AN UPDATE OF GLUCOCORTICOID THERAPY IN RHEUMATOID ARTHRITIS: DO BENEFITS OUTWEIGH THE RISKS?

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ABSTRACT

To use glucocorticoids prudently, it is important to weigh their risks and benefits. Some developments in the past decades have favored the use of low-dose glucocorticoids in rheumatoid arthritis. Firstly, the better handling of adverse effects, such as the prevention of glucocorticoid-induced osteoporosis by better disease control and modern drugs, and the prevention of gastrointestinal complications by using therapeutic strategies. Secondly, the probable disease-modifying potency of glucocorticoids. This article goes into detail about this latter effect of glucocorticoids.

Key-Words: Glucocorticoids; Rheumatoid Arthritis; Disease Modifying; Joint Sparing Effect; Adverse-effects.

RESUMO

Para usar os glicocorticóides com prudência é importante pesar os riscos e os benefícios. Alguns dados obtidos nas últimas décadas favoreceram o uso de doses baixas de glicocorticóides na artrite reumatóide. Em primeiro lugar, a maior capacidade para lidar com os efeitos adversos, como por exemplo a prevenção da osteoporose induzida pelos glicocorticóides através de um melhor controlo da doença e fármacos mais modernos, e a prevenção das complicações gastrointestinais através de estratégias terapêuticas. Em segundo lugar, o provável efeito modificador dos glicocorticóides na doença. Este artigo detalha este último efeito dos glicocorticóides.

Palavras-Chave: Glicocorticóides; Artrite Reumatóide; Fármacos Modificadores da Doença; Redução Progressão Radiológica; Efeitos Adversos.

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Introduction

The introduction of glucocorticoids by Hench in 1948 was a revolution in the treatment of rheumatoid arthritis.[1] The use of high doses generated dramatic results, which led to enthusiasm for this therapy. The positive opinion about glucocorticoids was reversed when the toxicity of this therapy, and especially high-dose therapy, became apparent some years after its introduction. Despite this, the general opinion is that with low-dose glucocorticoids the adverse effects are balanced by positive symptomatic effects.[2] A substantial proportion of patients with rheumatoid arthritis is treated on a daily basis with low-dose glucocorticoids as additive therapy for their symptomatic effect. Despite a series of older trials and publications on the positive effects of glucocorticoids on radiographic disease progression, albeit in high doses in therapeutic strategies without disease-modifying antirheumatic drugs (DMARDs),[3-7] up to about a decade ago there was no firm proof that glucocorticoids had joint-sparing, disease-modifying potential. Recent studies demonstrating the potential of glucocorticoids in rheumatoid arthritis have renewed the debate on the risks and benefits of glucocorticoids.

We here review more recent articles on the disease-modifying effects of glucocorticoids. We then draw a conclusion about the use of glucocorticoids, weighing risks and benefits of glucocorticoids in the light of new data, and give recommendations for the use of glucocorticoids in daily practice.

Studies on disease-modifying potential of glucocorticoids

In the double-blind Arthritis and Rheumatism Council low-dose glucocorticoid study,[8] 128 patients with active, relatively early rheumatoid arthritis (duration less than 2 years) were randomly allocated to 7.5 mg prednisolone (n = 61) or placebo (n = 67) once daily for 2 years in addition to other therapies, including DMARDs, in more than 70% of the patients. The statistical analysis of radiographic scores was restricted to 106 patients for whom there were films at baseline and 2 years later. During this period, the mean Larsen score increased by 0.7 units in the prednisolone group but by 5.4 units in the placebo group, a clinically and statistically significant difference. At 2 years, 15 of the 68 hands with no erosions at the start of the study in the prednisolone group (22%) and 36 of the 79 non-erosive hands in the placebo group (46%) had acquired erosions ($p < 0.01$). The reductions in joint scores, pain, and disability at 3 months; in pain at 6 months; and in disability at 6, 12, and 15 months were greater in the prednisolone group than in the placebo group (all p values < 0.05). The conclusion was that in patients with early, active rheumatoid arthritis, prednisolone (7.5 mg daily) given for 2 years in addition to other treatments substantially reduced the rate of radiographic disease progression and clinical signs and symptoms. At the end of the study period, the study medication was discontinued and follow-up was maintained for a further year.[9] Of the 75 patients with radiographs at baseline and at years 1–3, the mean progression in the prednisolone group was 0.2, 0.04, and 1.0 Larsen units at year 1, year 2, and year 3, respectively. The equivalent scores for the placebo group were 2.3, 1.0, and 1.6 Larsen units. The percentage of hands which showed erosions at each time point was 28, 29, 35, and 39 for the prednisolone group and 28, 49, 59, and 67 for the placebo group, respectively. No clear flare in clinical symptoms was observed after prednisolone was stopped in the third year. The conclusion after this additional year of follow-up was that joint destruction resumed after discontinuation of prednisolone.

