Effects on joint destruction and remission, bone turnover and lack of influence on atherogenesis: a review of the BARFOT low-dose prednisolone studies on patients with early RA

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ABSTRACT

As early as in 1948 a woman with severe rheumatoid arthritis (RA) was successfully treated with glucocorticoids. However, not until recently has the role of GCs in the treatment of RA been clarified and supported by scientific evidence in a limited number of randomised studies. The present article reviews four reports from the BARFOT (Better Anti-Rheumatic FarmacOTherapy) low-dose prednisolone study based on 250 patients with early RA. These patients were randomised to have either DMARDs only or DMARDs plus prednisolone 7.5 mg daily for two years.

It was shown that low-dose prednisolone in addition to a DMARD was superior to DMARDs alone in the ability to inhibit joint damage and induce clinical remission. A follow-up study demonstrated that remission after 2 years with low-dose prednisolone was associated with reduced joint destruction also after 4 years. Prednisolone had no or minor effects on bone density and the frequency of adverse effects was small. A third article measuring markers of bone synthesis and resorption demonstrated that the suppressive effect on bone synthesis exerted by prednisolone was counteracted by the ability of prednisolone to hamper the inflammatory mediated increase in bone resorption. In a fourth article assessing intima-media thickness and endothelial function, no influence of prednisolone 7.5 mg daily on atherosclerosis was observed. Altogether, these four studies provide evidence for recommending low-dose prednisolone treatment in combination with DMARDs for at least two years to patients with recent onset RA.

Introduction

The outcome of rheumatoid arthritis (RA) has gradually and considerably improved. The reason for this is diverse, early diagnosis, early institution of conventional and biologic DMARDs, orthopaedic surgery and tight control regimens are the most important reasons.

We present in this article a review of four studies concerning our experience in a randomised controlled trial of prednisolone conducted in the early 2000s (1-4).

A milestone was reached in September 1948 when Dr Philip Hench with dramatic success for the first time ever treated a woman with severe RA with a corticosteroid, Compound E (5). Shortly after that, in the 1950s, systematic studies found beneficial effects of glucocorticoids (GCs) on clinical symptoms and joint destruction in patients with recent RA (6).

The early studies had little impact on clinical practice after the 1950s because of adverse effects of glucocorticoids. Glucocorticoids were advocated and used in different arbitrary ways by some rheumatologists as bridging therapy while awaiting results of DMARD therapy or only for life-threatening extra-articular disease, such as vasculitis, while others adopted an adverse attitude excluding glucocorticoids entirely from therapeutic options. In recent years, the role of glucocorticoids in treatment of RA has been clarified and supported by new scientific evidence. Thus in 1995, Kirwan *et al*. for the ARC (Arthritis and Rheumatism Council) (7) presented the exciting observation that prednisolone 7.5 mg daily together with optional DMARDs slowed down radiographic joint damage in patients with early RA (disease duration ≤2 years), while the effects of GCs on clinical symptoms and signs were less impressive.

This study aroused a great deal of attention from the world of rheumatology and was followed by a few other randomised low-dose prednisolone

Table I. Van der Heijde Sharp scores (median (IQR) and mean (SD)) from study start to two years in patients in the prednisolone (pred) and no prednisolone (no pred) groups (1).

		Median (IQR)			Mean (SD)	
		pred	no pred	*p*-value	pred	no pred
Baseline	TS score	1.5 (0–4.0)	1.5 (0–4.0)	0.88	4.1 (9.2)	4.8 (9.6)
	E score	0.5 (0–1.5)	0.5 (0–1.5)	0.49	1.9 (5.0)	1.9 (4.0)
	JSN score	1.0 (0–2.5)	0.5 (0–2.5)	0.94	2.2 (4.6)	2.9 (6.4)
One year	Change in TS score	1.0 (0–3.0)	2.0 (0–5.0)	0.035	2.4 (4.6)	5.3 (9.3)
	Change in E score	0.0 (0–1.5)	0.5 (0–3.0)	0.005	0.8 (1.6)	2.4 (4.0)
	Change in JSN score	0.0 (0–2.0)	0.5 (0–2.5)	0.14	1.5 (3.8)	2.9 (6.0)
Two years	Change in TS score	1.8 (0.5–6)	3.5 (0.5–10)	0.019	5.2 (9.0)	9.1 (14.3)
	Change in E score	0.5 (0–2.0)	1.5 (0–4.5)	0.019	1.9 (3.6)	4.0 (6.8)
	Change in JSN score	1.0 (0–4.0)	2.0 (5–5.0)	0.08	3.3 (6.4)	5.0 (8.6)

studies with different design (8, 9) and the studies by the BARFOT study group (1, 2). In the BARFOT studies we tried to reproduce Kirwan's study as closely as possible.

