A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis

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Abstract

Objective. To compare the clinical efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis (RA).

Methods. In this multicentre, double-blind trial, 999 subjects with active RA were randomized to leflunomide ($n = 501$; loading dose 100 mg/day for 3 days, maintenance dose 20 mg/day) or methotrexate ($n = 498$; 10–15 mg/week) for 52 weeks. After 1 yr the subjects could choose to stay for a second year of double-blind treatment. The primary end-points were tender and swollen joint counts and overall physician and patient assessments. Analyses were of the intent-to-treat group.

Results. After 1 yr, the mean changes in the leflunomide and methotrexate groups, respectively, were -8.3 and -9.7 for tender joint count; -6.8 and -9.0 for swollen joint count; -0.9 and -1.2 for physician global assessment; -0.9 and -1.2 for patient global assessment; -14.4 and -28.2 for erythrocyte sedimentation rate. Improvements seen with methotrexate were significantly greater than those with leflunomide. No further improvement occurred after the second year of treatment and the distinction between the two treatments in terms of tender joint count and patient global assessment was lost. During the first year of treatment, a small and equivalent degree of radiographically assessed disease progression was seen with both drugs. After 2 yr, disease progression was significantly less with methotrexate. The most common treatment-related adverse events in both groups were diarrhoea, nausea,

alopecia, rash, headache, and elevated plasma liver enzyme levels. Over 2 yr, 21 subjects receiving methotrexate were withdrawn due to elevated plasma liver enzymes *vs* eight subjects taking leflunomide. Two drug-related deaths from pulmonary causes were recorded with methotrexate *vs* no drug-related deaths among the subjects receiving leflunomide.

Conclusions. Both leflunomide and methotrexate are efficacious for prolonged treatment of RA. At the doses used, some clinical benefit of methotrexate over leflunomide was observed in the first year of treatment. This benefit must be weighed against the potential toxicity of this drug when used without folate supplementation.

KEY WORDS: Leflunomide, Methotrexate, Clinical trial, Folate supplementation, Rheumatoid arthritis, Radiographic assessment of disease progression.

As knowledge of the pathogenic progression of rheumatoid arthritis (RA) has increased, it has become clear that permanent joint damage begins relatively early in the course of the disease, generally within 2 yr of onset in subjects with active, polyarticular RA [1, 2]. Based on this observation, current treatment guidelines emphasize the early use of disease-modifying anti-rheumatic drugs (DMARDs), a class of therapeutic agents that have the potential to minimize or prevent joint damage [3]. Unfortunately, long-term maintenance of patients on DMARDs has proven to be difficult and is frequently limited by loss of efficacy and/or development of serious adverse events [4, 5].

Leflunomide, an isoxazole derivative, is a new DMARD for the treatment of RA. Leflunomide is converted by first-pass metabolism in the liver and gut to an active metabolite, A77 1726, that blocks *de novo* synthesis of pyrimidines by inhibiting dihydroorotate dehydrogenase, the rate-limiting enzyme in the pyrimidine synthesis pathway [6, 7]. During the initiation of RA, activated CD4+ T cells proliferate rapidly, a process that requires an expansion of the pyrimidine nucleotide pool within lymphocytes by 8–16-fold to support synthesis of new DNA [8]. A77 1726 inhibits this proliferation by preventing T cells from generating the pyrimidines required for the synthesis of new DNA prior to cell division.

In recent phase III clinical trials, leflunomide was found to be clinically superior to placebo and equivalent to sulphasalazine and methotrexate for improving the symptoms of RA [9, 10]. Additionally, leflunomide was shown to be similar to sulphasalazine and superior to methotrexate for slowing the progression of radiographically assessed joint damage. The present phase III clinical trial compared both short-term and long-term (up to 2 yr) clinical efficacy and safety of leflunomide and methotrexate in patients with active RA.

Materials and methods

Subjects

Women and men, 18 yr or older, were eligible for enrolment. All subjects recruited for this study had diagnosed RA according to American College of Rheumatology (ACR) criteria [11] for at least 4 months but no longer than 10 yr and active disease as defined by the following criteria at enrolment: at least six joints that were swollen and six that were tender by 28-joint count [12]; overall assessment of RA activity by patient and physician as fair, poor, or very poor; C-reactive protein (CRP) > 2.0 mg/dl or erythrocyte sedimentation rate (ESR) > 28 mm/h. Previous use of DMARDs was permitted only if they were discontinued at least 28 days before trial enrolment. Non-steroidal anti-inflammatory drugs (NSAIDs) and steroids ($\leqslant 10$ mg/day prednisolone or equivalent) were allowed, provided the subject had been receiving a stable dose for at least 28 days prior to study entry. Intra-articular corticosteroid injections were not allowed within 6 weeks of an efficacy assessment. Women of childbearing age were required to use adequate contraception and were given blood tests to ensure that they were not pregnant prior to enrolment.

Study design

This 104-week study was a multicentre, randomized, double-blind, parallel-group evaluation of the efficacy and safety of leflunomide and methotrexate. The study was performed in 117 centres in Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, The Netherlands, Norway, South Africa, Spain, Sweden, and the UK. The study was approved by the human research committee of each participating institution, and written informed consent was requested and received from all subjects in the study.