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In the double-blind «combination therapy in early rheumatoid arthritis» (COBRA) trial, 155 patients with early (duration less than 2 years) rheumatoid arthritis were randomly allocated to one of two groups of treatment: COBRA treatment or sulphasalazine monotherapy.[10] COBRA treatment comprised (i) a starting dose of 60 mg/day prednisolone, which was rapidly tapered to 7.5 mg/day within 6 weeks, continued unchanged for 20 weeks, and then withdrawn completely after 26 weeks; (ii) a low dose of methotrexate (7.5 mg/week at one time) for 40 weeks, and then withdrawn in 4 weeks; and (iii) a maintenance dose of sulphasalazine (2000 mg/day). Patients randomized to the sulphasalazine monotherapy group received a maintenance dose of sulphasalazine (2000 mg/day). Outcomes were the pooled index (a weighted change score of five disease activity measures) and the Sharp/Van der Heijde radiographic score of hands and feet. At week 28, the mean pooled change index was 1.4 in the COBRA treatment group and 0.8 in the sulphasalazine group ($p < 0.0001$). At this time, 55 (72%) and 39 (49%) patients showed improvement according to American College of Rheumatology criteria, respectively. However, after prednisolone was stopped the clinical difference between the groups decreased and was no longer significant. At 28 weeks, the radiographic damage score had increased by a median of 1 in the COBRA group and by 4 in the sulphasalazine group ($p < 0.0001$). The increases at week 56 (2 versus 6) and at week 80 (4 versus 12) were also significant. Because in two other double-blind randomized trials the effect of the combination of methotrexate and sulphasalazine was not superior to that of either drug alone,[11,12] it is our hypothesis that the superior effect of combination therapy in the COBRA trial can be ascribed to prednisolone. In a 4-5 year follow-up extension of the COBRA study, analysis of the data on an intent-to-treat basis revealed long-term beneficial benefits of the combination strategy on radiographic damage.[13] The Sharp/Van der Heijde progression rate was 8.6 points per year in the sulphasalazine group and 5.6 in the COBRA group. After adjustment for differences in treatment and disease activity during follow-up, the between-group difference in the rate of radiographic progression was 3.7 points per year. The health-assessment questionnaire (HAQ) score did not change significantly over time.

In a 1-year randomized study by Hansen et al. 102 patients with active established rheumatoid arthritis were allocated to treatment with a DMARD alone or a DMARD plus prednisolone, the latter given in a dose regimen adapted to the disease activity of the individual patient.[14] At entry, the median disease duration in the prednisolone plus DMARD group was significantly less than that in the DMARD alone group (2.8 versus 8.5 years, $p < 0.05$). The mean dose of prednisolone was 6 mg daily. At 1 year 26 patients had withdrawn from the investigation, leaving 76 patients for evaluation. Disease activity in the prednisolone-treated group was reduced within 2 weeks versus after some months in the DMARD alone group. At 6 months, no difference was observed between the groups, as evaluated by an improvement score using a number of criteria of the American College of Rheumatology. Prednisolone was not able to protect significantly against radiographic disease progression, although a trend toward less progression in the Larsen score was observed in the prednisolone group. The conclusion was that the beneficial effects of prednisolone are not as clear-cut in established rheumatoid arthritis as in early disease.

Another double-blind low-dose (5 mg/daily) prednisolone trial was performed by Wassenberg et al. with 192 patients with active early rheumatoid arthritis (duration less than 2 years) who were also treated with either intramuscular gold or methotrexate for 2 years.[15] Findings from this 2-year study have only been published as an abstract. Analyses were based upon 76 patients who completed the study according to protocol, of whom 34 were treated with prednisolone and 42 with placebo. At 24 months, the mean Sharp/Van der Heijde radiographic score increased from 10 at baseline to 15 in the prednisolone group, but from 12 to 24 in the placebo group. The authors concluded that treatment with 5 mg prednisolone daily plus conventional DMARD therapy (intramuscular gold or methotrexate) decreased radiographic progression in early rheumatoid arthritis.