Low-dose prednisolone reduces joint damage and increases remission rate

Two hundred and fifty patients with early RA (≤ one year after onset) who entered the BARFOT observational study of RA in southern Sweden were included (1).

At the start of the study all patients were DMARD and glucocorticoid naïve with sufficiently active disease of a DAS28 >3.0 to have a DMARD initiated. The 250 patients were randomised to daily prednisolone (n=119) or no daily prednisolone (n=131) for 2 years. Joint damage in hands and feet was assessed by the Sharp van der Heijde modified score (total score, TS, erosion score, ES and joint space narrowing score, JSN) (10). The smallest detectable change (SDC) in TS from baseline to two years (SDC) was calculated to be 5.8. Remission was defined as a DAS28 below 2.6 (11). Function was assessed by the Swedish version of the HAQ score (12).

Radiographic joint damage was inhibited by prednisolone

At the end of two years, all but eight patients had completed the study. The progression of radiographic joint damage was less pronounced in the prednisolone (P) group compared with the group without prednisolone (NoP group), which was shown in the following ways:

- The increase in TS and ES was significantly smaller in the P group compared with that in the NoP group after one and two years (Table I).
- The number of new erosions increased less frequently in the P group. Thus, after 1 and 2 years the median number of newly eroded joints was 0 and 0.5 in the P group and significantly higher in the NoP group, 0.5 and 1.25, p=0.004 and 0.007, respectively.
- At the end of the study, a smaller proportion of patients, 25.9%, in the P group had radiographic progression above SDC compared with 39.3% of patients in the NoP group, p=0.033.

Frequency of remission increased and function improved

Disease activity, measured by DAS28, decreased over the 2 years from mean 5.3 to 2.7 in the P group which was significantly more than in the NoP group, from 5.4 to 3.2,. p=0.005 (Fig. 1). Remission was more common among patients who were treated with prednisolone. Thus, after 2 years 55.5% in the P group compared with 32.8% in the NoP group (p=0.001) benefited from remission.

Function improved significantly more in the P group where the mean HAQ decreased over 2 years from 1.0 to 0.5, while the decrease in the NoP group was mean 1.0 to 0.7, p=0.003.

Adverse effects were acceptable in both the P and NoP groups

Prednisolone was well tolerated and the frequency of adverse reactions was low in both treatment groups and most often due to the DMARD given. However, in the P group prednisolone was judged to be the cause in five cases; diabetes (1); proteinurea (2); striae and ecchymoses (1) and cushingoid appearance (1) while there was none of these in the NoP group. As to the effects on bone, see below.

Remission after 2 years treatment with low-dose prednisolone was associated with reduced joint destruction also after 4 years

In an extension of the ARC study (13), the rate of joint destruction resumed during the third year, during which prednisolone was discontinued. How-

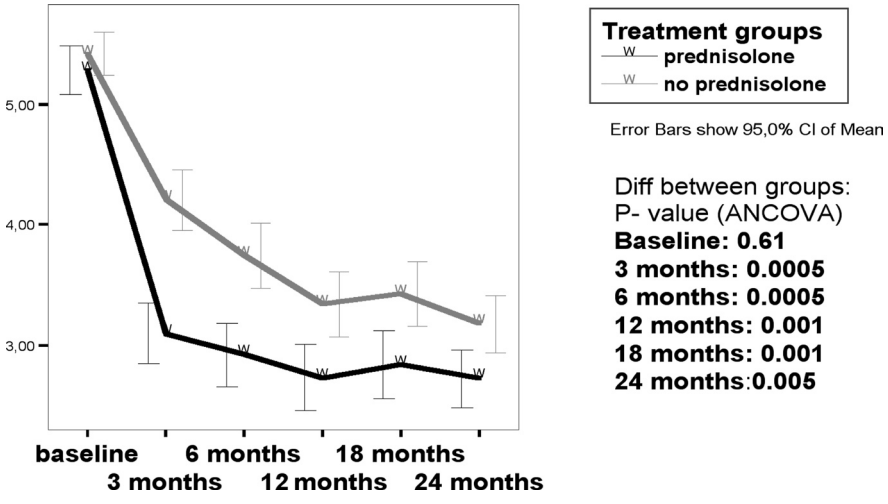

Fig. 1. DAS28 in the prednisolone group was significantly lower than DAS28 in the no prednisolone group at each follow-up visit (1).

Table II. Van der Heijde Sharp scores (median (IQR)) after four years in patients with or without remission at two years, broken up by treatment groups (2).

