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## Glucocorticosteroids in the management of rheumatoid arthritis

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### Abstract

Glucocorticosteroids are used frequently in the management of patients with rheumatoid arthritis. Data supporting their efficacy and safety are still meagre. Glucocorticosteroids may be used systemically with different routes of administration (oral, i.m. and i.v.), in different doses and for different periods of time. The effectiveness of glucocorticosteroids in reducing inflammation in the short term has been shown for oral treatment in a dose of 7.5 mg prednisolone daily or more, for i.m. pulses (120 mg methylprednisolone every 4 weeks) and for i.v. methylprednisolone pulses. For longer periods of treatment, the evidence suggesting effectiveness of low-dose oral glucocorticosteroids is more limited. Some data suggest that different regimens of glucocorticosteroids may retard the development of erosions in patients with rheumatoid arthritis. The toxicity of short-term treatment is relatively low. For long-term treatment, the development of osteoporosis is a serious problem. Concomitant therapy with either calcitriol or bisphosphonates may reduce this risk.

KEY WORDS: Glucocorticosteroids, Rheumatoid arthritis, Mode of action, Joint damage, Toxicity.

A previous contribution to the disease-modifying drugs series in this journal, addressing the use of methotrexate in rheumatoid arthritis (RA), notes in its introduction the wealth of articles on this subject in the recent literature [1]. For glucocorticosteroids, the situation is rather different. In a recent meta-analysis studying their moderate-term effectiveness, only nine studies could be included: four comparing glucocorticosteroids to placebo and five to other active drugs, the authors being unable to evaluate radiographic outcomes [2]. This paper attempts to summarize the effects of glucocorticosteroids on disease activity and on the progression of joint damage in RA. Some emphasis will be given to the most recent contributions to the literature [3, 4]. The toxicity of glucocorticosteroids will also be discussed briefly.

### Mode of action of glucocorticosteroids

Comprehensive reviews have been published on this topic [5]. The basic mechanism of action involves passive diffusion of free circulating glucocorticosteroids through the plasma membrane and subsequent binding to specific intracellular cytoplasmic receptors, which are present in

all cell types. The activated hormone–receptor complex is bound to specific sites within DNA in the nucleus, causing modulation of specific genes.

Favourable effects of glucocorticosteroids in patients with rheumatoid arthritis may be explained either by their general anti-inflammatory and immunomodulatory effects or, hypothetically, by more disease-specific mechanisms.

#### *General effects [5]*

Glucocorticosteroids have effects on different cell types involved in the inflammatory process. Proliferation, differentiation, and function of macrophages and fibroblasts are inhibited by glucocorticosteroids. Effects include the inhibition of the production and release of cytokines such as interleukin-1, interleukin-6 and tumour necrosis factor alpha. They also influence the production of arachidonic acid metabolites, including both prostaglandins and leukotrienes. Induction of inhibitors of phospholipase A2, like lipocortin, may be central to this effect. They also decrease expression of cyclooxygenase type 2. Glucocorticosteroids further inhibit many pro-inflammatory responses of endothelial cells.

Treatment with glucocorticosteroids causes redistribution of lymphocytes, resulting in circulating lymphopenia. In addition, they inhibit the generation, proliferation and activation of T cells by multiple

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mechanisms. B cells and plasma cells are less affected, high doses of glucocorticosteroids being necessary for suppression of immunoglobulin production.

#### Disease-specific effects

Chikanza *et al.* [6] have found that the hypothalamic–pituitary–adrenal axis of patients with RA responds less to surgical stress than that in patients with osteoarthritis or osteomyelitis. The numbers studied so far have been few. Their results suggests that patients with RA may have a defective hypothalamic regulation of the pituitary–adrenal axis. As a consequence, these patients could be more prone to develop chronic arthritis. These interesting data have as yet not been confirmed by others [7].

