
A dose of only 5 mg prednisolone daily retards radiographic progression in early rheumatoid arthritis – the Low-Dose Prednisolone Trial

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Received and accepted on August 15, 2011.

Clin Exp Rheumatol 2011; 29 (Suppl. 68): S68-S72.

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Key words: prednisolone, radiographic progression, rheumatoid arthritis

Competing interests: H. Zeidler has received honoraria from Merck KGaA for giving lectures; the other co-authors have declared no competing interests.

ABSTRACT

Glucocorticoids (GC) have been used to treat rheumatoid arthritis (RA) for more than 60 years. Despite this very long experience, there remains considerable debate concerning the adequate dosing and timing of these medications, primarily because of frequent and sometimes serious side effects, particularly in high doses. GCs are documented to provide immediate symptomatic relief and to decrease signs of inflammation in active disease. At the time when the Low-Dose Prednisolone Trial (LDPT) was designed, no clear evidence was available concerning whether low doses of GCs given over a long period add to slowing of structural damage in RA. The trial was therefore designed to test the hypothesis that even a low dose of prednisolone that was thought to cause no or only very limited harm could slow radiographic progression. The trial therefore included patients with active early RA (disease duration less than two years) who received either prednisolone 5 mg/day or placebo on concomitant DMARD therapy with parenteral gold or methotrexate for two years. Radiographs of hands and feet were taken at baseline, and at 6, 12 and 24 months. Structural damage was assessed using change in the Ratingen score (0–190 scale) as the primary outcome, and change in the Sharp/van der Heijde score (0–448 scale) for additional information concerning the same radiographs. Of 192 patients in the study, 166 were available for intention to treat analysis (ITT), and 76 completed the study per protocol (PP). Progression of the Ratingen score was significantly less at all consecutive time points in the prednisolone group compared to the control group, with the greatest difference after 6 months. At 24 months the increase in score in the prednisolone group was 1.2 ± 3.5 , (95% CI 0.4–2.1)

and in the placebo group 4.3 ± 6.8 (95% CI 2.7–5.9) ($p=0.006$, ITT-analysis). This was confirmed by the results of the Sharp/van der Heijde erosion and total score with an increase of the total score of 5.3 ± 10.7 units in the prednisolone compared to 11.4 ± 19.1 in the placebo group ($p=0.022$) at 24 months. The LDPT trial therefore confirmed that a very low daily dose of 5 mg prednisolone given over two years in combination with background DMARD therapy substantially decreases radiographically detectable damage in patients with early RA.

Introduction

Disease-modifying effects of glucocorticoids were recognised a few years after their introduction in the 1950s (1). Early open randomised studies using high doses of cortisone or prednisolone (2–4) provided conflicting results, but severe adverse effects occurring with high doses were unacceptable for long-term use. Nevertheless glucocorticoids are widely used in the treatment of rheumatoid arthritis. Studies from the US and from the large German database of the German Collaborative Arthritis Centers show that about 60% of outpatients are treated with these medications, with the majority receiving doses equivalent to ≤ 7.5 mg/day prednisolone (5, 6).

The Low-Dose Prednisolone Study was therefore undertaken to investigate whether a very low dose of prednisolone of 5 mg daily has an effect on radiographically detectable damage in patients with early (less than two years disease duration) RA. The radiographic, clinical and safety data have been reported previously (7). This paper focusses on the interpretation of the radiographic results and on bone density measurements. Patients with active disease were enrolled from Janu-

ary 1993 to December 1995 while starting concomitant treatment with either parenteral gold or methotrexate, the mostly widely-used disease-modifying anti-rheumatic drugs (DMARDs) at the time. These drugs were also chosen to avoid a possible confounding effect of the concomitant treatment, as both had been shown to have an almost identical effect on radiographic progression in the German comparative trial of parenteral gold and methotrexate in early erosive RA (8).

Methods

The patients were randomised to receive either 5 mg prednisolone or placebo at the time treatment with parenteral gold or methotrexate was commenced. The choice of which agent was left to the treating physician. Gold sodium thiomalate was initiated with a 10 mg intramuscular (i.m.) injection, followed by 20 mg a week later, and then by 50 mg injections once weekly up to a total dose of 2,000 mg; thereafter, patients were treated with a maintenance dose of 50 mg every other week. Methotrexate was initiated with a dose of 7.5 mg/week for three weeks, followed by 10–15 mg weekly (i.m., i.v. or orally) depending on tolerability. If gold or methotrexate was discontinued because of lack of efficacy (not before 6 months of therapy), or because of toxicity, the other DMARD had to be initiated within six weeks. If complete remission was achieved for more than six months, the gold or methotrexate dose could be decreased by the treating physician.