Subjects were randomized to receive either leflunomide or methotrexate in a ratio of 1:1. Subjects assigned to the leflunomide group were given 100 mg daily for 3 days followed by a daily maintenance dose of 20 mg for the remainder of the treatment period. At the discretion of the investigator, the dosage could be reduced to 10 mg/day after week 4 in subjects who experienced significant clinical adverse events. Subjects in the methotrexate group were given 7.5 mg in weeks 1–4, 10 mg in weeks 5–12, and 10 or 15 mg in weeks 13–52. After week 4, the dosage could be reduced from 10 to 7.5 or from 15 to 10 mg/week if adverse events occurred. Folate supplementation for the subjects taking methotrexate was not mandated by protocol. All subjects in both groups received one weekly and one daily dose of drug, one of which was a placebo.

All subjects who completed the initial 52-week treat-

ment phase were given the opportunity to continue double-blind treatment for an additional 52 weeks. During this period, the subjects were maintained in the treatment group to which they had been previously assigned and continued to receive the drug dosage they had been taking at the end of the 52-week period.

Efficacy and safety measures

Clinical assessments of RA activity were obtained every 2 weeks for the first 8 weeks and at weeks 12, 24, 36, 52, 76, and 104. The following efficacy end-points were assessed: counts of tender and swollen joints based on a 28-joint count [12]; physician and patient assessments of global RA disease activity based on a five-point scale from 1 (very good) to 5 (very poor); duration of morning stiffness; pain intensity assessment on a visual analogue scale of 0 (no pain) to 10 (severe pain); values of Westergren ESR, CRP and rheumatoid factor (RF). Functional disability was measured with a health assessment questionnaire (HAQ) that rated the subjects' ability to perform daily activities from 0 (without difficulty) to 3 (unable to perform tasks). Plain radiographs of both hands, including the wrists, and both forefeet were taken in posteroanterior view at baseline and at weeks 52 and 104.

The four primary efficacy end-points in this study were tender and swollen joint count and global physician and patient assessment of disease activity. Overall patient clinical response to therapy was assessed by ACR criteria [13]. To be considered an ACR 20% responder, a subject had to have a $\geqslant 20\%$ improvement in tender and swollen joint count and in at least three of the following five criteria: patient global assessment, physician global assessment, pain intensity, HAQ, CRP or ESR. The time to first response in the two treatment groups and the percentage of responders during the first and second years of treatment were also compared.

Radiographs at baseline and after 1 yr of treatment were blinded for treatment and sequence and were assessed by Dr Arvi Larsen according to the Larsen technique as modified for use in clinical trials [14]. Radiographs after the second year of treatment were read separately and blinded only for treatment. Initial and final radiographs of 40 joints in the hands and feet were scored on a scale of 0–5, where an increasing score indicated worsening disease. Individual scores were then summed and divided by the number of joints assessed to give a mean Larsen score per joint. The number of eroded joints was also counted. The joint involvement was expressed as a mean score and eroded joint count.

The safety assessment included a complete medical history at baseline and a complete physical examination before the study and at 6-month intervals over the course of the study or as clinically indicated. Vital signs and weight were taken at monthly intervals. A 12-lead electrocardiogram (ECG) and chest radiographs were taken at baseline. The ECG was repeated at 6-month intervals or as clinically indicated. Chest radiographs were repeated only if clinically indicated. Pill counts were performed to assess compliance with medication protocols.

Laboratory tests consisting of haematological measurements, determination of blood chemistry, and urinalysis were performed at each monthly visit. All adverse events reported spontaneously by the subjects or observed or elicited by the investigator were recorded. The intensity of the adverse event and the possible relationship of the adverse event to the study medication were assessed by the investigator who recorded the event. An adverse event was classified as serious if it met any of the following criteria: fatal or life-threatening; permanently or significantly disabling; requiring hospitalization; involving cancer or a congenital anomaly; occurring with overdose; or suggestive of a significant hazard.

Statistical analysis

The null hypothesis of this study was that the effects of leflunomide *vs* methotrexate on any of the four primary efficacy end-points differed by more than 50% from the known differences between methotrexate and placebo. Sample sizes for the study were calculated assuming that the superiority of methotrexate over placebo is five joints for tender and swollen joint count and 0.5 categories for physician and patient assessments of disease. Standard deviations (S.D.) for the effect of treatment on the primary efficacy end-points were assumed to be 8.5 and 6 for tender and swollen joint count, respectively, and 1.0 for both patient and investigator global disease assessments. Assuming a significance level of 0.05, power of 0.80, and that 30% of the data could not be evaluated, it was calculated that a total sample size of at least 670 per-protocol completers would be required to show equivalence for all four primary efficacy variables with 95% confidence intervals.

All analyses were performed on the intent-to-treat population. For the first year of the study, the intent-to-treat population was defined as those subjects who had a baseline measurement and at least one follow-up measurement. For the second year of the study, the intent-to-treat population consisted of all subjects who received at least one dose of medication after week 52 of the study. If a subject dropped out of the study prior to week 52, data from the last observation were carried forward in the analysis of the first year data. A similar procedure was used for the analysis of the results from subjects who dropped out during the second year of the study.

