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TREATMENT WITH LEFLUNOMIDE SLOWS RADIOGRAPHIC PROGRESSION OF RHEUMATOID ARTHRITIS

Results from Three Randomized Controlled Trials of Leflunomide in Patients with Active Rheumatoid Arthritis

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Objective. **To determine whether treatment with leflunomide (LEF), methotrexate (MTX), or sulfasalazine (SSZ) for 6–12 months retards progression of radiographic damage and to identify clinical variables that correlate with radiographic progression.**

Methods. **Radiographs of the hands and feet were performed at baseline and at the end of study or early exit in 3 randomized controlled trials. Protocol US301 was a 12-month controlled trial of LEF or MTX treatment compared with placebo in 482 patients randomized in a 3:3:2 ratio. Protocol MN301 compared 6 months of LEF or SSZ treatment with placebo in 358 patients, randomized in a 3:3:2 ratio, with continued blinded treatment in the active control arms for 12 months. Protocol MN302 compared 12 months of LEF treatment with MTX in 999 patients. Radiographs were blinded for sequence and treatment and were scored for erosions and joint space narrowing. All analyses were by intent-to-treat. Sensitivity analyses were performed to account for missing data.**

Results. **LEF, MTX, and SSZ treatment resulted in statistically significantly less radiographic progression compared with placebo at 6 and 12 months: for protocol US301, LEF versus placebo $P = 0.0007$ and MTX versus placebo $P = 0.0196$; for protocol MN301, LEF versus placebo $P = 0.0004$ and SSZ versus placebo $P = 0.0484$. The effect of LEF treatment was similar to that of MTX and SSZ.**

Conclusion. **These are the first 6- and 12-month randomized placebo- and active drug–controlled trials to demonstrate retardation of radiographic progression by a new disease-modifying antirheumatic drug (DMARD), LEF, as well as 2 commonly used DMARDs, MTX and SSZ.**

A few of the currently available therapies for rheumatoid arthritis (RA) have been demonstrated to retard structural damage as measured by progression in serial radiographs of erosions and joint space narrowing (1–8). None are curative, and their use is frequently limited by tolerability and/or insufficient efficacy. Leflunomide (LEF; Arava; Hoechst Marion Roussel, Kansas City, MO), a recently approved antirheumatic drug, inhibits de novo pyrimidine synthesis in rapidly dividing cells, such as activated lymphocytes, resulting in reversible cell cycle arrest. The efficacy of LEF, initially demonstrated in a phase II randomized, placebo-controlled study in 402 patients, was confirmed in the 3 phase III studies (2 placebo controlled and all 3 active-drug controlled) presented here, which compared LEF treatment with methotrexate (MTX), sulfasalazine (SSZ), and/or placebo (9,10).

For a treatment to be accepted as a structure-modifying antirheumatic drug, there must exist convincing evidence that the agent alters the course of disease progression by slowing or stopping joint destruction as measured radiographically (11). Two principal methods and several modifications of scoring radiographic damage have been widely used, and the reproducibility of

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radiographic scoring in RA has been defined in multiple studies (12–18). Recent OMERACT (Outcome Measures in Rheumatology Clinical Trials) conferences have reached consensus in recommending that all new drugs must demonstrate efficacy in retarding the progression of structural damage in order to be accepted as disease-modifying or disease-controlling antirheumatic therapy (19).

PATIENTS AND METHODS

Study design. Three multicenter, randomized, controlled trials were performed to assess the clinical efficacy of LEF; 2 were placebo controlled, and all 3 included active drug treatment. All 3 studies were approved by appropriate ethical review boards and were conducted in accordance with the principles established by the Declaration of Helsinki and all relevant regulations. The members of the Leflunomide RA Investigators Groups are shown in Appendix A.

In protocol US301, initial treatment with LEF or MTX was compared with placebo given for 4–12 months, using a 3:3:2 randomization ratio, in 482 patients. To alleviate the risk of disease progression causing severe, irreversible damage during prolonged placebo treatment, patients were allowed to exit initial therapy on or after 4 months of treatment if they had a documented lack of efficacy and/or tolerability and were allowed to enter alternate therapy set by the protocol. After a 4-week washout period, patients who chose alternate therapy and were originally assigned to the placebo or MTX groups received LEF; patients originally assigned to receive LEF subsequently received MTX.

Protocol MN301 compared 6 months of LEF or SSZ treatment with placebo in 358 patients randomized in a 3:3:2 ratio; blinded treatment was continued in the active control arms for 12 months.

Study MN302 compared 12 months of LEF treatment with MTX treatment in 999 patients.

Radiographs. Radiographs of the hands and feet were obtained at baseline and followup, which was at 6 months (MN301) and 12 months (US301, MN302, and MN301/303 blinded followup), or at early exit, whichever occurred first. In conformity with recommendations from the World Health Organization Conference on Outcomes in Rheumatoid Arthritis Clinical Trials (20), every effort was made in protocol US301 to obtain radiographs 12 months following entry into initial therapy, regardless of when the patient exited protocol treatment, and to determine whether the patients were receiving alternate therapy as specified by the protocol or active treatment outside the protocol.