Non-steroidal anti-inflammatory drugs (NSAIDs) and osteoporosis prophylaxis (calcium, vitamin D supplementation and oestrogen replacement) were allowed, whereas osteoporosis treatment with fluorine, bisphosphonates and calcitonin was not allowed.

X-rays of hands and feet were taken at baseline and at 6, 12 and 24 months, lumbar spine radiographs in lateral projection at baseline and 24 months. All radiographs were collected for central evaluation, and evaluated with known sequence of the films, as this was advised to detect minimal clinically relevant changes (9). Hand and feet radiographs were scored twice, with an

interval of more than 6 weeks, with the Ratingen Score (10) and the van der Heijde's modified Sharp Score (11), respectively.

The Ratingen Score includes 38 joints, each graded according to the amount of joint surface destruction on a 0 to 5 scale leading to Score results ranging from 0 to 190. The van der Heijde/Sharp Score comprises an Erosion Score (ES) that evaluates 44 joints of the hands and feet, graded 0–5 in the hands and 0–10 in the feet according to the number and size of erosions, and a separate Joint Space Narrowing Score (JSN) that grades 42 joints on a 0–4 scale. The ES ranges between 0 and 280, and the JSN between 0 and 168; both are added to yield the Total Score (TS), ranging from 0 to 448.

Secondary clinical and functional outcome parameters (pain and overall condition, morning stiffness, 38 joint count for swelling and tenderness to calculate the Thompson Index (12), the Hannover functional questionnaire (Funktionen-Fragebogen Hannover, FFbH) (13), the questionnaire published by Hautzinger (14) to capture depressed mood, and the items relevant for the American Rheumatism Association (ARA) criteria for clinical remission (15) were recorded at each visit (0, 6, 12, 18 and 24 months).

New osteoporotic fractures were evaluated on the lumbar spine x-rays. Bone density measurement was performed at 0, 12 and 24 months only in centres with access to densitometry (Q-CT or DEXA). Side effects, body weight, blood pressure and blood glucose were recorded at each follow-up visit. Ophthalmologic examinations were performed at the beginning and end of the study to examine patients for signs of cataract or glaucoma.

Statistical analysis

Statistical analysis was performed in the intention to treat (ITT) and the per protocol (PP) group (7). The primary outcome measure of efficacy in this study was change in the Ratingen score from baseline to 24 months in the PP group, because of the completeness of the data. Secondary outcomes for PP and ITT analysis included chang-

es in the Ratingen score at six and 12 months, the number of eroded joints (Ratingen score ≥ 1), and changes in Sharp/van der Heijde scores at each follow-up compared to baseline.

Results

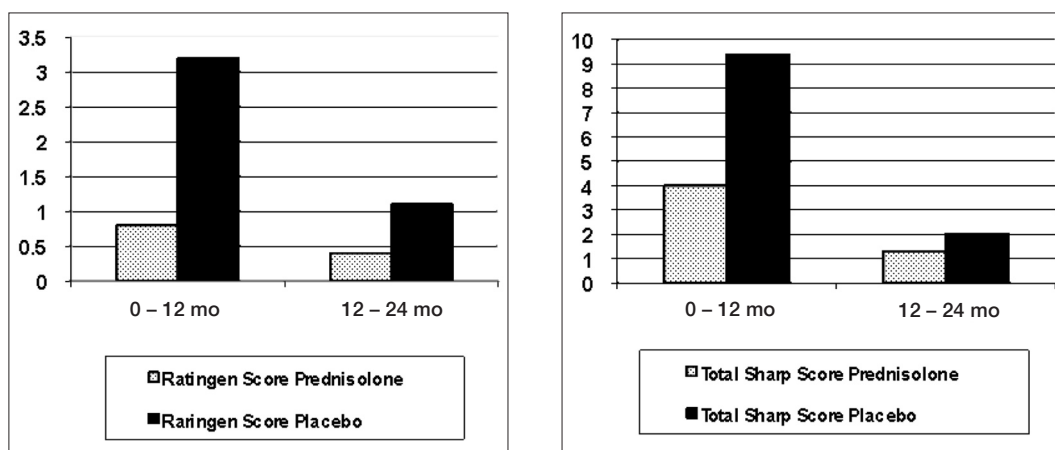
Of the 192 patients enrolled, 93 received at least one dose of prednisolone and 96 placebo to be considered for the safety analysis. 166 patients (80 on prednisolone / 86 on placebo) were included in the intention to treat (ITT) analysis; 103 patients completed the study but only 76 (34/42) fulfilled the strict criteria predefined for the per protocol (PP) analysis.