Descriptive statistics of all variables were calculated and are presented as means and S.D. The baseline comparability of categorical variables in the treatment groups was assessed by χ^2-test or Fisher's exact test. Continuous variables were compared by an analysis of variance (ANOVA) model that included treatment group, investigator, and treatment–investigator interaction as factors. Comparisons of the mean changes of efficacy end-points were performed by analysis of covariance (ANCOVA). Treatment, investigator, RA duration ($\leqslant 2$ yr or > 2 yr), treatment–investigator interaction, and treatment–RA duration interaction were included as fixed effects, and baseline score was a covariant in

the model. All statistical tests were two-tailed and a probability (*P*) < 0.05 was considered significant.

Results

Patient characteristics

A total of 1244 subjects were enrolled in this study. Of these, 244 subjects were withdrawn in the screening phase, and one additional subject was randomized but not treated. Of the 999 subjects randomized and treated, 501 received leflunomide and 498 received methotrexate. A total of 736 subjects (349 leflunomide and 387 methotrexate) completed the initial 52-week treatment phase. Of these 736 subjects, 612 (292 leflunomide and 320 methotrexate) were recruited for a second year of treatment and 497 subjects (233 leflunomide and 264 methotrexate) completed 2 yr of double-blind treatment.

The demographic characteristics of the initial treatment groups and of the subgroup of subjects that continued through the second year of the study are shown in Table 1. The mean age of all subjects was 57–59 yr, all treatment groups were approximately 71% female, and the average duration of disease was 3.5–3.8 yr. In all treatment groups, approximately 66% of the subjects had failed to respond to at least one previous DMARD. Approximately 35% of all subjects were using corticosteroids and 80–85% were taking NSAIDs prior to beginning the first year of the study. In the subset of subjects who went on to a second year of treatment, lower but equivalent rates of NSAID and corticosteroid use were seen in leflunomide- and methotrexate-treated subjects.

At week 12, the weekly methotrexate dosage was increased from 10 to 15 mg in 263 (53%) of the subjects receiving methotrexate. Overall, the dosage of study medication was decreased due to an adverse event or abnormal laboratory finding in 128 (37 leflunomide, 91 methotrexate) subjects. The percentage of subjects whose medication was decreased was higher in the methotrexate- (18%) than in the leflunomide-treated group (7%).

Withdrawals during treatment are shown in Table 2. In both treatment groups, the most common reason for withdrawal during the first year of treatment was adverse events. This accounted for 19% of the withdrawals in the leflunomide group and 15% in the methotrexate group. During the second year of treatment the most common reason for withdrawal in both treatment groups was still adverse events, but the rates were less than half those seen during the first year. Lack of efficacy was the next most common reason for withdrawal and was cited as the reason for 7% of withdrawals in leflunomide- and 3% of withdrawals in methotrexate-treated subjects during the first year of treatment. Similar rates were seen in the subset of patients who received a second year of treatment.

Clinical efficacy

Changes in the four primary clinical efficacy end-points over the first year of treatment with leflunomide and methotrexate are shown in Table 3. Both treatments resulted in significant improvement in all primary efficacy end-points. However, the difference between baseline and end-point measurements of all efficacy end-points was significantly greater in methotrexate- than in leflunomide-treated subjects.

Changes in primary clinical efficacy end-points in the subset of subjects who continued the second year of treatment are shown in Table 4. During the second year of treatment, little or no further improvement occurred in any of the primary efficacy end-points with either leflunomide or methotrexate. The differences between treatments in terms of efficacy end-points tended to narrow such that the improvements in tender joint count and patient global assessment from baseline were not statistically different in the two treatment groups after 2 yr.

The changes in secondary clinical efficacy end-points after 1 yr of treatment are shown in Fig. 1. Both leflunomide and methotrexate resulted in significant improvement in all variables examined (morning stiffness, pain intensity, HAQ score, ESR, CRP, and RF). For most variables, the quantitative difference between the responses to the two treatments was minimal, despite the fact that the response to methotrexate was statistically greater for all variables except RF.

TABLE 1. Demographics of subjects receiving leflunomide (LEF) or methotrexate (MTX)

	Year 1		Year 2	
	LEF (*n* = 501)	MTX (*n* = 498)	LEF (*n* = 292)	MTX (*n* = 320)
Age				
Mean ± s.d.	58.3 ± 10.1	57.8 ± 10.8	57.7 ± 9.8	57.0 ± 11
⩾65 yr (%)	30.7	30.1	25.7	27.2
Women (%)	70.7	71.3	71.2	71.3
Duration of RA				
Mean ± s.d. (yr)	3.7 ± 3.2	3.8 ± 3.5	3.5 ± 3.1	3.8 ± 3.5
⩽2 yr (%)	43.7	43.2	45.2	44.1
Previous DMARD treatment (%)	66.3	66.9	64.7	66.9
DMARDs failed (mean ± s.d.)	1.1 ± 1.1	1.1 ± 1.1	1.0 ± 1.0	1.1 ± 1.2
Concomitant corticosteroids (%)	36.3	33.5	14.0	11.3
Concomitant NSAIDs (%)	80.0	84.7	37.3	42.5