### How are glucocorticosteroids used in rheumatoid arthritis?

Over the years, glucocorticosteroids have been employed in several ways. In this paper, the intra-articular use of glucocorticosteroids is not discussed. For the systemic use of these drugs, different regimens can be classified according to the route of administration, the dose used and the expected duration of treatment (Table 1). Glucocorticosteroids are used either as a single agent or in combination with other anti-rheumatic drugs. In short-term (duration of use <1 yr) regimens, treatment is often aimed at controlling symptoms in periods of high disease activity either with unchanged background anti-rheumatic therapy or while awaiting the effects of newly started other disease-modifying drugs. This kind of use is commonly referred to as bridge therapy. In patients in whom other drugs have failed to control the arthritic symptoms sufficiently, due to inadequate efficacy or to the occurrence of side-effects, glucocorticosteroids are used for prolonged periods of time. Glucocorticosteroids may also be prescribed specifically to prevent progression of joint damage as assessed by radiological scores. In the recent literature, two different approaches have been presented. Kirwan [3] proposed long-term treatment with low-dose oral glucocorticosteroids in addition to other anti-rheumatic treatments. Boers *et al.* [4] have studied the effects of intensive early combination therapy including short-term high-dose glucocorticosteroids.

TABLE 1. Studies on the use of glucocorticosteroids in rheumatoid arthritis\*

Duration of treatment	Route of administration			
	Oral		Intramuscular	Intravenous
	Low dose†	High dose†		
<1 yr	[9, 10]	[4]	[19, 20]	[21–36]
≥1 yr	[3, 11–18]			

\*Details of these studies are mentioned in the text.

†Low dose defined as 15 mg/day prednisolone equivalent or less.

### Effects on disease activity

#### Oral glucocorticosteroids

*Short-term use.* Recently, two meta-analyses of the effectiveness of low-dose glucocorticosteroids have been published [2, 8]. One of them addresses the short-term (1–2 weeks) efficacy of low-dose prednisone in RA [8]. The authors conclude that prednisolone has a marked symptomatic effect when used in doses of 15 mg daily or less. Saag *et al.* [2] studied the intermediate term (3 months or longer) efficacy. The results indicate that glucocorticosteroids, in doses equivalent to up to 15 mg/day prednisolone and in the first 6 months of their use, are more effective than placebo in improving the number of tender and swollen joints and the erythrocyte sedimentation rate. The size of the effect seems to be similar to that of traditional second-line agents. However, the small number of studies that could be included in the meta-analysis, the small number of patients included in most studies, and differences between these studies with respect to the precise dose used, limit the conclusions that can be drawn from this meta-analysis.

The use of oral low-dose glucocorticosteroids as bridge therapy has been studied in only two placebo-controlled trials, which together represent a major part of the intermediate term meta-analysis mentioned above [9, 10]. Harris *et al.* [9] added prednisone (5 mg/day) to other drugs including non-steroidal anti-inflammatory drugs and constant doses of gold salts or penicillamine over 24 weeks. Nearly all variables related to disease activity failed to show a significant difference between the prednisone ( $n = 18$ ) and placebo ( $n = 16$ ) treated patients. After abrupt cessation of prednisone at week 24, disease activity markedly exacerbated, inflammation being significantly worse in the prednisone group at week 36. The efficacy of 10 mg/day prednisone was studied in 40 patients who started treatment with i.m. gold salts by van Gestel *et al.* [10]. Rapid improvement was observed in the prednisone-treated patients ( $n = 20$ ), the difference with the placebo-treated patients ( $n = 20$ ) already being significant after 1 week. Responses to prednisone were noticed in 60% of patients only. After gradual tapering of prednisone, a rebound deterioration was observed in the majority of the responders.