One investigator (JTS) used an established method (12,14) to interpret radiographs in patient sets that had been randomized and blinded as to sequence and treatment. Both erosions and joint space narrowing were scored, since these 2 aspects of joint damage do not proceed in lock step and since each contributes to anatomical damage that results from persistent joint inflammation.

Erosions were scored in 34 joints in the hands and 12 in the feet, and joint space narrowing in 36 joints in the hands and 12 in the feet (12,14). The scale for erosions ranged from 0 to 5, 0 for normal joints and increasing grades for progressively more involvement. Progression from one grade to the next was scored when a discrete new erosion appeared in a previously uninvolved quadrant of the joint or carpal bone or when a preexisting erosion increased sufficiently in size to be judged greater than what could have occurred because of artifacts caused by changes in position or differences in radiation exposure or film development. Joint space narrowing was scored on a scale of 0–4, where 0 = normal, 1 = asymmetric or minimal narrowing $<11\%$, 2 = 11–50%, 3 = 51–99%, and 4 = complete loss of joint space and presumptive ankylosis.

Erosion and joint space narrowing scores were summed to obtain the total radiographic score for each patient, giving a maximum possible total score of 422. Even with severe damage, scores above 200 are seen infrequently (15).

Treatment. In all 3 studies, a 3-day loading dose of LEF (100 mg/day) was followed by 20-mg daily doses. This loading dose was used to more rapidly achieve steady-state plasma levels, given the mean half-life of 14–16 days.

In protocol US301, MTX was initiated at 7.5 mg/week and increased to 15 mg/week over weeks 6–9 in 60% of the patients, all of whom had active disease at week 6.

In MN301, SSZ was started at 500 mg/day and increased to 2,000 mg/day in weekly increments of 500 mg.

In MN302, MTX treatment was initiated at 7.5 mg/week, increased to 10 mg/week at week 4 and to 15 mg/week on or after week 12, at the discretion of the investigator, in 53% of the patients.

Statistical analysis. All analyses were performed on an intent-to-treat basis. That is, patients were assigned to their initial treatment group even if they entered alternate therapy or discontinued protocol participation before the 12-month assessment. The primary measure of the effects of treatment on radiographic progression was the total radiographic score (the sum of erosion and joint space narrowing scores) by an analysis of covariance. Secondary analyses included changes in erosion and joint space narrowing scores calculated separately, the number of patients with newly eroded joints, and the number of patients with radiographic progression defined as an increase in erosion scores >3.

Sensitivity analyses were performed to investigate the potential impact of missing radiographic data on the results of the radiographic findings based on nonmissing data. Four different approaches were used (21). These included, first, a bootstrap method to find the boundary value for the least squares mean difference between the LEF and placebo missing data cohorts which would result in losing the statistically significant difference; second, imputing the missing data cohort by sampling from the opposite treatment group; third, holding the mean change scores in one treatment group constant and iteratively "worsening" the missing cases in the opposite group until loss of statistical significance; and fourth, substituting the mean value from the opposite group for all missing cases.

Summary statistics of demographic characteristics, baseline radiographic scores, and change in radiographic scores from baseline were examined in various subgroups based on duration of disease, baseline radiographic score, absence of erosions at baseline, concomitant steroid use, prior and no prior disease-modifying antirheumatic drug (DMARD) use, and combinations of these subsets.

To test the association of clinical variables with radiographic progression, the change from baseline of all observations of the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and Health Assessment Questionnaire (HAQ) scores were averaged for each patient and tested by Pearson correlation coefficients. The American College of Rheumatol-

Table 1. Baseline demographics and disease characteristics, by study*

	US301			MN301			MN302	
	LEF (n = 182)	PL (n = 118)	MTX (n = 180)	LEF (n = 131)	PL (n = 91)	SSZ (n = 134)	LEF (n = 498)	MTX (n = 487)
Age, years								
Mean	54.2	54.6	53.3	58.3	54.6	58.9	58.3	57.8
% <65	78	82	81	71	82	62	70	70
% ≥65	23	18	19	29	18	38	31	30
% female	73	70	75	76	75	69	71	71
Mean disease duration, years	7.0	6.9	6.5	7.6	5.7	7.4	3.7	3.8
Disease duration, years								
% ≤2	39	33	40	38	45	42	44	43
% >5	44	45	37	46	38	42	31	31
% >10	25	21	20	30	24	28	2	4
Mean no. of DMARDs failed	0.8	0.9	0.9	1.0	0.8	0.9	1.1	1.1
% DMARD-naive	45	40	44	40	53	51	34	33
% taking corticosteroids	54	56	53	45	45	46	49	45
% RF positive	65	60	59	76	83	76	74	76
% with erosions at baseline	70	78	66	78	79	74	74	74
Mean ESR, mm/hour	39.0	37.3	33.8	55.7	52.3	50.5	51.0	51.6
Mean CRP, mg/dl	2.08	2.47	1.88	4.45	4.10	3.40	4.22	4.07
Mean baseline TJC (of 28)	15.5	16.5	15.8	18.8	16.3	16.7	17.2	17.7
Mean baseline SJC (of 28)	13.7	14.8	13.0	16.2	15.8	15.3	15.8	16.5
Mean baseline HAQ Disability Index	1.30	1.31	1.30	1.89	1.82	1.70	1.50	1.52

