Leflunomide for the Treatment of Rheumatoid Arthritis: A Systematic Review and Metaanalysis

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ABSTRACT. ***Objective.*** To systematically review the evidence from clinical trials on the efficacy and toxicity of leflunomide for the treatment of active rheumatoid arthritis (RA).

Methods. We searched Medline, Embase, Current Contents, and the Cochrane Controlled Trial Register for human randomized controlled trials (RCT) and controlled clinical trials up to December 2001. We also hand-searched reference lists and conference proceedings and consulted content experts. Relative benefit (RB), and weighted mean differences or standardized mean differences with their 95% confidence interval (95% CI) were calculated.

Results. Six RCT totaling 2044 patients with RA were included in this review. Using specific criteria, all trials were considered of high methodological quality. Leflunomide improved the ACR20 response rate roughly 2 times over placebo both at 6 months (RB = 1.93, 95% CI 1.51, 2.47) and at 12 months (RB = 1.99, 95% CI 1.42, 2.77). Other clinical outcomes of disease activity and function and radiological scores were also significantly better for leflunomide patients than those taking placebo. No significant differences for most of the outcomes were observed between leflunomide and sulfasalazine (SSZ) or methotrexate (MTX). Adverse events were more common in the leflunomide group, but withdrawal rates were fewer than for placebo. Overall, withdrawal rates and adverse events in the leflunomide group were not different from SSZ or MTX.

Conclusion. Leflunomide improves all clinical outcomes and delays radiographic progression at 6 and 12 months of RA treatment compared to placebo. Its efficacy and adverse events at 2 years of treatment are comparable to SSZ and MTX. Longterm efficacy and toxicity remain to be established. (J Rheumatol 2003;30:1182–90)

Key Indexing Terms:
LEFLUNOMIDE RHEUMATOID ARTHRITIS SYSTEMATIC REVIEW METAANALYSIS

Rheumatoid arthritis (RA) is a chronic inflammatory, destructive joint disease that affects around 1% of the population[1]. This disease can cause progressive joint destruction and deformity despite treatment. Several medications known as disease modifying antirheumatic drugs (DMARD) have been shown to decrease inflammation, delay bone erosion, and improve the functional ability[2-4] in the majority of patients with RA. DMARD are more effective if administered within 2 years of disease duration[3]. However, not all RA patients benefit from treatment with DMARD. A number of patients have progressive bone and joint damage although joint inflammation is well suppressed.

Among the different DMARD currently used for treating RA, methotrexate (MTX) and sulfasalazine (SSZ) are most frequently prescribed[5]. Newer DMARD include cyclosporin A and leflunomide, and biological agents such as etanercept and infliximab are increasingly used for RA treatment. These newly developed agents can be used as single drugs or in combination with other DMARD for the treatment of RA.

Leflunomide is a novel immunoregulatory drug that has a different structure and mechanism of action than the other DMARD. Leflunomide is an isoxazole derivative and its active metabolite, A77 1726, acts as an inhibitor of pyrimidine synthesis[6-8]. Since pyrimidine nucleotides are required for the proliferation of activated autoimmune T lymphocytes, reduction of pyrimidine synthesis will reduce the number of these T cells, downregulating the related autoimmune responses. Because T cells play an important role in

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the pathogenesis of RA, these effects are expected to lead to clinical benefits[6,8].

A number of clinical trials have evaluated the efficacy of leflunomide in RA; most of them were multicenter randomized controlled trials (RCT) comparing leflunomide with placebo, MTX, or SSZ. The objective of this study was to systematically review and pool data from trials of leflunomide to increase the precision and accuracy of estimates of efficacy and toxicity, and to compare its performance with other drugs. Efficacy outcomes included measures of clinical improvement as defined by the American College of Rheumatology (ACR)[9] and functional ability.

MATERIALS AND METHODS

Inclusion Criteria

Study design: RCT and controlled clinical trials (CCT) comparing leflunomide treatment with placebo or other DMARD.