A much larger ( $n = 155$ ) double-blind randomized trial was recently published by Boers *et al.* [4]. They compared the combination of sulphasalazine (2 g/day), methotrexate (7.5 mg/week) and high-dose prednisolone with sulphasalazine alone. The daily prednisolone dose was 60 mg in week 1, 40 mg in week 2, 25 mg in week 3, 20 mg in week 4, 15 mg in week 5, 10 mg in week 6 and 7.5 mg thereafter. The glucocorticosteroids were gradually withdrawn between week 28 and week 35. Methotrexate was gradually withdrawn between week 40 and week 46. Rapid improvement of disease activity was seen in the combination therapy prednisolone-treated patients who had a clear advantage over the single treatment group. This advantage was lost after

withdrawal of the glucocorticosteroids. The magnitude of the effect was greater than in the study by van Gestel *et al.* [10] who did not initially use high-dose glucocorticosteroids. With similar baseline values, the combined disease activity score (DAS) improved with 2.1 at week 28 in the high-dose study and with 1.6 at week 12 in the low-dose study. Responses to the combined treatment were observed in 72% of patients. Flares after withdrawal of glucocorticosteroids were less of a problem than in previous studies.

*Long-term use: glucocorticosteroids as a single agent.* Soon after the introduction of glucocorticosteroids in the treatment of rheumatoid arthritis, large randomized trials were performed by the Empire Rheumatism Council (ERC) and the Medical Research Council (MRC) in co-operation with the Nuffield Foundation [11–15]. The trials were designed to compare the effects of glucocorticosteroids with those of aspirin. In the initial trials, cortisone was used in doses equivalent to ~15 mg prednisolone daily. The ERC trial included patients with variable disease duration [11, 12], while the MRC trial involved patients with early disease [13–15]. These early studies were unable to show clear benefits of glucocorticosteroids over aspirin in the long term, although initial responses were better in the cortisone-treated patients. A study initiated some years later also in patients with early disease used prednisolone in a comparison with aspirin or phenylbutazone. Prednisolone was started at 20 mg/day and gradually tapered to 10 mg/day after 2 and 3 yr [16, 17]. The prednisolone-treated patients experienced a rapid improvement both in clinical and biochemical indices of disease activity, which was statistically significantly better than in the aspirin or phenylbutazone group. The improvement was maintained in the long term.

More recently, Van Schaardenburg *et al.* [18] compared disease activity in 28 active elderly-onset RA patients treated with prednisone (15 mg daily during 1 month, followed by a tapering scheme according to clinical success) with 28 patients receiving chloroquine in a prospective randomized study with a follow-up of 2 yr. Functional capacity and disease activity improved significantly, but similarly in both groups, except for a greater improvement in the corticosteroid group at 1 month. Other disease-modifying anti-rheumatic drugs, however, were warranted in 43% of the chloroquine- vs 29% of the corticosteroid-treated group.

*Long-term use: glucocorticosteroids in combination with other second-line drugs.* Kirwan [3] recently published a double-blind randomized trial in which a comparison was made of the addition of prednisolone (7.5 mg daily) or placebo to other anti-rheumatic treatments in 128 early RA patients. Primary outcome variables were related to radiological joint damage scores and will be discussed later. Secondary outcomes included disease activity variables and functional capacity. After 3 months, the patients in the prednisolone group had greater reductions in an articular index (accounting for both tender and swollen joints), pain and disability, but not in the acute-phase response. In the remainder

of the follow-up of 2 yr, these advantages gradually disappeared.

*Minimally effective dose?* The dose–response relationship has not been studied well for oral glucocorticosteroids. Combining the results from various studies suggests that the minimally effective dose lies somewhere between 5 and 10 mg prednisolone daily [3, 4, 9, 10]. Individual patients may, of course, respond to lower doses or be in need of higher doses.