TABLE 2. Reasons for withdrawal from treatment with leflunomide (LEF) or metrotrexate (MTX)

| | Year 1 | | Year 2 | |
Reason for withdrawal	LEF (*n* = 501)	MTX (*n* = 498)	LEF (*n* = 292)	MTX (*n* = 320)
Lack of efficacy	37 (7%)	15 (3%)	17 (6%)	14 (4%)
Adverse events	94 (19%)	74 (15%)	24 (8%)	19 (6%)
Death	4 (1%)	5 (1%)	1 (<1%)	7 (2%)
Non-compliance	11 (2%)	14 (3%)	6 (2%)	6 (2%)
Other	6 (1%)	3 (<1%)	11 (4%)	10 (3%)
Total	152 (30%)	111 (22%)	59 (20%)	56 (17%)

Changes in secondary efficacy end-points in the sub-group of subjects treated with leflunomide and methotrexate for 2 yr are shown in Table 5. As was noted for the primary efficacy end-points, there was little or no further improvement in any of the secondary efficacy end-points during the second year of treatment with either leflunomide or methotrexate, and the differences between responses to leflunomide and methotrexate tended to narrow with time. After 2 yr of treatment, the improvements in morning stiffness, pain intensity, HAQ, and RF from baseline were not statistically different in the two groups.

During the first year of treatment, 50.5% (250/495) of the subjects in the leflunomide intent-to-treat group met the criteria for ACR 20% response. The corresponding percentage for subjects receiving methotrexate was 64.8% (317/489) (*P* < 0.0001 *vs* leflunomide). In the subset of subjects who subsequently received a second year of treatment, the percentages of ACR 20% responders in the two treatment groups after 1 yr were higher than in the overall study population [64.6% (185/286) and 76.7% (241/314) in the leflunomide- and methotrexate-treated subjects, respectively]. There was no further increase in the percentage of ACR 20% responders after the second year of either treatment, and after 2 yr, the ACR 20% response rate in the leflunomide-treated subjects was not significantly different from the response rate of the subjects given methotrexate (64.3 *vs* 71.7%).

Radiographic assessment of RA progression

The overall Larsen score is a radiographically determined index of bone and joint damage in both hands and feet. Mean baseline overall Larsen scores were statistically equivalent for the two treatment groups prior to beginning the first year of the study (1.25 ± 0.48 *vs* 1.29 ± 0.45 in leflunomide- and methotrexate-treated patients, respectively). After 1 yr of treatment, there was a small (0.03) and equivalent increase in overall Larsen score with both treatment protocols. The subset of subjects treated for 2 yr had baseline overall Larsen scores similar to the total population of subjects (1.27 ± 0.47 *vs* 1.31 ± 0.52 in leflunomide- and methotrexate-treated patients, respectively). There was no further increase in joint damage in the subjects treated with leflunomide and a small improvement in the subjects treated with methotrexate. The net result was a small

TABLE 3. Changes in primary clinical efficacy end-points (mean ± S.D.) after 1 yr of treatment with leflunomide (LEF) or methotrexate (MTX)

	LEF (*n* = 495)	MTX (*n* = 489)	*P*
Tender joint count			
Baseline	17.2 ± 6.8	17.7 ± 6.7	
Δ	− 8.3 ± 7.9	− 9.7 ± 7.9	0.006
Swollen joint count			
Baseline	15.8 ± 6.0	16.5 ± 5.9	
Δ	− 6.8 ± 7.3	− 9.0 ± 7.3	0.0001
Physician global assessment			
Baseline	3.5 ± 0.6	3.6 ± 0.6	
Δ	− 0.9 ± 1.0	− 1.2 ± 1.0	< 0.001
Patient global assessment			
Baseline	3.6 ± 0.6	3.6 ± 0.7	
Δ	− 0.9 ± 1.1	− 1.2 ± 1.0	< 0.001

TABLE 4. Changes in primary clinical efficacy end-points (mean ± S.D.) after 2 yr of treatment with leflunomide (LEF) or methotrexate (MTX)

	LEF (*n* = 273)	MTX (*n* = 298)	*P*
Tender joint count			
Baseline	16.9 ± 6.7	17.2 ± 6.5	
Δ (1 yr)	− 10.2 ± 7.7	− 11.0 ± 7.1	
Δ (2 yr)	− 10.5 ± 8.1	− 10.9 ± 8.2	NS
Swollen joint count			
Baseline	16.0 ± 6.0	16.1 ± 6.0	
Δ (1 yr)	− 8.6 ± 7.2	− 10.0 ± 7.0	
Δ (2 yr)	− 9.1 ± 7.7	− 10.3 ± 7.3	0.017
Physician global assessment			
Baseline	3.5 ± 0.6	3.6 ± 0.6	
Δ (1 yr)	− 1.3 ± 0.9	− 1.5 ± 0.9	
Δ (2 yr)	− 1.1 ± 1.0	− 1.4 ± 1.0	0.015
Patient global assessment			
Baseline	3.5 ± 0.6	3.6 ± 0.7	
Δ (1 yr)	− 1.2 ± 1.0	− 1.4 ± 1.0	
Δ (2 yr)	− 1.2 ± 1.1	− 1.3 ± 1.0	NS

NS, not significant.

but significant treatment difference in the change in radiographic scores of the two treatment groups after 2 yr.

