the risk of glucocorticoid-induced osteoporosis should be based on risk factors, including bone mineral density measurement.	96 (92-99)	93	IB-III
6	Full proposition (6A + 6B)	95 (89-100)	100	
7	Patients treated with glucocorticoids and concomitant non-steroidal anti-inflammatory drugs should be given appropriate gastro-protective medication, such as proton pump inhibitors or misoprostol, or alternatively could switch to a cyclo-oxygenase-2 selective inhibitor.	91 (84-98)	93	1A-IB
8	All patients on glucocorticoid therapy for longer than 1 month, who will undergo surgery, need perioperative management with adequate glucocorticoid replacement to overcome potential adrenal insufficiency.	91 (84-99)	93	IV
9	Glucocorticoids during pregnancy have no additional risk for mother and child.	87 (78-96)	86	IB-III
10	Children receiving glucocorticoids should be checked regularly for linear growth and considered for growth hormone replacement in case of growth impairment.	93 (85-100)	93	IB
	*A+B%, percentage of the taskforce members that strongly to fully recommended this proposition, based on an A - E ordinal scale; CI, confidence interval; SOR, strength of recommendation; VAS, visual analogue scale (0–100 mm, 0 = not recommended at all, 100 = fully recommended).			

Table 4 / Evidence delivered by the proposition-specific searches.

Proposition	Proposition-specific search, n studies:	N studies meeting inclusion criteria:	Type of evidence*
1	2699	34	Circumstantial
2	556	16	Partially direct
3	464	29	Circumstantial
4	131	4	Circumstantial
5	401	4	Circumstantial
6	71	19	Indirect
7	157	15	Indirect
8	303	13	Circumstantial
9	86	19	Partially indirect and partially direct
10	221	19	Indirect
Total	5089	172 (165 minus duplicates	

* Indirect = Data indirectly supports the proposition / Circumstantial = No data directly or indirectly supports the proposition, but there is circumstantial data which is useful to the proposition. Partially direct = part of the proposition is directly supported by data.

Experts' opinion approach

The Delphi exercise was performed after the taskforce experts had discussed the results of the general literature search. Initially, 153 (partly overlapping) propositions were produced and after 2 anonymous Delphi rounds, 10 final propositions were agreed upon (Table 3).

Assesment of the propositions

The proposition specific searches resulted in 5089 possibly useful studies. Of these studies, 165 were included to provide (circumstantial) evidence for the propositions (Table 4).

RECOMMENDATIONS

1. The adverse effects of glucocorticoid therapy should be considered and discussed with the patient before glucocorticoid therapy is started. This advice should be reinforced by giving

information regarding glucocorticoid management. If glucocorticoids are to be used for a more prolonged period of time, a "glucocorticoid card" is to be issued to every patient, with the date of commencement of treatment, the initial dosage and the subsequent reductions and maintenance regimens.

Level of evidence: IV

Strength of recommendation (95% CI):

Overall: 91 (86-96)

Pre-treatment advice: 92 (85-100)

Information: 88 (80-96)

Glucocorticoid card: 78 (67-89)

The taskforce experts recommend that the occurrence of AEs during GC-therapy (Table 2) should be categorized following WHO guidelines: very common (>1/10); common (>1/100); uncommon (>1/1000); rare (>1/10 000); very rare (<1/100 000).[7] Thorough explanation of common and very common AEs of therapy is an integral part of the management of any disease and of patient education. An AE-survey in a population based cohort of GC-users showed that 68% of patients who used GCs recalled discussing potential GC-related AEs with their practitioner.[8] This recall might be influenced by the perception of severity of GC-related AEs, which may differ amongst patients .[9] Patient perspective has been studied in patients who used other types of drugs than GCs. Cancer patients who used taxane chemotherapeuticum perceived symptom status and improvement to be more important than toxicity of this medication.[10] RA patients, who had to choose between different DMARDs (not including GCs), based their preference on safer short term AE profile,[11] and older patients with knee osteoarthritis preferred a lower risk of AE to treatment effectiveness too.[12] In Japanese patients with chronic diseases, non-adherence to prescribed medication was strongly associated with anxiety.[13] For patients who were treated with sumatriptan subcutaneously, important issues of

this migraine therapy were safety and AEs.[14]

Whether discussion of possible AEs before GC-therapy has any beneficial effect on disease outcome, e.g. by improving patient compliance, is unclear because of lacking data regarding GCs. However, circumstantial evidence exists that general patient education, including discussing possible AEs of treatment, positively influences outcome of therapy. A controlled clinical study showed that a structured patient education program in 100 RA patients reduced disability and pain for 3 months, although this reduction was no longer seen after 12 months.[15] A quasi-experimental study of 183 RA patients who were taking MTX showed that knowledge of the toxicity and safe use of MTX was significantly improved by a patient education program utilizing a rheumatology nurse.[16] Patient education also proved to be beneficial for the outcome of therapy in diabetic patients,[17] in cancer patients,[18] and in ambulatory clinic population.[19] Patient education is not always beneficial, however. A controlled clinical study showed that knowledge about adverse effects of beta-blockers could produce anxiety,[20] so in giving information, individual patient psychological characteristics should be taken into account.

Patient education could therefore have an effect on outcome of drug therapy, but the format of patient education has not been investigated. No study looked at the use of information leaflets in long-term GC-therapy specifically, which also leaves this part of the recommendation to be supported by expert opinion only. It was nevertheless shown that information leaflets did not have an impact on incidence and reporting of adverse effects,[21] whereas it did help patients to recognize an adverse reaction due to drug consumption,[22] and it increased patients' recall of a surgical procedure,[23,24] and knowledge about asthma[25] or clinical trials.[26] Several factors showed to influence recall of written information: narrative style,[27] understandability and cultural relevance,[28] readability,[29,30] time after information supply,[31-33] patient's age,[16,34,35] IQ and cognitive function.[34,35] Besides the use of an information leaflet, other techniques also showed to be worthwhile options: supplemental pocket-cards,[16] patient information videos,[36-38] and multimedia, such as touch screen computers.[39,40]

In the final part of this recommendation the use of "glucocorticoid cards" is advocated.

No evidence was found to corroborate this, but the use of a pocket card in methotrexate (MTX) users improved their knowledge on safety and toxicity of MTX-treatment.[16]

In conclusion, although there is no research based justification specific to AEs of GC-therapy (category IV), information and, if necessary, education of patients on AEs of their treatment is generally accepted to be an ethical prerequisite and worthwhile. One should realise that patients' perspective on AEs might differ from doctors' perspective; patient information should include both perspectives. If next to oral information an additional source of information is considered, several factors that influence its usefulness, the specific individual patients' perspective and characteristics, and different techniques of providing information should be taken into account.

2. Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, disease activity, risk factors and individual responsiveness of the patient. Timing may be important, with respect to the circadian rhythm of both the disease and the natural secretion of glucocorticoids.

2

Level of evidence: I-III

Strength of recommendation (95% CI):

Overall: 83 (70-97)

Dose regimens: 92 (83-100)

Dose timing: 74 (59-89)

The only rheumatic disease in which dosing schemes of GCs were compared is polymyalgia rheumatica (PMR)/giant cell arteritis (GCA): after initial medium dose, subsequent dose reduction depended on disease activity. In a retrospective study, the records of 91 patients with PMR or GCA were reviewed: mean initial prednisolone dose in PMR-patients was 18 mg/day and mean duration of treatment was 17 months. In patients with GCA mean initial dose was 31 mg/day and mean duration of treatment was 16 months. In both groups the

GC-treatment was stopped within 24 months.[41] Dosing strategies were assessed in one retrospective and three prospective studies on short to intermediate term GC-treatment in PMR and GCA: patients needing low initial dosages had less relapses, lower maintenance dose, and experienced less toxicity.[42-45] In early RA (disease duration <2 years), the use of low-dose GCs is not based solely on disease activity, but also on long-term outcome. A meta-analysis on multiple RCTs in early RA has shown that low-dose GCs are joint sparing on the long-term and can therefore be categorized as DMARDs.[3] Different regimens with GCs have been used for joint sparing purposes in early RA, usually in combination with other DMARDs. These different schemes could result in different outcome of the treatment, but data is lacking.

A relation between dose strategies and risk factors, such as diabetes, hypertension, and osteoporosis, can only be shown indirectly. In several studies in renal transplant patients, including a prospective observational study[46] (category IIB), reduction of GC-dose was related to improved insulin sensitivity.[46-48] Hypertension was related to higher initial GC-dosage in a comparative study on liver transplant patients[49] (category III). High initial dose and long-term use of GCs are associated with osteoporosis; this relation is elaborated upon in proposition 6.

Specific abnormalities in the GC-receptor gene have been associated with eighter an increased or reduced receptor function in 6.6% and in 2.3% of a healthy elderly population, respectively. In this population there was no association with individual response to GC, but abnormalities in the GC-receptor may contribute to the variable sensitivity to GC-therapy observed in a normal population.[50] It is unknown whether an individual response is different among individuals for the same GC-dose, since no study was found on the relation between dose strategies and individual responsiveness of patients.

Timing of GC-administration might influence its efficacy. This assumption is based on the fact that both symptoms (such as morning stiffness) and clinical signs of RA[51] as well as several pro-inflammatory cytokines[52] vary within 24 hours and show a circadian flare in

the beginning of the day. Administration of GCs early in the morning[53] (category IB), or the use of modified release (MR) tablet formulation of prednisone, delivering the GC early in the morning (abstract)[54] gave more improvement of RA symptoms than conventional timing of GC-therapy.

In conclusion, there is category III evidence on dosing regimens of GCs in PMR/GCA and category IA evidence showing a benefit for the use of low-dose longterm GCs in early RA. The relation between risk factors, AEs, high GC-dosages and longterm GC-use was indirectly shown for diabetes (category IIB) and hypertension (category III). No studies were identified that show a relation between GC-dosing regimens and individual responsiveness (category IV). There is category IB data on a superior effect of circadian administration of GCs.

3. When it is decided to start glucocorticoid treatment, comorbidities and risk factors for adverse effects should be evaluated and treated where indicated. These include hypertension, diabetes, peptic ulcer, recent fractures, presence of cataract or glaucoma, presence of (chronic) infections, dyslipidemia and co-medication with non-steroidal anti-inflammatory drugs.

Level of evidence: IV

Strength of recommendation (95% CI): 92 (87-96)

The relation between the risk factors mentioned above and GCs is well-known, and literature on the AEs that are associated with the above mentioned risk factors has recently been reviewed.[55] Although it is common sense to treat risk factors to diminish the chance of GC-related AEs, no study looked directly at the effects of evaluation and treatment of the above mentioned risk factors before the start of GC-treatment. The rationale for pre-treatment screening and treatment is that these risk factors are also known AEs of GCs, so these conditions could deteriorate and cause complications during GC-treatment. Data on the deterioration of the following risk factors and AEs were found:

- Diabetes and hypertension:[55] these preexistent conditions may worsen during GC-pulse therapy[56] and diabetes has also been shown to worsen during longterm oral GC-therapy.[57]
- Peptic ulcer and concomitant NSAID use: Incidence of peptic ulcers was slightly increased by therapy with GCs alone in some studies,[58-61] but not in all.[62] Undoubtly the risk of peptic ulcers increases when GCs are prescribed concomitant with NSAIDs.[62] Patients should be asked about the use of 'over the counter'- NSAIDs, since many patients use this approach.[63]
- Recent fractures: GCs increase the risk of fractures.[64] Unfortunately, the majority of patients on GC-therapy with osteoporotic fractures has not been prescribed bisphosphonates or other anti-osteoporotic therapy.[65-67] This indicates that, in many cases, neither bone mineral density nor fracture status is evaluated before the start of GC-therapy. Nevertheless, rheumatologists are increasingly aware of the risk of fractures[68] and they prescribe more frequently bisphosposphonates than GC-prescribing internal medicine specialists do.[69]
- Glaucoma and cataract: GCs can increase ocular pressure, and thus may induce glaucoma in predisposed individuals. Pre-existing glaucoma[70] and age[71] increase this risk of worsening of glaucoma due to GCs. Ocular GCs are believed to be more prone to induce glaucoma.[72] Research data on the incidence of cataract with long-term low dose systemic GC-treatment is scarce,[55] but the occurence of cataract is associated with longer term and higher dosed GC-use.[8,60]
- (Chronic) Infections: GCs increase the risk of infection[73,74] and may mask the symptoms of infection. No data on the usefulness or effect of systematic screening for infections before start of GC-therapy is available, but nevertheless it should be performed. It should be kept in mind that GCs could also have an effect on the screening-tests themselves, i.e. in a population with a high prevalence of tuberculosis, only 29% of 112 RA patients, of whom 87% used prednisone ≤7.5mg daily, had a positive mantoux test, versus 71% of the healthy matched control group.[75]

- Dyslipidemia: GCs may induce dyslipidemia,[76] but we found no studies on the effects of GC-treatment upon preexisting dyslipidemia. High disease activity in RA and SLE may deteriorate lipid levels,[77,78] while effective disease modifying therapy, including GCs, has been shown to improve the altered lipid spectrum.[79-81] Classical risk factors, such as lipid levels, nevertheless explain the higher risk of cardiovascular disease only partially, since the disease itself might increase the risk of cardiovascular disease.[82]

In conclusion, even though risk factors for GC-associated AEs are well-known and there is obvious face validity trying to prevent these from occurring by assessing and treating comorbidities and risk factors at baseline, there is no evidence to show that this is effective (category IV).

4. For prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity. The reasons to continue glucocorticoid therapy should be regularly checked.

Level of evidence: IV

Strength of recommendation (95% CI): 81 (68-94)

Since there is no evidence from appropriately designed studies to support this proposition, it is supported by expert opinion alone (category IV). Nevertheless, this proposition has obvious face validity since the occurrence of GC-related AEs, osteoporosis in particular (proposition 5 and 6), is dependent of dose and duration of therapy. Concomitant GC-sparing therapy like methotrexate was successful in facilitating GC-tapering in some but not all trials in PMR-patients.[83-85] The risk-benefit ratio of tapering and stopping GCs in RA has not been studied systematically. In a placebo-controlled RCT of 12 weeks, low dose GCs had a small effect on HPA function and all patients showed response to the ACTH-stimulation test the day afer stopping treatment,[86] suggesting that the abrupt stopping of low dose GC-therapy in these patients did not result in HPA insufficiency.

5. During treatment, patients should be monitored for body weight, blood pressure, peripheral oedema, cardiac insufficiency, serum lipids, blood and/or urine glucose and ocular pressure depending on individual patient's risk, glucocorticoid dose and duration.

Level of evidence:IV

Strength of recommendation (95% CI): 89 (81-97)

Since there is no direct evidence from appropriately designed studies to support this proposition, it is supported by expert opinion alone (category IV). Certain parts of the proposition deserve further attention:

Firstly, risks of AEs during GC-treatment are related to GC-dose and duration of treatment, monitoring should be dependent on both variables. For instance, changes in both body weight and blood glucose have been shown to be time and dose dependent.[8] Additionally, a review on low-dose GCs in RA showed that the toxicity of low dosages was modest.[55] Furthermore, not all AEs mentioned in this proposition occur in low dose GC-therapy; the same review found no relation of low dose GCs with hypertension, peripheral oedema, cardiac insufficiency, dyslipidemia, or hyperglycaemia.[55] In line with this, a retrospective

Table 5 / Theoretical framework of criteria which can be used to decide whether monitoring for specific AEs is useful.

	Number needed to screen? (1/prevalence per year)	**Severity?** (Low / moderate / high)	**Cost of screening?** (Low / moderate / high)	**Feasibility of scoring?** (Low / moderate / high)
Body weight	1.5 [8]	Low	Low	High
Blood pressure	?	Moderate	Low	High
Peripheral oedema	?	Low	Low	High
Heart failure	?	High	Moderate	Moderate*
Dyslipidemia	?	Moderate	Moderate	Moderate*
Blood/urine glucose	12.5 [8]	Moderate	Moderate	High
Glaucoma	18.1 [60]	Moderate	Moderate	Moderate*

* Scoring in daily practice depends on presence of accurate laboratory tests and / or eye pressure measurement equipment.

cohort study did not show a significant relation between GC-dosage lower than 5 mg/day and serious AEs.[60] However, a recent analysis did show a relation between GC-dosage lower than or equal to 5 mg/day and pneumonia, hazard ratio 1.4 (1.1-1.6)[74] .

Secondly, monitoring for treatable and preventable AEs is especially useful if the AE is common (i.e. low number needed to screen), the AE is severe or has a significant impact on quality of life, the cost of screening is low, and scoring is feasible in daily clinical practice. A theoretical framework showing elements of the discussion on monitoring the above mentioned AEs is found in Table 5, based upon group consensus after discussing all propositions. However, also non-modifiable AEs should be assessed, as they could be important from the patient's perspective and could be a surrogate marker for other AEs (e.g. reflecting patient's sensitivity to GCs), alerting the physician.

6. If a patient is started on prednisone ≥ 7.5 mg daily and continues on prednisone for more than 3 months, calcium and vitamin D supplementation should be prescribed. Antiresorptive therapy with bisphosphonates to reduce the risk of glucocorticoid-induced osteoporosis should be based on risk factors, including bone mineral density measurement.