#### *Intramuscular glucocorticosteroids*

Intramuscular methylprednisolone pulse treatment (120 mg three times at 4-weekly intervals) has been shown to be an effective bridge therapy when initiating chrysotherapy [19]. An advantage of this regimen over the oral equivalent already discussed before [10] is the lack of a rebound deterioration. This is probably due to the slow fall in serum levels by using an i.m. depot regimen. No clear advantage of a similar treatment could be shown in the initial phase of sulphasalazine treatment [20]. The reason for the apparent discrepancy between the responses to i.m. methylprednisolone pulses in patients starting gold salts or sulphasalazine has not been clarified. Possibly, glucocorticosteroids may interfere with the efficacy in the initial phase of sulphasalazine treatment. Bridge therapy with i.m. glucocorticosteroids has not been studied with other second-line anti-rheumatic drugs.

#### *Intravenous glucocorticosteroids*

Various regimens of i.v. methylprednisolone pulse treatments have been published in the past two decades and this topic has been reviewed recently [21]. Doses in the different studies vary between 40 and 1000 mg. Some have studied the effects of a single infusion, while others have employed repeated administrations (three on consecutive days, three on alternate days or monthly for 6 months). All studies have involved only relatively small numbers of patients [22–36]. In general, these studies have shown beneficial effects on disease activity parameters including both clinical and biochemical variables related to the acute-phase response. Sustained responses have been observed in some patients, especially for the clinical variables. The optimal dose has not been established. In some but not all studies, higher doses seem to be more effective than lower doses. Successful bridge regimens involving three infusions of 1000 mg methylprednisolone on alternate days have been reported with concomitant start of D-penicillamine or sulphasalazine [25] and i.m. gold salts [31], but not with azathioprine [26]. Lower doses of i.v. methylprednisolone pulses may not be effective as bridge therapy [34, 36].

### Effects on joint damage

#### *Long-term low-dose oral glucocorticosteroids*

As mentioned earlier, Kirwan [3] recently reported the results of a double-blind randomized trial that evaluated primarily the effects of a fixed dose of 7.5 mg prednisolone daily in addition to other anti-rheumatic drugs on the progression of joint damage. The trial was designed

after re-evaluation of the earlier ERC and MRC trials [37]. Although not generally recognized at the time of publication, the earlier prednisolone trial [16, 17] seemed to suggest that glucocorticosteroids could retard structural joint damage as assessed by radiological scores. Kirwan included 128 patients with early disease in the study. The Larsen score was used to evaluate the progression of joint damage in the hands after 1 and 2 yr. Two primary end points were defined: the mean progression in the (log-transformed) Larsen scores and the development of erosions on hands that had no erosions at baseline. After 2 yr, the Larsen score increased by a mean of 0.72 unit in the prednisolone group and by 5.37 units in the placebo group ( $P = 0.004$  for the difference between the two groups). In the prednisolone group, erosions developed in 22.1% of initially normal hands, and in 45.6% in the placebo group ( $P = 0.007$ ). The authors conclude that in patients with early active RA, prednisolone (7.5 mg daily) given for 2 yr reduces the rate of radiologically detected progression of disease, despite the lack of a sustained effect on indices of disease activity. In our view, the findings of this study are certainly very interesting. Some points of concern, however, need to be expressed. Firstly, the data collection in this trial was incomplete and the conclusions are based on only ~80% of the randomized patients. Secondly, the placebo group included patients with more severe disease according to several baseline characteristics. Although the differences between the two groups were not statistically significant, an influence on the results cannot be excluded. Thirdly, we find it difficult to interpret the second primary end point in a clinically meaningful way. In this study, one patient can be part of two groups at the same time: one hand developing erosions and the other not! It would have been more relevant to evaluate the proportion of patients who had become erosive instead of the proportion of hands. In this issue, Hickling *et al.* [38] present the data of an additional follow-up study of 1 yr after discontinuation of prednisolone or placebo in a double-blinded fashion. Unfortunately, adjustments had to be made to the raw data, as changes in reader sensitivity had occurred in comparison with the original trial [3]. Surprisingly, more correction was needed for the placebo than the prednisolone group. The mean Larsen score increased both after discontinuation of placebo and prednisolone. However, the advantage of the prednisolone-treated patients over the placebo group was maintained 1 yr after discontinuation of the drug. Because of the methodological issues that we mentioned in relation to both studies, firm conclusions cannot be reached. Although promising, the results need to be confirmed in another study before we can recommend long-term treatment with a fixed dose of prednisolone for all patients with early, active RA.