Response time

The mean time to the first ACR 20% response was shorter in subjects receiving leflunomide than in methotrexate-treated subjects (74 ± 80 *vs* 101 ± 92.5 days;
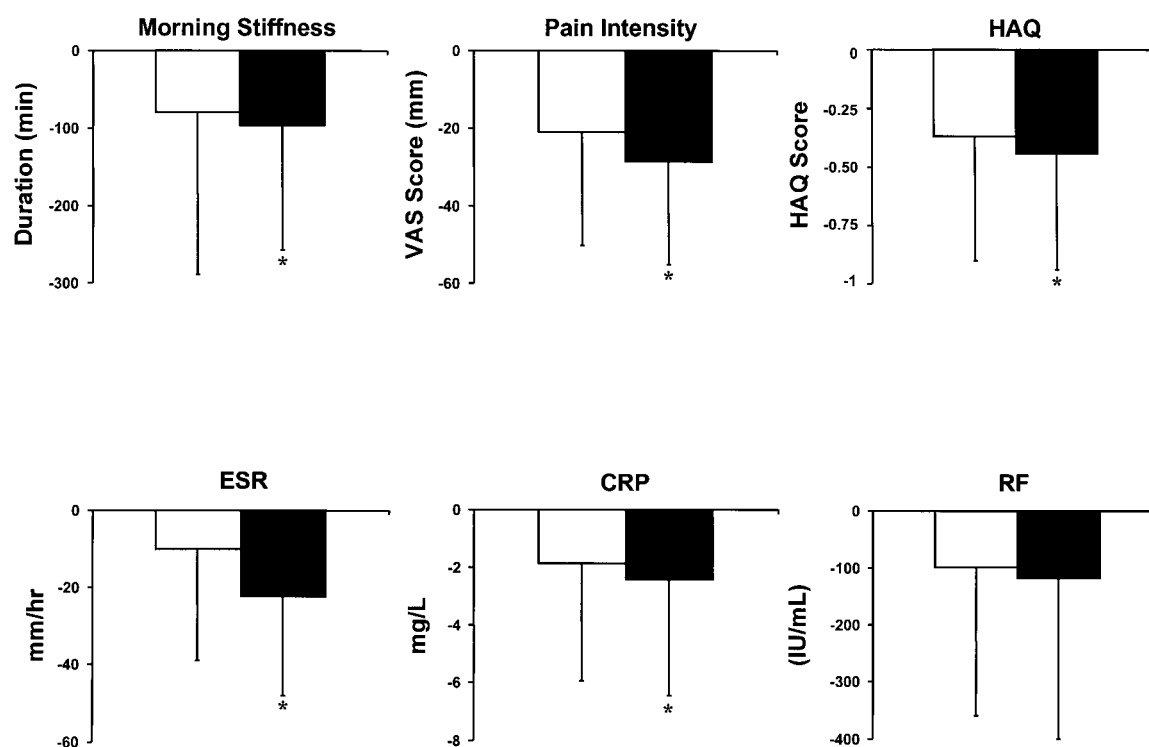
FIG. 1. Changes from baseline of secondary clinical efficacy end-points after 1 yr of treatment with leflunomide (open bar) or methotrexate (filled bar). All values are means ± s.d. Asterisks indicate a statistically significant difference ($P < 0.05$) between treatment effects with leflunomide and methotrexate. VAS, visual analogue scale.

TABLE 5. Changes in secondary clinical efficacy end-points after 2 yr of treatment with leflunomide (LEF) or methotrexate (MTX); all values are means ± s.d.

	LEF	MTX	P
Morning stiffness (min)	$n = 268$	$n = 292$	
Baseline	117.4 ± 101.3	123.6 ± 99.3	
Δ (1 yr)	− 87.3 ± 104.1	− 91.5 ± 94.4	
Δ (2 yr)	− 76.3 ± 105.9	− 87.6 ± 103.6	NS
Pain intensity (mm)	$n = 273$	$n = 297$	
Baseline	55.1 ± 21.8	58.5 ± 19.6	
Δ (1 yr)	− 27.3 ± 26.6	− 35.2 ± 24.2	
Δ (2 yr)	− 27.1 ± 27.7	− 31.8 ± 25.9	NS
HAQ	$n = 252$	$n = 278$	
Baseline	1.03 ± 0.62	1.01 ± 0.58	
Δ (1 yr)	− 0.48 ± 0.50	− 0.54 ± 0.47	
Δ (2 yr)	− 0.45 ± 0.56	− 0.50 ± 0.55	NS
ESR (mm/h)	$n = 266$	$n = 282$	
Baseline	51.2 ± 23.2	52.5 ± 22.5	
Δ (1 yr)	− 14.4 ± 24.1	− 28.2 ± 22.7	
Δ (2 yr)	− 14.1 ± 26.3	− 27.0 ± 24.3	0.0001
CRP (mg/l)	$n = 260$	$n = 285$	
Baseline	4.3 ± 4.4	4.0 ± 3.6	
Δ (1 yr)	− 2.2 ± 6.9	− 2.9 ± 3.7	
Δ (2 yr)	− 2.6 ± 4.2	− 2.8 ± 3.8	0.008
RF (IU/ml)	$n = 259$	$n = 281$	
Baseline	277 ± 345	284 ± 364	
Δ (1 yr)	− 126 ± 252	− 120 ± 249	
Δ (2 yr)	− 125 ± 277	− 120 ± 279	NS

NS, not significant.