* Baseline for entire intent-to-treat populations in each protocol. Two patients in US301, 2 in MN301, and 14 in MN302 did not complete 1 followup examination and were not assigned treatment. The population of patients with radiographic data was not significantly different. The remainder of the tables are based on radiographic subsets. LEF = leflunomide; PL = placebo; MTX = methotrexate; SSZ = sulfasalazine; DMARDs = disease-modifying antirheumatic drugs; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; TJC = tender joint count; SJC = swollen joint count; HAQ = Health Assessment Questionnaire.

ogy (ACR) response criteria (22) were scored 1 if the ACR20 criteria were met and 0 if they were not. The sum of the number of weeks in responder status 1 was taken as the area under the curve (AUC) and tested for association with radiographic progression by the Pearson correlation coefficient in the entire population in each study. In addition, the final ACR response was tested against radiographic progression in the subset of patients who met the predefined criterion for radiographic progression, which was an increase in radiographic score ≥3 units.

RESULTS

Demographics and baseline disease characteristics. Demographics and disease characteristics were similar across treatment groups within each of the 3 clinical studies (Table 1). Enrollment criteria in protocols US301 and MN302 required that patients had not previously taken MTX (MTX-naive). Patients recruited into MN302 had the shortest disease duration (mean 3.7 years) and had failed a mean of 1.1 DMARDs; 34% were DMARD-naive. Mean disease duration was ~7 years in both placebo-controlled trial populations (US301 and MN301). Despite the long disease duration in MN301, 40–53% were DMARD-naive and only 33% had previously received MTX. In US301, a bimodal distribution was observed, with ~40% of patients with ≤2 years' and another 40% with >5 years' disease duration; 42% were DMARD-naive.

Radiographic analysis. In US301, paired radiographs were obtained in 352 patients (73% of 482) at baseline and at 12 months or at early exit. Among these 352 patients, 305 (87% of 352) had final films at 12 months and 47 (13% of 352) had films at early exit (Table 2). In MN301 and MN302 baseline and end point films were successfully obtained in 65% and 64% of patients who were evaluable for efficacy, respectively.

In US301, of the 83 patients (70% of 118)

Table 2. Radiographic data analyzed in US301*

	LEF	PL	MTX
No. with radiographs analyzed at end point	131	83	136
Radiographs at month 12, %			
Patient taking initial therapy	63	37	70
Patient taking alternate therapy	9	33	10
Mean time on initial therapy, weeks	24	23	21
Mean time on alternate therapy, weeks	23	25	27
Patient exited protocol early	17	10	10
Mean time on initial therapy, weeks	20	19	24
Radiographs at early exit, %	11	21	12

* LEF = leflunomide; PL = placebo; MTX = methotrexate.

Table 3. Radiographic outcomes*

Study, treatment	Mean (SD) change		*P*	
	After 6 months	After 1 year	Active drug vs. placebo (95% CI)	LEF vs. active drug (95% CI)
US301				
LEF (n = 131)		0.53 (4.53)	0.0007 (−3.98, −1.09)	–
PL (n = 83)		2.16 (3.95)	–	–
MTX (n = 136)		0.89 (3.27)	0.0196 (−2.57, −0.23)	0.0499 (−2.31, −0.00)
MN301 (6 months)				
LEF (n = 87)	1.23 (2.85)		0.0004 (−6.17, −1.80)	–
PL (n = 62)	5.88 (10.00)		–	–
SSZ (n = 84)	2.32 (10.11)		0.0484 (−6.86, −0.24)	0.3394 (−3.34, 1.16)
MN303 (12 months)				
LEF (n = 60)		0.97 (6.11)	–	–
SSZ (n = 53)		1.38 (2.88)	–	0.6854 (−2.20, 1.45)
MN302				
LEF (n = 302)		2.48 (5.36)	–	–
MTX (n = 324)		1.62 (13.38)	–	0.2940 (−2.24, 7.38)

* After 6 months of treatment under protocol MN301, patients who had received LEF or SSZ were offered the option of continuing the same medication blinded for another 6 months under protocol MN303. 95% CI = 95% confidence interval; LEF = leflunomide; PL = placebo; MTX = methotrexate; SSZ = sulfasalazine.

randomized to receive placebo who had followup radiographs, 31 patients (37%; 31 of 83) continued with initial therapy at 12 months, 27 (33%; 27 of 83) had entered alternate therapy for a mean of 25 weeks, and 8 (10%; 8 of 83) had exited the protocol for unspecified active drug treatment (presumed to be MTX) for a mean of 33 weeks. In comparison, 12 (9%) of the LEF-treated and 13 (10%) of the MTX-treated patients received alternate therapy for a mean of 23 and 27 weeks, respectively. In the LEF group, 22 patients with end-point radiographs (17%) were receiving active treatment outside the protocol, for a mean of 28 weeks; 13 MTX-treated patients (10%) were treated outside the protocol for a mean of 25 weeks (Table 2).