Level of evidence: I

Strength of recommendation (95% CI):

Overall: 95 (89-100)

Calcium and vitamin D: 95 (91-99)

Bisphosphonates: 96 (92-99)

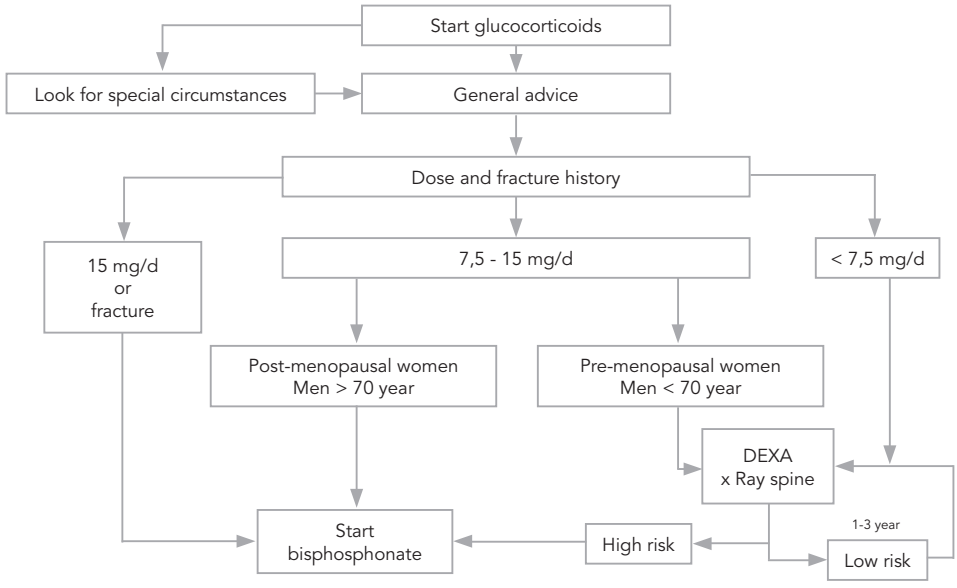
Bone loss commences early after the start of GC-therapy;[87] further rationale for this proposition is given by a large case-control study that showed an increase of the risk of both vertebral and hip fractures in patients using prednisone 7.5 mg daily or more compared to

patients using lower dosages.[88] Several European guidelines took 7.5 mg of prednisone or equivalent daily as a cutoff value for the decision to perform bone mineral density (BMD) measurements or the start of preventive treatment for osteoporosis.[89,90] Nevertheless, a meta-analysis showed already an increased risk of fractures for GC-dosages as low as 5 mg daily within 3 to 6 months of treatment.[64] In contrast, two studies that measured BMD in early RA patients didn't show a detrimental effect of low dose GCs,[91,92] which could indicate that GC-induced osteoporosis might not only be related to dose but could also be disease specific.[93]

There is no direct evidence to support this proposition entirely, but indirect evidence does: Calcium, vitamin D, and vitamin D analog supplementation have been shown to decrease GC-induced loss of BMD and to reduce fractures in several meta-analyses of RCTs (category IA). A meta-analysis of 5 trials (274 patients, duration 9-36 months) comparing therapy with calcium and vitamin D to calcium alone or to placebo in patients taking GCs (prednisone equivalent of 5.6 - 18.9 mg daily) demonstrated less bone loss with vitamin D and calcium.[94] A review that included two meta-analyses of 32 studies (1531 patients, mostly RCTs) in transplant-patients using high doses of GCs showed that active vitamin D3 analogues resulted in less bone loss and less fractures than no treatment, placebo, plain vitamin D3 and/or calcium.[95] Nevertheless, vitamin D and calcium do not totally prevent GC-induced bone loss, whereas bisphosphonates generally do. Bisphoshonates have been proven superior in increasing BMD compared to calcium and/or (active) vitamin D in a meta-analysis of 13 trials (842 patients, duration 6-24 months)[96] (category IA). Another meta-analysis showed that bisphosphonates were more effective in preserving bone and decreasing the risk of vertebral fractures than active vitamin D3 analogues.[95] This superiority in increasing BMD as well as in preventing fractures was also shown in both a large RCT comparing the effects of alfacalcidol and alendronate,[97] as in a meta-analysis of 5 randomised placebo-controlled trials with etidronate in postmenopausal women.[98]

It has been justified by several studies that bisphosphonate therapy should be based on the following risk factors: decreased BMD, female gender, older age, postmenopausal status

Figure 2:
Example of an algorithm for osteoporosis prevention in glucocorticoid users.



and low body mass index (BMI). A cross-sectional study in 394 female RA-patients from a county based register indicated that age >60 years, low BMI, and current use of GCs were risk factors for low BMD[99] (category IIB). A review of 2 RCTs (296 patients) on risedronate showed that both GC-dose and low BMD were predictors of fractures. Additionally, at the same BMD level, postmenopausal patients on GCs were more prone to get fractures than postmenopausal patients who were not receiving GCs[100] (category 1B). The ACR has published a clear guideline on the treatment of GC-induced osteoporosis[101] and algorithms have been proposed to decide whether or not to start with bisphosphonates based on GC-dosage, preexistent fractures, age and gender, menopause, and BMD-measurement[90,102] (Figure 2).

Preventive therapy against GC-induced osteoporosis in long-term GC-users is still inconsistently prescribed, however.[103,104] This might result in more osteoporosis-related morbidity than necessary.

In conclusion, this proposition is supported by indirect evidence (category IA),

which shows a decreased incidence of fractures resulting from calcium and vitamin D supplementation, and an even better protective effect with bisphosphonates in patients on prolonged treatment with GCs. Decreased BMD is a good predictor of future fractures (category I B) and advanced age and low BMI are associated with low BMD (category IIB).

7. Patients treated with glucocorticoids and concomitant non-steroidal anti-inflammatory drugs should be given appropriate gastro-protective medication, such as proton pump inhibitors or misoprostol, or alternatively could switch to a cyclo-oxygenase-2 selective inhibitor (coxib).

Level of evidence: I

Strength of recommendation (95% CI): 91 (84-98)

No study investigated gastro-protective measures in GC-using patients specifically, but the rationale for this proposition is given by the fact that gastro-intestinal (GI) toxicity possibly increases by treatment with GCs alone (see proposition 3). This is corroborated by a post-marketing surveillance program of more than 11000 arthritis patients, that showed that osteoarthritis and RA patients are 2.5 to 5.5 times more likely than the general population to be hospitalized for GI events which are NSAID-related. In these patients independent risk factors are GC-use, NSAID dose, age, disability level, and previous NSAID-induced GI symptoms.[105] Strikingly, gastro protective agents (i.e. antacids, histamin$_2$-receptor antagonists, proton pump inhibitors (PPI), and cytoprotective agents (i.e. misoprostol)) are used in only 35% to 40% of patients with multiple risk factors for gastrointestinal ulceration, such as advanced age, active disease, NSAID therapy concomitant with GCs, low dose aspirin or anti-coagulants.[106] Established risk factors for NSAID-associated gastrointestinal toxicity have been shown to be poor predictors of prescription of a coxib. In contrast, the prescribing physician's preference was an important determinant.[107]

Although not studied in GC-using patients specifically, several treatment regimens

have been shown to be gastro-protective for conventional NSAID users. This indirect evidence shows that:

- Proton pump inhibitors and misoprostol reduce the risk of gastric and duodenal ulcers in patients taking conventional NSAIDs (category I B).[108,109]
- Coxibs cause less GI-toxicity than conventional NSAIDs in RA patients (category I B)[110,111]. Furthermore, in a subgroup of aspirin-using patients, celecoxib reduced gastric ulcers by 51% compared to conventional NSAIDs, whereas this reduction was 71% among patients not taking aspirin.[112]
- Conventional NSAIDs combined with PPI cause less dyspepsia than coxibs do, when both treatments are compared with conventional NSAIDs (category I A).[113]
- In deciding on the prescription of coxibs and conventional NSAIDs, cardiovascular risk factors should be taken into account.[114-119]

In conclusion, this proposition is supported by indirect evidence (category IA-IB).

8. All patients on glucocorticoid therapy for longer than one month, who will undergo surgery, need perioperative management with adequate glucocorticoid replacement to overcome potential adrenal insufficiency.

Level of evidence: IV

Strength of recommendation (95% CI): 91 (84-99)

Adrenal insufficiency due to surgical stress has already been described in the 1950's. As patients with RA and PMR are considered to have relative adrenal insufficiency,[121] they might be more prone to adrenal insufficiency at surgery. The incidence and duration of GC-induced adrenal insufficiency depends, apart from possible individual differences in sensitivity for GC, of two factors. First, type and dosage of GC: a single dose of 50 mg prednisone or equivalent depresses the hypothalamic-pituitary-adrenal axis for 1.25 to 1.5 days, a dose of 40 mg triamcinolone for

2.25 days, and a dose of 5 mg dexamethasone for 2.75 days.[122] Intramuscular administration of a single dose of 40 to 80 mg triamcinolone acetonide depresses the hypothalamic-pituitary-adrenal axis for 2 to 4 weeks, and after 40 to 80 mg intramuscular methylprednisolone, suppression lasts 4 to 8 days.[122] After an intra articular injection with 20 to 160 mg of methylprednisolon, the hypothalamic-pituitary-adrenal axis function is supressed for 1 day in half of the patients and recovers in 95 % of the patients within 2 weeks.[123] Second, duration of therapy: although, acute stopping without consequences of low dose GCs in ambulant RA patient seems possible (see proposition 4), for patients in stress, like those undergoing surgery, the case is completely different. In such circumstances acute cessation after a daily dose of 7.5 mg or more prednisolone or equivalent for at least 3 weeks could lead to problems.[124] Treatment of less than 3 weeks or alternate-day therapy does not exclude the risk of suppression of the hypothalamic-pituitary-adrenal axis,[125,126] but the risk is still dose depended.[127] Stopping GCs perioperatively because of fear for infections can cause severe harm to patients and should not be done without sound consideration of risk and benefit.

GC-replacement is recommended in case of surgery for patients at risk of adrenal insufficiency. A replacement scheme has been proposed for different (surgical) procedures:[128] 1. For moderate physical stress inducing procedures, a single dose of 100 mg hydrocortisone intravenously. 2. For major surgery, 100 mg hydrocortisone intravenously before anesthesia and every 8 hours four times thereafter. The dose can be tapered by half per day afterwards. Several other schemes of GC-replacement exist. However, at this moment there is insufficient evidence to propopse any specific recommendation for different surgical procedures. Possibly, low dose schemes could be applied, given the fact that acute stopping of low dose GCs in RA patients had only a small effect on HPA function,[86] suggesting little or non adrenal suppression.

Although GC-replacement is recommended in patients at risk,[129] the necessity of supraphysiological replacement has been questioned by the result of a randomized double-blind study of 18 patients with known prednisone induced adrenal suppression (abnormal ACTH test) caused by chronic prednisone use, who underwent major surgery.[130] These patients did not experience hypotension due to adrenal insufficiency while only continuing

daily GC-dose perioperatively, indicating adrenal suppression does not necessarily mean that there will be clinical signs of adrenal insufficiency. Other data, in 40 renal allograft recipients on long-term low dose GC-treatment with significant physiologic stress (i.e. sepsis, metabolic abnormalities, or surgery), suggests too that baseline GC-therapy might be sufficient to prevent adrenal insufficiency.[131]

In conclusion, since early studies show the occurrence of adrenal insufficiency during surgery, it is common to increase the dose of GCs around surgical interventions in patients on GCs for longer than one month. There is no research investigating this (category IV) and it seems that in certain circumstances the continuation of usual daily GC-dosages might be sufficient. Stopping of GC-therapy perioperatively should not be done.

9. Glucocorticoids during pregnancy have no additional risk for mother and child.

Level of evidence:

Mother: IV

Child: I-III

Strength of recommendation (95% CI): 87 (78-96)

Safety of GC-usage during pregnancy has two aspects: safety for the mother and safety for the unborn child.

Firstly, the safety of GCs for the pregnant mother: AEs associated with the use of GCs are believed not to differ between a pregnant patient and a non-pregnant patient, but no evidence was found to support this (category IV). As pregnant or lactating women are more at risk for pregnancy-associated AEs (e.g. osteoporosis,[132] diabetes,[133] hypertension[134]), this risk could be increased by GC-therapy, but no data are available.

Secondly, the safety of GCs for the fetus and neonate. The ability to pass the placenta and the rate of metabolization (inactivation) within the placenta differ for different types of GCs. So different GCs have different indications during pregnancy. Dexamethasone can be

used to treat fetal conditions such as immature lungs, because it is not metabolized well by the placenta nor predominantly protein bound and thus higher dosages are available to the fetus. Prednisone, prednisolone, and methylprednisolone, are less available to the fetus (10% of the maternal dose) and therefore these substances are preferred for the treatment of maternal disorders.[135] GCs prior to and during pregnancy do not seem to have a negative impact on the development of the fetus. GCs in high doses have caused cleft palate in experimental animal models and low birth weight in humans.[136,137] However, there is no evidence that in humans either prednisone or methylprednisolone are teratogenic (Food and Drug Administration risk category B,[138] the increased risk of cleft palate in animals was not confirmed in controlled studies in women in the first trimester, nor in the later trimesters).

In a large retrospective cohort of GC-treated pregnant asthma-patients no increased incidence of birth defects compared with the general population was found. Most women were receiving low-dose prednisone (the mean daily dose was 8 mg) and were taking GCs at the time of conception (category III).[139] An increased incidence of prematurity among neonates exposed to GCs in utero was shown by a RCT, which compared the effects of high dose GCs (0.5 to 0.8 mg per kilogram of body weight per day) with those of aspirin (100 mg daily) or placebo to treat unexplained recurrent fetal loss in SLE patients with a history of recurrent fetal loss (category I B).[140] On the other hand, disease activity itself has been associated with increased risk of abortions in SLE.[141,142] GCs have been suggested to improve fetal survival in SLE-patients with lupus anti-coagulant,[143,144] but this was not confirmed by the above mentioned RCT.[140] Finally, the incidence of infection was not increased in neonates who were exposed to GCs in utero (category I B).[145]

During lactation, GCs are excreted minimally into breast milk[146,147] and breast feeding by women with low dose GC-therapy is generally considered to be safe.[148] Exposure of an infant can be further minimized if breast-feeding is avoided during the first 4 hours after GC-intake, because there is an equilibrium between the concentration of prednisolone in mother milk and serum.[147]

The influence of bisphosphonates on the fetus is not known, but concern exists for

use in fertile and in pregnant women because of the very long half-life of these drugs, which are presumed to be able to cross the placenta.[149] Furthermore, fetal hypocalciemia has been reported once during bisphosphonate therapy.[150] Until now, the treatment of osteoporosis with a bisphosphonate has not proved to be teratogenic during pre and early pregnancy in a case series of 24 patients,[149] but caution seems warranted.

In conclusion: There is category IV evidence that GCs are safe for mothers during pregnancy. Category III indirect evidence shows that GCs are not teratogenic for the fetus, and there is category I B evidence that they do not contribute to perinatal infections. Category I B evidence exists that high dose GCs may contribute to fetal prematurity in SLE patients.

10. Children receiving glucocorticoids should be checked regularly for linear growth and considered for growth hormone replacement in case of growth impairment.

Level of evidence: I

Strength of recommendation (95% CI): 93 (85-100)

GCs can cause growth retardation in children. The pathogenesis of this growth impairment is multifaceted. Several studies showed the negative effects of long-term GC-therapy on growth: Studies in juvenile idiopathic arthritis (JIA) (category III),[151] early onset Crohn's disease (category III),[152] and asthma patients (category II B).[153] In addition, the growth impairment remained long after GC-treatment had been stopped in cystic fibrosis patients (category I B).[154] Growth hormone replacement (GHR) can be used to prevent growth impairment due to GCs: increase of linear growth with GHR was shown in several studies of GC-using JIA-patients (category I - III),[155-160] and in studies of "slowly growing GC-treated patients" (category II),[161,162] The daily GC-doses used in these studies varied between 0.2 and 0.5 mg/kg prednisolone equivalent and the duration GHR-therapy was 2 to 4 years.

Contrary to oral GCs, topical GC-administration does not seem to induce growth impairment,[163] whereas there is doubt whether inhalation GCs might influence linear growth.

In one study of asthma patients, inhalation GCs had a negative influence on linear growth,[164] but in a meta-analysis, this finding was not confirmed.[153] Alternate day GC-administration in JIA patients resulted in less inhibition of body growth than daily usage did.[165]

An extra feature of GHR is its effect on bone: an increase of bone mineral content (BMC) was shown in addition to an increase of linear growth (category III).[166]

If GHR is considered, referral to an experienced paediatrician is indicated and additional testing can confirm GH deficiency. The most frequently used test is the clonidine provocation test.[167] Additionally, the dexamethasone response test appears to be promising for the detection of GH deficiency.[168] Routine usage of GHR in GC-using patients is hampered by several factors: the therapy exists of daily injections (subcutaneously or intramuscularly), the length gain is relatively small, and it is a very costly therapy (between 15,000 € and 50.000 €, depending on the weight of the individual child[169]).

In conclusion, there is evidence (category I B) that GCs may cause growth impairment in children, which can be treated with GHR (category I B). GH deficiency can be confirmed with provocation tests and GHR should be under expert supervision.

DISCUSSION

This EULAR document is an attempt to give recommendations for the safer use of systemic GCs, in rheumatic diseases. A similar design was used as in earlier taskforces,[170-173] i.e. a combination of both evidence and expert opinion. The added value of this taskforce, like previous ones, is provided by the fact that they (a) are a broad representation of experts in the field of GCs within and outside Europe; (b) use recent research data; and (c) use a thorough evidence based format. This format was applied in this taskforce and generated 10 key propositions on the use of GCs by anonymous Delphi procedure, which was followed by a systematic search for evidence per proposition. The order of propositions in the paper does not reflect importance, neither does the level of evidence of propositions, but reflects

the logical order of patient management. Finally, both the level of evidence of the studies in support of each proposition as well as the strength of each recommendation are descibed. The benefits of this approach are reduction of personal bias, good external validity and generalisability, and clear identification of areas of clinical practice where more research data are required.[174] These propositions aim promoting the safer use of GCs among physicians and patients alike and they will form the basis for further EULAR research and education.