$P < 0.05$). Overall, 62% of the subjects treated with leflunomide and 54% of the subjects receiving methotrexate responded during the first 12 weeks of treatment. After 1 yr of treatment, the percentage of subjects who had met the criteria for ACR 20% response at least once during treatment had risen to 82.8 and 86.8%, respectively. In the subgroup of subjects treated for 2 yr, approximately 90% of both treatment groups fulfilled the criteria for ACR 20% response at least once during treatment.

Safety

Adverse events leading to withdrawal from the study were seen in 94 (19%) of the subjects treated with leflunomide and 75 (15%) of the subjects receiving methotrexate after 1 yr of treatment. In the subset of subjects treated for a second year, 24 (8%) of the subjects treated with leflunomide and 19 (6%) of the subjects receiving methotrexate withdrew because of adverse events. The overall frequency of treatment-related serious adverse events was low and comparable in both treatment groups (leflunomide 7%, methotrexate 8%). Over the 2-yr course of the study, there were two treatment-related deaths among the subjects receiving methotrexate (one from pneumonitis and the other from pancytopenia followed by pneumonia) and none among the leflunomide-treated subjects.

The most common adverse events resulting in withdrawal during the first year of treatment were elevations of plasma liver enzyme levels (eight leflunomide, 16 methotrexate), nausea (seven leflunomide, nine methotrexate), diarrhoea (seven leflunomide, four methotrexate), and alopecia (transient reversible hair loss) (seven leflunomide, one methotrexate). No pattern was discernible in the adverse events leading to withdrawal during the second year of treatment. The only adverse event that resulted in withdrawal reported in more than three subjects in a treatment group during the second year was abnormal liver enzyme levels, a condition that was seen in five subjects receiving methotrexate.

Treatment-related adverse events seen in ⩾5% of subjects and associated withdrawals in both treatment groups during the first and second years of treatment with leflunomide or methotrexate are shown in Tables 6 and 7, respectively. During the first year of treatment, the most common treatment-related adverse events in subjects receiving leflunomide were diarrhoea, alopecia, and nausea. The frequency of both nausea and diarrhoea was highest during the first 2 weeks of treatment with leflunomide or methotrexate and declined thereafter. The most notable difference in the adverse event profile of the two treatment groups was the high incidence of abnormal plasma liver enzyme levels in subjects receiving methotrexate; the 16.3%, increase was three times higher than that seen in subjects receiving leflunomide. Withdrawal rates for all adverse events were comparable in both treatment groups, with the exception of those for diarrhoea, alopecia, and rash, which were more common in leflunomide-treated subjects, and nausea and abnormal plasma liver enzyme levels, which were more common in methotrexate-treated subjects.

In the second year of treatment, hypertension and rash were the most common treatment-related adverse events seen with leflunomide. Over the 2 yr of treatment with leflunomide, the mean increases in systolic and diastolic blood pressure were 4.6 ± 20 and 3.4 ± 11 mmHg, respectively. Severe hypertension was seen in only two subjects treated with leflunomide and in both cases concomitant cardiovascular disease was present. In subjects receiving methotrexate, upper respiratory infections and abnormal plasma liver enzyme levels were seen more often. Withdrawal rates for individual adverse events were comparable in both treatment groups with two exceptions. Rash was more common in leflunomide-treated subjects and abnormal plasma liver enzyme levels were observed more frequently in methotrexate-treated subjects.

In both treatment groups, some adverse events were recurrent. In the second year of the study, 14 subjects experienced treatment-emergent alopecia and of these, seven had reported alopecia as an adverse event during the first year of treatment. Other second year recurrences of adverse events with leflunomide included 11 of 29 subjects with diarrhoea, three of 10 subjects with nausea, and two of nine subjects with abnormal liver function tests. With methotrexate, 10 of the 27 patients reporting nausea during the second year of treatment had also reported this adverse event during the first year of treatment. The same was true for four of the 22 subjects

TABLE 6. Treatment-related adverse events (AEs) occurring in ⩾5% of subjects during the first year of treatment with leflunomide (LEF) or methotrexate (MTX) and associated withdrawal rates

	LEF ($n = 501$)		MTX ($n = 498$)	
	AE (%)	Withdrawal (%)	AE (%)	Withdrawal (%)
Diarrhoea	18.0	2.0	6.8	0.8
Alopecia	16.6	1.4	9.8	0.2
Nausea	11.2	1.2	15.7	2.2
Rash	7.4	1.2	4.8	0.2
Headache	6.2	0.6	4.8	1.0
Gastrointestinal pain	5.6	0.8	5.6	0.8
Abnormal plasma liver enzyme levels	5.4	1.6	16.3	3.2
Upper respiratory infection	5.2	0.2	5.0	0
Mouth ulceration	3.0	0.2	5.6	0.2
Dyspepsia	2.4	0.4	5.8	0.4

TABLE 7. Treatment-related adverse events (AEs) occurring in ⩾ 5% of subjects during the second year of treatment with leflunomide (LEF) or methotrexate (MTX) and associated withdrawal rates

	LEF ($n = 292$)		MTX ($n = 320$)	
	AE (%)	Withdrawal (%)	AE (%)	Withdrawal (%)
Hypertension	6.8	0	2.5	0
Rash	6.5	1.0	3.8	0
Alopecia	4.5	0.3	5.0	0
Upper respiratory infection	4.5	0	5.6	0.3
Abnormal plasma liver enzyme levels	2.7	0	5.9	1.6

reporting abnormal liver function tests during the second year of treatment.