Patient population: Patients aged at least 18 years with clinical diagnosis of RA according to the ACR 1987 revised criteria[10]. Patients must have had active disease determined by number of tender and swollen joints, duration of morning stiffness, and acute phase reactants.

Dosage of leflunomide: 20–25 mg/day with a loading dose of 100 mg daily given in the first 1–3 days.

Duration of the trial: At least 6 months.

Outcome Measures

Primary outcome measures were the number of patients who fulfilled the ACR20 response criteria (improvement by ≥ 20% of the number of tender joints and swollen joints and 3 of 5 of the following: pain, function, patient and physician global assessments of disease activity, and acute phase reactants)[9] and individual outcome measures defined as the ACR core set of disease activity measures for RA clinical trials, which were endorsed by the European League Against Rheumatism (EULAR) and the Outcome Measures in Rheumatology Clinical Trials (OMERACT)[11,12]. These measures include number of tender joints, number of swollen joints, patient and physician global assessments of disease activity, pain, function, erythrocyte sedimentation rate (ESR), and radiographic changes of hand joints for trials of one year or more. Secondary outcome measures included function and health status [Medical Outcome Study Short Form-36 Health Survey (SF-36), Health Assessment Questionnaire (HAQ) modified HAQ, Problem Elicitation Technique: (PET)], adverse reactions, total number of withdrawals and dropouts, and withdrawals due to adverse events.

Search Strategies

We searched Medline, Embase, and Current Contents from 1966 to December 2001 as well as the Cochrane Controlled Trials Register (Issue 4, 2001) and the Cochrane Musculoskeletal Specialized Register (Issue 4, 2001). The search strategy was conducted as recommended by Haynes, *et al*[13] and was modified for the Cochrane Musculoskeletal Group.

Reference lists were hand-searched for further identification of published work and presentation at scientific meetings. In addition, we reviewed related abstracts published in the proceedings from the ACR Annual Scientific Meetings between 1994 and 2000. Medical Subject Headings (MeSH) terms used in the database search included leflunomide, isoxazole, rheumatoid arthritis, and randomized controlled trial. Content experts were also contacted for unpublished data. Our search included articles in any language.

Data Extraction and Analysis

All studies were assessed independently by 2 reviewers (MO, BS) to select the trials that fulfilled the inclusion criteria. Differences were resolved by consensus. Data extracted from each trial included: information regarding the trial design, characteristics of study population, treatment regimen and duration, and outcome measures at baseline and end-of-study. Data at intermediate timepoints (e.g., 6 months in a one-year trial) were also extracted when available. The data extraction was performed independently by the same 2 reviewers using standardized forms. Differences were resolved by consensus, after reexamination of the original articles. A third reviewer (VR) was consulted to help resolve differences. When necessary, the authors of the primary studies were contacted to obtain additional information.

The outcome measures from all trials were pooled to obtain the overall estimate of efficacy of leflunomide. Where possible, the analyses were based on intention-to-treat data from individual trials. Sensitivity analyses were conducted to test the robustness of results in relation to the methodological quality of the study and patient characteristics. Publication bias (i.e., negative studies not being published) was evaluated with funnel plots. These are scatter plots of effect estimates (on horizontal axis) against sample size (on vertical axis). Asymmetric or skewed shape funnel plots suggest publication bias. For continuous data, results were presented as weighted mean differences (WMD) (patient and physician global assessments, ESR). However, when different scales were used to measure the same outcome, standardized mean differences (SMD) were used instead (number of tender and swollen joints, pain, function). For dichotomous data, relative benefit (RB) was calculated as relative improvement from leflunomide compared to placebo, MTX, or SSZ (number of patients meeting the ACR20 criteria) and relative risk (RR) for the number of patients withdrawn from the study. Homogeneity among trials was evaluated using a chi-square test with n – 1 degrees of freedom (n = number of studies) at a significance level of < 0.05. Initially all the data were pooled using fixed effects models. For measures showing heterogeneity, random effects models were used.

When data were available, the following timepoints were analyzed for efficacy: 6 months, 12 months, and 24 months. For toxicity, the report and pooling were performed on end-of-study results.