In a 2-year randomized, double-blind, placebo-controlled clinical trial (the Utrecht study) involving 81 patients with early active rheumatoid arthritis who had not been treated with DMARDs, 41 patients were assigned to oral prednisone (10 mg/day) and 40 were assigned to placebo.[16] After 6 months, sulphasalazine (2 g/day) could be prescribed as rescue medication. After month 6, radiographic scores showed significantly less progression in the prednisone group than in the placebo group, see Figure 1. In the first 6 months, the prednisone

group also showed more clinical improvement than the placebo group, but this effect was not seen after 6 months, probably because the use of additional therapies, such as nonsteroidal anti-inflammatory drugs (NSAIDs), was significantly higher in the placebo group than in the prednisone group.[17]

In a double-blind trial (WOSERAC, West of Scotland Early Rheumatoid Arthritis Corticosteroid-trial), 167 patients with early rheumatoid arthritis (median disease duration 12 months, range 2–84 months) were started on the DMARD sulphasalazine and randomly allocated to prednisolone (7 mg) or placebo prednisolone for 2 years. Prednisolone was given to 84 patients. At 2 years, 61 (73%) of the patients were still on prednisolone and 59 (70%) were still on sulphasalazine. Of the 83 patients on placebo at 2 years, 80% still used placebo and 64% sulphasalazine. No significant difference in radiographic scores (Sharp/Van der Heijde) or in clinical and laboratory measures was observed between both groups at 0 and 2 years.[18]

The conclusion that can be drawn from these studies is that prednisolone seems to have the potential to retard the development of joint damage in rheumatoid arthritis, but probably not in all patients. The disease-modifying potency of glucocorticoids probably depends on the dosage used, the stage of the disease (duration, joint damage), the activity of the disease, and therapeutic strategies (intensity of treatment). These factors differed in the aforementioned trials. Furthermore, in these trials the intensity of DMARD therapy was not tailored to the disease activity of individual patients in order to achieve remission, which is an objective of modern daily clinical practice for patients with early rheumatoid arthritis. In neither trial were biological agents used, a therapeutic modality that is being increasingly used in developed countries and which inhibits the development of joint damage in rheumatoid arthritis.[19] So, the results of these trials cannot directly be translated to daily clinical practice. But in patients with early active rheumatoid arthritis, treatment with prednisolone at doses of at least 7.5 mg daily not only provides symptomatic relief but probably also retards the development of joint damage.

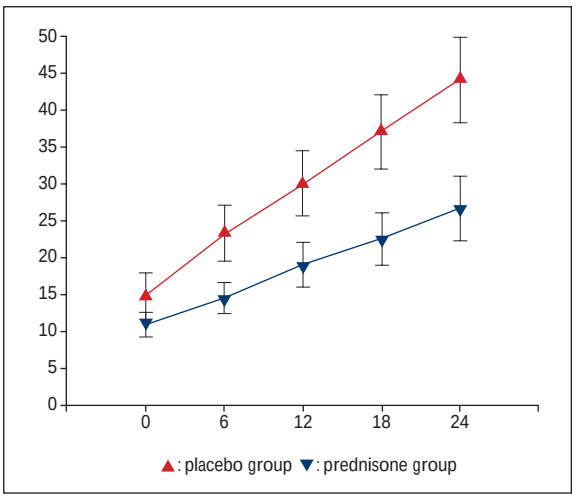

Figure 1. Radiographic joint damage over time (months) in the prednisone group *versus* the placebo group in the Utrecht study.[16]

Y-axis: radiographic score of hand and feet (Sharp/Van der Heijde score), means and standard errors of the mean; X-axis time in months. At month 12 and further on, joint damage is significantly less in the prednisone group compared to the placebo group (p=0,04 at 12 months and 0,02 at 24 months).

Weighing benefits and risks of therapy with low-dose glucocorticoids in rheumatoid arthritis

Rheumatoid arthritis probably is the only rheumatic disease in which therapy with glucocorticoids is often started and then continued, in low doses, as adjunct therapy.[20] Glucocorticoids are highly effective in relieving symptoms in patients with active rheumatoid arthritis when used in doses lower than 10 mg; many patients are functionally dependent on this therapy and continue it long-term.[21] An explanation for the symptomatic effect of this low-dose therapy could be a relative insufficiency of the adrenal gland in patients with rheumatoid arthritis.[22,23] A review of seven studies (in total 253 patients) concluded that glucocorticoids, when administered for about 6 months, are effective for the treatment of rheumatoid arthritis.[24] However, after 6 months of therapy the beneficial effects of glucocorticoids seem to diminish.[8,16,25] Nevertheless, if this therapy is then tapered and stopped, patients often experience an aggravation of symptoms for several months. As described above, in patients with early active rheumatoid arthritis, treatment with prednisolone in doses of at least 7.5 mg daily not only provides symptomatic relief but possibly also retards the development of joint damage.

