The clinical efficacy of 3 mg/day prednisone in patients with rheumatoid arthritis: evidence from a randomised, double-blind, placebo-controlled withdrawal clinical trial

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ABSTRACT

A randomised, double-blind, placebo-controlled, withdrawal clinical trial was conducted of prednisone <5 mg/day versus placebo in 31 patients with rheumatoid arthritis (RA). These patients had been treated with long-term 1–4 mg/day of prednisone, 22 with 3 mg/day, in usual clinical care at a single academic clinical setting. Stable clinical status over 12 weeks prior to screening for the trial was documented quantitatively by patient questionnaire scores. The protocol involved three phases: a) "equivalence" – 1–4 study prednisone 1-mg tablets taken for 12 weeks, to ascertain their efficacy versus the patient's usual prednisone tablets prior to randomisation; b) "transfer" – substitution of a 1-mg prednisone or identical placebo tablet at a rate of a single 1-mg tablet every 4 weeks (over 0–12 weeks) to the same number as baseline prednisone; c) "comparison" – observation over 24 subsequent weeks taking the same number of either placebo or prednisone tablets as at baseline. The primary outcome was withdrawal due to patient-reported lack of efficacy versus continuation in the trial for 24 weeks. Thirty-one patients were randomised, 15 to prednisone and 16 to placebo, with 3 administrative discontinuations. In "intent-to-treat" analyses, 3/15 prednisone and 11/16 placebo participants withdrew (p=0.03). Among participants eligible for the primary outcome of withdrawal for lack of efficacy, 3/13 prednisone versus 11/15 placebo participants withdrew (p=0.02). No meaningful adverse events were reported, as anticipated. These data document statistically significant differences between the efficacy of 1–4 mg prednisone vs. placebo in only 31 patients, which may suggest a robust treatment effect.

Introduction

Systemic glucocorticoids generally continue to be recommended in patients with rheumatoid arthritis (RA) primarily as "bridging therapy" while awaiting anticipated benefits of disease modifying anti-rheumatic drugs (DMARDs) and not appropriate for possible long-term therapy (1). Nonetheless, prednisone or prednisolone are used quite commonly in many usual care rheumatology clinical settings. In the quantitative clinical assessment of patients with rheumatoid arthritis (QUEST-RA) study of 4,363 RA patients seen in usual care at 48 clinical sites (~100 patients per site) in 15 countries, 66% of patients were taking glucocorticoids, including more than 70% in Argentina, Finland, France, Ireland, Serbia, and USA, more than 50% in Germany, Italy, Poland, Spain, Sweden, Turkey, and UK – fewer than 50% only in Denmark (43%) and the Netherlands (26%) (2).

The author developed a practice between 1980 and 2004 of treating more than 80% of RA patients seen at a weekly academic clinical setting with low-dose prednisone, generally <5 mg/day, maintained indefinitely. Almost all patients were treated with concomitant methotrexate after 1990. It was noted in long-term studies (see *Pincus* chapter p. S-130) that higher doses were initiated in patients with higher scores for physical function, pain, and routine assessment of patient index data (RAPID3) (3, 4) on a multidimensional health assessment questionnaire (MDHAQ) (5). Similar improvement was seen in these scores in patients whose initial dose was less than, equal to, or greater than 5 mg/day, and few adverse effects were seen – primarily bruising and skin thinning.

Prednisone in doses of 5 mg/day or less appears potentially attractive for long-term use in a chronic rheumatic disease

such as RA, as these doses do not lead to suppression of the hypothalamic-pituitary-adrenal axis and a need for supplementation at surgery or other stressful events (6-9). Furthermore, as noted by Da Silva *et al.*, "adverse effects associated with [low-dose prednisone] are modest, and often not statistically different from those of placebo" (10). However, the efficacy of prednisone in doses of less than 5 mg/day has not been extensively analysed in patients with RA. Rheumatologists continue to disagree on the relative risk/benefit ratio of long-term treatment with low-dose glucocorticoids.