An important part of the methodology of these recommendations is the use of the VAS and ordinal scales for the grading of the recommendations. The mean values of the scaling give a clear indication of the support of the taskforce for each proposition, and the confidence intervals show the degree of agreement within the taskforce. The same method has been used by a recent taskforce[171] and proved to be very adequate for procedures which cannot be, or have not been, assessed in RCTs, but need to be upgraded according to expert opinion.[6] The latter is of great importance for these recommendations, since evidence on the safety or AEs of GCs lacks comparative studies of high quality, such as RCTs.

Table 6 / Research agenda developed throughout 2 Delphi rounds.

1	What is the perception of patients, general physicians and rheumatologists on efficacy, safety and management of glucocorticoid therapy in rheumatic diseases? (exploring perceptions and environmental factors as barriers for the effective and safe use of glucocorticoids).
2	What is the influence of low dose glucocorticoid therapy on lipid profile and other cardiovascular risk factors in relation to active inflammation?
3	What is the pathophysiology of the skin side effects due to the use of glucocorticoids, and how can these be prevented?
4	What is the ideal timing of glucocorticoid treatment regarding safety as well as efficacy?
5	Regarding the use of glucocorticoids in early RA: is continuous low dose as effective as a step down dose (starting high and then tapering)?
6	Can we define biomarkers (including genetics) that predict glucocorticoid toxicity?
7	What is the best strategy for prediction, detection and prevention of glucocorticoid-associated cataract and glaucoma?
8	The mechanisms behind individual responsiveness and glucocorticoid resistance should be investigated and the clinical implications clarified.
9	Do glucocorticoids also inhibit radiographic progression in patients with long standing rheumatoid arthritis?
10	What is the pathophysiological mechanism of steroid myopathy and can we prevent this; is there a role for specific exercises?
11	Which genomic and non-genomic mechanisms of glucocorticoid actions are responsible for wanted and adverse effects, respectively?

These recommendations have some limitations. First, the search strategy could have been too specific and relevant studies might have been overlooked. Search results were often overwhelming, since GCs are used quite extensively. Therefore, search strings might have been more specific than ideally useful. Second, the selection of circumstantial evidence in the absence of direct evidence has some degree of subjectivity. Third, in literature the evidence hierarchy has focused on treatment efficacy, whereas evidence on safety is better graded by other study types than RCTs. The above mentioned grading methodology tries to overcome this problem, but other grading systems might be preferred for grading studies on safety in the future.

The literature search showed that studies on GCs lack systemic assessment of AEs, that AEs often are poorly described, let alone defined, which made it difficult to provide direct evidence for most propositions. It is therefore advised to monitor a well defined list of AEs in a standardised manner in future studies. Standardised scoring for most AEs has however yet to be developed. Hypertension, diabetes, osteoporosis, gastric ulcer, cataract, glaucoma, infections, and dyslipidemia are AEs that merit monitoring. Optimal ways of implementation of monitoring and its effect also are to be studied, including patients' perspectives. To point out the most important topics for future research on GCs a research agenda of 11 research questions has been formulated through 2 additional Delphi rounds (Table 6).

These recommendations, with all their limitations, are meant to give physicians some guidance for daily clinical pratice. For this purpose also, some additional practice points were formulated by the taskforce (Box 1).

Box 1 / Additional Practical Points

(During the process of formulating and discussing each propostion, several topics arose that merit extra emphasis).

- Starting GC-therapy before a clear diagnosis has been made, may hamper the making of a diagnosis.
- Worries of patients about GC-induced AEs are likely to differ from those of physicians.
- Faster tapering of GCs than described in schemes in the literature might often be possible.
- Avoid concomitant therapy with NSAIDs in patients on a daily dose >10 mg prednisolone or equivalent.
- Patients on GCs possibly are more prone to get fractures than postmenopausal patients not on GCs with the same BMD-levels/T-scores.
- Reminders on the use of anti-osteoporosis medication reduce the occurrence of fractures in high risk patients.
- Adrenal supression by GC, mirrored by an abnormal ACTH stimulation test, does not always predict signs and symptoms of adrenal insuficiency

APPENDIX 1

General systematic literature search:

Database	Search string	n
Pubmed	Naïve search: (“rheumatoid arthritis”[Title/Abstract] OR “arthritis, rheumatoid”[MeSH Terms] OR “polymyalgia rheumatica” [Title/Abstract] OR “polymyalgia rheumatica”[MeSH Terms] OR vasculit*[Title/Abstract] OR “vasculitis”[MeSH Terms] OR “systemic lupus erythematosus”[Title/Abstract] OR “lupus erythematosus, systemic”[MeSH Terms] OR “polymyositis”[Title/Abstract] OR “polymyositis”[MeSH Terms] OR “dermatomyositis”[Title/Abstract] OR “rheumatic disease”[Title/Abstract] OR “rheumatic diseases”[MeSH]) AND ((“adrenal cortex hormones”[Title/Abstract]) OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR *cortisone*[Title/Abstract]) AND (“low dose”[Title/Abstract] OR “medium dose”[Title/Abstract] OR (“2.5 mg” OR “5 mg” OR “7.5 mg” OR “10 mg” OR “12.5 mg” OR “15 mg” OR “17.5 mg” OR “20 mg” OR “22.5 mg” OR “25mg” OR “27.5 mg” OR “30 mg”)) MeSH-database search: “Glucocorticoids/adverse effects”[MAJR] AND “Glucocorticoids/adverse effects”[MESH] AND “Glucocorticoids/therapeutic use”[MESH]	999 1725
Embase	Naïve search: ((‘rheumatoid arthritis’/exp) OR (‘polymyalgia rheumatica’/exp) OR ‘vasculitis’/exp OR (‘systemic lupus erythematosus’/exp) OR ‘polymyositis’/exp OR (‘dermatomyositis’/exp) OR (‘rheumatic diseases’/exp)) AND ((‘adrenal cortex hormones’/exp) OR glucocort* OR predniso* OR *cortisone*) AND ((‘low dose’/exp) OR (‘low dose’/exp) OR ((‘2.5 mg’) OR (‘5 mg’) OR (‘7.5 mg’) OR (‘10 mg’) OR (‘12.5 mg’) OR (‘15 mg’) OR (‘17.5 mg’) OR (‘20 mg’) OR (‘22.5 mg’) OR (‘25 mg’) OR (‘27.5 mg’) OR (‘30 mg’))) AND [english]/lim AND [humans]/lim AND [embase]/lim Emtree-database search: (‘glucocorticoid’/exp/dd_ae,dd_to/mj AND [english]/lim AND [humans]/lim AND [embase]/lim) AND (‘glucocorticoid’/exp/dd_po/mj AND [english]/lim	1071 763
CINAHL	((rheumatoid arthritis) OR vasculit* OR (systemic lupus erythematosus) OR polymyositis OR dermatomyositis OR “rheumatic disease”[Title/Abstract] OR “rheumatic diseases”) AND ((adrenal cortex hormones) OR glucocorticoids OR prednisone OR prednison OR prednisolone OR prednisolon OR cortisone OR cortison OR hydrocortisone OR hydrocortison) AND ((Low dose) OR ((2.5 mg) OR (5 mg) OR (7.5 mg) OR (10 mg) OR (12.5 mg) OR (15 mg) OR (17.5 mg) OR (20 mg) OR (22.5 mg) OR (25 mg) OR (27.5 mg) OR (30 mg)))	87
Total number of studies minus duplicates:		4140

APPENDIX 2

Searchstrings proposition 1:

Part 1A.

"The adverse effects of glucocorticoid therapy should be considered before glucocorticoid therapy is started…"

Intervention / determinant: [patient education]

Outcome: [adverse effects]

Part 1B.

"…This advice should be reinforced by giving information regarding glucocorticoid medication..."

Intervention / determinant: [patients information] AND [information leaflets]

Part 1C. "…If glucocorticoids are to be used for a more porlonged period of time a "glucocorticoid card" is to be issued to every patient, with the date of commencement of treatment, the initial dosage and the subsequent reductions and maintenance regiments."

Patient: [GC]

Intervention: [steroid card]

Database	Search string	n
Pubmed	*Part 1A:* ("patient education"[Title/Abstract] OR "informed consent"[Title/Abstract] OR "patient instruction"[Title/Abstract] OR "patient perspective"[Title/Abstract] OR "patients perspective"[Title/Abstract] OR "patients' perspective" OR "patient viewpoint"[Title/Abstract] OR "patients viewpoint"[Title/Abstract] OR "patients' viewpoint") AND ("self report"[Title/Abstract] OR "adverse event"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "adverse effect"[Title/Abstract] OR "adverse effects"[Title/Abstract] OR "side-effect"[Title/Abstract] OR "side-effects"[Title/Abstract] OR "unwanted effect"[Title/Abstract] OR "unwanted effects"[Title/Abstract]) *Part 1B:* ("information leaflet"[Title/Abstract] OR "written information"[Title/Abstract] OR "information booklet"[Title/Abstract] OR "information brochure"[Title/Abstract] OR "information folders"[Title/Abstract] OR "information pamphlets"[Title/Abstract]) AND ("patient education"[Title/Abstract] OR "informed consent"[Title/Abstract] OR "patient instruction"[Title/Abstract]) *Part 1C:* ("steroid card"[Title/Abstract] OR "medication card"[Title/Abstract] OR "information card"[Title/Abstract] OR "information leaflets"[Title/Abstract] OR "written information" [Title/Abstract] OR "information booklet"[Title/Abstract] OR "information brochure"[Title/Abstract] OR "information folder"[Title/Abstract] OR "information folder"[Title/Abstract] OR "information pamphlet"[Title/Abstract]) AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR *cortisone*[Title/Abstract] OR "Glucocorticoids/adverse effects"[MESH] OR "Glucocorticoids/therapeutic use"[MESH])	1256 122 3
Embase	*Part 1A:* (('patient education'/mj OR 'informed consent'/mj OR 'patient instruction' OR 'patient perspective' OR 'patients perspective' OR 'patient viewpoint' OR 'patients viewpoint') AND ('self report'/mj OR 'adverse event' OR 'adverse effects' OR 'adverse effect'/mj OR 'adverse effects' OR 'side-effect'/mj OR 'side-effects' OR 'unwanted effect' OR 'unwanted effects')) AND [english]/lim AND [humans]/lim AND [embase]/lim *Part 1B:* ('information leaflet' OR 'written information' OR 'information booklet' OR 'information brochure' OR 'information folders' OR 'information pamphlets') AND ('patient education'/de OR 'informed consent'/de OR 'patient instruction') AND [humans]/lim AND [embase]/lim *Part 1C:* ("steroid card" OR "medication card" OR "information card" OR "information leaflets" OR "written information" OR "information booklet" OR "information brochure" OR "information folder" OR "information folder" OR "information pamphlet") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR *cortisone*):ti:ab:kw AND [humans]/lim AND [embase]/lim	166 181 1
Cochrane	*Part 1A:* ("patient education" OR "informed consent" OR "patient instruction" OR "patient perspective" OR "patients perspective" OR "patient viewpoint" OR "patients viewpoint") AND ("self report" OR "adverse event" OR "adverse effects" OR "adverse effect" OR "adverse effects" OR "side-effect" OR "side-effects" OR "unwanted effect" OR "unwanted effects"):ti:ab:kw *Part 1B:* ("information leaflet" OR "written information" OR "information booklet" OR "information brochure" OR "information folders" OR "information pamphlets") AND ("patient education" OR "informed consent" OR "patient instruction"):ti:ab:kw *Part 1C:* ("steroid card" OR "medication card" OR "information card" OR "information leaflets" OR "written information" OR "information booklet" OR "information brochure" OR "information folder" OR "information folder" OR "information pamphlet") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR *cortisone*):ti:ab:kw	942 27 1
Total number of studies minus duplicates: **Part 1A:** **Part 1B:** **Part 1C:**		896 619 47 230

Searchstrings proposition 2:

Part 2A.
"Initial dose, dose reduction and long-term dosing depend on the underlying rheumatic disease, disease activity, risk factors and individual responsiveness of the patient…"
Patient / domain: [rheumatic disease]
Intervention / determinant: [dosage]
Outcome: [glucocorticoids]

Part 2B.
"…Timing may be important, with respect to the circadian rhythm of both the disease and the natural secretion of glucocorticoids…"
Patients: [rheumatic diseases]
Intervention: [glucocorticoids]
Outcome: [circadian rhythm]

Database	Search string	n
Pubmed	*Part 2A:* ("rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms] OR "polymyalgia rheumatica" [Title/Abstract] OR "polymyalgia rheumatica"[MeSH Terms] OR vasculit*[Title/Abstract] OR "vasculitis"[MeSH Terms] OR "systemic lupus erythematosus"[Title/Abstract] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[Title/Abstract] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[Title/Abstract] OR "rheumatic disease"[Title/Abstract] OR "Rheumatic Diseases"[MeSH]) AND ("Initial dose" [Title/Abstract] OR "dose reduction" [Title/Abstract] OR "long-term dosing" [Title/Abstract] OR "long-term treatment" [Title/Abstract] OR "starting dose" [Title/Abstract] OR "dose-ranging" [Title/Abstract] OR "dose finding" [Title/Abstract] OR "low-dose" [Title/Abstract]) AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortisone*[Title/Abstract] OR "Glucocorticoids "[MESH]) *Part 2B:* ("rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms] OR "polymyalgia rheumatica" [Title/Abstract] OR "polymyalgia rheumatica"[MeSH Terms] OR vasculit*[Title/Abstract] OR "vasculitis"[MeSH Terms] OR "systemic lupus erythematosus"[Title/Abstract] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[Title/Abstract] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[Title/Abstract] OR "rheumatic disease"[Title/Abstract] OR "Rheumatic Diseases"[MeSH]) AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR hydrocortisone*[Title/Abstract] OR "Glucocorticoids" [MESH]) AND ("circadian"[Title/Abstract] OR "circadian rhythm"[Title/Abstract] OR "biological rhythm"[Title/Abstract] OR biorhythm[Title/Abstract] OR "body clock"[Title/Abstract] OR "circadian clock"[Title/Abstract] OR cycles [Title/Abstract])	550 54
Embase	*Part 2A:* ("rheumatoid arthritis" OR "polymyalgia rheumatica" OR vasculit* OR vasculitis OR "systemic lupus erythematosus" OR polymyositis OR dermatomyositis OR "rheumatic disease") AND ("Initial dose" OR "dose reduction" OR "long-term dosing" OR "long-term treatment" OR "starting dose" OR "dose-ranging" OR "dose-finding" OR "low-dose") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR *cortisone*):ti:ab:kw AND [humans]/lim AND [embase]/lim *Part 2B:* ("rheumatoid arthritis" OR "polymyalgia rheumatica" OR vasculit* OR vasculitis OR "systemic lupus erythematosus" OR polymyositis OR dermatomyositis OR "rheumatic disease") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR *cortisone*) AND ("circadian" OR "circadian rhythm" OR "biological rhythm" OR biorhythm OR "body clock" OR "circadian clock" OR cycles) :ti:ab:kw AND [humans]/lim AND [embase]/lim	113 5
Cochrane	*Part 2A:* ("rheumatoid arthritis" OR "polymyalgia rheumatica" OR vasculit* OR vasculitis OR "systemic lupus erythematosus" OR polymyositis OR dermatomyositis OR "rheumatic disease") AND ("Initial dose" OR "dose reduction" OR "long-term dosing" OR "long-term treatment" OR "starting dose" OR "dose-ranging" OR "dose-finding" OR "low-dose") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR *cortisone*):ti:ab:kw *Part 2B:* ("rheumatoid arthritis" OR "polymyalgia rheumatica" OR vasculit* OR vasculitis OR "systemic lupus erythematosus" OR polymyositis OR dermatomyositis OR "rheumatic disease") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR hydrocortisone*) AND ("circadian" OR "circadian rhythm" OR "biological rhythm" OR biorhythm OR "body clock" OR "circadian clock" OR cycles) :ti:ab:kw	68 11
Total number of studies minus duplicates: **Part 2A:** **Part 2B:** **Part 2C:**		556 512 54 3

Searchstrings proposition 3:

Intervention / comparison: Risk factors before start GC-therapy.
Outcome: prediction of (above mentioned) AEs.

