Clinical Trials Documenting the Efficacy of Low-Dose Glucocorticoids in Rheumatoid Arthritis

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Abstract
Twelve clinical trials have documented that prednisone or prednisolone in doses of 10 mg/day or less is efficacious to improve function, maintain status and/or slow radiographic progression in patients with rheumatoid arthritis (RA). An early trial reported by de Andrade et al. [Ann Rheum Dis 1964; 23:158–162] in 1964 indicated that 5 mg of prednisolone at night was preferred to 5 mg of prednisone in the morning. Harris et al. [J Rheumatol 1983; 10:713–721] documented the efficacy of 5 mg/day of prednisone in a non-double-blind trial in 1983. Two important trials in the 1990s by Kirwan [N Engl J Med 1995; 333:142–146] using 7.5 mg/day, and the COBRA study by Boers et al. [Lancet 1997; 350:309–318] with step-down from 60 mg rapidly tapered to 5 mg/day led to strong advocacy of low-dose glucocorticoids. In 2002, the first Utrecht Study [Ann Intern Med 2002; 136:1–12] indicated that 10 mg/day prednisone slowed radiographic progression, a finding confirmed and extended in 2005 by Svensson et al. [Arthritis Rheum 2005; 52:3360–3370] with 7.5 mg/day, and Wassenberg et al. [Arthritis Rheum 2005; 52:3371–3380] with 5 mg/day of prednisolone. In 2008, Buttgereit et al. [Lancet 2008; 371:205–214] reported CAPRA-1, which documented that modified-release prednisone or prednisolone taken at bedtime led to lower morning stiffness and IL-6 levels compared to usual morning prednisone. In 2009, Pincus et al. [Ann Rheum Dis 2009; 68:1715–1720] reported a withdrawal clinical trial, in which patients who took 3 mg/day were gradually withdrawn to placebo, and dropped out at a significantly higher rate than control patients who were ‘withdrawn’ to prednisone. In 2012, a second Utrecht Study [Ann Intern Med 2012; 156:329–339], CAMERA-II, documented that 10 mg of prednisone added to a ‘treat-to-target’ strategy with methotrexate provided incremental slowing of radiographic progression. An Italian study of patients with early RA who received step-up disease-modifying anti-rheumatic drug therapy over 2 years plus prednisolone or not indicated higher rates of clinical remission and sustained remission associated with 7.5 mg/day of prednisolone [Arthritis Res Ther 2012; 14:R112]. The CAPRA-2 trial [Ann Rheum Dis 2013; 72:204–210] documented that modified-release nighttime prednisone or prednisolone was significantly more efficacious than placebo. Taken together, these 12 clinical trials indicate that low-dose glucocorticoids prednisone or prednisolone provides symptomatic relief, improved functional status and slowing of radiographic progression for patients with RA.
Introduction

The introduction of glucocorticoids for treatment of rheumatoid arthritis (RA) in 1948 by Hench et al. [1] did not require randomized control clinical trials, which were first conducted only in the 1940s [2, 3]. Documentation of dramatic clinical responses in a report published in 1949 [1] was sufficient to allow glucocorticoids to be available for prescription by physicians. The 1950 Nobel Prize in Physiology and Medicine was awarded to Hench, Kendall and Reichstein for the discovery and clinical application of glucocorticoids [4].

The efficacy of glucocorticoids was obvious from the first administration. However, the absence of formal clinical trials left a void concerning both optimal dosage and adverse events. Of note, the Mayo Clinic group that discovered glucocorticoids recommended in 1955 that doses equivalent to 5–10 mg/day of prednisone be used in the treatment of RA [5]. However, a dose of 20 mg/day of prednisolone was used in clinical trials in 1960 (after glucocorticoids were available for treatment) to compare with aspirin [6, 7]. While disease-modifying properties were documented in patients with RA [6, 7], the ‘conventional wisdom’ at that time (and, to a large extent, at this time) was that low doses were not ‘disease modifying’, i.e. did not slow radiographic progression.