Baseline characteristics were similar regardless of whether patients were eligible for safety, intention to treat or per protocol analysis. Patients in the prednisolone group were slightly older and more often female than in the placebo group. Four patients of the 62 who initially took methotrexate switched to gold (two in each group) during the study, and 26 of the 104 who initially took gold switched to methotrexate (12 in the prednisolone and 14 in the placebo group).

Changes in the Ratingen Score as well as changes in the van der Heijde/Sharp Erosion and Total Score from baseline were significantly smaller at all consecutive time points in the prednisolone group compared to the placebo group, in both the PP and in the ITT analysis. Changes in van der Heijde/Sharp Joint Space Narrowing Score showed a significant difference in favour of prednisolone only at six months ($p=0.036$) but not at 12 or 24 months ($p=0.063$ and $p=0.133$, respectively). Of the 27 patients non-erosive at baseline in the prednisolone group, 7 became erosive during follow-up, compared to 14 of 22 patients non-erosive at baseline in the placebo group ($p=0.011$).

The greatest difference in radiographic progression was observed over the first year of treatment (Fig. 1). The mean changes in the Ratingen score over time decreased substantially not only in the prednisolone but also in the placebo group, from 3.2 (ITT analysis) and 3.3 (PP analysis) between baseline and month 12, to 1.1 and 1.1 between

Fig. 1. Change in Radiographic score between Year 1 and Year 2 in the LDPT Trial (ITT).



month 12 and 24. This must be attributed mainly to the potent disease-modifying effect of the concomitant DMARD therapy.

The improvements in the secondary clinical and functional outcome parameters compared to baseline were generally greater in patients who took prednisolone 5 mg compared to placebo, but did not differ significantly between treatments for any of these outcomes at each follow-up time point, with the single exception of the median change in Thompson score at month 6 (-116.0 in the prednisolone group vs. -81.5 in the placebo group; $p=0.029$). A trend in favour of prednisolone was also observed for the ACR remission criteria, with nearly twice as many prednisolone patients (16%) compared to placebo patients (9%) in remission at the conclusion of the study.

Safety

Evaluation of safety was performed in 93 patients in the prednisolone group

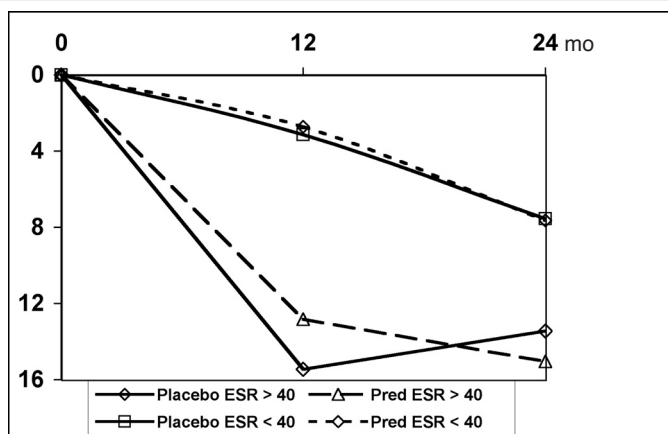
and 96 in the placebo group were evaluated for safety. The percentage of patients who experienced adverse events was very similar in both groups (71% in the prednisolone group and 74% in the placebo group), as was the percentage who experienced serious adverse events (29% vs. 33%). The most striking difference between the two groups was the mean weight increase of 5 kg in the prednisolone group compared to only 0.3 kg in the placebo group. Blood pressure and blood glucose levels were not different between the groups at the end of the study. All dropouts due to adverse events were clearly attributed to the concomitant treatment with gold or methotrexate. Two patients, both from the placebo group, died: one from myocardial infarction and the other secondary to right heart failure.

Osteoporosis was noted at initiation of therapy in the medical history of 12 patients in the prednisolone and 15 patients in the placebo group, and was reported during the trial in three addi-

tional patients in each treatment group. One of these reports concerned an osteoporotic fracture of the pubic ramus of the pelvis in a patient taking prednisolone. No vertebral fractures occurred during the study.

Bone density measurements were available at the end of the study for 23 patients of each treatment group. Decreasing values over time were found slightly more pronounced in the prednisolone group, but the differences were not statistically significant. When bone density was analysed according to baseline ESR values, the difference between patients with lower baseline ESR (<40 mm/h) compared to those with higher baseline values was much more pronounced than the difference between the two treatment groups (Fig. 2). This trend was particularly apparent during the first year, suggesting that the amount of inflammation has more impact on bone mass than the treatment with low-dose prednisolone (Fig. 2). These differences are not statistically significant, likely due to small numbers. No new lumbar spine fractures were found on lateral lumbar spine radiographs at 24-month follow-up in either group.