Database	Search string	n
Pubmed	((“risk factor”[title/abstract] OR “risk factors”[title/abstract]) AND (baseline[title/abstract] OR (therapy[title/abstract] AND (before[title/abstract] OR begin[title/abstract] OR start[title/abstract] OR “prior to”[title/abstract])))) OR (“predictor”[title/abstract] OR “predictors”[title/abstract]) AND (osteoporosis[Title/Abstract] 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 osteonecrosis[Title/Abstract] OR “avascular necrosis”[Title/Abstract] OR “muscle weakness”[Title/Abstract] OR myopathy[Title/Abstract] OR “diabetes mellitus”[title/abstract] OR “blood glucose”[title/abstract] OR “fasting glucose”[title/abstract] OR “urine glucose”[title/abstract] OR glycosuria[title/abstract] OR urinalysis[title/abstract] OR “glucose intolerance”[Title/Abstract] OR “glucose tolerance”[Title/Abstract] OR hyperglycaemia[title/abstract] OR “body weight”[title/abstract] OR “weight gain”[Title/Abstract] OR “adipositas”[Title/Abstract] OR “fat redistribution”[Title/Abstract] OR “Fat distribution”[Title/Abstract] OR “buffalo hump”[Title/Abstract] OR “serum lipids”[title/abstract] OR dyslipidemia[title/abstract] OR dyslipidaemia[title/abstract] OR dyslipidemias[title/abstract] OR dyslipidaemias[title/abstract] OR hyperlipidemias[title/abstract] OR hyperlipidaemias[title/abstract] OR hypercholesterolaemia[title/abstract] OR atherosclerosis[Title/Abstract] OR arteriosclerosis[Title/Abstract] OR “atherosclerotic plaque”[Title/Abstract] OR “coronary artery disease”[Title/Abstract] OR “angina pectoris” [title/abstract] OR “myocardial infarction”[title/abstract] OR hypertension[title/abstract] OR “blood pressure”[title/abstract] OR oedema[title/abstract] OR edema[title/abstract] OR “cardiac insufficiency”[title/abstract] OR “heart failure”[title/abstract] OR “swollen ankles”[title/abstract] OR “electrolyte disorder”[Title/Abstract] OR “electrolyte balance”[title/abstract] OR “electrolyte imbalance”[title/abstract] OR “fluid disorder”[Title/Abstract] OR “fluid retention”[Title/Abstract] OR hypernatremia[Title/Abstract] OR hypernatraemia[Title/Abstract] OR hypokalaemia[Title/Abstract] OR hypokalemia[Title/Abstract] OR “Cushing syndrome”[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 purpura[Title/Abstract] OR striae[Title/Abstract] OR “easy bruisability”[Title/Abstract] OR “easy bruising”[Title/Abstract] OR “wound healing”[Title/Abstract] OR acne[Title/Abstract] OR “hair loss”[Title/Abstract] OR hirsutism[Title/Abstract] OR alopecia[Title/Abstract] OR “gastric ulcer”[title/abstract] OR “gastroduodenal ulcer”[title/abstract] OR “stomach ulcer”[title/abstract] OR “peptic ulcer”[title/abstract] OR “peptic ulcer disease”[title/abstract] OR dyspepsia[title/abstract] OR dysfagia[title/abstract] OR “deglutition disorders”[title/abstract] OR “gastric hemorrhage”[title/abstract] OR “stomach hemorrhage”[title/abstract] OR “gastroduodenal hemorrhage”[title/abstract] OR cataract[title/abstract] OR glaucoma[title/abstract] OR “ocular pressure”[title/abstract] OR “intraocular pressure”[title/abstract] OR (infection[title/abstract] AND (viral[title/abstract] OR bacterial[title/abstract] OR fungal[title/abstract] OR respiratory[title/abstract] OR urinary[title/abstract] OR skin[title/abstract])) OR candida[title/abstract] OR “non-steroidal anti-inflammatory agents”[title/abstract] OR NSAID[title/abstract])	220
Embase	((“risk factor” OR “risk factors”) AND (baseline OR (therapy AND (before OR begin OR start OR “prior to”)))) OR (“predictor” OR “predictors”) AND (osteoporosis OR “bone loss” OR “Vertebral deformity” OR “Vertebral deformities” OR “fracture” OR “fractures” OR “bone mineral density” OR “bone density” OR osteonecrosis OR “avascular necrosis” OR “muscle weakness” OR myopathy OR “diabetes mellitus” OR “blood glucose” OR “fasting glucose” OR “urine glucose” OR glycosuria OR urinalysis OR “glucose intolerance” OR “glucose tolerance” OR hyperglycaemia OR “body weight” OR “weight gain” OR “adipositas” OR “fat redistribution” OR “Fat distribution” OR “buffalo hump” OR “serum lipids” OR dyslipidemia OR dyslipidaemia OR dyslipidemias OR dyslipidaemias OR hyperlipidemias OR hyperlipidaemias OR hypercholesterolaemia OR atherosclerosis OR arteriosclerosis OR “atherosclerotic plaque” OR “coronary artery disease” OR “angina pectoris” OR “myocardial infarction” OR hypertension OR “blood pressure” OR oedema OR edema OR “cardiac insufficiency” OR “heart failure” OR “swollen ankles” OR “electrolyte disorder” OR “electrolyte balance” OR “electrolyte imbalance” OR “fluid disorder” OR “fluid retention” OR hypernatremia OR hypernatraemia OR hypokalaemia OR hypokalemia OR “Cushing syndrome” OR “facial fullness” OR “facial swelling” OR “moon face” OR “cutaneous atrophy” OR “skin atrophy” OR “skin hemorrhage” OR “skin bleeding” OR purpura OR striae OR “easy bruisability” OR “easy bruising” OR “wound healing” OR acne OR “hair loss” OR hirsutism OR alopecia OR “gastric ulcer” OR “gastroduodenal ulcer” OR “stomach ulcer” OR “peptic ulcer” OR “peptic ulcer disease” OR dyspepsia OR dysfagia OR “deglutition disorders” OR “gastric hemorrhage” OR “stomach hemorrhage” OR “gastroduodenal hemorrhage” OR cataract OR glaucoma OR “ocular pressure” OR “intraocular pressure” OR (infection AND (viral OR bacterial OR fungal OR respiratory OR urinary OR skin)) OR candida OR “non-steroidal anti-inflammatory agents” OR NSAID):ti:ab AND [humans]/lim AND [embase]/lim	251
Cochrane	((“risk factor” OR “risk factors”) AND (baseline OR (therapy AND (before OR begin OR start OR “prior to”)))) OR (“predictor” OR “predictors”) AND (osteoporosis OR “bone loss” OR “Vertebral deformity” OR “Vertebral deformities” OR “fracture” OR “fractures” OR “bone mineral density” OR “bone density” OR osteonecrosis OR “avascular necrosis” OR “muscle weakness” OR myopathy OR “diabetes mellitus” OR “blood glucose” OR “fasting glucose” OR “urine glucose” OR glycosuria OR urinalysis OR “glucose intolerance” OR “glucose tolerance” OR hyperglycaemia OR “body weight” OR “weight gain” OR “adipositas” OR “fat redistribution” OR “Fat distribution” OR “buffalo hump” OR “serum lipids” OR dyslipidemia OR dyslipidaemia OR dyslipidemias OR dyslipidaemias OR hyperlipidemias OR hyperlipidaemias OR hypercholesterolaemia OR atherosclerosis OR arteriosclerosis OR “atherosclerotic plaque” OR “coronary artery disease” OR “angina pectoris” OR “myocardial infarction” OR hypertension OR “blood pressure” OR oedema OR edema OR “cardiac insufficiency” OR “heart failure” OR “swollen ankles” OR “electrolyte disorder” OR “electrolyte balance” OR “electrolyte imbalance” OR “fluid disorder” OR “fluid retention” OR hypernatremia OR hypernatraemia OR hypokalaemia OR hypokalemia OR “Cushing syndrome” OR “facial fullness” OR “facial swelling” OR “moon face” OR “cutaneous atrophy” OR “skin atrophy” OR “skin hemorrhage” OR “skin bleeding” OR purpura OR striae OR “easy bruisability” OR “easy bruising” OR “wound healing” OR acne OR “hair loss” OR hirsutism OR alopecia OR “gastric ulcer” OR “gastroduodenal ulcer” OR “stomach ulcer” OR “peptic ulcer” OR “peptic ulcer disease” OR dyspepsia OR dysfagia OR “deglutition disorders” OR “gastric hemorrhage” OR “stomach hemorrhage” OR “gastroduodenal hemorrhage” OR cataract OR glaucoma OR “ocular pressure” OR “intraocular pressure” OR (infection AND (viral OR bacterial OR fungal OR respiratory OR urinary OR skin)) OR candida OR “non-steroidal anti-inflammatory agents” OR NSAID) :ti:ab:kw	0
Total number of studies minus duplicates:		464

Searchstrings proposition 4:

Patient / Domain: [Rheumatic diseases AND GCs]
Intervention / Determinant: [long-term treatment]

Database	Search string	n
Pubmed	("rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms] OR "polymyalgia rheumatica" [Title/Abstract] OR "polymyalgia rheumatica"[MeSH Terms] OR vasculit*[Title/Abstract] OR "vasculitis"[MeSH Terms] OR "systemic lupus erythematosus"[Title/Abstract] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[Title/Abstract] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[Title/Abstract] OR "rheumatic disease"[Title/Abstract] OR "Rheumatic Diseases"[MeSH]) AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("long-term treatment"[Title/Abstract] OR "chronic treatment"[Title/Abstract] OR "long-term therapy"[Title/Abstract] OR "chronic therapy"[Title/Abstract])	109
Embase	(("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("long-term treatment" OR "chronic treatment" OR "long-term therapy" OR "chronic therapy")):ti :ab	42
Cochrane	(("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("long-term treatment" OR "chronic treatment" OR "long-term therapy" OR "chronic therapy")):ti:ab:kw	0
Total number of studies minus duplicates:		131

Searchstrings proposition 5:

Patient / domain: rheumatic patient
Intervention / determinant: Monitoring (for body weight, BP, etc…) during GC-treatment.
Outcome: Body weight, blood pressure, etc..

Database	Search string	n
Pubmed	("rheumatoid arthritis"[Title/Abstract] OR "arthritis, rheumatoid"[MeSH Terms] OR "polymyalgia rheumatica" [Title/Abstract] OR "polymyalgia rheumatica"[MeSH Terms] OR vasculit*[Title/Abstract] OR "vasculitis"[MeSH Terms] OR "systemic lupus erythematosus"[Title/Abstract] OR "lupus erythematosus, systemic"[MeSH Terms] OR "polymyositis"[Title/Abstract] OR "polymyositis"[MeSH Terms] OR "dermatomyositis"[Title/Abstract] OR "rheumatic disease"[Title/Abstract] OR "Rheumatic Diseases"[MeSH]) AND (evaluation[title/abstract] OR monitoring[title/abstract] OR assessment[title/abstract] OR control[title/abstract] OR evaluating[title/abstract] OR measurement[title/abstract] OR metaphylaxis[title/abstract] OR screening[title/abstract] OR surveillance[title/abstract]) AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("diabetes mellitus"[title/abstract] OR "blood glucose"[title/abstract] OR "fasting glucose"[title/abstract] OR "urine glucose"[title/abstract] OR glycosuria[title/abstract] OR urinalysis[title/abstract] OR "glucose intolerance"[Title/Abstract] OR "glucose tolerance"[Title/Abstract] OR hyperglycaemia[title/abstract] OR "body weight"[title/abstract] OR "weight gain"[Title/Abstract] OR "adipositas"[Title/Abstract] OR "fat redistribution"[Title/Abstract] OR "Fat distribution"[Title/Abstract] OR "buffalo hump"[Title/Abstract] OR "serum lipids"[title/abstract] OR dyslipidemia[title/abstract] OR dyslipidaemia[title/abstract] OR dyslipidemias[title/abstract] OR dyslipidaemias[title/abstract] OR hyperlipidemias[title/abstract] OR hyperlipidaemias[title/abstract] OR hypercholesterolaemia[title/abstract] OR atherosclerosis[Title/Abstract] OR arteriosclerosis[Title/Abstract] OR "atherosclerotic plaque"[Title/Abstract] OR "coronary artery disease"[Title/Abstract] OR "angina pectoris" [title/abstract] OR "myocardial infarction"[title/abstract] OR hypertension[title/abstract] OR "blood pressure"[title/abstract] OR oedema[title/abstract] OR edema[title/abstract] OR "cardiac insufficiency"[title/abstract] OR "heart failure"[title/abstract] OR "swollen ankles"[title/abstract] OR "electrolyte disorder"[Title/Abstract] OR "electrolyte balance"[title/abstract] OR "electrolyte imbalance"[title/abstract] OR "fluid disorder"[Title/Abstract] OR "fluid retention"[Title/Abstract] OR hypernatremia[Title/Abstract] OR hypernatraemia[Title/Abstract] OR hypokalaemia[Title/Abstract] OR hypokalemia[Title/Abstract] OR "Cushing syndrome"[Title/Abstract] OR "facial fullness" [Title/Abstract] OR "facial swelling"[Title/Abstract] OR "moon face"[Title/Abstract] OR glaucoma[title/abstract] OR "ocular pressure"[title/abstract] OR "intraocular pressure"[title/abstract])	181
Embase	(("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND (evaluation OR monitoring OR assessment OR control OR evaluating OR measurement OR metaphylaxis OR screening OR surveillance) AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("diabetes mellitus" OR "blood glucose" OR "fasting glucose" OR "urine glucose" OR glycosuria OR urinalysis OR "glucose intolerance" OR "glucose tolerance" OR hyperglycaemia OR "body weight" OR "weight gain" OR "adipositas" OR "fat redistribution" OR "Fat distribution" OR "buffalo hump" OR "serum lipids" OR dyslipidemia OR dyslipidaemia OR dyslipidemias OR dyslipidaemias OR hyperlipidemias OR hyperlipidaemias OR hypercholesterolaemia OR atherosclerosis OR arteriosclerosis OR "atherosclerotic plaque" OR "coronary artery disease" OR "angina pectoris" OR "myocardial infarction" OR hypertension OR "blood pressure" OR oedema OR edema OR "cardiac insufficiency" OR "heart failure" OR "swollen ankles" OR "electrolyte disorder" OR "electrolyte balance" OR "electrolyte imbalance" OR "fluid disorder" OR "fluid retention" OR hypernatremia OR hypernatraemia OR hypokalaemia OR hypokalemia OR "Cushing syndrome" OR "facial fullness" OR "facial swelling" OR "moon face" OR cataract OR glaucoma OR "ocular pressure" OR "intraocular pressure"))/MJ :ti:ab AND [humans]/lim AND [embase]/lim	83
Cochrane	(("rheumatoid arthritis" OR "polymyalgia rheumatica" OR "polymyalgia rheumatica" OR vasculit* OR "systemic lupus erythematosus" OR "lupus erythematosus, systemic" OR "polymyositis" OR "dermatomyositis" OR "rheumatic disease" OR "Rheumatic Diseases") AND (evaluation OR monitoring OR assessment OR control OR evaluating OR measurement OR metaphylaxis OR screening OR surveillance) AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("diabetes mellitus" OR "blood glucose" OR "fasting glucose" OR "urine glucose" OR glycosuria OR urinalysis OR "glucose intolerance" OR "glucose tolerance" OR hyperglycaemia OR "body weight" OR "weight gain" OR "adipositas" OR "fat redistribution" OR "Fat distribution" OR "buffalo hump" OR "serum lipids" OR dyslipidemia OR dyslipidaemia OR dyslipidemias OR dyslipidaemias OR hyperlipidemias OR hyperlipidaemias OR hypercholesterolaemia OR atherosclerosis OR arteriosclerosis OR "atherosclerotic plaque" OR "coronary artery disease" OR "angina pectoris" OR "myocardial infarction" OR hypertension OR "blood pressure" OR oedema OR edema OR "cardiac insufficiency" OR "heart failure" OR "swollen ankles" OR "electrolyte disorder" OR "electrolyte balance" OR "electrolyte imbalance" OR "fluid disorder" OR "fluid retention" OR hypernatremia OR hypernatraemia OR hypokalaemia OR hypokalemia OR "Cushing syndrome" OR "facial fullness" OR "facial swelling" OR "moon face" OR cataract OR glaucoma OR "ocular pressure" OR "intraocular pressure")):ti:ab:kw	137
Total number of studies minus duplicates:		401

Searchstrings proposition 6:

Patient / Domain: [GC]
Intervention / Determinant: [calcium OR vitamin D OR bisphosphonates]
Outcome: [review / meta-analysis]

Database	Search string	n
Pubmed	("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND (bisphosphonate[Title/Abstract] OR bisphosphonates[Title/Abstract] OR alendronate[Title/Abstract] OR ibandronate[Title/Abstract] OR etidronate[Title/Abstract] OR risendronate[Title/Abstract] OR calcitonine[Title/Abstract] OR Calcium[Title/Abstract] OR "vitamin D"[Title/Abstract] OR "vitamin D3"[Title/Abstract] OR Hydroxycholecalciferols[Title/Abstract] OR alphacalcidol[Title/Abstract]) AND ((meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])))))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti]))) BUTNOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt])	34
Embase	(("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND (bisphosphonate OR bisphosphonates OR alendronate OR ibandronate OR etidronate OR risendronate OR calcitonine OR Calcium OR "vitamin D" OR "vitamin D3" OR Hydroxycholecalciferols OR alphacalcidol) AND ((meta-analysis:it OR meta-analysis OR metanalysis) OR ((review:it OR guideline:it OR consensus:ti OR guideline*:ti OR literature:ti OR overview:ti OR review:ti) AND ((Cochrane OR Medline OR CINAHL OR (National AND Library)) OR (handsearch* OR search* OR searching) AND (hand OR manual OR electronic OR bibliographi* OR database* OR (Cochrane OR Medline OR CINAHL OR (National AND Library))))) OR ((synthesis:ti OR overview:ti OR review:ti OR survey:ti) AND (systematic:ti OR critical:ti OR methodologic:ti OR quantitative:ti OR qualitative:ti OR literature:ti OR evidence:ti OR evidence-based:ti))) NOT ((case*:ti OR report:ti OR editorial:it OR comment:it OR letter:it) NOT ((meta-analysis:it OR meta-analysis OR metanalysis) OR ((review:it OR guideline:it OR consensus:ti OR guideline*:ti OR literature:ti OR overview:ti OR review:ti) AND ((Cochrane OR Medline OR CINAHL OR (National AND Library)) OR (handsearch* OR search* OR searching) AND (hand OR manual OR electronic OR bibliographi* OR database* OR (Cochrane OR Medline OR CINAHL OR (National AND Library))))) OR ((synthesis:ti OR overview:ti OR review:ti OR survey:ti) AND (systematic:ti OR critical:ti OR methodologic:ti OR quantitative:ti OR qualitative:ti OR literature:ti OR evidence:ti OR evidence-based:ti))))):ti:ab	39
Cochrane	(("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND (bisphosphonate OR bisphosphonates OR alendronate OR ibandronate OR etidronate OR risendronate OR calcitonine OR Calcium OR "vitamin D" OR "vitamin D3" OR Hydroxycholecalciferols OR alphacalcidol)):ti:ab:kw	12
Total number of studies minus duplicates:		68

