Disease control with glucocorticoid therapy in rheumatoid arthritis

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Abstract

DMARDs aim to improve long-term prognosis of RA, as indicated by reduced progression of radiographic damage and maintenance of function. However, it may be more appropriate to consider disease-modifying strategies rather than drugs alone. Despite the challenges (e.g. lack of standard outcome measures, poor reporting of dose levels), a systematic review of 15 studies involving more than 1400 patients showed that glucocorticoid treatment for 1-2 years slowed radiographic progression compared with control treatment. Evidence for longer term disease-modifying benefits of glucocorticoids comes from individual studies with extended follow-up. In the Utrecht study, patients with early RA originally assigned to prednisone 10 mg/day for 2 years and then tapered off the therapy showed significantly less radiographic progression at follow-up after a further 3 years than patients originally assigned placebo, with no significant difference in the use of synthetic DMARD therapy. In the combination therapy in early RA (COBRA) study, patients with newly diagnosed RA treated with glucocorticoid (starting with 60 mg/day, quickly reduced to 7.5 mg/day for weeks 7-28 and subsequently stopped), MTX up to week 40 and SSZ showed significantly decreased radiographic progression compared with those treated with SSZ alone. The benefits of short-term combination therapy on disease progression were still apparent at 5-year and 11-year follow-up. In conclusion, there is clear evidence that treatment regimens including low-dose glucocorticoids given early in RA slow radiographic progression, meeting the definition of a DMARD. Furthermore, the evidence suggests that such treatment strategies favourably alter the disease course even after glucocorticoid discontinuation.

Key words: rheumatoid arthritis, glucocorticoids, radiological progression, disease-modifying antirheumatic drugs.

Glucocorticoids in RA

Glucocorticoids are an established therapy for inflammatory conditions, used in clinical practice for >60 years [1]. In RA, glucocorticoids were initially used at high doses for the short-term treatment of flares, but there is increasing interest in the use of lower dose therapy (<10 mg/day) given for prolonged periods (>6 months). The addition of long-term low-dose glucocorticoid therapy to standard disease-modifying treatments has been shown to reduce pain and improve patient quality of life, but also to reduce the development of erosions [2-6], suggesting a disease-modifying action.

Definition of a DMARD

A DMARD is used with the aim of achieving something more than immediate symptom control: it aims to improve long-term prognosis. The key long-term outcomes in RA are death and disability. Any potential DMARD must have intrinsic activity on these outcomes and must be used for sufficient time to alter the course of the disease. In practice, many therapies are stopped within a few years. Furthermore, death and disability are difficult to assess, as costly long-term studies are required to evaluate the impact of potential DMARDs on these outcomes. Consequently, an informal definition of a DMARD has been adopted, focusing on the ability to delay the progression of radiographic damage and to improve or maintain quality of life.
If a treatment has altered the course of disease, it might be expected that improved outcomes remain apparent, even after the drug has been discontinued. Yet there appears to be a dogmatic disconnect. Synthetic drugs traditionally seen as DMARDs, such as MTX, are expected to work when the patient is taking treatment but stop when it is discontinued, with fear of a flare-up keeping many patients on treatment even when it is unclear that treatment is still working. In contrast, glucocorticoids are expected to keep on working even after termination. Fear of toxicity means that the lowest possible dose of glucocorticoid is used (possibly a suboptimal dose) or the treatment is rapidly tapered or discontinued. Glucocorticoids may then be ‘blamed’ when the disease subsequently returns. However, there is now a considerable body of evidence that glucocorticoids can be considered disease modifying, at least in early RA.

Evidence from a systematic review of the literature

The disease-modifying effects of glucocorticoids in RA were evaluated in a systematic review of the literature [3]. All the studies included were randomized controlled trials with at least one arm including glucocorticoid treatment and one arm without this therapy. All studies measured radiographic change in joints of the hand and/or feet.

Conducting the review presented a number of challenges [3]. The quality of reporting was poor in many studies, with the dose of glucocorticoid not specified and few details given in the results. Furthermore, there was no standard outcome measure, with a variety of radiographic scoring systems used. Consequently the review focused on erosions with the score recoded as a percentage of the maximum score. Data were extracted in a standardized fashion, with change in erosions expressed as a standardized mean difference. A random-effects model was constructed to assess the results.

The review identified 15 studies meeting the inclusion criteria, comprising >1400 patients, mostly with early RA [3]. Most of the studies assessed the use of glucocorticoids with concomitant synthetic DMARD. The mean cumulative dose of glucocorticoid over 1 year was 2.3 g prednisone (or equivalent), ranging from 0.3 to 5.8 g. In all but one study, there was a numerical benefit of glucocorticoids. The standardized mean difference in the first year was 0.4 (95% CI 0.27, 0.54), in favour of glucocorticoids (Fig. 1). In studies lasting for 2 years (involving ~800 patients), the effect was retained.

