Steroid withdrawal favours joint erosion in rheumatoid arthritis

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**Aim:** In rheumatoid arthritis (RA) erosions frequently progress even when joint signs and symptoms seem to improve. The question of whether steroids act in the same way as DMARDs has been the subject of considerable debate. The study by Hickling and colleagues addresses this issue, its aim being to verify if prednisolone (P) may reduce the progression of joint erosion in RA.

**Methods:** Data from a prospective clinical study of the effects of P on erosive progression was re-analysed to address this issue. A randomized, double-blind, placebo-controlled trial was set up in which prednisolone 7.5 mg was given daily in addition to routine medication to a cohort of 128 patients with early RA over a period of 2 years. Both the patient and the physician remained blinded regarding the treatment received. Every joint examined was classified as “erosive” or “non-erosive” and was then scored by the method of Larsen. Secondary outcomes were assessed every 3 months, including changes in disability (according to the Health Assessment Questionnaire), joint inflammation, pain over the last 24 hrs, and the acute phase response. In the statistical analysis the χ² test was used to compare proportions and Student’s t-test to compare the means. All statistical tests were two-tailed and P = 0.05 was taken as the significance level.

**Results:** At baseline no significant differences in the proportion of erosive hands or in the Larsen score were found between prednisolone- and placebo-treated patients, nor between those patients included and those excluded from the analysis. After 2 years steadily progressive joint destruction was observed in the placebo group, while few changes were seen in the P-treated patients. During the third year after withdrawal of prednisolone, a significant increase in the Larsen score and in the number of erosive hands was found. The effects of prednisolone therapy persisted for 2 years, although the symptomatic benefit lasted only few months.

**Conclusion:** This study shows that prednisolone at a dose of 7.5 mg significantly reduces the progression of the Larsen index. The double-blind radiographic follow-up showed that after P withdrawal a significant deterioration in the Larsen index occurred. This reinforces the hypothesis that P suppresses the erosive progression of RA but only if initiated in the early phase of the disease and continued for a long period of time.

**Comment**

Three randomized controlled trials of corticosteroid treatment in patients with rheumatoid arthritis (RA) have assessed radiographic progression (1-3). The Kirwan trial supports the use of oral low dose prednisolone (7.5 mg daily) in patients with early disease (< 2 years duration). Despite relatively short term effects on disease activity, slowing of erosive disease persisted over the 2 years of treatment. The other two trials failed to identify a difference between corticosteroid treatment and the comparator treatments, aspirin or chloroquine, but neither was placebo-controlled. One of the above, and two additional controlled trials have evaluated the effect of low dose corticosteroid treatment on bone density in patients with RA, showing incrementally more bone loss in the group receiving steroids (3-5).

Taking these and other risks of long term corticosteroid therapy into account, the potential long term benefit of low dose steroids on disease progression has remained controversial. Further, 71% of patients in the Kirwan trial were receiving concomitant treatment with a variety of second line agents. Recently data have been published comparing clinical, radiographic and biochemical parameters during the third year when corticosteroids in the treated group were tapered and discontinued (6). Although the total Larsen erosion scores were significantly different between the groups at the end of 2 years treatment, off prednisolone the rate of yearly progression in erosion scores approached that in the control group. As might be expected, levels of the N-propeptide of type III procollagen and pro-MMP-1 were lower in the treated patients until prednisolone was withdrawn. Despite concomitant treatment with second line agents, surprisingly, pro-MMP-3 levels remained elevated during corticosteroid treatment.

These data appear to support, again, a positive role for concomitant low dose corticosteroid therapy in patients with early RA also receiving second line agents, although the disparity in pro-MMP-1 and -3 levels remains unexplained. However, over the time of the study a significant number of patients withdrew. In the first 2-year report, x-rays were available in 106 or 83% of the original 128 patient cohort. Biochemical data over 3 years of treatment were available in 79 (62%) and x-rays in 75 (59%) of the original cohort. We are assured that baseline demographics in the drop-out group did not differ from those who continued the protocol treatment, and that discontinuation rates were relatively equal between the treatment groups. Nonetheless, we must surmise that clinical responses at least in part determined continued protocol participation, such that a select group of patients completed the full 3-year evaluation. Admittedly, this may reflect more our limited therapeutic armamentarium than the protocol design.

Further studies will therefore be required to confirm the
reported long term benefit for low dose corticosteroid therapy in early disease, and to extend these observations to a larger RA population. It is likely such data will become available as newer biologic and synthetic therapeutic agents are studied for their potential effects in retarding x-ray progression. Hopefully these protocol populations will be sufficiently large to allow subset analyses of patients with/without concomitant low dose steroid treatment.

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References