Searchstrings proposition 7:

Part 7A:
Patient / domain: [GC-using patients with concomitant NSAID]
Intervention / determinant: [gastro-protective measures]
Part 7B:
Patient / domain: [NSAID-using patients]
Intervention / determinant: [gastro-protective measures]
Outcome: [Review OR Meta-analysis]

Database	Search string	n
Pubmed	*Part 7A:* ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("non-steroidal anti-inflammatory agents"[title/abstract] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR "anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR NSAID[title/abstract]) AND (gastro-protective[title/abstract] OR gastroprotective[title/abstract] OR "gastro-protection"[title/abstract] OR gastroprotection[title/abstract] OR "proton pump inhibitor"[title/abstract] OR "proton pump inhibitors"[title/abstract] OR PPI[title/abstract] OR "COX-2 inhibitor"[title/abstract] OR Coxib[title/abstract] OR "cyclooxygenase 2 inhibitors"[title/abstract]) *Part 7B:* ("non-steroidal anti-inflammatory agents"[title/abstract] OR "anti-inflammatory agents, non-steroidal"[MeSH Terms] OR "anti-inflammatory agents, non-steroidal"[Pharmacological Action] OR NSAID[title/abstract]) AND (gastro-protective[title/abstract] OR gastroprotective[title/abstract] OR "gastro-protection"[title/abstract] OR gastroprotection[title/abstract] OR "proton pump inhibitor"[title/abstract] OR "proton pump inhibitors"[title/abstract] OR PPI[title/abstract] OR "COX-2 inhibitor"[title/abstract] OR Coxib[title/abstract] OR "cyclooxygenase 2 inhibitors"[MESH] OR "cyclooxygenase 2 inhibitors"[title/abstract]) AND ((meta-analysis [pt] OR meta-analysis [tw] OR metanalysis [tw]) OR ((review [pt] OR guideline [pt] OR consensus [ti] OR guideline* [ti] OR literature [ti] OR overview [ti] OR review [ti]) AND ((Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw])) OR (handsearch* [tw] OR search* [tw] OR searching [tw]) AND (hand [tw] OR manual [tw] OR electronic [tw] OR bibliographi* [tw] OR database* OR (Cochrane [tw] OR Medline [tw] OR CINAHL [tw] OR (National [tw] AND Library [tw]))))) OR ((synthesis [ti] OR overview [ti] OR review [ti] OR survey [ti]) AND (systematic [ti] OR critical [ti] OR methodologic [ti] OR quantitative [ti] OR qualitative [ti] OR literature [ti] OR evidence [ti] OR evidence-based [ti]))) BUTNOT (case* [ti] OR report [ti] OR editorial [pt] OR comment [pt] OR letter [pt])	48 103
Embase	*Part 7A:* ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("non-steroidal anti-inflammatory agents" OR NSAID OR NSAIDs) AND (gastro-protective OR gastroprotective OR "gastro-protection" OR gastroprotection OR "proton pump inhibitor" OR "proton pump inhibitors" OR PPI OR "COX-2 inhibitor" OR Coxib OR "cyclooxygenase 2 inhibitors"):ti:ab *Part 7B:* ("non-steroidal anti-inflammatory agents" OR NSAID OR NSAIDs) :ti:ab AND (gastro-protective OR gastroprotective OR "gastro-protection" OR gastroprotection OR "proton pump inhibitor" OR "proton pump inhibitors" OR PPI OR "COX-2 inhibitor" OR Coxib OR "cyclooxygenase 2 inhibitors"):ti:ab AND ((meta-analysis:it OR meta-analysis OR metanalysis) OR ((review:it OR guideline:it OR consensus:ti OR guideline*:ti OR literature:ti OR overview:ti OR review:ti) AND ((Cochrane OR Medline OR CINAHL OR (National AND Library)) OR (handsearch* OR search* OR searching) AND (hand OR manual OR electronic OR bibliographi* OR database* OR (Cochrane OR Medline OR CINAHL OR (National AND Library))))) OR ((synthesis:ti OR overview:ti OR review:ti OR survey:ti) AND (systematic:ti OR critical:ti OR methodologic:ti OR quantitative:ti OR qualitative:ti OR literature:ti OR evidence:ti OR evidence-based:ti))) NOT ((case*:ti OR report:ti OR editorial:it OR comment:it OR letter:it) NOT ((meta-analysis:it OR meta-analysis OR metanalysis) OR ((review:it OR guideline:it OR consensus:ti OR guideline*:ti OR literature:ti OR overview:ti OR review:ti) AND ((Cochrane OR Medline OR CINAHL OR (National AND Library)) OR (handsearch* OR search* OR searching) AND (hand OR manual OR electronic OR bibliographi* OR database* OR (Cochrane OR Medline OR CINAHL OR (National AND Library))))) OR ((synthesis:ti OR overview:ti OR review:ti OR survey:ti) AND (systematic:ti OR critical:ti OR methodologic:ti OR quantitative:ti OR qualitative:ti OR literature:ti OR evidence:ti OR evidence-based:ti))))	6 48
Cochrane	*Part 7A:* ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("non-steroidal anti-inflammatory agents" OR NSAID OR NSAIDs) AND (gastro-protective OR gastroprotective OR "gastro-protection" OR gastroprotection OR "proton pump inhibitor" OR "proton pump inhibitors" OR PPI OR "COX-2 inhibitor" OR Coxib OR "cyclooxygenase 2 inhibitors"):ti:ab *Part 7B:* ("non-steroidal anti-inflammatory agents" OR NSAID OR NSAIDs) :ti:ab AND (gastro-protective OR gastroprotective OR "gastro-protection" OR gastroprotection OR "proton pump inhibitor" OR "proton pump inhibitors" OR PPI OR "COX-2 inhibitor" OR Coxib OR "cyclooxygenase 2 inhibitors"):ti:ab:kw	2 22
Total number of studies minus duplicates: **Part 7A:** **Part 7B:**		157 48 111

Searchstrings proposition 8:

Patients / Domain: [Long-term GCs]
Intervention / Comparison: [perioperative GC-substitution]
Outcome: [adrenal insufficiency due to surgical stress]

Database	Search string	n
Pubmed	((“adrenal cortex hormones”[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR “Glucocorticoids”[MESH] OR Glucocorticoids[Title/Abstract]) AND (“long-term”[Title/Abstract] OR “low-dose”[Title/Abstract] OR chronic[Title/Abstract])) OR (“substitution”[Title/Abstract] OR “replacement”[Title/Abstract] OR “perioperative”[Title/Abstract]) OR (“adrenal insufficiency”[Title/Abstract] OR “adrenal deficiency”[Title/Abstract] OR “adrenal crisis”[Title/Abstract] OR “adrenocortical insufficiency”[Title/Abstract] OR “adrenocortical deficiency”[Title/Abstract] OR surgery[Title/Abstract] OR “surgical stress”[Title/Abstract])	110
Embase	(“adrenal cortex hormones” OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND (“long-term” OR “low-dose” OR chronic) AND (“substitution” OR “replacement” OR “perioperative”) AND (“adrenal insufficiency” OR “adrenal deficiency” OR “adrenal crisis” OR “adrenocortical insufficiency” OR “adrenocortical deficiency” OR surgery OR “surgical stress”):ti:ab:kw AND [humans]/lim AND [embase]/lim	203
Cochrane	(“adrenal cortex hormones” OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND (“long-term” OR “low-dose” OR chronic) AND (“substitution” OR “replacement” OR “perioperative”) AND (“adrenal insufficiency” OR “adrenal deficiency” OR “adrenal crisis” OR “adrenocortical insufficiency” OR “adrenocortical deficiency” OR surgery OR “surgical stress”):ti:ab:kw	18
Total number of studies minus duplicates:		303

Searchstrings proposition 9:

Patient / Domain: [rheumatic diseases and GCs]
Intervention / Determinant: [pregnancy]
Outcome: [Safety]

Database	Search string	n
Pubmed	(“rheumatoid arthritis”[Title/Abstract] OR “arthritis, rheumatoid”[MeSH Terms] OR “polymyalgia rheumatica” [Title/Abstract] OR “polymyalgia rheumatica”[MeSH Terms] OR vasculit*[Title/Abstract] OR “vasculitis”[MeSH Terms] OR “systemic lupus erythematosus”[Title/Abstract] OR “lupus erythematosus, systemic”[MeSH Terms] OR “polymyositis”[Title/Abstract] OR “polymyositis”[MeSH Terms] OR “dermatomyositis”[Title/Abstract] OR “rheumatic disease”[Title/Abstract] OR “Rheumatic Diseases”[MeSH]) AND (“adrenal cortex hormones”[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR “Glucocorticoids”[MESH] OR Glucocorticoids[Title/Abstract]) AND Pregnancy[Title/Abstract] AND ((safety[title/abstract] OR “adverse event”[Title/Abstract] OR “adverse effects”[Title/Abstract] OR “adverse effect”[Title/Abstract] OR “adverse effects”[Title/Abstract] OR side-effect*[Title/Abstract] OR “unwanted effect”[Title/Abstract] OR “unwanted effects”[Title/Abstract] OR complication* [Title/Abstract] OR morbidity[title/abstract] OR toxicity[title/abstract]))	51
Embase	(“rheumatoid arthritis” OR “polymyalgia rheumatica” OR “polymyalgia rheumatica” OR vasculit* OR “systemic lupus erythematosus” OR “lupus erythematosus, systemic” OR “polymyositis” OR “dermatomyositis” OR “rheumatic disease” OR “Rheumatic Diseases”) AND (“adrenal cortex hormones” OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND Pregnancy AND (safety OR “adverse event” OR “adverse effects” OR “adverse effect” OR “adverse effects” OR side-effect OR side-effects OR “unwanted effect” OR “unwanted effects” OR complication* OR morbidity OR toxicity):ti:ab	31
Cochrane	(“rheumatoid arthritis” OR “polymyalgia rheumatica” OR “polymyalgia rheumatica” OR vasculit* OR “systemic lupus erythematosus” OR “lupus erythematosus, systemic” OR “polymyositis” OR “dermatomyositis” OR “rheumatic disease” OR “Rheumatic Diseases”) AND (“adrenal cortex hormones” OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND Pregnancy AND (safety OR “adverse event” OR “adverse effects” OR “adverse effect” OR “adverse effects” OR side-effect OR side-effects OR “unwanted effect” OR “unwanted effects” OR complication* OR morbidity OR toxicity):ti:ab:kw	8
Total number of studies minus duplicates:		72

Searchstrings proposition 10

Patient / Domain: [Children that receive GCs]
Intervention / Determinant: [linear growth OR growth hormone]

Database	Search string	n
Pubmed	Child*[Title/Abstract] AND ("adrenal cortex hormones"[Title/Abstract] OR glucocort*[Title/Abstract] OR predniso*[Title/Abstract] OR cortison*[Title/Abstract] OR hydrocortison*[Title/Abstract] OR "Glucocorticoids"[MESH] OR Glucocorticoids[Title/Abstract]) AND ("Growth impairment"[Title/Abstract] OR "growth hormone"[Title/Abstract])	176
Embase	(Child* AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("Growth impairment" OR "growth hormone")):ti:ab	106
Cochrane	(Child* AND ("adrenal cortex hormones" OR glucocort* OR predniso* OR cortison* OR hydrocortison* OR Glucocorticoids) AND ("Growth impairment" OR "growth hormone")):ti:ab:kw	39
Total number of studies minus duplicates:		281

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CHAPTER 8

SUMMARY

This thesis focuses on glucocorticoid (GC)-treatment of inflammatory rheumatic diseases, mostly in rheumatoid arthritis (RA) patients. In this chapter the findings of these studies are summarised and discussed; and the questions that have been formulated in chapter 1 are addressed.

X-axis: efficacy

RA is a chronic disease characterised by joint inflammation; approximately 1% of the population suffers from it. The consequences of the disease can be severe, such as severely damaged joints in the long run. This damage to the joints often results in surgical procedures in order to maintain or improve their function. Better drug treatment has improved symptomatic control of the disease and inhibits joint damage. A clinically relevant endpoint to study the long-term effects of disease modifying anti-rheumatic drugs (DMARDs) on joint damage is joint surgery. The study in **appendix A** shows that 27 % of RA patients underwent joint surgery during the first 10 years after diagnosis; 30% of all surgical procedures was joint replacement and half of the patients had multiple surgical interventions. The study reveals that an early start with DMARD therapy after diagnosis (as compared to a delayed start), little radiologic joint damage during the first two years of treatment and good response to treatment are positively associated with a low occurrence of joint replacement surgery. Based on results of studies like this, ongoing research worldwide past decades was aimed at developing strategies to better control the disease. This resulted in the successful treatment paradigm of tight control or treat-to-target, in which treatment is tailored to the individual patient to achieve a low level of disease activity within a limited period of time. To this aim, combination drug strategies are used; because of their strong anti-inflammatory effects, a GC would be an attractive candidate for such strategies. Therefore, the following question arose:

how are GCs used as co-therapy with DMARDs in RA? The theme 'X-axis: efficacy' details the disease-modifying properties of GCs, in conjunction with other DMARDs, to achieve optimal disease control in RA. **Chapter 2** reviews the full range of GC co-therapies with regards to their position in RA treatment strategies. Different usages of GCs in treatment strategies are summarized, including both the use of systemic and intra-articular GCs as part of combination regimens, and the use of high dose GCs for bridging therapies. DMARD combination therapy including GCs not only performs better regarding short-term symptoms and functionality, compared to therapy without GCs, but also has long-term benefits with regards to radiographic damage. In a previous meta-analysis of all studies of RA patients that compared GCs with placebo or active controls with radiographic analysis as outcome measure,[1] the standardised mean difference in progression was 0.40 in favour of strategies using GCs (95% confidence interval 0.26, 0.52). Incontrovertibly**,** GCs are DMARDS.

Another therapeutic use of GCs is 'bridging therapy'; studies are reviewed showing that temporary medium to high dosage GC therapies could well serve as DMARD bridging therapy because of their rapid clinical benefits. Often intramuscular high dose GCs, intravenous pulse GCs, and subcutaneous Synacthen® depots are used; the small number of studies addressing this topic is summarized. Finally the use of intra-articular GCs is described; mostly used for local control in single joint arthritis in otherwise not active RA, but also as part of combination strategies in active RA.

Y-axis: toxicity

The next theme of this thesis is GC-toxicity. The chapters of this theme discuss two of the most notorious adverse events associated with GCs: osteoporosis and glucose intolerance. Osteoporosis is a frequently occurring co-morbidity of rheumatic diseases, which is caused both by the disease itself through pro-inflammatory cytokines and by the deleterious effects of GCs that are often used for treatment. Osteoporosis prevention and treatment start with calcium and vitamin D replacement, and in case of long-term GC-use often with additional bisphosphonates, according to the guideline discussed also in this thesis. The latter drugs

prevented glucocorticoid-induced bone loss in patients with rheumatic diseases starting long-term GC therapy more effectively compared to alfacalcidol (active vitamin D) during the 18 months Steroid Osteoporosis Prevention (STOP)-trial.[2] However, in the long run alfacalcidol could theoretically decrease the risk of osteoporotic fractures by improving micro-architecture of bone and strength and coordination of muscles, reducing the risk of falling.[3] In **Chapter 3**, as a follow-up study of the STOP-trial, the long-term occurrence and type of vertebral fractures in inflammatory rheumatic patients after GC use are described. Patients with inflammatory rheumatic diseases had a 28% incidence of vertebral fractures according to the Genant score over a period of 4.2 years after starting long-term GC-treatment (18 months trial and 2.7 years follow-up). During this follow-up period, when anti-osteoporotic treatment was left to the treating physician, 28 (24%) of the patients developed a new vertebral fracture, 12 of whom had mild (>20%-25% vertebral height loss), 12 intermediate (>25-40%) and 4 severe (>40%) vertebral X-ray deformities. In addition, a considerable number of these fractures was of the crushed type. Age and cumulative GC dose were associated with these vertebral fractures, but former anti-osteoporotic trial-treatment with either a bisphosphonate (alendronate) or active vitamin D (alfacalcidol) was not. This shows that osteoporotic co-morbidity was considerable in long-term GC-using rheumatic patients, and suggests that beneficial effects of early treatment with alfacalcidol versus alendronate against osteoporotic fractures are short lived if intensive anti-osteoporotic treatment is not strictly continued.

Alfacalcidol, next to its positive effects on bone, has also been associated with anti-inflammatory effects.[4] This is particularly interesting, since inflammation and bone metabolism share mechanisms (‘osteo-immunity’), which can be influenced by both GCs and vitamin D. Several cytokine pathways have so far been identified to play a role, but of special interest is macrophage migration inhibitory factor (MIF). MIF is a cytokine with inhibitory effects on GCs and it seems to be a regulator of bone metabolism, possibly inhibiting bone resorption in situations of injured bone. The relation between MIF and bone metabolism in long-term GC-using patients with inflammatory rheumatic diseases was evaluated in **chapter 4.** In a sub-analysis of the STOP trial, we measured cytokine profiles of 20 RA patients in

the alfacalcidol and 20 in the alendronate group. MIF levels did not differ between both groups, which is attributed to inhibition by GCs. Increases in MIF levels were associated with increases in bone mineral density (beta = 0.02; 95% confidence interval (CI) 0.004 to 0.04), corrected for alfacalcidol effect, age, gender and cumulative GC-dose. As MIF is a known antagonist of GCs, this finding could mean MIF has bone-protecting capacities by preventing (or antagonising) GC-induced bone loss; further studies are needed.