The standardized mean difference assesses the difference in change in erosion score achieved with each treatment, expressed as a difference in s.d. units [3]. However, the clinical relevance of the findings was also considered. The absolute benefit is the difference in the change achieved with each treatment, expressed in the original units. The relative benefit is then the absolute benefit, expressed as a percentage of the change in erosion score achieved by the control treatment. With the exception of one study, a clear clinical benefit was demonstrated.

Long-term disease-modifying impact of glucocorticoids

Evidence of the disease-modifying effects of glucocorticoids in the systematic review described above comes from studies of up to 2 years duration. Although there is no systematic review of longer term studies as yet, some of the individual studies [e.g. Better Anti-rheumatic Farmacotherapy (BARFOT), the Utrecht study, BeSt, combination therapy in early RA (COBRA)] included in the existing review have now reported follow-up for >2 years [5, 7-10]. Information from these extended follow-up studies confirms the long-term disease-modifying impact of treatment strategies that include initial glucocorticoid therapy.

In the BARFOT study, the addition of prednisolone 7.5 mg/day to initial DMARD therapy retarded the progression of erosions after 2 years in patients with early RA and provided a higher remission rate than DMARD therapy alone [11]. Remission achieved after 2 years was associated with less radiographic damage still present after 4 years, which when analysed according to initial treatment group was statistically significant only for patients receiving early glucocorticoid therapy [7]. No incidence of hypertension, diabetes or weight gain were reported during years 2-4.

In the Utrecht study, patients with early RA received prednisone 10 mg/day or placebo as monotherapy (with SSZ as rescue therapy) for 2 years [6]. Radiographic progression was significantly reduced in the group receiving prednisone compared with the control group. At the end of the trial, prednisone treatment was reduced and stopped if possible. Patients were followed up ~3 years after the end of the study [8]. During the follow-up period, there was no significant difference in DMARD therapy used in the two groups, though 35% of the group originally taking prednisone continued with this therapy for ~1 year (mean ~5 mg/day) and two patients from the control group started prednisone treatment. Radiographic joint damage in the hands and feet was assessed using the Sharp–van der Heijde method in 24 (60%) of the patients originally treated with prednisone and 28 (68%) of the original control group. Compared with the original placebo group, there was significantly less progression in the original prednisone group with no accelerated rate of progression during the follow-up period. The results suggested that inhibition of radiographic joint damage in patients with early active RA treated with prednisone 10 mg/day for 2 years persists after the end of prednisone therapy, consistent with a long-lasting disease-modifying effect associated with early glucocorticoid treatment.

The BeSt study compared four treatment strategies: sequential monotherapy with synthetic DMARDs, step-up combination therapy with synthetic DMARDs, initial combination therapy with a synthetic DMARD and low-dose glucocorticoid, and initial combination of synthetic DMARD and biologic DMARD [12]. After 1 year, both strategies of initial combination therapy resulted...
in significantly improved outcomes compared with sequential monotherapy or step-up combination, with no difference between the alternative combination approaches. After 5 years, the initial benefit of combination therapy was maintained, with significantly less joint damage in patients assigned to these two groups than the other two groups [9]. During this period, the number of serious adverse events, serious infections, malignancies and deaths were comparable across all treatment groups, though one patient in the group assigned biologic DMARD died from infectious complications following disseminated tuberculosis. The authors concluded that starting with combination therapy resulted in earlier clinical improvement and less joint damage without an increase in toxicity.

In the COBRA study, patients with early RA received either synthetic DMARD, SSZ or a step-down combination regimen of high-dose glucocorticoid (initial treatment with 60 mg/day, rapidly reduced to 7.5 mg/day for weeks 7–28 and subsequently stopped) and MTX up to week 40 with continuing SSZ [2]. Compared with those receiving SSZ alone, patients receiving initial combination treatment showed significantly reduced radiographic progression at assessments conducted 28, 56 and 80 weeks after the start of treatment. The benefits of the combination regimen, evident early in the study, were still apparent after 5 years and after 11 years [5, 10]. After 11 years, clinical records were examined to determine therapy, survival and co-morbidities; hand and feet radiographs were also obtained [10]. During the follow-up period, 52% of patients in the step-down combination group and 37% of the patients initially in the control group received glucocorticoid therapy, giving a total cumulative dose from the start of the study of 12.5 and 10.2 g, respectively [10]. Slightly more patients in the step-down combination group had received treatment with biologic therapies than in the control group. There were 18 deaths, of which six were in the group receiving the initial step-down combination therapy and 12 in the control group receiving only SSZ (Fig. 2). The hazard ratio, corrected for age and sex, was 0.57 in favour of the patients in the combination group. Although this difference did not reach statistical significance because of the small number of events, the data do not support an increased mortality from the step-down combination therapy. With regard to co-morbidities, the only significant difference was the increased prevalence of treated hypertension in the group initially receiving step-down combination therapy. There were interesting trends, including increased diabetes and cataracts in this group, and increased