Methodological Quality of Included Studies

The quality of the included studies was assessed using a validated tool developed by Jadad, *et al*, which includes the appropriateness of randomization, appropriateness of blinding, and description of dropouts and withdrawals[14]. The range of possible scores is 0 (worst) to 5 (best). Studies with quality scores less than 3 were considered low quality studies, while those with scores 3 or higher were high quality studies. Quality was assessed independently by 2 reviewers (MO, BS). Differences were resolved by consensus. A third reviewer was consulted if necessary (VR).

RESULTS

One hundred twenty-four full articles and 27 abstracts were initially selected for review. Of the original articles, 6 were finally included in the systematic review[15-20]. The others were excluded because of the following reasons: 70 were review articles, 27 were letters and news, 11 contained data already presented in the included articles; and 2 each were (1) one-arm open-label trials, (2) studies using different outcome measures for assessing treatment response, (3) articles about immunologic changes of human synovial tissues, (4) articles about magnetic resonance imaging changes of the joints, and (5) editorial comments. Four original articles provided additional data on the functional ability[21,22] and radiographic changes[23,24] to the 3 trials included[16,17,20]. The data from these 4 articles were included in the systematic review but not the trials themselves (see Figure 1 for flow diagram of search results).

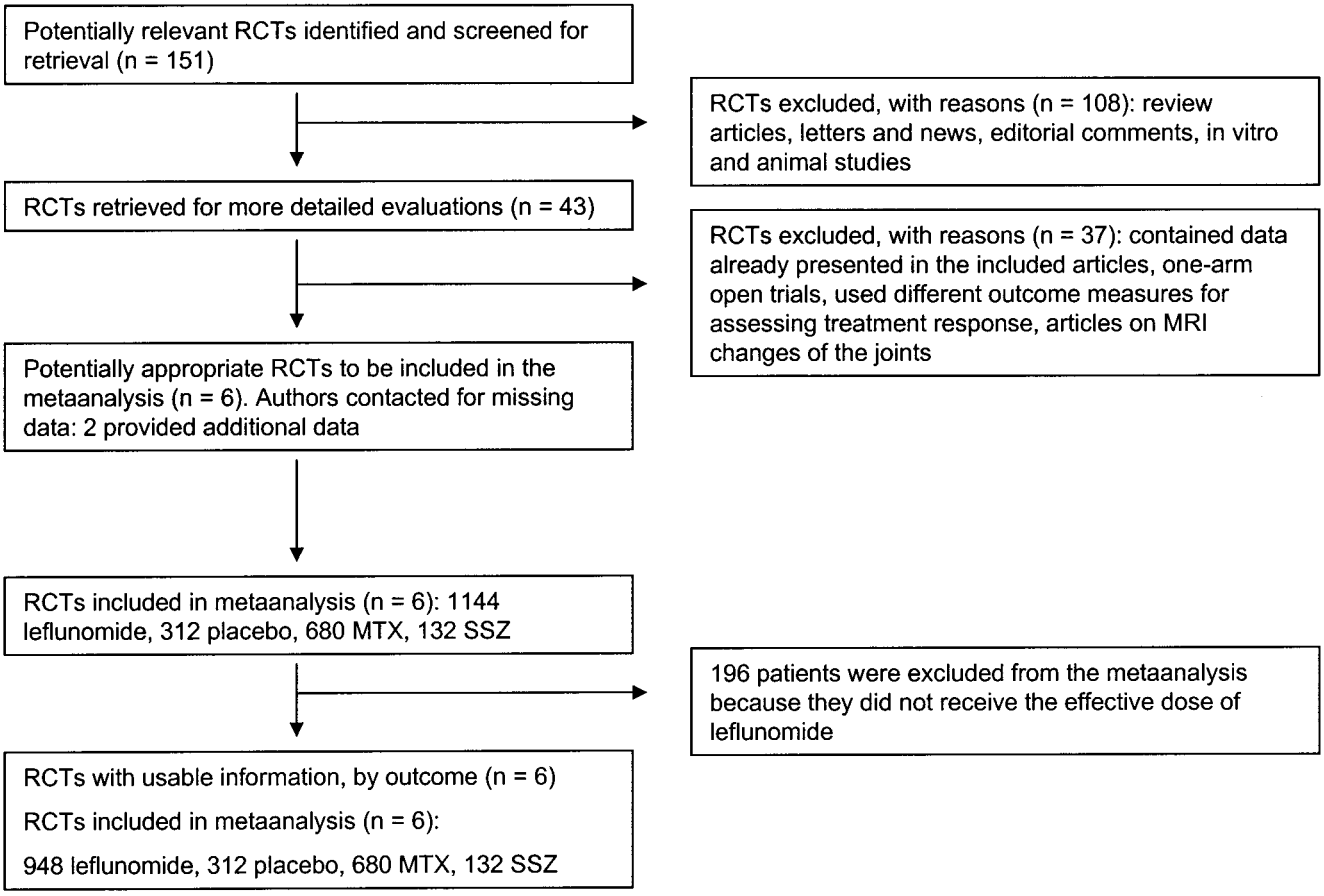

Figure 1. Results of search for eligible studies.

All of the 27 abstracts retrieved were preliminary reports of the included trials at 6, 12, and 24 months of treatment. The data from these abstracts were already present in the 6 original articles. None provided additional data to the trials included.

Of the 6 trials included in the systematic review and metaanalysis[15-20], all were RCT. One RCT by Mladenovic, *et al*, was a phase II study comparing 3 different doses of leflunomide with placebo at 24 weeks[15]. Three RCT were phase III studies — Strand, *et al* compared the efficacy of leflunomide with placebo and MTX at 12 months[16]; Smolen, *et al* compared leflunomide with placebo and SSZ at 6 months[17]; and Emery, *et al* compared leflunomide with MTX at 52 weeks and 2 years[18]. Another study by Strand, *et al*[21] reported