Glucose intolerance is the next topic, specifically: does RA affect glucose metabolism, and, if so, what is the influence of chronic GC-use on this interaction? In **chapter 5** we investigated glucose uptake and insulin secretion, by comparing glucose and insulin levels during frequently-sampled oral glucose tolerance tests (OGTTs) in both a GC naive and a long-term GC-using group of established RA patients and control subjects. The prevalence of known type 2 diabetes mellitus (T2DM) in both RA groups before the study was 8%; while 11% of RA patients had T2DM newly diagnosed during the study: 14% in the GC-group vs. 9% the GC-naïve group, p=0.3. Compared to control subjects RA patients were less insulin sensitive, and had more beta-cell dysfunction. GC-using patients did not differ in glucose metabolism from GC-naive RA patients; only high cumulative GC-dose was associated with newly diagnosed type 2 diabetes (P=0.04), when corrected for patient characteristics (age, gender, BMI, and waist circumference) and disease characteristics (DAS28, erosions of hands or feet, DMARD-usage history). Although confounding by indication of GC-therapy -preferentially prescribed in more severe RA- on glucose metabolism can not be solved in this retrospective study, its results seem to indicate -a disease activity related- metabolic influence of RA on glucose intolerance and seems to confirm the association between high cumulative doses of GCs and glucose intolerance.

Z-axis: safety

The final theme is safety during GC treatment, i.e. how to find the balance between efficacy and toxicity, the previous themes. In **chapter 6** a meta-analysis has been performed on the occurrence and profile of adverse events in rheumatic diseases and inflammatory bowel

disease. Only longitudinal studies of at least 1 month duration with low-to-medium dose GCs, (up to 30mg prednisone equivalent daily), which reported adverse events in a dichotomous manner were included. In 14 studies (796 patients) with rheumatoid arthritis the risk of adverse events was 43/100 patient-years (95% CI 30 to 55), in 4 studies of 167 patients with polymyalgia rheumatica it was 80/100 patient-years (95% CI 15 to146), and in 10 studies of 1419 patients with inflammatory bowel disease it was 555/100 patient-years (95% CI 391 to 718). However, high-quality studies with short follow-up (i.e. up to 6 months) such as those on inflammatory bowel disease, reported high rates of adverse events. Furthermore, in studies of patients with inflammatory bowel disease mainly gastro-intestinal adverse-events (AEs) were reported, which probably represented disease activity. Remarkably, in RA patients psychological AEs were most frequently reported (19 AEs per 100 patient years; 95% CI 4 to 34); these were mostly minor mood disturbances. Too much difference in study design hampered comparison of GC-related AE-rates in patients with different diseases.

This study served to inform a EULAR taskforce on GCs on the spectrum of adverse events reported in studies on GCs. This taskforce set out to formulate recommendations on safety measures a rheumatologist should adhere to during systemic low-to-medium dose GC-treatment of a patient (**chapter 7)**. Ten recommendations were generated using a combination of systematically retrieved research evidence and expert consensus as achieved using the Delphi method. Patient education and adequate evaluation of co-morbidities and risk factors for AEs at the start of treatment are emphasised and monitoring of these during treatment. Especially in case of long-term GC-use, the lowest possible dose and preventive therapies against GC-induced co-morbidities, such as osteoporosis and peptic ulcer disease in case of concomitant non-steroidal anti-inflammatory drugs usage, are advised. Finally, safety issues such as peri-operative GC replacement therapy are addressed and areas of importance that need further research are identified, such as cardiovascular risk and GCs.

GENERAL DISCUSSION

The compatibility triangle

As this thesis discusses, an incompatible situation arises when toxicity predominates over efficacy particularly in case high cumulative doses of GCs have been used. This has stigmatised their usage, which is often unwarranted when GC therapy is applied with sufficient precautionary measures (safety). The most obvious example is osteoporosis prophylaxis in patients on long-term GC therapy. When the three dimensions or axes related to the use of GCs namely efficacy, toxicity and safety of GC therapy are balanced, a good benefit-risk ratio and harmonious situation exist: a compatible triangle.

The main message from the first axis or theme 'efficacy' is that low-to-medium dose systemic GCs indeed deserve to be part of modern treat-to-target or tight control RA treatment strategies, as GCs are DMARDs and clearly improve the prognosis of RA patients. Whether the DMARD-effect of GC co-therapy persists after 2 years of treatment remains yet to be investigated, and also whether the triangle of dimensions stays compatible during chronic GC-treatment for this purpose.

The second theme 'toxicity' points out that patients on chronic GC-treatment still suffer from a high incidence of vertebral fractures; also disturbed glucose metabolism was detected in a substantial number of RA patients with established disease, both in those on GC therapy and those without GCs. With regards to these 2 co-morbidities, it is still not clear what the direct effects of GCs are, and what the effects of disease activity. More research on the basic mechanisms of GC-related osteoporosis and glucose intolerance, especially in randomised placebo-controlled GC studies with frequent longitudinal assessments is needed, also in patients chronically treated with GCs. The results of such investigations could suggest potential mechanisms for new (prophylactic) therapies, aimed at e.g. specific adipocytokines and bone regulating cytokines, through which the triangle of GC-use would become more compatible. Significant focus of future studies on long-term GC-use should be on other, e.g. cardiovascular AEs.

Safety is the third theme of GC-use and of crucial importance for the compatibility of the triangle of GC-use; associated with both efficacy and toxicity. Based on a review of GC-associated AEs, a broad set of recommendations has been formulated to prevent or treat these AEs during treatment. This enables safer long-term use of GCs and enhances the compatibility of the GC-use triangle. However, for interpretation of AEs, the direct effects of GCs and the effects of disease activity proved to be difficult to unravel; most recommendations are not fully evidence-based by lack of data.

Future improvement of the GC-triangle compatibility.

Several options are suggested to achieve more compatibility of the three dimensions concerning GC-use in the future. The first option is lowering the risk of GC-associated AEs; through further improvement of the AE-monitoring advices of chapter 7. Following these recommendations, the EULAR-taskforce on GCs developed more specific guidelines encompassing monitoring criteria and frequency of monitoring;[5] these furthermore differentiated monitoring in daily practice and in clinical trials. The second option, which could be called 'chrono-therapy' has recently been introduced for clinical practice. A modified release GC tablet that releases prednisone about 4 hours after intake, and as such adds to the circadian rhythm of endogenous GCs if taken in the evening, shows an impressive decrease of symptoms (i.e. morning stiffness) compared to prednisone taken early in the morning.[6] Future studies should evaluate the effects on other RA disease activity and outcome measures, such as long-term joint damage as compared to regular GCs. Finally, better compatibility of the GC-triangle could be achieved through the development of new GC-like drugs, so called SEGRAs (selective glucocorticoid receptor agonists), with the same efficacy but less AEs compared to current GCs.[7] These drugs under development aim at selective interaction with DNA-transcription by GCs after binding to their receptor: intact inhibition (transrepression) of pro-inflammatory mechanisms, but less induction (transactivation) of metabolic mechanisms, predominantly leading to AEs. Although these drugs have been announced some years ago, their introduction into the market is expected only in the next quinquennium. Even in earlier

stages of development augmenting their (local) anti-inflammatory effects are GCs coupled to nitric oxide, GCs combined with agents such as dipyridamole and GCs bound to liposomes.

Taken all of the above into account, the future of GC-use in rheumatic diseases is certainly going to be more ‘compatible’, from a triangular point of view…

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APPENDIX A

JOINT SURGERY IN THE UTRECHT RHEUMATOID ARTHRITIS COHORT: THE EFFECT OF TREATMENT STRATEGY

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Objectives

To investigate the prevalence and prognostic factors of joint surgery in a large cohort of patients with rheumatoid arthritis, whose treatment, clinical and radiographic data have been assessed at predefined points in time since disease onset.

Methods

Data on surgical interventions were retrospectively obtained from 482 patients with rheumatoid arthritis whose follow-up data for at least 2 years were available, including treatment and response to treatment during the first 2 years. Survival time until the first surgical intervention and until the first major surgical intervention was determined for the total study population by Kaplan–Meier survival curves. Three separate Cox regression analyses were carried out to determine which variables measured at baseline, during the first year and during the first 2 years were predictors for joint surgery.

Results

27% of the patients underwent surgical interventions. Mean survival time until the first surgical intervention was 10.4 years. The percentage of patients with a surgical intervention was 10% lower in the group with response to treatment when compared with the non-response group. Next to a delayed start with disease-modifying antirheumatic drugs, fast radiographic progression during the first year and first 2 years was a predictor of joint surgery in the multivariate regression analyses.

Conclusion

Treatment with disease-modifying antirheumatic drugs immediately after diagnosis results in less joint surgery when compared with a delayed start. Furthermore, joint surgery is carried out more often in patients who do not respond to treatment.

Rheumatoid arthritis is a chronic disease characterised by its fluctuating course, and heterogeneity of disease activity and joint damage. At the moment, treatment of rheumatoid arthritis is characterised by early administration of (combinations) disease-modifying antirheumatic drugs (DMARDs).

Although the efficacy of treatment has improved during the past decade, a group of patients still require one or more surgical interventions. Joint surgery can be seen as an outcome measure, reflecting the unfavourable course of rheumatoid arthritis. Surgical interventions vary from minor interventions such as the removal of noduli and arthroscopy to major interventions such as total joint arthroplasty. A few studies investigated the prevalence of joint surgery. In a study population including 1600 patients, it was estimated that 25% of the patients undergo total joint arthroplasty within 23 years after disease onset.[1] In two other studies with follow-up durations of 5 and 10 years, joint surgery was carried out in 17% and 19% of the patients, respectively. [2,3] The costs for surgical interventions are high and comprise a major part of the total direct costs.[4] In our study on direct costs, we found that the mean (standard deviation (SD)) annual cost for surgery was €152 (2222) and that for hospitalisation was €391 (1602).[5] The total costs of those patients (n=33) who underwent a surgical intervention were €93.383. Identification and modification of risk factors for joint surgery might postpone or prevent joint surgery and thus reduce these high costs related to rheumatoid arthritis.

In several studies, high erythrocyte sedimentation rate (ESR),[1-3] functional disability,[1,3,6] radiographic damage[1-3] and long disease duration[1-3] have been reported as risk factors for surgical interventions. Most often these variables were assessed at diagnosis. However, patients with severe disease activity at baseline might respond well to treatment in the initial years after diagnosis, which could retard joint damage later on and, with that, surgical interventions. We already found that response to treatment is a predictor of remission, irrespective of treatment.[7] Thus, the kind of treatment and response to treatment might also influence the chance of joint surgery later on and are therefore of interest in the prognostic analyses. Except for two studies,[1,2] treatment has not been included in the prediction analyses as a possible prognostic factor for surgical interventions.

Two studies investigated the prognostic ability of variables with increasing observation time. Prediction of joint surgery improves with duration of observation time,[1,2] because probably with longer observation time the effect of treatment is included indirectly. To determine the predictive ability of variables with increasing observation time, a cohort of patients whose data have been obtained since diagnosis is required. In the region of Utrecht, The Netherlands, we have followed patients with rheumatoid arthritis since disease onset and assessed several variables at predefined points in time. This inception cohort allows us to investigate the ability of treatment strategy and response to treatment, in addition to demographic characteristics and clinical and radiographic variables assessed at diagnosis and during the first 2 years after diagnosis, to predict the requirement of joint surgery later on.

METHODS

From 1990 until 1998, all patients with a disease duration of <1 year, visiting one of the outpatient clinics of the Utrecht Rheumatoid Arthritis Cohort (SRU), The Netherlands, and fulfilling the revised 1987 American College of Rheumatology (ACR) criteria for rheumatoid arthritis8 and who did not meet any of the exclusion criteria, were asked to participate in a clinical trial to compare the effects of two treatment strategies—that is, an early start with DMARDs versus a delayed start with DMARDs. In the first strategy group, patients were randomly assigned to one of the three following treatment arms at diagnosis: (1) the methotrexate arm; (2) the intramuscular gold arm; and (3) the hydroxychloroquine arm. In the delayed start with DMARD group, patients did not receive any DMARD immediately at diagnosis but started using DMARDs if necessary during follow-up. In this group patients started with non-steroidal anti-inflammatory drugs (NSAIDs), and therefore this group is hereafter referred to as the NSAID group. After 1994, all patients were randomised into one of the three treatment arms of the early start with DMARD group because planned interim analyses showed that this strategy was much more beneficial.[9-11]

Clinical variables and radiographic damage

Patients included in one of the two strategy groups visited the outpatient clinic once every 3 months during the first 2 years and once every 6 months thereafter for assessment of disease activity. At each outpatient visit, the following clinical variables were assessed: ESR (mm/h), pain on a visual analogue scale (VAS; mean score; 0–100 mm=worst score), VAS general well-being (0–100 mm=worst score), joint score according to the Thompson joint score (a weighted score including both swollen and tender joints, range 0–53412), duration of morning stiffness (0–720 min) and functional disability (Dutch Health Assessment Questionnaire13; 0–3=worst score). At baseline and every year thereafter, radiographs of hands and feet were scored according to the Sharp–van der Heijde method (range 0–448).[14] Differences in total scores of individual patients of >25% were discussed until agreement was reached. The intraclass correlation coefficient between two sets of scores was 0.98, indicating excellent agreement.[15] Annual radiographic progression rate was calculated for the first year and for the first 2 years.

Surgical interventions

Patients' medical records were checked for any surgical intervention as a consequence of rheumatoid arthritis. All recorded surgical interventions were grouped into minor, intermediate and major interventions; also, the date of the procedures was recorded. Minor interventions were defined as arthroscopy, carpal tunnel decompression and rheumatoid nodule removal. Intermediate interventions included arthrodesis, synovectomy, and replacement or resection arthroplasty of the smaller joints of hands and feet. Major interventions included joint replacement of hip, knee, shoulder, elbow, ankle and wrist.

Statistical analyses

Descriptive statistical analyses were carried out for patients who remained in the cohort for at least 2 years. Baseline characteristics were compared between patients with a surgical intervention and patients without a surgical intervention using either the unpaired t-test

for continuous variables or the x2 test for categorical data, as appropriate. In this study, we also evaluated whether a response to treatment at 1 year or at 2 years resulted in less joint surgery later on. Response to treatment was achieved when a minimum of three of four of the following criteria were met: morning stiffness (15 min, Thompson joint score (10, VAS pain (10 mm and ESR (30 mm/h. Kaplan–Meier analyses were applied to determine the estimated mean (95% confidence interval (CI)) survival time from inclusion until the first surgical intervention or until the first major surgical intervention.

As follow-up duration was different for individual patients, univariate and multivariate Cox proportional regression analyses were carried out to determine demographic, clinical and radiographic prognostic factors, measured during the first 2 years, for surgical interventions. For both univariate and multivariate Cox regression analyses, three different analyses are reported. The first analysis uses only baseline data as covariates. The second analysis includes the area under the curve (AUC) standardised to time (during the first year) of all clinical variables, the radiographic progression rate during the first year and response to treatment measured at 1 year after diagnosis. The third analysis includes the AUC obtained during the first 2 years of all clinical variables, the radiographic progression rate during the first 2 years and response to treatment measured at 2 years after diagnosis. To calculate the AUC, missing data between two visits were imputed by the mean of the previous and the next score. For the multivariate Cox regression analyses, a forward procedure was applied and all variables were entered in order of significance level as obtained in the univariate analyses. In both the second and third analyses, age, sex, rheumatoid factor test assessed at diagnosis (positive *vs.* negative) and treatment strategy at diagnosis (NSAID group *vs.* DMARD group) were also included as covariates. All data were analysed using SPSS V.11.5.

RESULTS

Patients

Of the 590 patients who were randomised between 1990 and 1998 in the SRU, 482 patients

had a follow-up duration of at least 2 years and medical records of these patients could be retrieved and were used in the present study. Table 1 shows the characteristics of the study population, assessed at disease onset. In all, 71% of the patients were women and 65% had a positive rheumatoid factor test at diagnosis. The average disease duration was 7.2 years (range 2–14 years) at the time of this study. No significant differences were found in baseline characteristics of the 482 evaluated patients and the other 108 non-evaluated patients of the original cohort, except that the non-evaluated patients were older (56 (SD 14) years v 61 (SD 15) years; p,0.01).

Table 1 / Baseline characteristics for the total study population and separately for patients with and without any surgical intervention during follow-up

	Total group n = 482	**Surgical intervention**		**p Value**
		No (n = 352)	*Yes (n = 130)*	
Age, years	56 (14)	56 (14)	54 (14)	0.407
Sex, % female	71	69	76	0.125
Rheumatoid factor, % positive	65	62	71	0.082
ESR, mm/h	40 (26)	39 (24)	43 (31)	0.055
Morning stiffness, min	110 (114)	107 (117)	105 (110)	0.937
General well-being on VAS, mm	50 (23)	49 (24)	50 (24)	0.333
Pain on VAS, mm	47 (26)	45 (26)	48 (26)	0.776
Thompson joint score	144 (96)	135 (91)	159 (104)	0.012
Functional disability, HAQ	1.3 (0.7)	1.3 (0.7)	1.4 (0.8)	0.415
Radiographic damage score	4.7 (7.2)	5 (7)	5 (7)	0.942
Treatment groups				
DMARD group	430 (89)	323 (92)	107 (82)	0.005
NSAID group	52 (11)	29 (8)	23 (18)	

DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NSAID, non-steroidal anti-inflammatory drug; VAS, visual analogue scale.
Data are mean (standard deviation) for continuous variables and percentages for categorical variables. Ranges for variables are as follows: ESR, 2–140 mm/h; morning stiffness, 0–720 min; general well-being on VAS, 0–100 mm= worst score; pain on VAS, 0–100 mm= worst score; joint score, Thompson joint score 0–534; functional disability, HAQ 0–3 = worst score; and radiological damage score, modified Sharp–van der Heijde score 0–448.

