CONCISE REPORT

Long term evaluation of radiographic disease progression in a subset of patients with rheumatoid arthritis treated with leflunomide beyond 2 years

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Objectives: To assess the effect of long term (>2 years) leflunomide treatment on radiographic progression in patients with RA.

Methods: Patients treated with leflunomide for >2 years in one of three phase III trials and subsequent extensions, for whom paired, evaluable radiographs at baseline and study end point were available, were included. Radiographs of hands and feet were assessed according to the modified Sharp/van der Heijde scoring method, for erosion, joint space narrowing, and total score. Changes from baseline were assessed, and a predicted yearly progression rate estimated for each patient.

Results: 128 of the original 824 patients were included, with mean disease duration 5.1 years and mean leflunomide treatment duration 4.3 years until the final x ray examination. The mean change from baseline in total score was 8.6 with yearly adjusted rate 1.9, and the median change was 2 with yearly adjusted rate 0.5, compared with 7.9 and 4.9, respectively, before leflunomide treatment. After treatment, the rate improved in 92/128 (72%) patients and deteriorated in 21/128 (16%). In 42 (33%) patients who had a total score >0 at baseline, no radiographic progression occurred after leflunomide treatment.

Conclusions: In a subset of patients who continued treatment long term, leflunomide treatment reduced the rate of radiographic damage.

Radiographic damage has been shown to occur early in the course of rheumatoid arthritis (RA), with most patients showing evidence of joint erosions within the first 2 years from disease onset.¹ Moreover, in studies specifically performed in patients with early RA, the joints of the feet have been shown to be affected much earlier and to a greater extent than the joints of the hands.^{2–3} Although the rate of radiographic progression can vary widely between people with RA, when assessed as a group, joint damage can be said to progress linearly over the first 20 years of RA. When the modified Sharp/van der Heijde method of scoring is used, a progression rate of 7.5 units/year has been estimated based on several longitudinal observational studies.⁴

Prevention of joint damage early in the course of RA is likely to preserve physical function. In three phase III studies, leflunomide has been shown to be effective in slowing disease progression, and improving signs and symptoms and functional ability in patients with RA as early as 4 weeks after the start of treatment, with a sustained long term response for up to 2 years.^{5–10} Leflunomide was also effective in slowing disease progression as assessed by radiographic analysis of joint damage up to and after 2 years of treatment.^{10–12}

This study aimed at evaluating long term x ray progression in patients with RA treated with leflunomide for >2 years, in order to assess the influence of leflunomide treatment on joint damage.

METHODS

Patients with active RA who completed 2 years of leflunomide treatment (100 mg loading dose for 3 days followed by 20 mg thereafter) in one of three randomised, double blind phase III trials (MN301, MN302, US301) were offered inclusion in one of two open label extension studies (3009 or 4003) until the drug became commercially available. Patients from these studies, who had paired, evaluable x ray findings from baseline and treatment end point were included in this analysis. Data from all three studies were pooled owing to small patient numbers.

The clinical study protocol and study related documents were approved by independent ethics committees. Written, informed consent to enter the study was required from all patients.

Radiographs of the hands and feet were assessed using the modified Sharp/van der Heijde method,^{12–13} and a single investigator who was unaware of patient identity and of the sequence of the radiographs performed the evaluation. Interobserver agreement was tested by a second investigator on 10 sets of radiographs and the intraclass correlation coefficient between the two investigators was 0.99 for time A, 0.96 for time B, and 0.87 for the change between these two times. Radiographs were scored for erosion and joint space narrowing (JSN), and these scores were summed to obtain a total radiographic score. Erosions were scored bilaterally and were based on a score range of 0–5 for 16 joints in each hand/wrist, and 0–10 for six joints in each foot. JSN was scored in 15 joints in each hand/wrist and six joints in each foot, based on a score of 0–4 for each joint. Therefore, at each time the erosion score ranged from 0 to 280, JSN score from 0 to 168, and total score from 0 to 448. Changes in x ray findings from baseline were analysed, and yearly progression rates estimated by adjustment for treatment duration. All statistical methods were descriptive only.

RESULTS

A total of 128 patients who were treated with leflunomide from enrolment in the original phase III studies and continued treatment in the extension studies had x ray data available at baseline and treatment end point. Figure 1 shows the numbers of patients enrolled in each study, and those continuing in the extension studies.

Baseline demographics were similar in the 128 patients with evaluable x ray data and in the 696 patients without

Abbreviations: CRP, C reactive protein; JSN, joint space narrowing; RA, rheumatoid arthritis; SJC, swollen joint count; TJC, tender joint count

Figure 1 Study design and patient numbers.

evaluable *x* ray data available. The mean (SD) age in the group with *x* ray data was 55.3 (10.2) years and 76% were female, compared with a mean age of 57.7 (10.9) years and 71.3% female patients in the group without *x* ray data. The mean (SD) duration of RA was 5.1 (6.2) years in the group with *x* ray data compared with 5.0 (6.1) years in the group without *x* ray data, and similar numbers of patients in each group had received previous DMARDs (69% *v* 62%, respectively). The distribution of American College of Rheumatology functional class at baseline was similar in both groups; 12% and 9.4% were class I, 62.5% and 60.5% were class II, 28.1% and 31.0% were class III, and 0% and 0.3% were class IV in the groups with and without *x* ray data, respectively. Mean tender joint count (TJC), swollen joint count (SJC), and C reactive protein (CRP; mg/l) were 16.4 (6.6), 15.4 (6.3), and 2.9 (3.0), respectively, in the group with *x* ray data, compared with 17.2 (6.8), 15.4 (6.1), and 3.9 (4.0), respectively, in the group without *x* ray data.