#### *Short-term high-dose oral glucocorticosteroids*

The design of the study by Boers *et al.* [4] comparing combined step-down high-dose prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in

early RA has already been described in an earlier section of this paper where we discussed the effects of this combination treatment on indices of disease activity. Radiological scores on the progression of joint damage were included in the secondary end points of this trial. Radiographs of hands and feet were scored for joint space narrowing and erosions according to van der Heijden's modification of Sharp's method. The authors report the median and ranges of progression of the scores after 28, 56 and 80 weeks. After 80 weeks, progression scores could be calculated for 121 of 155 randomized patients. In the combined treatment group, the progression of erosions was less than in the sulphasalazine alone group. At week 80, the median total progression score was 4 in the combined treatment group and 12 in the sulphasalazine alone group ( $P = 0.01$ ). Differences in scores for erosions were more marked than for joint space narrowing. The results of this study seem to suggest that the combination used (initial high-dose prednisolone, methotrexate and sulphasalazine) is associated with less progression of joint damage than treatment with sulphasalazine alone, although again conclusions are based on only ~80% of randomized patients. This beneficial effect may be due to either the addition of methotrexate, of prednisolone or the combination of both to sulphasalazine. Circumstantial evidence suggests that the inclusion of prednisolone in this treatment regimen is the most important factor. First, the clinical advantages experienced by the patients in the combination treatment group disappeared after the gradual discontinuation of prednisolone. Second, other studies evaluating the potential advantages of the combination of sulphasalazine and methotrexate in early RA do not suggest an important beneficial effect of this combination on the progression of joint damage [39].

#### Toxicity of glucocorticosteroids

The toxicity of glucocorticosteroids is well known. In general, adverse effects are more frequent and more severe with higher doses and with longer periods of treatment.

##### *Toxicity in general*

The relative safety of low-dose glucocorticosteroid treatment was documented in a well-written review by Caldwell and Furst in 1991 [40]. They distinguish between adverse effects that probably occur only with high-dose (>10 mg prednisolone daily) glucocorticosteroids and adverse effects that definitely or probably occur also with low-dose treatment. A slightly adapted summarizing table is presented here (Table 2). Short-term, high-dose glucocorticosteroid treatment, as studied by Boers *et al.*, may also be relatively safe. The 76 patients who used high doses of prednisolone in their study experienced no serious side-effects [4]. In a retrospective study of 50 patients given 1000 mg methylprednisolone i.v. pulse therapy on three alternate days, frequent (>5 patients) short-term complications were: rise in diastolic blood pressure (>10 mmHg), hyper-

TABLE 2. Toxicity of glucocorticosteroids<sup>a</sup>

Organ system	Dose <sup>b</sup>		
	Probably with high dose only	With high and low dose	
		Probably	Definitely
General	Infections		Weight gain Redistribution of body fat Moon face
Musculoskeletal	Osteonecrosis	Osteoporosis Myopathy Withdrawal symptoms Peptic ulcer <sup>c</sup>	
Gastrointestinal	Pancreatitis Bowel rupture Diverticular rupture		
Cardiovascular	Hypertension Lipoprotein abnormalities Atherosclerosis		
Reproductive	Fetal wastage Fetal malformation		
Neurological	Psychoses		
Eye			Cataracts Glaucoma
Cutaneous	Delayed wound healing		Acne Hirsutism Purpura Skin atrophy Spontaneous skin tearing
Endocrine		HPA dysfunction	Diabetes mellitus

<sup>a</sup>Adapted from Caldwell and Furst [40].