	Prednisolone group, n=64			No prednisolone group, n=86		
	In remission n=35	No remission n=29	*p*-value	In remission n=26	No remission n=60	*p*-value
	Scores at 4 years			Scores at 4 years		
TS score	7.5 (2.0–11.5)	13.5 (3.0–25.0)	0.009	7.0 (2.0–10.0)	16.0 (8.0–28.5)	0.001
ES score	1.0 (0.0–3.0)	3.0 (0.0–8.0)	0.005	1.0 (0.0–2.0)	3.5 (1.5–9.0)	0.002
JSN score	5.0 (2.0–9.5)	9.0 (2.0–15.5)	0.015	3.5 (2.0–9.0)	9.5 (6.5–19.5)	0.003
	Change 0 to 4 years			Change 0 to 4 years		
TS score	4.5 (2.0–7.5)	12.0 (4.0–24.5)	0.006	6.5 (1.5–12.0)	10.5 (1.0–20.0)	0.466
ES score	0.0 (0.0–1.0)	3.0 (1.0–9.0)	0.001	1.0 (0.0–2.5)	1.5 (0.0–6.0)	0.209
JSN score	3.0 (1.0–7.0)	8.0 (3.0–17.0)	0.020	4.5 (1.0–10.0)	6.5 (1.0–14.0)	0.527

ever, joint damage was still significantly lower compared with that in the placebo-treated patients. In contrast, the COBRA study (14) reported long-term reduction of radiological damage in a 4–5 year follow-up in patients who received triple therapy, including prednisolone. However, prednisolone was started in high dosage, followed by tapering and withdrawal at week 35. These studies did not address the possibility that the patients who showed remission with prednisolone treatment might have reduced joint damage. Therefore, we wanted to know if remission induced by the prednisolone, added to the first DMARD during the first 2 years of early RA, was associated with sustained effects on radiological damage and physical function over a period of 4 years (2).

Of the original 250 patients, 211 were eligible for the continuation study, of which 61 declined to participate in the study from year 2 to 4, mainly because they wanted to decide by themselves when to be treated by prednisolone. The remaining 64 patients from the P group were re-randomised to either discontinue or continue 7.5 mg prednisolone daily while the 86 patients from the NoP group continued without prednisolone. DMARDs were prescribed according to the recommendations in use at the time of the study.

Remission was associated with decreased radiological progression in prednisolone treated patients

Patients in remission at 2 years had, compared with those not in remission, significantly less change in radiographic scores also at 4 years (Table II). These results were in agreement with the observation in a longitudinal analysis that remission by DAS28 was associated with lower Sharp scores during the entire four-year follow-up. Furthermore, a post hoc analysis showed that patients *in remission with prednisolone* at 2 years had significantly less increase in radiographic scores at 4 years than patients *in remission with no prednisolone* at 2 years. This was supported by a longitudinal analysis showing that radiological progression in patients in remission was dependent on prednisolone use.

Irrespective of remission state, the patients randomised to no prednisolone increased more in total Sharp score than those with prednisolone during the four years period but this tendency (p=0.079) was significant only for the first two years (p=0.019).

Early remission was associated with better function irrespective of prednisolone treatment

Patients in remission at 2 years had significantly lower HAQ score at both 2 and 4 years, irrespective of whether they were treated with prednisolone or not. During the 2-year extension of the original study, side effects were few and never serious.

Effects of prednisolone treatment on bone mineral density

Dual x-ray absorptiometry (DXA) was performed in 189 of the patients both at baseline and after 2 years. The mean bone mineral density (BMD), expressed in g/cm^2, at the lumbar spine did not differ significantly between the P and NoP groups, neither at baseline nor after 2 years, 1.14 and 1.11 *vs*. 1.17 and 0.16, respectively. Similarly, the decrease in z- score during the 2 study years did not differ significantly between the P and NoP groups, -0.29 *vs*. -0.16, respectively (1).

Accordingly, at the femur neck there were no significant differences in BMD between the P and NoP groups at baseline and at 2 years, 0.91 and 0.90 *vs*. 0,90 and 0.87, respectively, or in the change in Z-score from baseline to 2 years, -0,07 *vs*. -0.16, respectively.

When looking at women separately, the decrease in BMD and Z-scores at lumbar spine was significantly higher in the P women than the in the NoP women, p=0.001. This increased loss affected the postmenopausal women, as there was no difference in bone loss between treatment groups when calculated on premenopausal women only.

The changes in BMD of lumbar spine and femoral neck during the 4 years did not differ significantly between the treatment groups, nor did the changes in BMD differ between patients in remission at 2 years and those not, irrespective of treatment group (2).

In the BARFOT study, prednisolone had thus no or only small effects on BMD except that postmenopausal women treated with prednisolone lost more bone during the first 2 years of treatment. However, at the time of the study, prevention of osteoporosis was carried out with supplement of calcium

only, not with vitamin D or bisphosphonates.