Interstitial pneumonitis, a rare but life-threatening adverse event associated with methotrexate treatment, was reported in five subjects treated with methotrexate over the 2 yr of the study and resulted in one death. No cases of interstitial pneumonitis were reported in subjects treated with leflunomide.

No clinically relevant changes in plasma electrolytes were noted with either treatment regimen in this study. Treatment with both leflunomide and methotrexate resulted in a significant increase in plasma haemoglobin and a significant reduction in leucocyte and platelet counts after both 1 and 2 yr of treatment. During the first year of treatment, leucopenia was reported as an adverse event possibly related to study medication in 20 subjects treated with leflunomide and eight subjects treated with methotrexate. None of the low leucocyte values was clinically noteworthy (i.e. $< 2 \times 10^9$ white blood cells/l), but mild leucopenia (leucocyte count $\geqslant 2.0$ and $< 3.0 \times 10^9$ cells/l) led to withdrawal of study medication in four subjects treated with leflunomide. During the second year of the study, mild treatment-related leucopenia was noted in eight subjects treated with leflunomide, three of whom were subsequently withdrawn from the study, and in 10 subjects treated with methotrexate. Additionally, one subject treated with methotrexate developed pancytopenia that was considered to be treatment related and died from pneumonia that subsequently developed.

After 1 yr of treatment with methotrexate, plasma creatinine and uric acid both increased significantly from baseline (92.2 ± 14.7 *vs* 89.0 ± 14.5 μM/l and 304 ± 78 *vs* 291 ± 74 μM/l, respectively). These increases were maintained during the second year of treatment. In contrast, treatment with leflunomide resulted in no change in plasma creatinine level over baseline after 1 yr of treatment (89.3 ± 14.1 *vs* 89.2 ± 13.8 μM/l) and significantly decreased plasma uric acid levels (223 ± 73 *vs* 286 ± 78 μM/l). In the subgroup of subjects treated with leflunomide for 2 yr, no change in plasma creatinine levels and no further changes in plasma uric acid levels were noted during the second year of treatment.

Clinically relevant elevations in plasma liver enzyme levels ($\geqslant 3 \times$ upper limit of normal) were noted in 32 subjects receiving leflunomide and 124 subjects treated with methotrexate for 1 yr. During the second year of treatment, 16 subjects treated with leflunomide and 20 subjects taking methotrexate had clinically relevant elevations in plasma liver enzyme levels. Over the entire 2 yr of the study, eight subjects receiving leflunomide and 21 subjects given methotrexate were withdrawn from treatment because of persistent elevations in plasma liver enzyme levels.

The body weights of the two treatment groups were statistically equivalent at the beginning of the study. After 1 yr of treatment, subjects treated with leflunomide had lost 1 ± 3 kg, while those taking methotrexate gained 1 ± 3.9 kg. In the subset of subjects treated for 2 yr, those receiving leflunomide lost 0.2 ± 4.7 kg while those taking methotrexate gained 1.6 ± 4.6 kg.

Discussion

DMARDs have been widely used for the treatment of RA for more than 20 yr [15, 16]. Their popularity has been based on their ability to relieve the signs and symptoms of active RA and, in some cases, to retard the radiographically assessed joint destruction that is a hallmark of disease progression. Unfortunately, chronic treatment with DMARDs is frequently limited by loss of drug efficacy over time and by the development of serious adverse effects that frequently necessitate a change in therapeutic regimen.

Leflunomide, the first new DMARD in more than 10 yr, has a unique mechanism of action. The active metabolite of leflunomide, A77 1726, inhibits dihydro-orotate dehydrogenase, the rate-limiting enzyme in the pyrimidine synthesis pathway [6, 7]. Since T cells rely heavily on newly synthesized pyrimidine for the production of DNA prior to cell division [8], the inhibition of pyrimidine synthesis markedly limits the expansion of T cells that is thought to be a primary event in the initiation and maintenance of the chronic joint inflammation of RA [17].

The present study compared the clinical efficacy and safety of leflunomide and methotrexate, a commonly used DMARD. The study was continued for 2 yr, a sufficient time period to allow the assessment of long-term efficacy and tolerability of leflunomide.

Both leflunomide and methotrexate resulted in significant improvement in the four primary clinical efficacy end-points of this study after 1 yr of treatment (Table 3). Although methotrexate treatment resulted in significantly more improvement than leflunomide in the first year of treatment, this distinction was not clinically meaningful and was largely lost after 2 yr of treatment (Table 4). A similar pattern of response was also seen in the secondary clinical efficacy end-points. For all efficacy end-points, virtually all of the improvement was seen during the first year of treatment with either leflunomide or methotrexate. During continued treatment, the degree of improvement seen after 1 yr was largely maintained.