LEF, MTX, and SSZ treatment were significantly better than placebo in slowing or stopping radiographic progression: LEF versus placebo $P = 0.0007$ in US301 and $P = 0.0004$ in MN301; MTX versus placebo $P = 0.0196$ in US301; SSZ versus placebo $P = 0.0484$ in MN301 (Table 3). Progression of erosion scores was significantly lower in LEF-treated patients compared with placebo-treated patients in US301 (0.23 compared with 0.84; $P = 0.0326$), and in MN301 (0.63 compared with 2.07; $P = 0.0070$). Joint space narrowing scores also increased at a significantly slower rate in LEF-treated patients in both studies (in US301 0.31 compared with 1.24; $P = 0.0002$; in MN301 0.60 compared with 3.81; $P = 0.0020$) (Table 4).

To provide an estimate of how rapidly joint destruction had occurred between disease onset and

Table 4. Change from baseline to end point in erosion and joint space narrowing scores in radiographs of the hands and feet*

Study, treatment	Change in erosion scores				Change in joint space narrowing scores			
	Mean	SD	*P* (vs. LEF)	95% CI	Mean	SD	*P* (vs. LEF)	95% CI
US301								
LEF (n = 131)	0.23	2.20	–	–	0.31	2.78	–	–
PL (n = 82)	0.84	1.82	0.0326	−1.46, −0.06	1.24	2.70	0.0002	−2.68, −0.86
MTX (n = 136)	0.48	1.84	0.1158	−1.08, 0.12	0.41	1.83	0.0521	−1.36, 0.01
MN301								
LEF (n = 87)	0.63	1.30	–	–	0.60	2.27	–	–
PL (n = 59)	2.07	4.09	0.0070	−2.14, −0.35	3.81	7.45	0.0020	−4.38, −1.01
SSZ (n = 84)	0.92	3.34	0.5399	−1.01, 0.53	1.40	6.92	0.2836	−2.41, 0.71
MN302								
LEF (n = 302)	1.00	2.76	–	–	1.48	3.49	–	–
MTX (n = 324)	0.54	6.92	0.4669	−1.56, 3.40	1.08	7.19	0.2243	−1.02, 4.32

* LEF = leflunomide; 95% CI = 95% confidence interval; PL = placebo; MTX = methotrexate; SSZ = sulfasalazine.

Table 5. Baseline radiographic scores and estimated yearly progression*

	US301			MN301			MN302	
	LEF (n = 131)	PL (n = 83)	MTX (n = 138)	LEF (n = 89)	PL (n = 62)	SSZ (n = 86)	LEF (n = 304)	MTX (n = 331)
% of patients with films	72	70	76	66	65	63	61	67
Baseline Sharp score	23.11	25.37	22.76	46.26	46.18	41.86	24.94	24.60
Estimated yearly progression	3.30	3.68	3.50	6.09	8.10	5.66	6.74	6.47

* Estimated yearly progression was calculated as the total baseline score divided by the number of years with disease. LEF = leflunomide; PL = placebo; MTX = methotrexate; SSZ = sulfasalazine.

study entry, a yearly rate of radiographic progression was estimated by dividing the individual baseline total radiographic score by disease duration for that patient. The mean for each treatment group was calculated and compared between studies and between treatment groups in each study as an indication of heterogeneity in the 3 populations. The estimated yearly progression at baseline was almost twice as rapid in the 2 European populations, MN301 and MN302, as in the US population, US301. However, this imputed baseline progression rate was comparable between treatment groups within each study, i.e., within each protocol, treatment groups had similar imputed yearly radiographic progression rates at baseline (Table 5).

Comparing the baseline estimated yearly progression to the observed change in total radiographic scores in the MN301 placebo-treated population, progression of joint destruction exceeded the predicted value at 6 months, increasing by 5.88 units compared with 4.05 (Table 5 and Figure 1). In US301, progression in radiographic scores in the placebo-treated population was less than the imputed baseline value (2.16 compared with 3.68) (Figure 1). However, as previously noted, 63% of the placebo-treated patients received active-drug treatment; almost half received LEF for a mean of 24 weeks, and the remaining were treated outside the protocol for up to 33 weeks.