Surgical interventions

Overall, 130 (27%) patients underwent a total of 240 surgical interventions, with a maximum of five interventions per patient: one intervention, n=65 (50%); two interventions, n=39 (30%); three interventions, n=15 (12%); four interventions, n=3 (2%); and five interventions, n=8 (6%). Of all surgical interventions, 17% was a minor intervention, 53% an intermediate intervention and 30% a major intervention. Of the 128 intermediate surgical interventions, the number of arthrodesis was 26 (20%), including 12 of the wrist or hand, 13 of the ankle or foot and 1 of the shoulder. In all, 48 patients underwent a total of 73 major surgical interventions; of these, the hip (51%) was the most frequently operated joint, followed by the knee (38%), the wrist (7%) and the shoulder (4%). The median (interquartile range) time from diagnosis to the first small intervention was 3.6 years (0.7–7.2), to the first intermediate intervention 4.7 years (2.2–6.4) and to the first major intervention 6.0 years (4.3–9.1). Table 1 shows the characteristics at diagnosis for the surgery group and the non-surgery group.

Survival analyses

Figure 1 shows the survival curve until the first surgical intervention of any kind and until the first major surgical intervention for the total study population since inclusion. The estimated mean (95% CI) survival time from inclusion until the first surgical intervention was 10.4 years (9.8 to 10.9) and that until the first major intervention was 12.5 years (12.1 to 12.9). Treatment strategy and response to treatment Forty-five (87%) of the patients in the NSAID group started using DMARDs within the first 2 years after diagnosis after a mean (SD) disease duration of 10 (5) months. Figure 2 shows the Kaplan–Meier survival curve for both treatment strategy groups. Patients in the NSAID group had an increased risk for surgical interventions when compared with those in the DMARD group (log rank test p=0.036). At 1 year, 25% of patients in the NSAID group and 44% of patients in DMARD group showed a good response to treatment (p=0.012). After 2 years these percentages were 48% and 47%, respectively (p=0.95). The percentage of patients needing a surgical intervention in the entire cohort after the first year was higher (albeit not significant) in the non-response group than

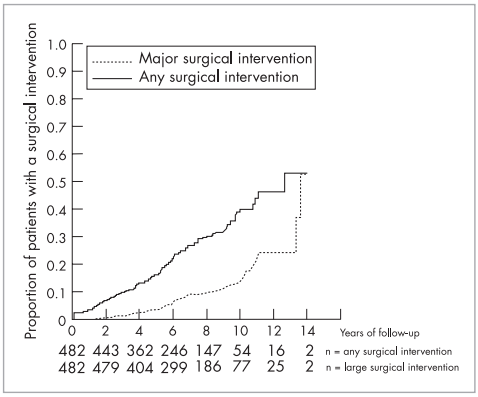

Figure 1 / Kaplan–Meier survival curve until the first surgical intervention (solid line) and until the first major surgical intervention (dotted line) since inclusion for the entire study population. At each 2-year interval, numbers indicate the remaining patients for follow-up.

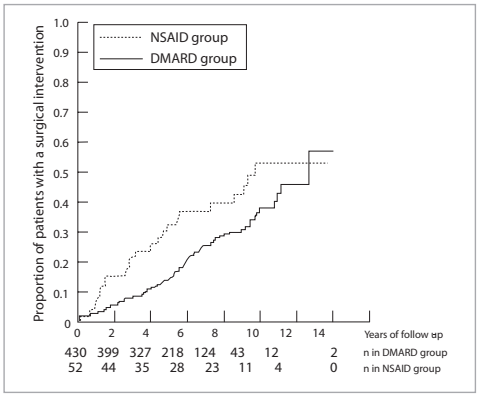

Figure 2 / Kaplan–Meier survival curve until the first surgical intervention for the disease-modifying antirheumatic drug (DMARD) group (solid line) and the non-steroidal anti-inflammatory drug (NSAID) group (dotted line). At each 2-year interval, numbers indicate the remaining patients for follow-up. Difference between treatment groups by log rank test = 0.036.

in the response group (30% *vs.* 23%; p=0.086). At 2 years this result became significantly different (i.e., 32% *vs.* 21%, respectively; p=0.012).

Prognostic factors for surgical interventions

Table 2 shows the results of the three univariate analyses comprising variables obtained at baseline, during the first year and during the first 2 years. For all three analyses, high Thompson joint score and high ESR were prognostic factors for joint surgery, and the prognostic ability became stronger in time. Not baseline, but functional disability and radiographic progression measured during the first year and during the first 2 years were significant prognostic risk factors for joint surgery. A response to treatment, both at 1 and 2 years, was associated with less surgery. Except for morning stiffness, all variables measured over 2 years were associated with joint surgery.

Table 3 shows the results of the three multivariate Cox regression analyses. An early start with DMARDs decreases the risk for surgical interventions when compared with a delayed start with DMARDs after controlling for all other clinical and demographic variables

Table 2 / Results of three univariate Cox regression analyses to determine prognostic factors of joint surgery, using data obtained at diagnosis, during the first year and during the first 2 years

	Baseline			**First year**			**First 2 years**		
	HR	*95% CI*	*p Value*	*HR*	*95% CI*	*p Value*	*HR*	*95% CI*	*p Value*
Sex, female v male	1.435	0.963 to 2.139	0.076	NA	NA	NA	NA	NA	NA
Age, years	1.000	0.988 to 1.013	0.982	NA	NA	NA	NA	NA	NA
Randomisation, NSAID group v DMARD group	1.620	1.029 to 2.553	0.037	NA	NA	NA	NA	NA	NA
Response to treatment, no v yes	NA	NA	NA	1.459	1.018 to 2.092	0.040	1.612	1.130 to 2.299	0.008
RF, positive v negative	1.244	0.849 to 1.823	0.263	NA	NA	NA	NA	NA	NA
ESR, mm/h	1.008	1.002 to 1.015	0.013	1.012	1.005 to 1.019	0.001	1.014	1.006 to 1.022	0.001
Joint score, Thompson joint score	1.002	1.001 to 1.004	0.004	1.003	1.001 to 1.005	0.001	1.004	1.002 to 1.007	0.000
Pain on VAS, mm	1.002	0.995 to 1.008	0.592	1.009	1.000 to 1.017	0.045	1.010	1.001 to 1.019	0.025
General well-being on VAS, mm	0.997	0.990 to 1.004	0.431	1.008	0.998 to 1.018	0.104	1.011	1.001 to 1.021	0.031
Morning stiffness, min	1.000	0.999 to 1.002	0.575	1.002	1.000 to 1.004	0.096	1.002	1.000 to 1.004	0.093
Radiographic damage, Sharp–van der Heijde	1.004	0.979 to 1.029	0.771	1.017	1.006 to 1.027	0.002	1.031	1.015 to 1.047	0.000
Functional disability, HAQ	1.145	0.910 to 1.441	0.248	1.393	1.068 to 1816	0.014	1.448	1.107 to 1.896	0.007

DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; RF, rheumatoid factor; VAS, visual analogue scale.
For each clinical variable (ESR, Thompson joint score, pain on VAS, general well-being on VAS, morning stiffness and functional disability), three separate univariate Cox regression analyses were carried out, including (1) baseline values; (2) values obtained during the first year (AUC standardised to time; AUC first year); and (3) values obtained during the first 2 years (AUC 2 years). Only sex (female v male), age, randomisation (NSAID v DMARD) and RF (positive v negative) were included in the baseline analyses. Only response to treatment (no response v response) was determined at 1 and at 2 years after diagnosis. Radiographic damage was determined at baseline, and radiographic progression was measured during the first year and during the first 2 years. The number of available radiographs for patients in the DMARD group and the NSAID group were, respectively: at baseline (328 (93%) v 120 (92%)); for radiographic progression over the first year (326 (93%) v 120 (92%)); and for radiographic progression during the first 2 years (317 (90%) v 118 (91%)).

in the three timedependent analyses. In addition, fast radiographic progression, either during the first year or during the first 2 years, increases the risk for joint surgery. When analysing the association between clinical, radiographic and demographic characteristics obtained during the first year with a large surgical intervention, we found less prognostic factors than when including all surgical interventions; these were at baseline, ESR and Thompson joint score; during the first year, ESR, radiographic progression and functional disability; and during the first 2 years, ESR, Thompson joint score, functional disability and radiographic progression.

Table 3 / Final models of three separate multivariate Cox regression analyses with increasing observation time to determine prognostic factors of joint surgery using data obtained at diagnosis, during the first year and during the first 2 years

	Baseline			**First year**			**First 2 years**		
	HR	*95% CI*	*p Value*	*HR*	*95% CI*	*p Value*	*HR*	*95% CI*	*p Value*
Randomisation, NSAID group v DMARD group	1.748	1.094 to 2.793	0.020	1.881	1.180 to 2998	0.008	1.938	1.200 to 3.130	0.007
Joint score, Thompson joint score	1.002	1.000 to 1.004	0.014						
Radiographic progression, Sharp–van der Heijde				1.018	1.006 to 1.030	0.003	1.035	1.017 to 1.053	<0.001

DMARD, disease-modifying antirheumatic drug; NSAID, non-steroidal anti-inflammatory drug.
A total of 438 patients were included in these analyses, as baseline radiographic or rheumatoid factor data were missing for 44 patients.

In the multivariate analyses, Thompson joint score at baseline and ESR measured over the first and first 2 years were the only prognostic factors associated with a large surgical intervention.

DISCUSSION

The percentage of patients needing a surgical intervention in the SRU was 27% and that of patients needing a major surgical intervention was 10%. Estimated mean survival time until the first surgical intervention was about 10 years. These data are in line with those of other studies, of which one was also carried out in an inception cohort,[2] which resembled our cohort.

In this study, we found that treatment with conventional DMARDs prevents surgery later on. This finding is in contrast with an older study in which treatment effect was investigated, and the use of DMARDs increased the risk for total joint replacement.[1] This contrast can be explained by the randomisation of patients to the DMARD group in our cohort irrespective of disease activity and the non-random design of the other study in which supposedly patients who did worse were treated with DMARDs—in other words, bias by indication. In general, it is to be expected that this effect of treatment on joint surgery will be more pronounced for the newer more intensive treatment strategies, including treatment

with biologicals, as it has already been shown that radiographic progression is for a major part inhibited or even halted by intensive treatment strategies.[16-23] In line with our previous findings that a good response to treatment predicts remission,[7] in the present study the response to treatment reduced the risk for joint surgery.

In univariate regression analyses the number and the predictive power of individual clinical variables became larger with longer observation time. Demographic factors were not predictive for joint surgery. High ESR and joint score were the only two clinical variables, which were identified as prognostic factors with increasing observation time in all three analyses. Both these clinical variables have also been found to predict joint surgery in many other studies,[1,2,6] and are also indicators for the development of radiographic damage.[24,25] Not radiographic damage at baseline, as seen in other studies,[1,2] but annual radiographic progression rate was a prognostic risk factor for surgical interventions in our study. Functional disability has often been found to be a predictor of an unfavourable outcome measure such as joint replacement,[1-3,6] mortality,[26,27] and work disability.[28] In this study, functional disability was associated with joint surgery only in the univariate analyses, but it was excluded from the final model in the multivariate analyses by treatment and by radiographic progression during the first 2 years. Unfortunately, we did not have data on human leucocyte antigen status, which was also found to be a predictor of joint surgery in previous studies.[2,29,30]

There might be some shortcomings in this study, especially with respect to collecting data on joint surgery. Some patients might have undergone joint surgery in another institution. To deal with this problem, all rheumatologists checked the list of interventions of their patients and, in addition, telephone calls were made to a random sample (n=30=5%) of all patients. Data retrieved from the medical records seemed reliable. Another bias might be the underlying reason for joint surgery. Primary osteoarthritis could have been an additional cause for joint surgery, but whether this was the primary indication for joint surgery could not always be confirmed from the medical record. In another inception report it was shown that after controlling for primary osteoarthritis age at onset became a weaker prognostic factor, whereas associations with variables of disease activity and joint surgery became

stronger.[2] Another drawback of the study might have been the discrepancy in follow-up time between the DMARD group (mean 7.1 years) and the NSAID group (8.4 years) because after 1994 all patients were randomised into one of the three treatment arms of the early start with DMARD group. However, when including data of only those patients who had been randomised between 1990 and 1994, the difference in percentage surgery between the NSAID and the DMARD groups remained significant (log rank test; p=0.017). Although all patients with recent onset of rheumatoid arthritis fulfilling the revised ACR criteria for rheumatoid arthritis had been asked to participate in the study on the effects of an early start with DMARDs versus a delayed start with DMARDs between 1990 and 1998, we included only those patients who were willing to participate in the randomised trial in this study in order to determine the effect of treatment. The non-randomised (n=62) group did not, however, differ from the randomised group with respect to percentage of patients (18%) undergoing surgical interventions (data not shown), and therefore the results of this study are representative of a population with rheumatoid arthritis fulfilling the ACR criteria and visiting an outpatient clinic in The Netherlands.

In conclusion, in our study 27% of 482 patients underwent joint surgery, of whom 10% had a large joint replacement after a mean disease duration of 7.2 years. Treatment with DMARDs immediately after diagnosis results in less joint surgery when compared with a delayed start. Other factors consistently predictive of joint surgery were ESR and joint score measured at baseline, and the annual radiographic progression rate. Furthermore, patients responding to treatment during the first 2 years need less surgery later on compared with patients not responding. This suggests that early intensive treatment can prevent joint surgery later on.

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DUTCH SUMMARY (NEDERLANDSE SAMENVATTING)

Dit proefschrift bespreekt de toepassing van glucocorticoïden (GC) in de behandeling van inflammatoire reumatische aandoeningen, voornamelijk in patiënten met reumatoïde artritis (RA). In deze samenvatting worden de bevindingen van de uitgevoerde studies beschreven en bediscussieerd.

X-as: effectiviteit

RA is een chronische ziekte die gekenmerkt wordt door ontstekingen van het synovium in gewrichten en komt bij ongeveer 1% van de bevolking voor. De gevolgen van deze aandoening, zoals het optreden op de lange termijn van irreversibele gewrichtsschade, kunnen ernstig zijn. Deze gewrichtsschade leidt vaak tot chirurgisch ingrijpen waarbij getracht wordt de functie van de gewrichten te handhaven en/of te herstellen. Een betere behandeling van RA met geneesmiddelen heeft geleid tot verbeterde symptomatische controle van de ziekte en verminderde gewrichtschade. Een klinisch relevant eindpunt om de effecten van 'antireumatica in engere zin', DMARDs (afkorting van 'disease-modifying antirheumatic drugs'), op gewrichtsschade te bestuderen, is gewrichtschirurgie. De studie in **bijlage A** toont aan dat 27% van alle RA patiënten binnen 10 jaar na diagnose, gewrichtschirurgie heeft ondergaan, 30% van deze chirurgische ingrepen waren vervangingen van het gewricht en de helft van de patiënten had meerdere chirurgische ingrepen. Verder laat dit onderzoek zien dat een vroege start met DMARDs na diagnose (vergeleken met een latere start), weinig radiologische schade en een goede respons op behandeling gedurende de eerste twee jaar van behandeling, geassocieerd zijn met minder gewrichtsvervangende chirurgie. Resultaten van studies als deze hebben ertoe geleid dat er wereldwijd, in de afgelopen decaden, onderzoek is gedaan naar de ontwikkeling van nieuwe behandelingstrategieën om RA beter te kunnen behandelen. Deze onderzoeken hebben geleid tot de eerste stap in behandelingen op maat voor individuele RA patiënten, het zogenoemde 'tight control' of 'treat-to-target'. Hierbij wordt binnen een kort tijdsbestek een lage ziekteactiviteit bereikt en om dit te bereiken worden behandel-combinatie strategieën gebruikt van meerdere DMARDs tegelijkertijd; GC zouden hiervoor een aantrekkelijke kandidaat kunnen zijn, door hun sterke onderdrukking van ontsteking zoals dit bij RA voorkomt. Vandaar dat in dit proefschrift de vraag werd gesteld: hoe worden GC gebruikt in de behandeling van RA, als co-medicatie naast DMARDs? Het thema 'X-as: effectiviteit' gaat in op de ziekte

modificerende eigenschappen van GC, indien gebruikt als toevoeging aan DMARDs, die leiden tot een optimale ziektecontrole van RA. **Hoofdstuk 2** geeft een volledig overzicht van de toepassingsmogelijkheden van GC binnen de behandeling van RA. De verschillende toepassingsmogelijkheden van GC worden samengevat, inclusief het gebruik van systemische en intra-articulaire GC als onderdeel van behandelcombinaties, als ook het gebruik van hoge GC doseringen als overbruggingstherapie. Combinatie therapieën van DMARDs met GC, in vergelijking met DMARDs niet gecombineerd met GC, werken niet alleen beter op korte termijn symptomen en functionaliteit, maar dragen ook bij aan een verminderde radiologische schade op de lange termijn. In een eerder uitgevoerde meta-analyse, waarin alle studies werden meegenomen die GC gebruik in RA patiënten met placebo of actieve controles met radiologische analyse als uitkomst maat vergeleken, werd een gestandaardiseerd gemiddeld verschil gevonden in progressie van 0.40, in het voordeel van behandelcombinaties met GC (95% betrouwbaarheidsinterval (BI) 0.26, 0.52); op deze wijze is onweerlegbaar vastgesteld dat GC DMARDs zijn. Een andere therapeutische toepassingsmogelijkheid van GC ligt in overbruggingstherapie. Verscheidene studies tonen aan dat door hun snelle klinische effecten, tijdelijke behandeling met matige tot hoge doseringen van GC therapieën dienst kan doen als overbruggingstherapie tussen behandeling met 2 verschillende soorten DMARDs; hiervoor worden vaak intramusculaire hoog gedoseerde GC, intraveneuze pulse GC, en subcutane Synacthen® depots gebruikt. Het kleine aantal studies dat overbruggingstherapie beschrijft wordt samengevat. Tenslotte wordt in dit deel het gebruik van intra-articulaire GC therapie beschreven. Deze toepassing ligt voornamelijk in lokale controle van mono-artritis in niet actieve RA, maar wordt ook toegepast als onderdeel in behandel-combinatie strategieën in actieve RA.