Radiographic measurements in the present study indicate an equivalent degree of RA disease progression following 1 yr of treatment with either leflunomide or methotrexate. During the second year of treatment, no further progression was seen during leflunomide treatment, and a small degree of disease regression was noted with methotrexate. In the absence of placebo-treated control subjects, the effect of treatment on disease progression cannot be evaluated. However, it should be noted that both leflunomide and methotrexate have been shown to slow radiographically assessed joint damage relative to placebo-treated controls a in 1-yr clinical

study with a design similar to that of the present trial. In that study, leflunomide was significantly more effective than methotrexate in slowing progression of RA after 1 yr of treatment [10].

The onset of action of DMARDs is usually relatively slow, a factor that may limit patient compliance with medication. In the present study, the mean time to ACR 20% response with leflunomide was almost 4 weeks shorter than that of methotrexate, and after 12 weeks the ACR 20% response had been seen in 62 and 54% of the leflunomide- and methotrexate-treated subjects, respectively. This rapidity of onset may result from the initial loading dose of leflunomide that is given on the first 3 days of treatment to ensure fast attainment of steady-state therapeutic levels of drug in the plasma [18].

The efficacy results in the present study differ from those of another recent comparison of leflunomide and methotrexate reported by Strand *et al.* [10]. This 52-week study was placebo-controlled but otherwise had a design similar to that of the present trial. The results of the study indicated that treatment with either leflunomide or methotrexate resulted in statistically significant improvement in tender and swollen joint count and in patient and physician disease assessments compared with placebo, and that the degree of improvement was equivalent with both drugs. Responses to leflunomide in terms of the major efficacy end-points were consistent across the two studies. In contrast, the improvement in tender and swollen joint count and patient and physician global assessments following 1 yr of methotrexate treatment in the present study was 30–70% greater than the response noted by Strand *et al.* [10]. There are at least two differences in these studies that presumably contributed to the difference in methotrexate efficacy. First, the subjects in the study by Strand *et al.* [10] had a longer disease duration (6.5–7.0 *vs* 3.7–3.8 yr in the present study) and thus, presumably, more advanced disease. Second, an obvious difference in the two studies is the use of folate supplementation. Folate was mandated in the study by Strand *et al.* [10] but was taken by <10% of the subjects in the present study. Although folate supplementation has been reported to ameliorate many of the toxic effects of methotrexate, particularly gastrointestinal-related side-effects, without compromising drug efficacy for therapy of RA [19, 20], these conclusions have been contradicted by a more recent study by Van Ede *et al.* [21] that was specifically designed to test whether supplementation with either folic acid or folinic acid affects the efficacy or side-effect profile of methotrexate. In this randomized, double-blind trial, 38% of the patients treated with methotrexate (7.5–25 mg/week) alone discontinued treatment within 48 weeks, *vs* 17% of patients receiving methotrexate plus 2 mg/day folate. Virtually all of the difference in withdrawals was due to differences in hepatotoxicity. Although the authors concluded that folate supplementation had no effect on the efficacy of methotrexate, the mean dose of methotrexate required to achieve the same degree of efficacy was significantly higher in the group given methotrexate without folate supplementation [21]. The results of the

present study, when contrasted with those of Strand *et al.* [10], are consistent with the findings of Van Ede *et al.* [21] and suggest that folic acid supplementation may decrease both the efficacy and toxicity of methotrexate.

The adverse events seen during this trial were similar to those seen in other clinical studies of leflunomide [9, 10]. Drug-related adverse events tended to be more common in the first year of treatment with both leflunomide and methotrexate. The most common adverse events resulting in treatment withdrawal during the first year of leflunomide treatment were elevated plasma liver enzyme levels, nausea, diarrhoea, and alopecia (Table 6). A similar pattern was seen in the subjects treated with methotrexate, but the number of withdrawals due to elevations of plasma enzyme levels was twice as high as that seen with leflunomide. The overall incidence of treatment-related elevations of plasma liver enzyme levels in the first year of the trial was 3-fold higher with methotrexate than with leflunomide.

During the second year of treatment, hypertension, rash, and alopecia were the most common treatment-related adverse events leading to withdrawal in subjects taking leflunomide (Table 7), but there was no predominant cause of withdrawal, nor were there any treatment-related deaths. In contrast, elevation of plasma liver enzyme levels continued to be the most common drug-related adverse event in subjects receiving methotrexate and resulted in more than 25% of the withdrawals from methotrexate treatment during the second year. The high incidence of liver toxicity during methotrexate treatment noted in this study presumably results, at least in part, from the lack of folate supplementation. Folate has been reported to reduce the gastrointestinal and mucosal toxicity of methotrexate [19, 20]. Two methotrexate-related deaths, one from pneumonitis and one from pneumonia following pancytopenia were also reported during the second year of the study.

In summary, the results of this study indicate that both leflunomide and methotrexate are effective drugs for the long-term treatment of RA. Although methotrexate was statistically more efficacious in terms of improvements in the clinical efficacy variables after 1 yr of treatment, differences in efficacy were largely lost after 2 yr of treatment. Additionally, any extra benefit in terms of symptomatic improvement of RA with methotrexate must be weighed against the potentially life-threatening pulmonary toxicity and serious hepatotoxicity that are associated with methotrexate use. A full evaluation of the clinical benefit of leflunomide relative to methotrexate will only become available after additional years of use and will be determined by how well subjects can be maintained on the drug, given the propensity of DMARDs to lose efficacy over time.

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