Physicians tended to prescribe doses of glucocorticoids higher than 10 mg/day, or even 20 mg/day, and many adverse events were seen in many patients after taking these high doses over more than a few months [8]. Although the efficacy of parenteral and intra-articular glucocorticoids was recognized for particular clinical situations, a poor risk/benefit ratio was widely acknowledged for high-dose oral glucocorticoids because of long-term adverse events [8]. Therefore, by the late 1950s, oral glucocorticoids were regarded as appropriate in RA only for severe, potentially life-threatening situations or as short-term ‘bridging therapy’, while awaiting results of what were regarded as ‘remission-inducing’ disease-modifying anti-rheumatic drugs, such as parenteral gold therapy [8, 9](the long-term effectiveness of which was greatly exaggerated [10]).

An Early Clinical Trial of Prednisolone 5 mg/Day

The first clinical trial involving low-dose glucocorticoids was reported by de Andrade et al. [9] of the Oxford Regional Rheumatism Research Center, Stoke Mandeville Hospital, Aylesbury, UK. This report will be discussed in some detail, as it is not well known and appears to provide important lessons not only about glucocorticoids but also about how knowledge is disseminated in clinical medicine. These investigators reported using low-dose glucocorticoids in routine clinical care [9], on the basis of recommendations by the Mayo Clinic group to use doses equivalent to 5–10 mg/day of prednisone [5]. They stated that their clinical practice of treating all patients with 7.5 mg/day or less was also based on ‘observations made in the course of studying the phenomenon of morning stiffness’ [9].

The clinical trial included 56 patients, all of whom were reported never to have received doses higher than 5 mg of prednisolone (in the early 1960s!). The investigators compared preferences for 5 mg/day of prednisolone as an evening dose versus a 5-mg morning dose, giving a placebo in the reciprocal pattern in a cross-over design. Overall, 28 of the 56 (50%) patients preferred the evening dose, only 2 the morning dose, 18 were inconsistent, 1 had no preference and 7 did not have suitable data for analysis due to a limited understanding of the trial [9]. The conclusion was that 5 mg of prednisolone at night was more efficacious than in the morning for the management of most RA patients [9].

The report noted that most patients in a clinical trial as well as in usual care experienced ‘few severe adverse effects throughout the treatment of prednisolone in daily doses of 5–7.5 mg. The mild adverse effects, notably, bruising, seem[ed] to be related to duration of treatment’ [9]. The prevalence of adverse events was substantially lower in patients who received <10 mg compared to 10 mg or more, after 25 weeks, at 25–50 weeks and, most strikingly, after 50 weeks of treatment. Prolongation of therapy ‘rarely produced fresh adverse effects, though the incidence of purpura and bruising continued to increase. … Pituitary adrenocortical reserve was found to be present in all of ten patients who had taken 5 mg prednisolone daily for up to 3.5 years’ [9]. The authors concluded that ‘our present policy is not to exceed a daily total of 7.5 mg in any but the most exceptional circumstances’ [9].

The report also concluded that ‘it would be surprising if so low a dose could retard deterioration in the joints, assessed radiographically’. As noted, this inference was consistent with the ‘conventional wisdom’, i.e. the prevailing paradigm at the time. However, that idea likely is incorrect, in view of recent data from subsequent clinical trials documenting that doses of 10 mg/day or less, including two trials of 5 mg/day [11, 12], slow radiographic progression [11–17]. Furthermore, a cohort of patients treated over indefinite periods by the authors (T.P.), in-
including all seen in 2000, 80% with prednisone at doses less than 5 mg/day, had Larsen radiographic scores that were only 3% of maximum, far lower than expected [18].

It is not possible to attribute the slowing of radiographic progression entirely to prednisone, since almost all patients were also treated with methotrexate. However, this low level of radiographic progression is rarely seen only with long-term methotrexate monotherapy. Thus, it appears a possible consideration that doses as low as 3 mg/day of prednisone not only provide symptomatic relief [18], but can also slow radiographic progression, though this has not been documented in a formal clinical trial.