However, there are risks to glucocorticoid therapy (see Table 1). In part, the negative effects of

Table 1. Common Adverse Effects of Glucocorticoids

System	Adverse effect
Skeletal	Osteoporosis, osteonecrosis, myopathy
Gastrointestinal	Peptic ulcer disease (in combination with NSAIDs), pancreatitis, fatty liver
Immunological	Predisposition to infections, suppressed delayed hypersensitivity
Cardiovascular	Fluid retention, hypertension, accelerated arteriosclerosis, arrhythmias
Ocular	Glaucoma, cataract
Cutaneous	Skin atrophy, striae, ecchymoses, impaired wound healing, acne, buffalo hump, hirsutism
Endocrine	Cushingoid appearance, diabetes mellitus, changes in lipid metabolism, enhanced appetite & weight gain, electrolyte abnormalities, hypothalamus-pituitary-adrenal axis suppression, suppression gonadal hormones
Behavioral	Insomnia, psychosis, emotional lability, cognitive effects

glucocorticoids can be prevented or diminished by taking precautions before therapy is started and by screening for adverse effects (see Table 2). Osteoporosis is a well-known adverse effect of glucocorticoids but can be prevented to a large extent. Internationally accepted guidelines have been developed to minimize the occurrence of glucocorticoid-induced osteoporosis.[26] Bisphosphonates are, at present, the only class of drugs proven to be effective in the prevention and treatment of glucocorticoid-induced osteoporosis, and once weekly regimens of effective bisphosphonates are available nowadays. Active rheumatoid arthritis in itself is a risk factor for the development of osteoporosis, being induced by inflammatory cytokines. In addition, impaired mobility, a consequence of rheumatoid arthritis, leads to fewer weight-bearing activities and diminished exposure to sunlight, which weaken bone and increase the risk of falls. The better control of the activity of rheumatoid arthritis achieved with modern agents and combination therapy diminishes this risk.[27-29] Also beneficial in the light of the risk of osteoporosis is the trend to prescribe patients with rheumatoid

Table 2. Safe Usage of Glucocorticoids Therapy: Guidelines*

Before starting treatment, screen:
- blood pressure, check for peripheral edema and cardiac insufficiency
- other risk factors for osteoporosis than (consequences of) rheumatoid arthritis
- co-medication, especially NSAIDs; history of peptic ulcer
- family history of glaucoma
- serum lipids
- urine glucose test

At the start of treatment, prescribe:
- calcium and vitamin D suppletion always; biphosphonates on indication (see guidelines)
- in case of co-medication with NSAIDs, co-medication with proton pump inhibitors or prescribe a COX-1-sparing NSAID

During treatment, check: **
- blood pressure, check for peripheral edema and cardiac insufficiency
- serum lipids
- urine glucose test
- ocular pressure in patients with a family history of glaucoma or on a high dose of glucocorticoids

*International guidelines not yet available. COX-1 = cyclo-oxygenase 1
**Frequency depends on individual patient's risk or problems, assessed at screening before the start of therapy.

arthritis exercise, although this should not be overdone.[30]

The risk of gastrointestinal complications with the combination of NSAIDs and glucocorticoids can nowadays be tackled by comedication with proton pump inhibitors or by prescribing a cyclooxygenase-1 (COX-1)-sparing NSAID. However, the jury is still out on to whether the group of cyclooxygenase-1 (COX-1)-sparing NSAIDs increases the incidence of cardiovascular incidents. Especially in patients with rheumatoid arthritis using glucocorticoids, this is a serious issue as rheumatoid arthritis itself and glucocorticoids could increase cardiovascular morbidity.[31-33] Recently, a record linkage database study on 68781 glucocorticoid-users (of whom 1115 patients with RA) and 82202 nonusers was published.[34] The incidence of all cardiovascular diseases, including myocardial infarction, heart failure and cerebrovascular disease was not increased in patients using < 7.5 mg prednisolone on a chronic basis. However, it was increased in patients using dosages ≥ 7.5 mg daily: relative risk adjusted for all known risk factors 2.6, 95% confidence interval 2.2 to 3. So in rheumatoid arthritis patients on *low-dose* glucocorticoids, the disease itself seems to be more a risk factor for cardiovascular diseases than this medication. Possibly intensive treatment of rheumatoid arthritis can diminish the risk.[35]

Conclusion

The past decades several positive developments have tipped the balance further in favor of the use of low-dose glucocorticoid therapy (on indication) in rheumatoid arthritis. For example, glucocorticoids may have disease-modifying potency in subsets of patients, and adverse effects can now be dealt with more effectively, such as glucocorticoid-induced osteoporosis and gastrointestinal complications. Low-dose glucocorticoid therapy seems safe if monitoring for adverse effects (Table 2) is part of the therapeutic strategy. Guidelines still have to be developed on how and when and in which dose to use low-dose glucocorticoids in (early) rheumatoid arthritis.

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