In both placebo-controlled trials, the number of

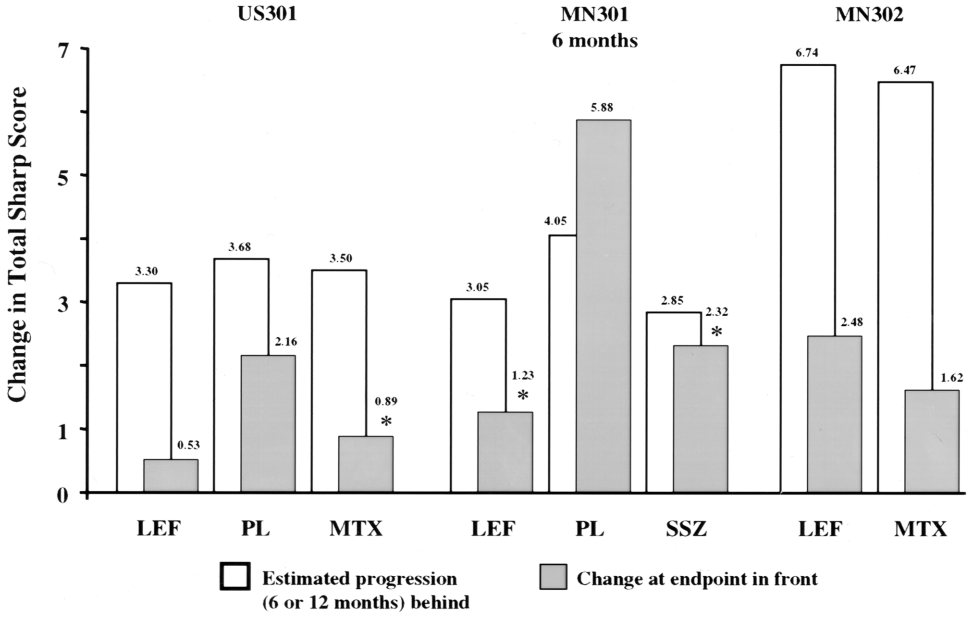

Figure 1. Change in total Sharp scores at end point and estimated progression in studies US301, MN301, and MN302. The observed radiographic progression in active-drug treatment groups was significantly less than in the placebo-treated group and less than the estimated progression over 6 months or 12 months. In study MN301, progression in the placebo group exceeded the imputed 6-month value. In study US301, progression in the placebo group was less than the imputed 12-month value, in part because 63% of the patients had received active-drug treatment. * = $P \leq 0.01$ versus placebo. LEF = leflunomide; PL = placebo; MTX = methotrexate; SSZ = sulfasalazine.

Table 6. Percentage of patients with radiographic progression*

Study, treatment	Progression	No progression	*P*
US301			
LEF (n = 131)	3	97	0.0197
PL (n = 83)	12	88	
MTX (n = 136)	4	96	0.0578
LEF vs. MTX			0.7496
MN301			
LEF (n = 87)	3	97	0.0070
PL (n = 59)	17	83	
SSZ (n = 84)	5	95	0.0216
LEF vs. SSZ			0.7169
MN302			
LEF (n = 302)	11	89	0.8975
MTX (n = 324)	10	90	

* Radiographic progression was defined as an increase in erosion scores of >3 units. *P* values are for active drug versus placebo unless stated otherwise; all *P* values were determined by Fisher's exact test. LEF = leflunomide; PL = placebo; MTX = methotrexate; SSZ = sulfasalazine.

patients with progressive radiographic disease (defined as an increase in erosion scores of >3 units) was significantly greater in the placebo groups than in the LEF groups (US301 $P = 0.0197$; MN301 $P = 0.0070$) (Table 6).

Even in the placebo treatment groups, however, only a small number of radiographs demonstrated this magnitude of change in erosion scores (US301 12%, MN301 17% versus 3% and 5% in the active-drug treatment groups). Similarly, the percentages of patients with newly eroded joints in the placebo treatment groups were small: in US301 28% compared with 21% and 23% in active-drug treatment groups; in MN301 34% compared with 31% and 27% (Table 7).

The radiographic effect of LEF administration was not statistically significantly different from that of SSZ administration in MN301 at 6 months ($P = 0.3394$) and 12 months ($P = 0.6854$) (Figure 2). In the 2 trials in which LEF and MTX treatment were compared, the two treatments were not statistically significantly different (for US301 $P = 0.0499$ without Bonferroni correction, 95% confidence interval −2.31, 0.00; for MN302 $P = 0.2940$, 95% confidence interval −2.24, 7.38); neither erosion nor joint space narrowing scores were significantly different.

Progression of radiographic damage correlated with a number of clinical and laboratory variables (Table 8). In all 3 protocols and in 6 of 8 treatment groups, radiographic progression was greater in patients with erosions at baseline than in those without (all groups 1.62 versus 1.28; US301 1.46 versus 0.48; MN301 1.29 versus 1.00; MN302 2.16 versus 1.56).