<sup>b</sup>Low dose defined as 10 mg prednisolone daily or less.

<sup>c</sup>Especially in combination with non-steroidal anti-inflammatory drugs.

glycaemia or glycosuria, facial flushing, headache, bitter taste, vertigo, palpitations or tachycardia. In these patients, possible long-term complications that were not infrequently seen were peptic ulceration, moon face, cataract, osteoporosis, purpura and skin atrophy, presenting within a mean follow-up of 3.8 yr. Many of these patients received more than one i.v. methylprednisolone pulse, while the majority were also on oral prednisone. Therefore, it remains difficult to attribute these complications to i.v. pulses that sometimes had been given years previously [21].

#### *Glucocorticosteroid-induced osteoporosis*

Whether low-dose glucocorticosteroid treatment is associated with increased bone loss and the development of osteoporosis has been much debated. Two recent articles illustrate the controversy nicely. In their review, Deodhar and Woolf [41] conclude that the use of oral glucocorticosteroids in a dose of 5 mg prednisone daily or more is a risk factor for the development of osteoporosis in RA. In contrast, Verhoeven and Boers [42], in their meta-analysis, conclude that the use of glucocorticosteroids by RA patients is probably not associated with clinically important bone loss. Certainly, this topic remains controversial. At this moment, there is still only one double-blind randomized trial that evaluates the effects on bone mineral density of unopposed glucocorticosteroid treatment in patients with active RA. After 20 weeks treatment with initially 10 mg prednisone and without concomitant calcium supplementation or other

bone-active drugs, bone mineral density decreased substantially. The effects on bone were present despite beneficial effects on functional capacity. After discontinuation of the glucocorticosteroid treatment, this negative effect appeared to be reversible for the greatest part [43]. Reversibility of glucocorticosteroid-induced bone loss has also been demonstrated after cure of Cushing's syndrome or disease [44]. Other recent studies which used calcium supplements in the glucocorticosteroid-treated patients have not shown similar deleterious effects, even with initially higher dosed regimens [4, 18]. All studies have limited themselves to relatively short-term studies. The long-term effects of prolonged (low-dose) glucocorticosteroid treatment are not and probably will not be studied in randomized trials. The available data from other types of studies indicate that long-term low-dose use of glucocorticosteroids is probably associated with an increased risk of osteoporosis and related fractures [41, 45].

Several drugs are available to prevent glucocorticosteroid-induced bone loss. Calcitriol and cyclical etidronate have been proven effective in double-blind randomized controlled trials [46–49]. More data on different bisphosphonates may be expected shortly. The best strategy for employing these drugs remains to be determined, however.

#### Conclusions

Oral glucocorticosteroids in doses of 7.5 mg prednisolone daily or more effectively reduce disease activity in

patients with RA in the short term. The effectiveness is more dubious when treatment periods are prolonged over 1 yr. The need to use much higher doses of glucocorticosteroids has not been demonstrated. Initial high doses may be more effective than standard low-dose regimens. However, the dose-response relationship needs to be documented better. Alternatives for oral treatment may be i.m. methylprednisolone pulses, which have been demonstrated to be effective as bridge therapy when starting i.m. gold salts, and i.v. methylprednisolone pulses, which should probably be reserved for patients refractory to other treatments.

Evidence for a disease-modifying role of glucocorticosteroids is limited. One study suggests that a fixed dose of 7.5 mg prednisolone daily, added to other anti-rheumatic treatment, may retard the development of erosions. Another study suggests a beneficial effect of a combination treatment including a short course of initially 60 mg prednisolone daily. Toxicity of short-term treatments is very limited. In clinical practice, however, many patients use glucocorticosteroids for prolonged periods of time. The development of osteoporosis is one of the main concerns. The availability of bone-active drugs like calcitriol and bisphosphonates increases the opportunities to treat these patients more safely.

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