Y-as: toxiciteit

Het volgende thema in dit proefschrift betreft GC-toxiciteit. De hoofdstukken binnen dit thema behandelen twee van de meest bekendste bijwerkingen die geassocieerd zijn met het gebruik van GC, namelijk osteoporose en glucose intolerantie. Osteoporose is een frequent voorkomende comorbiditeit van reumatische aandoeningen; welke enerzijds veroorzaakt wordt door de aandoening zelf via zogenaamde pro-inflammatoire cytokinen en immobiliteit en anderzijds door de direct schadelijke effecten van GC op bot. Volgens de richtlijnen die tevens in dit proefschrift worden behandeld, wordt osteoporose voorkomen en behandeld door de inname van calcium en vitamine D, vaak in combinatie met biphosphonaten indien

er sprake is van langdurig GC gebruik. Van Biphosphonaten is in de 18 maanden durende Steroid Osteoporosis Prevention (STOP)-trial in patiënten met reumatische aandoeningen die met langdurig GC gebruik startten, aangetoond dat ze GC geïnduceerd bot verlies effectiever voorkwamen vergeleken met alfacalcidol (actief vitamine D). Op de lange termijn echter, kan alfacalcidol het risico op osteoporotische fracturen theoretisch doen afnemen door het verbeteren van de microarchitectuur van botten en de spierkracht en coördinatie van spieren, waardoor de kans op vallen afneemt. Als vervolgstudie op de STOP trial wordt in **hoofdstuk 3**, het lange termijn voorkomen en type van wervelfracturen na het gebruik van GC in patiënten met een inflammatoire reumatische ziekte beschreven. Patiënten met inflammatoire reumatische aandoeningen hadden gedurende een periode van 4,2 jaar na start van langdurige GC behandeling (18 maanden trial met 2,7 jaar follow-up), een incidentie van vertebrale fracturen volgens de Genant score van 28%. Gedurende de follow-up periode, waarin de osteoporose behandeling werd overgelaten aan de behandelende arts, ontwikkelde 28 (24%) van de patiënten een nieuwe vertebrale factuur. Van deze patiënten hadden twaalf patiënten milde (>20-25% vertebrale hoogte verlies), twaalf patiënten intermediaire (>25-40%) en vier patiënten ernstige (>40%) misvormingen op de röntgenfoto van de wervelkolom. Leeftijd en cumulatieve GC dosering waren geassocieerd met deze vertebrale fracturen in tegenstelling tot eerdere osteoporose behandeling met hetzij biphosphonaten (alendronaat) hetzij actief vitamine D (alfacalcidol). Hiermee werd een aanzienlijke comorbiditeit ten gevolge van osteoporose aangetoond in patiënten met reumatische aandoeningen die gedurende lange tijd met GC behandeld werden. Dit suggereert dat de positieve effecten van een vroege behandeling met alendronaat, c.q. alfacalcidol, bij osteoporose teniet gedaan worden indien er geen strikte continuatie is van een intensieve osteoporose behandeling.

Alfacalcidol is naast zijn positieve effecten op het bot, ook geassocieerd met anti-inflammatoire effecten. Ontstekingen en botmetabolisme delen een gezamenlijk mechanisme (‘osteoimmunity’), dat door zowel GC als vitamine D beïnvloed kan worden. Tot nu toe zijn er verscheidene cytokine *pathways* geïdentificeerd die een rol spelen, waarbij speciale interesse is in het pro-inflammatoire cytokine macrofaag migratie- remmende factor (MIF). MIF is een cytokine dat de unieke eigenschap heeft om de effecten van GC te remmen. Daarnaast reguleert MIF, door remming van bot resorptie in bepaalde situaties, mogelijk bot metabolisme. De relatie tussen MIF en bot metabolisme in patiënten met reumatische aandoeningen die langdurig GC gebruiken is beschreven in **hoofdstuk 4**. In een subanalyse

van de STOP trial zijn cytokine profielen gemeten van 20 alfacalcidol gebruikende RA patiënten en van 20 alendronaat gebruikende RA patiënten. Tussen beide groepen bleek er geen verschil in MIF spiegels te zijn, waarschijnlijk door de remmende eigenschappen van GC. Toename in MIF spiegels was echter geassocieerd met een toename in bot mineraal dichtheid (beta = 0.02; 95% BI 0.004 to 0.04), gecorrigeerd voor effect van alfacalcidol, leeftijd, geslacht en cumulatieve GC dosering. Aangezien MIF een bekende antagonist is van GC, kan deze uitkomst mogelijk betekenen dat MIF botbeschermende eigenschappen heeft door het voorkomen (of tegenwerken) van GC geïnduceerde bot afbraak. Toekomstige studies zijn nodig voor verdere bevestiging van deze eigenschappen van MIF.

Glucose tolerantie en met name de vraag of RA invloed heeft op glucose metabolisme en indien dat zo is, wat dan de invloed is van chronisch GC gebruik op deze interactie, is het volgende onderwerp. **Hoofdstuk 5** beschrijft onderzoek naar glucose opname en insuline uitscheiding. Dit is gedaan door het vergelijken van glucose en insuline spiegels in frequent verzamelde orale glucose tolerantie testen (OGTTs) van zowel GC naïve RA patiënten als in RA patiënten die reeds lang GC gebruikten en in controles. De prevalentie van vastgestelde type 2 diabetes mellitus (T2DM) was voorafgaand aan de studie in beide RA groepen 8%; terwijl T2DM in 11% van alle RA patiënten tijdens de studie werd vastgesteld: 14% hiervan in de GC groep versus 9% in de GC naïve groep, p=0.3. RA patiënten waren, vergeleken met de controles, minder gevoelig voor insuline en hadden meer beta-cel dysfunctie. GC gebruikende patiënten verschilden niet in glucose metabolisme van niet-GC gebruikende patiënten. Bij hoge cumulatieve doseringen van GC werd wel een associatie gevonden, indien gecorrigeerd voor patiënt eigenschappen (leeftijd, geslacht, body mass index (BMI) en taille omtrek) en ziekte gerelateerde eigenschappen (ziekte-activiteit ‘disease activity score 28 (DAS28)’, erosies van handen en voeten, gebruik van DMARDs in de voorgeschiedens) met het ontstaan van T2DM (p=0.04). Alhoewel ‘confounding by indication’ van GC therapie op glucose metabolisme, waarbij GC therapie voornamelijk wordt voorgeschreven bij RA patiënten met ernstiger ziekte, door deze retrospectieve studie niet kan worden opgelost, wijzen de uitkomsten van deze studie naar een ziekte activiteit gerelateerde metabolische invloed van RA op glucose intolerantie en lijkt het de associatie tussen hoge cumulatieve doseringen van GC en glucose intolerantie te bevestigen.

Z-as: veiligheid

Het laatste thema van dit proefschrift betreft veiligheid gedurende GC behandeling, met andere woorden de balans vinden tussen effectiviteit en toxiciteit zoals beschreven in de vorige thema's. **Hoofdstuk 6** beschrijft een uitgevoerde meta-analyse op het voorkomen en het profiel van bijwerkingen in reumatische aandoeningen en in inflammatoire darmziekte. In deze meta-analyse werden longitudinale studies van tenminste 1 maand met lage tot middel hoge GC doseringen (tot maximaal een equivalent van 30mg prednison dagelijks) en waarbij bijwerkingen dichotoom werden vermeld meegenomen. Het risico op bijwerkingen bedroeg 43 per 100 patiëntjaren (95% BI 30 – 55) in 14 studies met 796 RA patiënten, 80 per 100 patiëntjaren (95% BI 15 – 146) in 4 studies met 167 polymyalgia reumatica patiënten en 555 per 100 patiëntjaren (95% BI 391 – 718) in 10 studies met 1419 patiënten met inflammatoire darmziekte. Studies van hoge kwaliteit, zoals in inflammatoire darmziekte, met een korte follow-up (tot maximaal 6 maanden) rapporteerden een hoog voorkomen van bijwerkingen. Verder werden in deze studies voornamelijk gastro-intestinale bijwerkingen gerapporteerd, wat waarschijnlijk duidt op actieve ziekte. Opmerkelijk was dat in RA patiënten psychologische bijwerkingen, voornamelijk kleine stemmingswisselingen, het meest gerapporteerd werden (19 per 100 patiëntjaren; 95% BI 4 – 34). De vele verschillen in studie opzet bemoeilijkten een directe vergelijking tussen patiënten met verschillende aandoeningen wat betreft GC gerelateerde bijwerkingen.

De zojuist beschreven meta-analyse heeft gediend om een EULAR taskforce over GC te informeren op het spectrum van bijwerkingen zoals die gerapporteerd zijn in studies naar GC gebruik. Deze taskforce heeft o.a. aanbevelingen geformuleerd op het gebied van veiligheid die een reumatoloog in acht dient te nemen wanneer deze een patiënt behandelt met lage tot middelhoge doseringen van GC (**hoofdstuk 7)**. Door een combinatie van systematisch verkregen literatuur en expert consensus, hetgeen bereikt werd door gebruik te maken van de Delphi methode, zijn tien aanbevelingen gegenereerd. Hierin worden patiënteducatie en adequate evaluatie van co-morbiditeit en risico factoren voor het optreden van bijwerkingen bij start van de behandeling, alsook het monitoren hiervan gedurende behandeling, benadrukt. Vooral bij langdurig GC gebruik wordt de laagst mogelijke (doch effectieve) dosering geadviseerd en ook preventieve therapieën tegen GC geïnduceerde co-morbiditeit, zoals osteoporose en ulcus pepticum bij gelijktijdig gebruik van niet-steroïde ontstekingsremmende pijnstillers. Ook worden veiligheidskwesties zoals peri-operatieve GC

substitutie therapie behandeld en tot slot worden belangrijke gebieden geïdentificeerd die verder onderzoek nodig hebben, zoals cardiovasculair risico tijdens het gebruik van GC.

Algemene conclusie: De coherente driehoek

In dit proefschrift wordt beschreven dat laag tot middelhoge GC een plaats hebben in moderne behandelstrategieën van RA; omdat zij effectieve DMARDs zijn. Echter, een onverenigbare situatie ontstaat indien toxiciteit van GC over hun effectiviteit domineert, zoals in het geval van gebruik van hoge cumulatieve doseringen van GC. Bij patiënten die chronisch GC gebruiken, komen wervelfrakturen en verstoorde glucose tolerantie veel voor. Deze wervelfracturen zijn geassocieerd met cumulatief GC dosering en ook insuline sensitiviteit en beta-cel functie worden verstoord door cumulatieve dosering van GC. Het is echter nog steeds niet duidelijk in welke mate dit direct door GC en in welke mate door de ziekte RA zelf wordt veroorzaakt. Daarom zal toekomstig onderzoek zich meer moeten richten op de basale mechanismen van GC gerelateerde osteoporose en glucose intolerantie; bijvoorbeeld de rol van het cytokine MIF binnen osteo-immuniteit. In dit proefschrift werd aangetoond dat verschil in MIF concentraties waren geassocieerd met die in bot mineraal dichtheid waarden.

De onverenigbare situatie die ontstaat bij het gebruik van hoge (cumulatieve) dosering GC, heeft het gebruik van GC gestigmatiseerd, hetgeen onnodig is wanneer veiligheid voldoende in acht wordt genomen tijdens het gebruik van GC. Immers, de bijwerkingen die worden beschreven in longitudinale studies met laag tot middelhoge GC, kunnen worden voorkomen of behandeld indien EULAR richtlijnen in acht worden gehouden. In dit proefschrift wordt beschreven hoe de drie dimensies die een rol spelen bij het gebruik van GC met elkaar een figuur kunnen vormen; wanneer tijdens het gebruik van GC effectiviteit, toxiciteit en veiligheid - in balans zijn, dan ontstaat er een harmonieuze situatie: Een coherente driehoek.

Toekomstig onderzoek naar GC dient bij voorkeur te geschieden middels gerandomiseerde studies met longitudinale metingen in patiënten die langdurig met GC worden behandeld. Ook moet in dergelijke studies voldoende aandacht zijn voor cardiovasculaire bijwerkingen van GC. In het geval van langdurig gebruik van GC en zolang er nog vraagtekens bestaan over de toxiciteit van GC versus hun effectiviteit, dient veiligheid een prominente rol te spelen bij het gebruik ervan.

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no parque sem destino, os melhores dias em casa a cozinhar waffles, as melhores voltas de bicicleta, as melhores conversas em restaurantes de tapas, os melhores dias de cafezinho, os melhores dias do terrível gato Tigre Pampus, mas acima de tudo têm sido anos de amor intenso. Eu aprendi contigo coisas muito significativas, como a importância de comprar computadores Apple e a edição especial da colecção remasterizada dos Beatles, de ver várias e repetidas vezes a 2ª parte do Senhor dos Anéis. A tua capacidade de fazeres várias coisas ao mesmo tempo (o PhD, limpar a casa, praticar desporto 3 vezes por semana, costurar, tocar flauta, ir às compras, ir ter com os amigos, ler muitos livros, etc...) continua a surpreender-me e completa-me na totalidade... Estou ansioso que chegue Junho para segurar a nossa "pequenina" nos braços, que esperemos que seja muito parecida contigo - a minha 'brown eyed girl' -; e aguardo com alegria pelas aventuras que vamos encontrar no futuro, esperando que muitas delas sejam no teu (ou poderei dizer "nosso") Portugal?!

CURRICULUM VITAE

Josephus Nicolaas (Jos) Hoes was born on the 21st of August in 1980 in Alphen aan den Rijn, the Netherlands. In 1998 he finished secondary school (gymnasium) at the Petrus Canisius College in Alkmaar.

He obtained his Bachelor of Science degree (major Life Science) at University College Utrecht (University of Utrecht) in May 2001. During his stay at the campus of UCU he co-founded the fraternity Primus (Disputum Primus Erectus est. 1998) of which he was (proud to be) made honorable member in 2008.

In November 2006 Jos obtained his Medical Doctor degree at the University of Utrecht. During his studies the basis for this thesis was founded. A meta-analysis was performed during an internship at the departments of Rheumatology & Clinical Immunology and the Julius Center for primary care, University Medical Center Utrecht (UMCU); under supervision of dr. G.J.M.G. van der Heijden, MD, PhD and dr. S.M.M. Verstappen, PhD, next to prof. J.W.J. Bijlsma, MD, PhD and J.W.G. Jacobs, MD, PhD. This work served as introduction for the EULAR taskforce on glucocorticoids, in which he took part as fellow during the formulation of recommendations on the safe use of systemic glucocorticoids in the rheumatic diseases; under supervision of J.W.G. Jacobs, MD, PhD and prof. J.W.J. Bijlsma, MD, PhD.

In December 2006 he performed further research for this thesis as a research-physician at the department of Rheumatology & Clinical Immunology of the UMCU; part of this research was in collaboration with the departments of Rheumatology and Endocrinology of the VUMC as part of the Top Institute Pharma (project T1-106) and another part was in collaboration with the Steroid Osteoporosis Prevention study group. From May 2008 until January 2010 he was a trainee of internal medicine at the Diakonessenhuis Utrecht (supervisors A.F. Muller, MD, PhD and W.N. Hustinx, MD, PhD), and from January 2010 until January 2011 he finished this thesis at the department of Rheumatology & Clinical Immunology of the UMCU. All but one (pending) of the articles in his thesis have been published in peer-reviewed journals.

Since January 2011 he continues his training in internal medicine (supervisors prof. E.W. Ter Braak, MD, PhD and prof. M.M. Schneider, MD, PhD), to be followed by a rheumatology traineeship (supervisor prof. J.W.J. Bijlsma, MD PhD).

Since May 2009 he is happily married to Joëlle Hoebert; the couple expects their first child mid-2011.

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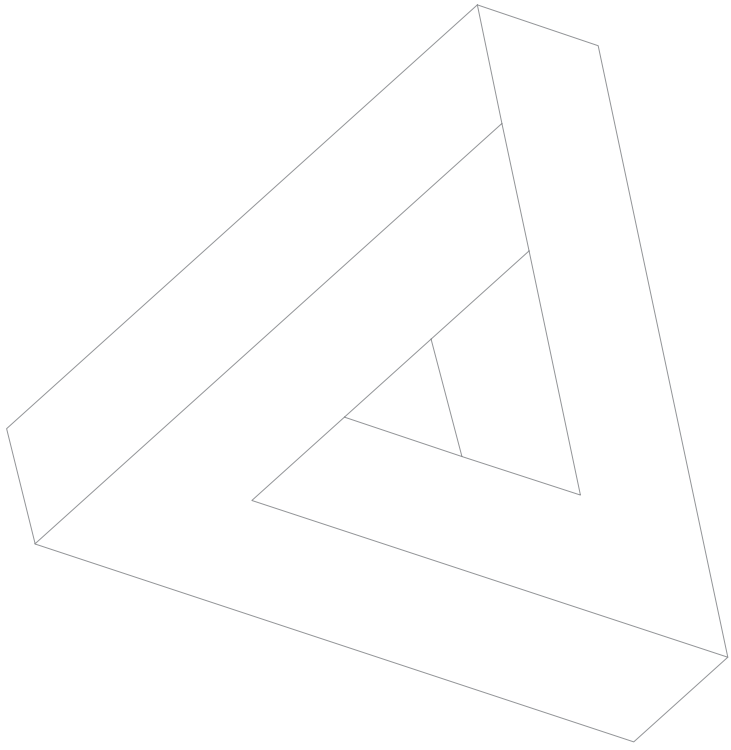

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