This effect was greater in the placebo treatment groups (placebo 4.65 versus 1.13; active-drug treatment 1.34 versus 1.1). Radiographic progression was greater in patients with concomitant corticosteroid therapy in 1 of the European protocols (MN301 3.1 versus 1.17), not different in the other European protocol (MN302 1.72 versus 1.67), and less in the North American protocol (US301 0.9 versus 1.27).

In patients with progressive disease (US301 and MN301), the final ACR20 responder status was associated with slower radiographic change, and in all patients, the AUC for the ACR20 response, the average decreases in ESR and CRP levels, and the HAQ scores were associated with slower radiographic change (results not shown). The correlation with final ACR20 response status among patients with progressive disease was the strongest of these associations, but none exceeded 0.4, indicating only mild correlation at best (Table 9).

To better define the relationship between radiographic progression and clinical response, all patients were divided into responder and nonresponder subsets defined by the ACR20 criteria. In 6 of the 8 treatment groups in these 3 studies, patients classified as responders had slower progression of joint damage than did nonresponders in the same group, with a difference in progression of 0.8–3.82 units. Among the 2 treatment groups that experienced greater radiographic progression in the nonresponders, the difference was 0.1 and 1 units. This association of radiographic progression with responder status is consistent with the weak associations found between clinical variables and radiographic changes during treatment.

To determine any bias that was potentially introduced by the large number of patients who discontinued protocol treatment early and did not have an exit radiograph, sensitivity analyses using a variety of approaches were performed (21). These confirmed the

Table 7. Percentages of patients with newly eroded joints*

Study, treatment	New joint erosions				
	1	2	3	>3	Total
US301					
LEF (n = 131)	15	2	1	2	21
PL (n = 83)	19	5	0	4	28
MTX (n = 138)	17	4	1	2	23
MN301					
LEF (n = 89)	14	8	7	2	31
PL (n = 62)	9	3	5	17	34
SSZ (n = 85)	14	5	1	7	27
MN302					
LEF (n = 304)	18	3	4	7	32
MTX (n = 331)	12	7	3	8	30

* Rounding of values in columns 1 through >3 accounts for apparent discrepancy in total percentages of patients with new erosions. LEF = leflunomide; PL = placebo; MTX = methotrexate; SSZ = sulfasalazine.

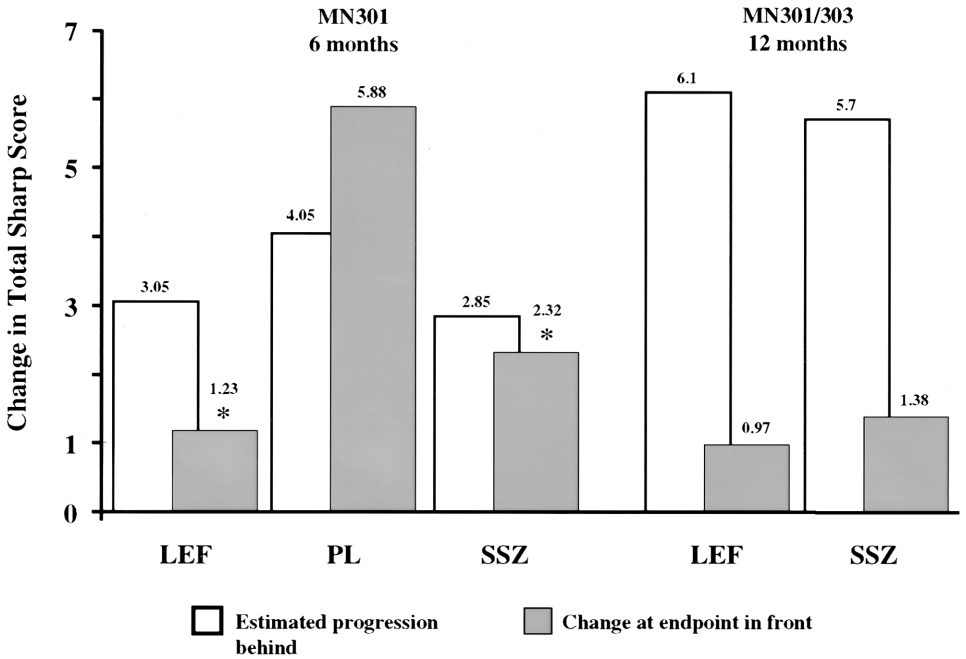

Figure 2. Change in total Sharp scores at end point and estimated progression in study MN301 at 6 months and 12 months. Progression in the placebo (PL) group exceeded the imputed value at 6 months. Radiographic progression was less in the active-drug treatment groups at 6 months (leflunomide [LEF] n = 87; sulfasalazine [SSZ] n = 84) compared with the placebo treatment group and in view of estimated progression. At 12 months, this effect continued in a smaller population of the active treatment groups (LEF n = 60; SSZ n = 53), indicating that the benefit observed over the first 6 months was sustained. $* = P \leq 0.01$ versus placebo.

results of the original analyses. None provided evidence that the effect of treatment would have been insignificant if 100% followup had been achieved. The original least squares mean difference of the total radiographic score between LEF and placebo in the US301 study was −2.53 ($P = 0.0007$) in favor of LEF. In 1 approach, the average of the least squares mean difference in 100 iterations between LEF and placebo in patients with missing data could be as high as 3.26 in favor of placebo without voiding the statistical significance ($P < 0.05$) of the original findings.