Total radiographic scores of 0 were present at baseline in 16 (12.5%) patients, indicating no signs of joint destruction. All but one of these patients retained this score of 0 at the end point after 3–5 years' leflunomide treatment. The mean change in erosion score from baseline to the end point was 3.0 with a yearly adjusted rate of 0.7, and the median change in erosion score was 0. In addition, the mean change from baseline to the end point in JSN score was 5.6 with a yearly adjusted rate of 1.2, and the median change in JSN score was 2.0 (table 1).

The mean change from baseline (25.9) to the end point (34.5) in total score was 8.6, with a yearly adjusted rate of 1.9, and the median change from baseline (12.5) to the end point (20) in total score was 2, with a yearly adjusted rate of 0.5 (table 1). The yearly rates were significantly lower than the mean and median estimated yearly progression rates at baseline (7.9 and 4.9, respectively). Progression rates based on erosion scores only, or on JSN scores only showed a similar decrease from baseline after leflunomide treatment (fig 2).

A comparison of the yearly adjusted change in total score after leflunomide treatment with the estimated yearly progression rate before treatment showed that 92/128 (72%) patients had a slower rate of progression, while only 21/128 (16%) had a more rapid rate. In addition, in 42 (33%)

patients who had a total score >0 at baseline progression had stopped.

The mean changes from baseline in disease activity measures for patients with and without *x* ray data were compared. In patients with *x* ray data available, the mean (SD) changes from baseline in TJC, SJC, and CRP were −11.9 (8.0) (*n* = 112 at end point), −10.8 (7.2) (*n* = 112 at end point), and −1.8 (3.2) (*n* = 118 at end point), respectively. The changes from baseline in patients without *x* ray data available were −7.7 (8.2) (*n* = 631 at end point), −6.0 (7.3) (*n* = 631 at end point), and −1.7 (3.9) (*n* = 526 at end point) for mean TJC, SJC and CRP, respectively. Therefore, improvements in disease measures were greater in patients with *x* ray data available than in those without such data.

DISCUSSION

It has been reported that joint damage at a group level occurs at a linear rate of about 7.5 units/year, as measured using the Sharp/van der Heijde total score across several longitudinal studies.⁴ In this study in a subset of patients who completed >2 years of leflunomide treatment, the mean estimated yearly progression rate at baseline was consistent with this historical control at 7.9 units/year. However, after leflunomide treatment the mean rate of disease progression in this population was significantly reduced to 1.9 units/year. Furthermore, the median yearly adjusted rate of disease progression was 4.9 at baseline compared with 0.5 after leflunomide treatment.

Reduced radiographic scores after leflunomide treatment compared with baseline was apparent in 72% of treated patients, with no progression in radiographic damage in 33% of patients. However, it should be recognised that this was a small, highly selective subset of patients who were responding well to leflunomide treatment after 2 years and who elected to continue open label treatment.

Greater improvements in measures of disease activity were seen in those patients who used leflunomide long term and had radiographs available than in those who did not have *x* ray data available. This indeed indicates that there was a selection of patients showing a good clinical response who continued to use leflunomide.

In this study, *x* ray findings of the hands and feet were assessed by a single investigator who was unaware of patient

Table 1 Total score, erosion score, and joint space narrowing score for all patients in the study

	Baseline	End point	Change	Yearly adjusted rate at end point*	Yearly adjusted rate at baseline
Total score					
Mean (SD)	25.9 (33.9)	34.5 (42.6)	8.6 (18.2)	1.9 (4.0)	7.9 (9.5)
Median (IQR)	12.5 (36.5)	20.0 (42.0)	2.0 (11.0)	0.5 (2.6)	4.9 (9.4)
Erosion score					
Mean (SD)	8.1 (15.6)	11.1 (21.0)	3.0 (8.8)	0.7 (2.0)	2.1 (3.6)
Median (IQR)	2.0 (7.5)	3.0 (10.5)	0.0 (2.0)	0.0 (0.54)	0.7 (3.0)
Joint space narrowing					
Mean (SD)	17.8 (21.6)	23.4 (25.2)	5.6 (11.3)	1.2 (2.4)	5.8 (7.2)
Median (IQR)	9.0 (23.5)	16 (29.5)	2.0 (7.0)	0.5 (1.7)	3.2 (6.4)

Results are shown as mean (SD) and median (interquartile range (IQR))

*A change was only looked for during treatment and not during the period from diagnosis.

Figure 2 Rate of disease progression before and during leflunomide treatment compared with a historical control.⁴

identity and sequence of the radiographs, and interobserver agreement was tested by a second investigator. A recent review suggests that a minimum of two observers are required to score radiographs during clinical studies and that the average of these two observers should be used in the analysis.¹⁴ A further study suggests that films should preferably be read in chronological order as this leads to an increase in detection of clinically relevant changes without serious overestimation of non-relevant changes, but this is an issue which still leads to much debate.¹⁵ These findings, however, do not diminish the importance of the present study, as estimated yearly progression rates can act as a benchmark to allow comparisons between different treatment groups and different treatment periods.¹⁶

In summary, long term leflunomide treatment is associated with significantly reduced radiographic damage compared with both historical controls and pretreatment estimated yearly progression rates. This study has demonstrated that disease progression was delayed in a selected group of patients with RA who continued leflunomide treatment long term for up to 5.8 years. Leflunomide has the potential to prevent joint damage and, consequently, preserve physical function.

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