results on function and health-related quality of life for the leflunomide versus placebo and MTX trial, while the study by Sharp, *et al*[22] provided the radiographic changes for all phase III trials. The study by Cohen, *et al* was the Year 2 extension of the Strand, *et al* study, which compared leflunomide with MTX[19]. The study by Scott, *et al* was the Year 1 and 2 extension of Smolen, *et al* comparing leflunomide with SSZ[20]. The study by Kalden, *et al*[23] provided the results of functional ability and health status outcomes for the Scott, *et al* study.

The included trials reported data on 1144 patients randomized to leflunomide, 312 to placebo, 680 to MTX, and 132 to SSZ. However, only 948 patients randomized to leflunomide were used in the metaanalysis because only the effective dosage was analyzed[15]. In the Year 2 extension studies, the number of patients continuing to take leflunomide was 158, SSZ 60, and MTX 101. The characteristics of the included studies are shown in Table 1.

Median quality score of the included trials was 3.5. Three studies scored 3, one scored 4, and the other 2 scored 5. All 6 trials involved patients with active RA and reported intent-to-treat data[15-20].

Efficacy of Leflunomide Compared to Placebo

Statistically significant improvements in all of the clinical outcomes were observed in leflunomide-treated patients compared to placebo. Figure 2 shows the RB and 95% confidence interval (CI) comparing leflunomide with placebo, and leflunomide with other DMARD. Patients in the leflunomide group were 2 times more likely than those receiving placebo to respond to treatment according to the ACR20 criteria at 6 months (RB 1.93, 95% CI 1.51, 2.47) and 12 months (RB 1.99, 95% CI 1.42, 2.77). There were a few differences in some of the outcome measures in the

RCT. The trial by Mladenovic, *et al*[15] based the number of joint counts on the evaluation of 66 or 68 joints, while the others were based on the 28-joint evaluation. For functional assessment, this trial used total HAQ scores while the others used HAQ disability index. The pooled estimates of these outcomes were analyzed by using SMD. In addition to the improvement of the clinical outcomes, leflunomide also significantly delayed radiographic changes of hand joints as measured with the Sharp scores compared to placebo at both 6 and 12 months. The WMD and SMD of the outcome measures are shown in Table 2.