DISCUSSION

In the 3 active drug–controlled and the 2 placebo-controlled phase III trials reported here, LEF effectively delayed progression of erosions and joint space narrowing compared with placebo, as measured radiographically over 6 and 12 months of treatment, as did MTX and SSZ. The benefit of SSZ and LEF treatments in protocol MN301 was evident after only 6 months of therapy. A few other studies have demonstrated radiographic slowing after 6 months of treatment, but many investigators have continued to hold the view that trials should be 1 year or longer to improve the chances of demonstrating positive treatment effects on radiographic measures (3,4,23). Until data are available to allow power calculations on 6-month versus 1- or 2-year trials, this problem will not be resolved. The MN301 trial of 6 months' duration reported here suggests that collecting such data for those calculations might provide important time- and money-saving advantages for future trials.

The benefit of LEF and MTX treatments were apparent in the US301 protocol despite the fact that the intent-to-treat analysis included all patients originally assigned placebo therapy, although 33% received alternate treatment for a mean of 25 weeks and 31% received treatment outside the protocol for up to 33 weeks. Thus, a significant number of patients initially assigned to placebo eventually received active-drug treatment. Almost twice as many placebo-treated patients as LEF- or MTX-treated patients switched to alternate therapy or dropped out. Although the intent-to-treat analysis considered placebo-treated patients who received active-drug therapy to be the same as those who continued placebo treatment for the entire 12 months, LEF and MTX administration resulted in significantly greater efficacy than was seen in the placebo group.

The imputed yearly progression rate of radiographic scores at baseline provides a better estimate for

Table 8. Radiographic changes in subgroups of patients*

	US301			MN301			MN302	
	LEF	PL	MTX	LEF	PL	SSZ	LEF	MTX
Without concomitant steroid use								
No. of patients	60	36	64	48	30	48	85	110
Baseline Sharp score	21.4	28.0	23.1	46.3	47.2	43.3	26.6	26.3
End point Sharp score	22.3	30.5	24.0	44.8	52.4	44.5	29.6	27.4
Change in Sharp score	0.9	2.5	0.9	−1.5	5.2	1.2	3.0	1.1
With erosions at baseline								
No. of patients	79	57	78	71	46	60	221	232
Baseline Sharp score	35.0	35.7	37.7	58.8	59.3	56.3	32.8	32.8
End point Sharp score	35.8	38.3	39.0	59.1	66.5	59.2	35.7	34.3
Change in Sharp score	0.8	2.6	1.3	0.3	7.2	2.9	2.9	1.5
Without erosions at baseline								
No. of patients	52	26	58	20	13	24	81	82
Baseline Sharp score	5.0	2.7	3.4	6.4	10.5	4.5	3.2	3.9
End point Sharp score	5.2	3.9	3.8	7.6	11.5	5.3	4.5	5.7
Change in Sharp score	0.2	1.2	0.4	1.2	1.0	0.8	1.3	1.8

* LEF = leflunomide; PL = placebo; MTX = methotrexate; SSZ = sulfasalazine.

comparing radiographic disease severity at study entry than do absolute scores since it takes into account how rapidly joint destruction has occurred. Based on this estimate, patients in the 2 European studies had more severe disease than those in the North American study, but within each study, treatment groups were comparable. This is consistent with the higher values for the ESR, CRP, and HAQ scores at baseline in MN301 and MN302. During the studies, radiographic progression in the placebo group in MN301 exceeded the baseline imputed rate, but in US301, placebo-treated patients progressed at a slower rate than the baseline estimate. The greater progression rate in MN301 is most likely due to normal variation in the disease activity. The slower and greater variation observed in the progression rate in the US301 placebo group probably reflects both the usual disease variation and the large number of placebo-treated patients who received active therapy.

Regardless, in both protocols, the observed radiographic progression in the active-drug treatment groups was highly statistically significantly less than in placebo-treated patients and considerably less than the estimated yearly progression in all 3 protocols. Furthermore, sensitivity analysis defined conditions under which protocol dropout rates and/or entry into alternate therapy (protocol US301) would be associated with loss of significant treatment effects and these conditions were not clinically credible. Thus, the case for concluding that LEF, MTX, and SSZ are true structure-modifying therapies, as demonstrated in these 3 phase III, randomized, controlled trials, is compelling.

Previous studies have established that MTX is more effective than azathioprine and oral gold and that SSZ is better than hydroxychloroquine in suppressing radiographic progression (3–5). The demonstration for the first time in these protocols that MTX and SSZ were better than placebo confirms these previous reports and firmly establishes their effectiveness as structure-modifying therapies.