A large, multicentre prospective randomised double-blind clinical trial in RA patients with no previous glucocorticoid therapy, to analyse the efficacy of <5 mg/day of prednisone along with usual therapies, might appear ideal. However, resources for such a multicentre clinical trial have not been available. Therefore, a single-centre withdrawal trial of prednisone <5 mg/day was conducted in the course of usual care (11).

Description of withdrawal clinical trial protocol

All patients were recruited from one academic clinical care setting of TP at Vanderbilt University; all clinical trial visits were conducted during usual clinical care. Most RA patients in this clinical setting were treated with long-term prednisone 1–5 mg/day from their first visit; the usual initial dose was 3 mg/day since the mid-1990s. Most patients experienced clinical effectiveness and few adverse effects – primarily bruising and skin thinning after months to years of therapy, similar to recent experience described in usual care in Germany (12). Almost all patients were also treated with methotrexate after 1990 (13), so the specific efficacy of prednisone could not be analysed without a clinical trial. The protocol included three phases:

a. <u>Equivalence</u> – All participants were given a 12-week (84-day – actually 100 days to ensure availability) supply of "study prednisone" tablets to take at the same dose as at baseline, prior to entry into the clinical trial, to ascertain similar efficacy of the study prednisone to usual prednisone.

Table I. Plan to "transfer" patients from low-dose prednisone tablets to study prednisone or placebo tablets.

Dose	Medication	Week of "transfer" phase				
		Week 0	Week 4	Week 8	Week 12	Week 16*
1 mg	Bottle A (prednisone)	0				
	Bottle B (unknown)	1				
2 mg	Bottle A (prednisone)	1	0			
	Bottle B (unknown)	1	2			
3 mg	Bottle A (prednisone)	2	1	0		
	Bottle B (unknown)	1	2	3		
4 mg	Bottle A (prednisone)	3	2	1	0	
	Bottle B (unknown)	1	2	3	4	
5 mg	Bottle A (prednisone)	4	3	2	1	0
	Bottle B (unknown)	1	2	3	4	5

Each participant was given an individual schedule outlining specific dates to make changes in the number of tablets to be taken from Bottle A and Bottle B.
*No patients taking 5 mg at baseline were enrolled in the study.

b. <u>Transfer</u> – Participants who reported "equivalence" over the 12-week period were assigned randomly to be "transferred" at a gradual rate (to avoid abrupt reduction of prednisone usage in subjects randomised for transfer to placebo) of a single 1-mg tablet per 4 weeks over the next 0–12 weeks, from study prednisone tablets to either 1-mg prednisone or identical placebo tablets (Table I).

c. <u>Comparison</u> – Participants were maintained over 24 weeks, following the "transfer" phase, taking the same number of either 1-mg prednisone or identical placebo tablets as at baseline.

Patients with RA who were taking stable doses of prednisone 1–4 mg per day in 1-mg tablets or one 5 mg tablet per day (although no patients who were taking 5 mg were actually enrolled) were eligible for the clinical trial. All patients were required to have stable clinical status over the previous 12 weeks documented by stable MDHAQ scores (14) for physical function, pain and global estimate of status, each scored 0–10 (15) and RAPID3, a composite of theses 3 RA core data set measures, scored 0–30 (3). (An MDHAQ is completed by all patients at all visits as a component of the infrastructure of standard care [16]). Few exclusion criteria were listed, including clinical improvement (RAPID3 lower by ≥3 units), clinical decline (RAPID3 higher by ≥3 units), severe fibromyalgia, a stable prednisone dose greater than 5 mg/

day (only 12% of all patients), severe clinical status for whom the investigator regarded it as inappropriate clinically to discontinue prednisone (fewer than 5% of all patients), pregnancy or nursing, substantial comorbidities, and planned elective surgery.