In retrospect, it appears that the assumption widely held in the 1960s that low-dose prednisone was unlikely to slow radiographic progression may have been unfortunate. Certainly, it appears to have deterred further development of these doses over 20–30 years. Until 19 years after the report by de Andrade et al. [9], no clinical trials involving low-dose prednisone were reported [11].

Clinical Trials of Low-Dose Prednisone during the 1980s and 1990s

Over the last 3 decades, 11 additional clinical trials have been conducted to document the efficacy of low-dose glucocorticoids in RA [10–17, 19–22] (Table 1). Documentation of efficacy is summarized briefly in this article; documentation of safety in these clinical trials is summarized in the article by Da Silva in this special issue, p. 57.

Interest in low-dose glucocorticoids was given impetus by observations during the mid-1980s of severe functional declines [23, 24], radiographic progression [25], premature mortality [23] and frequent work disability [26] in patients with RA. These observations suggested that adverse effects associated with glucocorticoid therapy might be justified on the basis of severity of RA. For example, the use of glucocorticoids, even in doses of 60 mg/day, for treatment of malignant diseases is generally accepted by doctors and patients, although severe RA was shown to have a 5-year survival comparable to stage 4 Hodgkin’s disease [27].

In 1983, a 24-week open non-blinded clinical trial of 5 mg/day of prednisone was reported with positive results to maintain functional status and slow radiographic progression in the prednisone versus control group [11]. This clinical trial began the modern era of low-dose glucocorticoid treatment. A greater risk/benefit ratio of low-dose glucocorticoid therapy compared to high-dose glucocorticoids was reported, including disease-modifying properties with 5 mg/day of prednisone, now confirmed in 6 further clinical trials with different designs and endpoints [12–17], although only 5 mg/day of prednisone was used in only one other clinical trial [12].

Two important clinical trials of low-dose glucocorticoids were reported in the 1990s. Kirwan [13] reported significant slowing of radiographic progression over 2 years in patients treated with 7.5 mg/day of prednisolone compared to placebo. Landewé et al. [28] reported on the long-term statistical benefits of the COBRA study [see the article by Rasch et al. in this special issue; pp. 51–56], which began with 60 mg of prednisolone, rapidly tapered to 5 mg/day, as well as sulfasalazine and methotrexate, compared to sulfasalazine. Again, significant slowing of radiographic progression was seen, which was maintained years later after discontinuation of prednisolone.

Table 1. Clinical trials documenting the value of low-dose prednisone in RA [10–17, 19–22]

<table>
<thead>
<tr>
<th>First author</th>
<th>Reference</th>
<th>Dose, mg/day</th>
<th>Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Andrade</td>
<td>[9]</td>
<td>5</td>
<td>Morning stiffness</td>
</tr>
<tr>
<td>Kirwan</td>
<td>[12]</td>
<td>7.5</td>
<td>X-ray</td>
</tr>
<tr>
<td>Boers (COBRA Trial)</td>
<td>[14]</td>
<td>60→5</td>
<td>ACR criteria, X-ray</td>
</tr>
<tr>
<td>van Everdingen</td>
<td>[15]</td>
<td>10</td>
<td>Tender joint count, X-ray</td>
</tr>
<tr>
<td>Svensson</td>
<td>[16]</td>
<td>7.5</td>
<td>X-ray</td>
</tr>
<tr>
<td>Wassenberg</td>
<td>[17]</td>
<td>5</td>
<td>X-ray</td>
</tr>
<tr>
<td>Buttgeret (CAPRA-1)</td>
<td>[18]</td>
<td>5 (modified release)</td>
<td>Morning stiffness</td>
</tr>
<tr>
<td>Pincus</td>
<td>[19]</td>
<td>≤5</td>
<td>Discontinuation of prednisone or placebo</td>
</tr>
<tr>
<td>Bakker</td>
<td>[20]</td>
<td>10</td>
<td>X-ray</td>
</tr>
<tr>
<td>Montecucco</td>
<td>[21]</td>
<td>12.5→7.5</td>
<td>Remission</td>
</tr>
<tr>
<td>Buttgeret (CAPRA-2)</td>
<td>[22]</td>
<td>5 (modified release)</td>
<td>ACR20, 50</td>
</tr>
</tbody>
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The two senior investigators, Dr. Kirwan and Dr. Boers, became strong advocates of common use of low-dose glucocorticoids in patients with RA.