These 3 phase III trials were designed in 1993 and implemented in 1994 and 1995. At that time, the maximum dosage of MTX that was labeled for use in RA in the United States was 20 mg/week. Protocols US301 and MN302 allowed escalation to a maximum dosage of 15 mg/week within the first year of treatment, although increases to 17.5 and 20 mg/week were allowed in the second year of US301. Regardless, the mean dosages of MTX used in these 2 protocols over the 12-month period of treatment compare favorably with recently published data regarding a beneficial effect of MTX therapy on disease progression as measured by radiography. In an unselected group of 24 RA patients receiving MTX as initial DMARD therapy, Rich et al reported a mean weekly dose of 6.9 ± 1.7 mg and a final dose of 10.6 ± 3.6 mg (mean ± SD) following a mean of 32 weeks of treatment (24). Similarly, Maravic et al pub-

Table 9. Correlation of change in radiographic score and clinical outcomes*

	ESR	CRP	HAQ	AUC of ACR20	ACR20†
US301	0.08	0.17‡	0.08	−0.13‡	−0.27‡
MN301	0.10	0.22	0.12	−0.10	−0.03
MN302	0.13‡	0.15‡	0.05	−0.06	−0.14

* ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; HAQ = Health Assessment Questionnaire; AUC = area under the curve; ACR20 = American College of Rheumatology 20% response criteria (responders).
† All correlations were with entire patient population in each study except for the final ACR20, which was tested against a subset of patients with a change from baseline total score of ≥3.
‡ $P \leq 0.05$.

lished data on 29 RA patients with early disease (mean 0.5 years' duration) treated with MTX for 13 ± 3.8 months (mean ± SD) in which stabilization of radiographic progression was observed (25). The mean ±SD weekly dose of MTX at initiation was 8.9 ± 2.5 mg and at followup was 10.0 ± 3.2 mg as required to control disease activity.

Treatment effects were evident across a broad span of disease duration. This is of interest, since a substantial number of patients in all 3 phase III protocols (31–46%) had a disease duration of >5 years, and baseline radiographic scores were substantial in all groups. These results present a contrast to currently held beliefs that radiologic progression is best demonstrated in RA patients with early disease.

Slowing of radiographic progression was greater in patients who had erosions on baseline radiographs but benefit was also seen in those without erosions at baseline. This is consistent with previous reports, as well as with the small series recently reported by Rich et al, where radiographic progression occurred more rapidly in patients who had erosions at baseline (24). Across all 3 protocols, 22–30% of patients did not have erosions evident on baseline radiographs. The lower rates of progression in patients without erosions may have reduced the differences between treatment with LEF, MTX, or SSZ and placebo but could not have spuriously altered the positive effects of active-drug treatment observed in these protocols.

Treatment effects were more evident in the joint space narrowing scores, similar to what has been observed in many previous trials using radiographic analysis. This finding suggests that loss of cartilage occurs in RA with considerable regularity, even in the absence of bony erosion, and may be more frequent than we have appreciated, in that it cannot solely be attributed to having studied patients with long disease duration, as evidenced by the populations enrolled in these phase III trials.

Concomitant use of corticosteroids did not have a consistent effect on treatment outcome, an observation in agreement with that of a previous study comparing patients taking nonsteroidal antiinflammatory drugs who received prednisone in low doses with patients who were not taking concomitant steroids (26). This is of particular interest because among those taking steroids, the average prednisone dosage was <10 mg/day, which is in the range of dosages used by Kirwan et al, who reported beneficial effects of steroid therapy on radiographic progression (27) and which is consistent with several other studies using even larger dosages of steroids or combinations of steroids with multiple drugs (7,8,28).

The correlation between clinical and radiographic responses in the 3 protocols was less strong than expected from previous reports. In general, the correlations were weak, <0.5, and were not consistent across the protocols. Even in US301, where the correlation with HAQ scores was highest, the AUC analysis for ACR20 responders showed only a weak association with slower radiographic progression. Analyses of changes in ESR and CRP levels over time were less closely correlated with radiographic progression than has been reported in other studies (29–34). Although a number of factors may contribute to this poor correlation (including the narrow spread in observed progression rates and measures of disease severity and the relatively short observation period during which radiographic progression rates were observed), it remains largely unexplained.

In summary, these studies demonstrate that LEF joins a small group of DMARDs that have been repeatedly demonstrated to slow radiographic progression in RA and a somewhat larger group for which there is limited evidence of slowing of disease progression. In addition, MTX and SSZ were shown for the first time in placebo-controlled trials to retard joint destruction as measured radiographically, confirming previous reports comparing MTX and SSZ with other therapies. Although its relative ranking among intramuscular gold, MTX, SSZ, cyclosporine, and the interleukin-1 receptor antagonist remains to be firmly established, provided its efficacy is sustained and long-term tolerability remains favorable after extensive use in the clinic, LEF promises to be an important addition to the pharmacopoeia of effective agents for the treatment of RA.

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