Low-dose prednisolone treatment and bone turnover

Suppressive effects of GCs on bone synthesis have been well documented, especially when high doses are used. RA has been shown to be associated with an increased risk of osteoporosis. Since a great number of patients with RA are treated with GCs it is usually difficult to sort out the relative effects on bone formation and resorption obtained by the disease and its treatment. However, the randomised design of the present study makes this possible.

We compared the P and NoP groups as to the performance of the procollagen type 1 N-terminal propeptide (P1NP) (bone formation), the C-telopeptide crosslaps of type I collagen (CTX-1) and the C-terminal telopeptide of type I collagen (1CTP) (bone resorption) (3). It was then shown that P1NP decreased more in the P group than in the NoP group, $p<0.001$. CTX-1 and 1CTP decreased in both treatment groups, significantly more in the P group, $p=0.019$ and $p<0.001$, respectively. Thus, in the P group the decrease in bone resorption balanced the decrease in bone formation.

The data suggest that the suppressive effect on bone synthesis exerted by prednisolone was compensated by its ability to hamper disease activity and thereby the inflammatory mediated increase in bone resorption.

Effect of low-dose prednisolone treatment on atherosclerosis and endothelial function

Patients with rheumatoid arthritis (RA) run a significant risk of cardiovascular disease (CVD), independent of traditional risk factors. In addition, treatment with GCs has been associated with an increased risk of CVD. Therefore, we deemed it of interest to use patents from the randomised prednisolone study to assess the influence of low-dose prednisolone on atherosclerosis, endothelial function and risk factors for atherosclerosis.

In this study 67 patients were recruited from one of the participating centres, 34 from the P group and 33 from the NoP group. In the P group, 21 patients were treated for two years and 13 for at least five years with prednisolone (4). After a mean of five years the intima-media thickness (IMT) of the carotid arteries was determined by B mode ultrasound and endothelial function was assessed by flow-mediated dilatation of the brachial artery (FMD).

The median IMT did not differ between the P and NoP groups, 0.675 mm *vs*. 0.673 mm, respectively, nor did the prevalence of atherosclerotic plaques, 82.3% *vs*. 81.9% or endothelial function, FMD percentage change (mean±SD); 3.88±2.8 *vs*. 3.74±2.9%, respectively. Moreover, there was no difference in lumen diameter of carotid arteries, levels of lipoproteins and glucose. Patients treated for all five years with prednisolone had at that time-point significantly higher cholesterol levels, 5.6±1.39 as compared with non-treated, 4.9±28, $p=0.03$ and showed a trend to higher systolic blood pressure, 157±29 mm Hg *vs*. 141±28 mm Hg, $p=0.06$. In the whole cohort, age and high-density lipoproteins (HDL) were independently associated with IMT, while age and serum creatinine were associated with presence of atherosclerotic plaques.

All together, treatment with prednisolone 7.5 mg daily did not influence atherosclerosis and endothelial function in RA. However, total cholesterol increased during prednisolone treatment.

Comments and conclusions

The first article in the present series of studies on low-dose prednisolone in early RA demonstrated that low-dose prednisolone in combination with a DMARD inhibits joint damage for two years. The second study provides some evidence for a continued effect during two additional years. Moreover, to be in remission is a further advantage since it was shown that prednisolone treated patients, who were in remission after two years benefited from reduced joint damage also during the following two years.

The DXA data indicate that prednisolone had no or only small effects on BMD except that postmenopausal women treated with prednisolone lost somewhat more bone during the first two years of treatment. Other side effects were few and infrequently serious and were considered acceptable.

The third article focused on the effects of the disease and its treatment on bone turnover. The main conclusion of this study was that the suppressive effect on bone synthesis exerted by prednisolone was counteracted by the ability of prednisolone to hamper disease activity and thereby the inflammatory mediated increase in bone resorption.

Finally, the fourth article addressed the relation of atherosclerosis, RA and its treatment with GCs. No influence of prednisolone 7.5 mg daily on atherosclerosis or endothelial function was observed. However, total cholesterol increased during prednisolone treatment.

To conclude, these articles provide evidence for recommending low-dose prednisolone treatment in combination with DMARDs for at least two to four years to patients with recent onset RA. This treatment reduced joint damage substantially and increased remission rates significantly and was associated with few serious side effects. A negative effect on BMD was only seen in the spine of postmenopausal women, which may probably be avoided by a more up to date prevention of osteoporosis. Low-dose prednisolone treatment alleviated the catabolic effect of bone induced by the inflammatory process and, finally, no evidence of an atherogenic effect of low-dose prednisolone treatment could be demonstrated.

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