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**Table 1**

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Glucocorticoids N</th>
<th>Comparator N</th>
<th>SMD (random)</th>
<th>Weight, %</th>
<th>SMD (random)</th>
</tr>
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<tr>
<td>Boers (1997)</td>
<td>70</td>
<td>65</td>
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<td>Capell (2004)</td>
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<td>55</td>
<td>8.4</td>
<td>0.08</td>
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<tr>
<td>Choy (2005)</td>
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<td>30</td>
<td>5.2</td>
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<td>-0.44</td>
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<tr>
<td>Empire (1957)</td>
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<td>31</td>
<td>5.5</td>
<td>0.10</td>
<td>-0.39</td>
</tr>
<tr>
<td>Goekeop (2005)</td>
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<td>115</td>
<td>12.9</td>
<td>0.15</td>
<td>-0.44</td>
</tr>
<tr>
<td>Hansen (1999)</td>
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<td>6.2</td>
<td>0.10</td>
<td>-0.20</td>
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<tr>
<td>Harris (1983)</td>
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<td>16</td>
<td>3.1</td>
<td>0.10</td>
<td>-0.54</td>
</tr>
<tr>
<td>Joint (1960)</td>
<td>41</td>
<td>35</td>
<td>6.0</td>
<td>0.10</td>
<td>-0.70</td>
</tr>
<tr>
<td>Kirwan (1995)</td>
<td>49</td>
<td>54</td>
<td>7.7</td>
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<td>-0.38</td>
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<tr>
<td>Schaardenburg (1995)</td>
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<td>24</td>
<td>4.5</td>
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<td>-0.17</td>
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<tr>
<td>Suponitsкая (2004)</td>
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<td>20</td>
<td>3.7</td>
<td>0.10</td>
<td>-0.10</td>
</tr>
<tr>
<td>Svensson (2005)</td>
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<td>112</td>
<td>12.1</td>
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<td>-0.51</td>
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<td>Wassenberg (2005)</td>
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<td>-0.63</td>
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<tr>
<td>van Everdingen (2002)</td>
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<td>0.10</td>
<td>-0.48</td>
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<td>van Gestel (1995)</td>
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<td>1</td>
<td>0.0</td>
<td>0.10</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>722</td>
<td>699</td>
<td>100.0</td>
<td>0.00001</td>
<td>-0.39</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square = 18.03 df = 13 P = 0.16 I² = 27.9%

Test for overall effect z = 5.96 P < 0.00001

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SMD: standardized mean difference

Erosions at 1 year as proportion of maximum score

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hypercholesterolaemia, infection and cancer in the control group receiving SSZ initially.

Importantly, the prevalence of cardiovascular events such as myocardial infarction and stroke, as well as clinical fractures and osteoporosis, was highly similar in both groups.

The impact of early step-down combination treatment on radiographic progression was assessed, with radiographs collected after 5, 8 and 11 years, scored by two independent observers using the Sharp-van Heijde method [10]. When patients are followed up over time, the observations at different time points in a single person are correlated. To account for this, generalized estimation equations were used in the analysis. There were considerably more drop-outs among those initially treated with SSZ alone. Taking this into account, the analysis showed that the benefit of combination therapy obtained in the first 5 years remained throughout the study (Fig. 3a). However, if data on the likely progression rate of those patients who dropped out of the study are extrapolated forward and included in the analysis, the results are compatible with a sustained benefit of step-down combination therapy on radiological progression and a significant difference between the groups of three Sharp points per year (Fig. 3b).

Although the findings reported here suggest that low-dose glucocorticoid treatment may have long-term disease-modifying effects, in a number of the studies (e.g. the COBRA study [5, 10]) it is not possible to differentiate between the contributions made by different components in a combination regimen that includes both glucocorticoids and synthetic DMARD. Such a difficulty has recently been discussed in regard to the reporting of studies with biologic DMARDs, many of which do not adequately report concomitant therapy with glucocorticoid treatment [13]. As a result, it may be more appropriate to consider disease-modifying strategies rather than focusing on the individual disease-modifying drugs used to achieve beneficial long-term outcomes.

Conclusions
In conclusion, there is now clear evidence that glucocorticoid therapy slows radiographic progression by at least 50% when given to patients with early RA, so satisfying the conventional definition of a DMARD. Furthermore, long-term follow-up data suggest that treatment strategies that include glucocorticoid therapy may favourably alter the disease course even after discontinuation of the glucocorticoids.

Rheumatology key messages
- Glucocorticoids are disease modifying, at least in early RA.
- Treatment strategies including glucocorticoid therapy may favourably alter the disease course even after glucocorticoid discontinuation.

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References