Functional ability and health status assessed with HAQ, MHAQ, PET, work productivity, and SF-36 improved significantly in the RA patients treated with leflunomide compared to placebo (data not shown). The only exception was the improvement of the mental component of the SF-36, which did not significantly differ between leflunomide and placebo (WMD –0.7, 95% CI –3.5, 2.1).

Efficacy of Leflunomide Compared to SSZ or MTX

Tests of homogeneity showed that the results of the study by Emery, *et al*[18] comparing leflunomide with MTX were significantly different from the other trials[16,19] ($p < 0.05$, chi-square test). Thus, the comparisons between leflunomide and MTX were based on random effects models.

No statistically significant differences were observed between leflunomide and MTX or SSZ in most of the clinical outcomes, except that leflunomide did better than SSZ in improving the ACR20 response rate at 24 months (RB 1.37, 95% CI 1.07, 1.75). The RB and 95% CI for ACR20 response rates comparing leflunomide with the SSZ or MTX group are shown in Figure 2. For leflunomide versus SSZ at 6 months, improvement of ESR was significantly better in the SSZ-treated group (WMD 9.2 mm/h, 95% CI 3.48, 14.92), while leflunomide significantly improved the HAQ scores (WMD –0.25, 95% CI –0.42, –0.08). For leflunomide versus MTX at 12 months, a significant improvement in the MHAQ scores (WMD –0.14, 95% CI –0.25, –0.03), PET scores (WMD –3.5, 95% CI –5.62, –1.38), and physical component of the SF-36 (WMD –3.0, 95% CI –5.41, –0.59) was observed in the leflunomide group.

Table 1. Characteristics of the trials of leflunomide efficacy in the treatment of RA.

Study	No. of subjects	Type	Interventions	Duration	Outcome Measures	Quality Score[14], n	Intention-to-Treat
Mladenovic[15], 1995	206*	Double blind, RCT	Leflunomide 100 mg/day for 1 day then 25 mg/day; placebo	24 wks	ACR core set of disease activity measures**, ACR20 and Paulus criteria, adverse events	4 (R2, B1, W1)	Yes
Strand [16], 1999	482	Double blind, RCT	Leflunomide 100 mg/day for 3 days then 20 mg/day; MTX 7.5–15 mg/wk; placebo	12 mo	ACR20, ACR50, ACR70, ACR success, ACR core set of disease activity measures, X-ray changes (Sharp scores), function and HRQOL, adverse events	5 (R2, B2, W1)	Yes
Smolen[17], 1999	357	Double blind, RCT	Leflunomide 100 mg/day for 3 days then 20 mg/day; SSZ 2 g/day; placebo	24 wks	ACR core set of disease activity measures, ACR20, ACR50, Paulus criteria, X-ray changes (Sharp scores), adverse events	5 (R2, B2, W1)	Yes
Emery[18], 2000	999	Double blind, RCT	Leflunomide 100 mg/day for 3 days then 20 mg/day; MTX 7.5–15 mg/week	52 wks	ACR core set of disease activity measures*, ACR20 and Paulus criteria, X-ray changes (Sharp scores), adverse events	3 (R1, B1, W1)	Yes
Cohen[19], 2001	199	Double blind, RCT	Leflunomide 10–20 mg/day; MTX 15–20 mg/wk with 1–2 mg folate daily	12 mo (year 2 extension of Strand study)	ACR20, ACR50, ACR70, ACR core set of disease activity measures, X-ray changes (modified Sharp scores), function and HRQOL, adverse events	3 (R1, B1, W1)	Yes
Scott[20], 2001	197 (6–12 mo) 146 (12–24 mo)	Double blind, RCT	Leflunomide 20 mg/day; SSZ 2 g/day	18 mo (year 2 extension of Smolen study)	ACR20, ACR50, ACR70, ACR core set of disease activity measures, X-ray changes (Larsen scores), function and adverse events	3 (R1, B1, W1)	Yes

R: random allocation, B: double-blinding, W: description of withdrawals, RCT: randomized controlled trial, ACR: American College of Rheumatology, MTX: methotrexate, SSZ: sulfasalazine, HRQOL: health-related quality of life. * Only the number of patients assigned to receive leflunomide 25 mg/day and placebo were included in the metaanalysis. ** Number of tender and swollen joints, patient and physician global assessments of disease severity, functional status, pain, ESR.

