

Viewpoint

Corticosteroids in rheumatoid arthritis: Is a trial of their 'disease modifying' potential feasible?

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After three decades of experience the use of corticosteroids to treat rheumatoid arthritis (RA) remains a matter of personal taste and generates much debate. Although their role in life threatening complications is apparently acceptable, one standard text¹ suggests that less than 5% of patients with predominantly articular disease will require them, and in a recent survey British rheumatologists reported using corticosteroids only 'occasionally' or 'very infrequently'.² However, when making clinical decisions a physician's opinion does not necessarily reflect his clinical practice.³ Recent studies have found that 24 of 100 consecutive RA patients seen at one British hospital were taking a mean daily dose of 5.6 mg of prednisolone² and that 15% of outpatients seen at a Dutch clinic were also receiving steroid treatment.⁴

EFFECT OF STEROIDS

Although corticosteroids are very effective in diminishing pain, swelling, and stiffness, to maintain

suppression of inflammation the dose must be increased to levels too toxic for long term administration.^{5,6} Yet even at lower doses there are marked effects on the immune system.⁷ Might we not expect a 'disease modifying' action (like gold and penicillamine) even when an anti-inflammatory effect, like that of aspirin, is no longer present?

Results of some studies of the effects of corticosteroids in RA are difficult to interpret in this respect because they are poorly controlled,^{8,9} too short term,¹⁰ or use large doses.⁹ However, tantalising evidence of a possible disease modifying effect derives from the combined MRC and Nuffield Foundation study of the 1950s^{5,6} and a follow up study by West.¹¹ Eighty four patients were randomly allocated to receive either analgesics or (effectively) analgesics plus prednisolone, initially at a dose of 20 mg daily but subsequently tailored to each patient so that the mean daily dose at two years was 10 mg. Radiological progression was much less in the steroid treated group (Table 1). This was clearly significant even when a more stringent statistical analysis was applied than that originally employed.

These overall assessments may, however, conceal the answer to arguably the most important

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Table 1 Evaluation of hand radiographs in the combined MRC and Nuffield Foundation trial^{4,5}

Therapy	Time	Erosion grade					Total number of patients in trial
		0	1	2	3	4	
Analgesics	Initially	13	5	11	5	1	39
	*At two years	4	1	13	11	6	36
Prednisolone and analgesics	Initially	15	8	13	4	1	45
	*At two years	9	8	16	4	4	41

* $\chi^2=51$, $p<0.01$.

Table 2 Follow up study of MRC and Nuffield Foundation trial by West¹¹

Therapy	Number of patients	Duration of follow up (years)	Number developing new erosions
Analgesics	34	5	32 (94%)
Prednisolone and analgesics	39	4	9 (23%)

question—Do corticosteroids prevent the development of *new erosions*? In a follow up study of 73 of the original patients⁸ only 23% of those taking prednisolone (mean daily dose 11 mg) for four years developed new erosions, while 94% of those receiving analgesics alone (for five years) did so (Table 2).

When the data from the original study^{5,6} are reviewed and the patients most likely to show evidence of new erosion development (that is, patients with an initial x ray classification of 'none' or 'doubtful' change) are considered it can be seen that most of this deterioration occurred over the first two years; 20% in the steroid group and 60% in the analgesic group. Therefore, a two year test of the effects of lower dose steroid treatment should provide clear cut evidence about its ability to prevent the development of erosions in patients with minimal initial x ray changes. If a linear dose-response relationship is assumed then 7.5 mg prednisolone daily would be expected to reduce the number of patients developing new erosions from 60% to 33%.

TRIAL DESIGN

How many patients should be entered in a clinical trial in order to be reasonably sure (with a power of say 90%) of identifying such a clinically important advantage of treatment? By referring to published tables¹² it can be seen that 80 would be required in the test and in the control groups, i.e., 160 patients in all. Some patients would be lost to follow up and a few (probably very few) withdrawn from treatment. A reasonable final estimate would be 180 patients fitting the original trial criteria and having no erosive change. The effects of other 'disease modifying' drugs, such as gold or penicillamine, on radiological progression are small¹³ and would be negligible in a trial this size. It would not be necessary to restrict their use.

FEASIBILITY

Would such a trial be feasible? Fifteen rheumatologists recruiting one patient per month would reach



Fig. 1 Age and duration of disease for 24 patients taking corticosteroids for rheumatoid arthritis.

the target in one year, and the study would be completed in three years. Organisation on this scale seems practicable. Could suitable patients, relatively young and early in the course of their disease, ethically be entered? In current practice many patients are less than 60 years old when steroid treatment is started and have had a short duration of disease, making it likely that they would satisfy the entry criteria. Fig. 1 shows the distribution of age and disease duration at commencement of therapy for one group of patients.²

Conclusion

It seems that a trial of low dose corticosteroids for the prevention of erosion development is feasible but should it be performed? The answer depends on whether the result (positive or negative) would influence prescribing and whether a fixed dose of 7.5 mg prednisolone daily is an acceptable long term treatment in relation to potential adverse reactions. We would be interested in the views of others on both these issues.

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