Results of withdrawal clinical trial
Although few exclusion criteria were listed, only 37 of 156 patients seen volunteered. Reasons for non-participation included: 21 (13.5%) unwilling to discontinue taking prednisone, often noting previous efforts without success, at the advice of physicians, relatives and others; 21 (13.5%) clinically improving (RAPID3 lower by ≥3 units) with new RA therapies; 9 (5.8%) clinically declining (RAPID3 higher by ≥3 units) with need for new therapies; 14 (9%) with severe fibromyalgia; 15 (9.6%) too far away for 3 monthly visits; 1 (0.6%) could not complete an English-language questionnaire; 19 (12.2%) took a prednisone dose greater than 5 mg/day (all initiated by other physicians); 5 (3.2%) not taking any prednisone; 4 (2.6%) with severe clinical status for whom the investigator regarded it as inappropriate clinically to discontinue prednisone; 3 (1.9%) pregnant or nursing; 5 (3.2%) with substantial comorbidities; and 2 (1.3%) with planned elective surgery.
Of 37 patient volunteers, 6 decided not to continue after the first 12 week "equivalence" phase, with an impression that the study prednisone did not

Table II. Clinical trial results in 31 participants who were randomised to prednisone or placebo, following gradual withdrawal of prednisone, according to baseline prednisone dose.

| Study group | Clinical trial results | Baseline prednisone dose | | | | |
		1 mg	2 mg	3 mg	4 mg	Total
Prednisone	Number randomised	1	2	10	2	15
	Withdrew – lack of efficacy	0	0	3	0	3*
	Completed trial	1	2	6	1	10*
	Withdrew – administrative	0	0	1	1	2
Placebo	Number randomised	0	1	12	3	16
	Withdrew – lack of efficacy	0	1	9	1	11*
	Completed trial	0	0	2	2	4*
	Withdrew – administrative	0	0	1	0	1
TOTAL		1	3	22	5	31

*For 28 participants who either completed the trial or withdrew because of lack of efficacy, $p=0.021$ by Fisher's exact test (prednisone *vs*. placebo). For all 31 randomised participants, $p=0.032$ by Fisher's exact test (prednisone *vs*. placebo).

have efficacy comparable to their usual prednisone; no explanation for this phenomenon was found. Therefore, 31 patients were randomised: 15 to prednisone and 16 to placebo (11). Among these 31 patients, 22 took 3 mg/day prednisone, one 1 mg/day, three 2 mg/day, and five 4 mg/day. The mean prednisone dose at baseline was 2.9 mg/day and the median dose 3 mg/day in both groups; patients had taken prednisone for 1–15 years. Methotrexate was taken at dosages between 5 and 25 mg/week by all but 2 participants.

Patients in the two groups did not differ significantly in age, duration of disease, or any quantitative or laboratory measure, including scores for physical function, pain, patient global estimate of status, or RAPID3 (11). Mean RAPID3 scores were 4.07 and 4.87; RAPID3 low activity is 3.01–6 (of 30) (15, 17), so most patients, but not all, were in low activity or remission.

Of the 15 participants who were randomised to prednisone, one took 1 mg/day, two took 2 mg/day, ten took 3 mg/day and two took 4 mg/day. Two patients were withdrawn for administrative reasons: one for an unanticipated hysterectomy and the other for a recurrence of breast cancer. Of the 13 remaining prednisone participants, 3 withdrew for lack of efficacy and 10 completed the 24-week "comparison" observation period (11) (Table II).

Of the 16 participants who were randomised to placebo, one took 2 mg/day, twelve took 3 mg/day and three took 4 mg/day as their stable dose. One patient

was withdrawn for administrative reasons; the patient had severe weight loss, ultimately found based on depression, with discontinuation of all medications. Of the 15 remaining placebo participants, 11 withdrew for lack of efficacy and 4 completed the 24-week "comparison" observation period (Table II).

Differences between withdrawal in the prednisone group *versus* the placebo group (Table II) were statistically significant ($p=0.021$). An intent-to-treat analysis of all randomised participants also indicated significant differences ($p=0.032$) (Table II).

Participants in the placebo group had higher median changes (indicating poorer status) with worsening scores for physical function, pain, patient global estimate, RAPID3 and fatigue. Participants in the prednisone group remained similar to baseline at the conclusion of the trial (11), although none of the differences compared to the placebo group were statistically significant ($p>0.05$). Furthermore, no significant differences between the groups were seen for change in ESR or CRP. No meaningful toxicities were reported by the participants in either group, as anticipated.