Fig. 2. Bone density measurement. Percentage of change to baseline according to baseline ESR (prednisolone n=16, placebo n=17)



Discussion

Disease-modifying effect of glucocorticoids

Several controlled studies found that glucocorticoids in daily dosages between 7.5 mg and 10 mg reduced the progression of joint damage (16-18). However, the long-term administration of higher doses of glucocorticoids

(≥ 7.5 mg) is associated with more and sometimes even severe side effects. Several attempts to examine a disease-modifying effect of lower doses have been reported. The first study by Harris was unable to demonstrate a significant difference *versus* placebo, likely because of the small sample sizes (19). However, two studies using 6 mg and < 5 mg daily could not confirm an effect on radiographic progression (20, 21).

The LDPT-trial is the only study to date to find evidence for a significant decrease in radiographic progression with only 5 mg prednisolone daily. This was confirmed by the results obtained with two radiological scoring systems, *i.e.* the Ratingen Score and van der Heijde modified Sharp Score, with very similar results. Only the subanalysis of joint space narrowing scores failed to show a significant difference between treatment groups at 12 and 24 months. The phenomenon that joint space narrowing is less likely to respond to treatment interventions than erosions was also observed in other recently-published trials in early RA patients (22) including the Swedish trial on low-dose prednisolone, the BARFOT Study (18).

The observation that the progression of radiographic damage was slower during the second year of the present trial, both in the prednisolone and in the placebo group, reflects the strong effect of the concomitant DMARD therapy on disease progression. This observation suggests the possible merit of van Gestel's proposal to use glucocorticoids as bridging therapy only until DMARD therapy takes effect (23). This idea is also adopted by the recent EULAR recommendations on the use of systemic glucocorticoids that advocate consideration of dose reduction and cessation of therapy whenever patients reach a state of low disease activity or remission (24).

The probability plots depicting radiographic change over time that are available for the LDPT Trial and also for the BARFOT Study (18) clearly reflect that only a minority of patients show a considerable and clinically relevant progression over time; the majority remain stable and some even improve. This observation highlights the fact

that therapeutic decisions in individual patients cannot be based only on mean changes observed in randomised trials of selected patients, but must take into account all the information available for that individual patient. The decision for prolonged treatment even with very low doses of prednisolone therefore must be based not only on the actual disease activity, but also on whether (and how much) radiographic progression is documented on regular follow-up. The possible disease-modifying effect of long-term prednisolone treatment must be weighed against the individual patient's risk for adverse effects, including age, history of infections, comorbidities, bone density and socioeconomic status.

Safety of low-dose glucocorticoids

A group of experts (25) stated that the overall fear of toxicity of low-dose GCs in RA, as quoted in textbooks and review articles, is probably overestimated, based on an analysis of controlled trials with low doses of prednisolone and an extensive literature review. The usual admonitions generally are based on extrapolation from observations with higher dose treatment. The adverse effects of high-dose GCs have been described extensively, including significantly more fractures, cataracts and, most importantly, deaths in the prednisolone group *versus* matched controls (26). The meta-analysis by Saag *et al.* came to the same conclusion, but could not rule out confounding by indication (27).

In the present study and other recently published controlled studies, between-group differences in the incidence of adverse effects were only minor. Nevertheless the same group of experts came to the conclusion that the chronic use of glucocorticoids, even in low doses, doubles the already increased risk of osteoporosis in RA (25). van Staa *et al.* reported, from a retrospective analysis of fractures occurring in glucocorticoid-treated patients in a very large cohort of 244,235 patients, that doses of 5 mg/day or less are least likely to be associated with fractures (28). Therefore, the importance of dose reduction is highlighted, even if frac-

ture incidence can be decreased in patients treated with GCs by the use of bisphosphonates (29). The results of the bone density measurement in our study support the idea that the positive effect of better disease control and the decrease in inflammation is more important than the possible negative effect of 5 mg prednisolone.

Altogether, the safety profile of 5 mg/day low-dose prednisolone therapy as documented in our trial does not exclude its long-term use, but dose reduction and timely limitation of treatment should always be considered.

Conclusion

The final conclusion from the LDPT Study is that a single oral daily dose of 5 mg prednisolone as an adjunct to DMARD therapy decreases the progression of radiological joint destruction in patients with early RA, with an acceptable low level of risk. Future studies must address whether doses even lower than 5 mg/day may provide a similar benefit with even fewer side effects, how long treatment should be continued in individual patients, and whether the same disease-modifying effect can be achieved in patients with more advanced disease.

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