Clinical Trials of Low-Dose Prednisone since 2000

Since 2000, 8 clinical trials have documented significant benefits of low-dose glucocorticoids [12, 15–17, 19–22]. The first Utrecht Study compared 10 mg of prednisolone to placebo with benefits documented for joint count and slowing of radiographic progression [15]. Svensson et al. [16] performed the Barfot Study in which 7.5 mg of prednisolone was shown to retard radiographic progression. A similar study by Wassenberg et al. [12], published simultaneously in Arthritis and Rheumatism, indicated slowing of radiographic progression with 5 mg/day of prednisolone.

The CAPRA-1 (Circadian Administration of Prednisone in Rheumatoid Arthritis) clinical trial [19] showed substantial differences in morning stiffness, as well as in IL-6 levels, associated with 12 weeks of modified-release prednisone, compared to immediate-release prednisone taken in the conventional morning dose. There was no significant difference in other efficacy measures, and the safety profile did not differ between the two treatment groups [19].

A withdrawal clinical trial of patients taking 5 mg/day or less was conducted to recognize whether patients might have clinical efficacy at this low dose [20]. This clinical trial was based on long-term therapy using 3 mg of prednisone as the initial dose in 83% of patients treated in this clinical setting after 2000, compared to 10.6 mg/day in 1980–1985, 20 years earlier [29]. Only 31 patients volunteered for this clinical trial, as many patients refused to participate since they had already tried to taper and discontinue prednisone on several occasions, at the advice of other physicians and family, but were convinced that prednisone was helpful. Among participants, the rate of withdrawal was significantly higher in patients who had been gradually tapered to placebo compared to those who remained on identical prednisone tablets in doses less than 5 mg/day [20].

Since the endpoint was withdrawal from therapy, there was no attempt to judge effects on maintaining functional status or slowing radiographic progression [20]. However, analyses of patients treated over a 25-year period [29] and of 150 patients treated by the author in the year 2000 [30] revealed Larsen scores that were only 3% of maximum. These data strongly suggest slowing of radiographic progression, although that cannot be isolated definitively, since most patients also were treated with methotrexate and/or other disease-modifying antirheumatic drugs.

In 2012, a second Utrecht Study, CAMERA-II, documented that 10 mg of prednisone, added to a ‘treat-to-target’ strategy with methotrexate, provided incremental slowing of radiographic progression [16]. A second clinical trial involving modified-release prednisone, CAPRA-2, indicated that addition of modified-release prednisone to existing DMARD treatment led to higher ACR20 and ACR50 responses compared to placebo, and with similar adverse events in both groups, establishing that modified-release prednisone is superior to placebo treatment [22].

Conclusions

Taken together, these studies document that low-dose prednisone or prednisolone provide both symptomatic relief with improved functional status and slowing of radiographic progression. Low doses are also associated with few adverse events and prednisone doses of 5 mg or less/day do not affect the hypothalamic-pituitary-adrenal axis [30, 31].

Randomized controlled clinical trials are the optimal method to analyze the efficacy and adverse effects of low-dose glucocorticoids, but have many limitations, particularly in chronic diseases – including a short time frame, inflexible dosage schedules and patient selection – which inevitably limit the application of results in actual clinical care [32–34]. Furthermore, it is extremely difficult or impossible to study the adverse effects of glucocorticoids adequately over fewer than 5 years. Therefore, clinical trials require supplementation with observational data, as discussed in another article in this special issue (see Pincus et al., p. 89). Knowledge of the risk/benefit ratio of low-dose glucocorticoids over long periods requires both clinical trials as well as long-term observational studies.

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