Interpretation of results

The clinical trial results indicate that patients who were transferred from long-term prednisone doses of 1–4 mg/day to identical placebo tablets were significantly more likely to withdraw over a subsequent 6- to 9-month period than those participants who were randomised to prednisone (11). Most rheu-

matologists initiate (and often maintain) prednisone therapy at doses higher than 3 mg. By contrast, most participants in the clinical trial had never taken prednisone at a dose higher than 3 mg, a dose that is attractive as no suppression of the hypothalamic-pituitary-adrenal (HPA) axis is seen (6-9). The efficacy of this dose compared to placebo was documented in the trial (11).

The withdrawal period involved reduction of the prednisone dose by 1 mg/day each month. In actual clinical practice, patients may be advised to alternate for 2–3 weeks between the dose that they were taking and the new 1 mg/day lower dose (11). Another approach to withdrawal used in the Netherlands involves decreasing the daily dose by 1 mg over 7 weeks, with the lower dose taken one day more among the days of the week progressively each week (18). These withdrawal schemes allow the patient to titrate the dose, and find a level that seems to be "required" to control symptoms optimally, or to taper completely and to discontinue all prednisone (a minority in the author's experience). The most important principle is that the withdrawal must be gradual, or the patient may experience a flare of symptoms. Further research concerning optimal withdrawal schemes for prednisone appears of value.

The reported clinical trial had many limitations:

a) Only 31 patients were randomised, although statistically significant differences with only 31 participants may imply a robust treatment effect.

b) The study was conducted in only one academic clinical site, which may not be representative of all RA patients.

c) Clinical status was assessed only according to patient questionnaire scores, although these scores yield results similar to joint counts and laboratory tests in clinical trials of adalimumab (19), abatacept (20) and certolizumab (17).

d) The trial was conducted entirely in the course of usual clinic visits, without a study coordinator, who might have added rigor to results. However, costs were substantially lower than in usual clinical trials, and the primary outcome was accounted for in all 31 enrolled patients at 24 weeks.

At the same time, this clinical trial may provide proof-of-concept that a simple clinical trial can be conducted in the course of usual clinical care, with minimal additional expense. A need for simple clinical trials is recognised to analyse results of therapy in most situations in clinical medicine, in which resources might not be available for the type of elaborate clinical trials sponsored by pharmaceutical companies to gain registration of new medications (21, 22). A simple trial with the flaws noted above and other limitations would appear preferable to the absence of any effort to study the important question concerning whether prednisone 3 mg/day is efficacious in RA.

The capacity to perform a simple clinical trial in usual clinical care is provided by routine completion of the MDHAQ in every patient at every visit in the clinical setting in which it was performed. This practice also allowed recognition of "stable clinical status" as a requirement for entry into the trial on the basis of quantitative documentation, rather than "gestalt" clinical judgment, the usual practice at this time. Exclusion of patients whose status was improving or declining may have been critical to demonstration of statistically significant differences between prednisone and placebo in only 31 patients.

"Add-on" clinical trials of biological agents involving patients with "incomplete responses" to methotrexate generally indicate ACR20 responses in the range of 20–30% in patients randomised to control treatment (23, 24). This finding may be explained in part by description of "incomplete responses" to methotrexate on the basis of clinical judgment rather than quantitative data. A requirement for stable questionnaire scores over a 3-month period to document incomplete (or complete, stable or unstable) responses, as in the reported trial (11), could reduce background responses in control arms of RA clinical trials.

The reported trial may underestimate treatment effects of prednisone, given that a primary reason for non-participation was a desire of many patients not to discontinue prednisone, on the basis of failure of (often many) previous attempts. Most participants in the clinical trial never took doses of prednisone greater than 3 mg/day, with mean RAPID3 scores at baseline of less than 2 on a scale of 0–10, or 6 on a scale of 0–30, indicating low severity (15). A multicentre (>2 year) *de novo* clinical trial of <u>initiation</u> of 3 mg prednisone per day *versus* placebo in patients who had never been treated previously with prednisone, rather than withdrawal from prednisone, might give more definitive information, and would appear of considerable value.

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