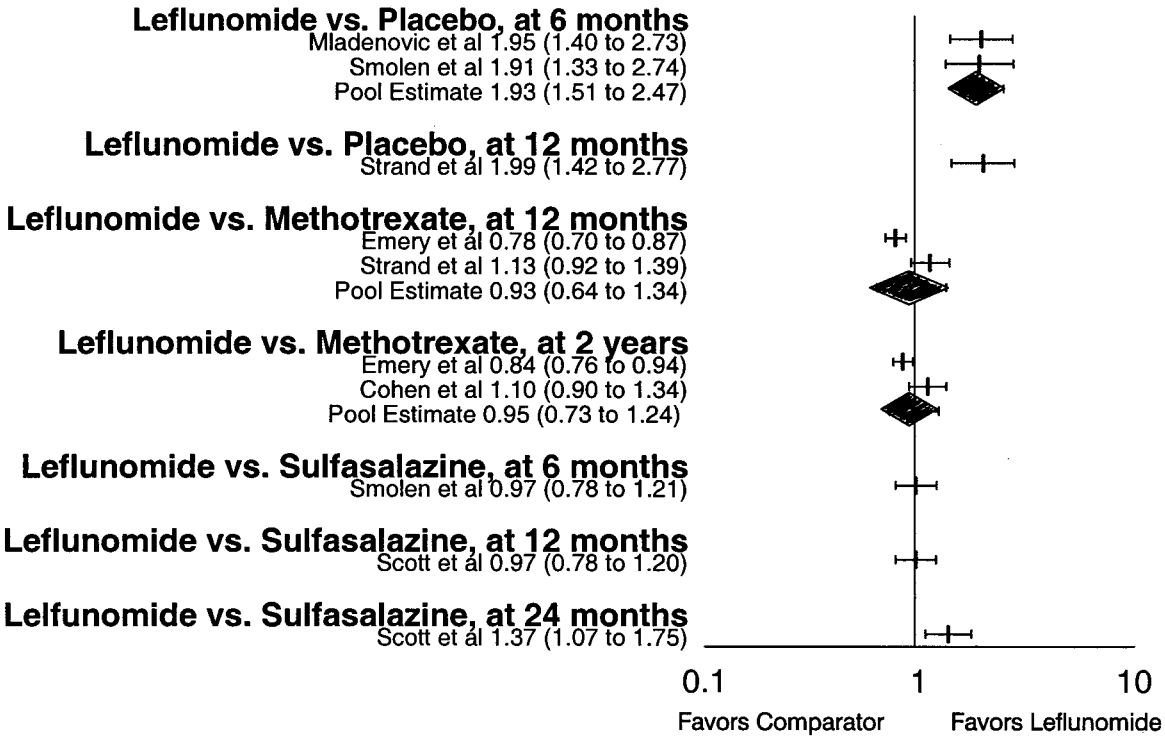

Figure 2. Relative benefits with 95% CI for ACR20 response rate of RA patients treated with leflunomide compared with placebo and other DMARD.

Table 2. Pooled estimates and 95% CI of the mean changes of the RA outcome measures: leflunomide versus placebo.

Outcome Measures	Evaluation Timepoints, mo	WMD/SMD (95% CI)	Effects Model Used
Tender joint count	6	SMD –0.59 (–0.72, –0.42)	Fixed
	12	WMD –4.7 joints (–6.59, –2.81)	Fixed
Swollen joint count	6	SMD –0.49 (–0.64, –0.34)	Fixed
	12	WMD –8.6 joints (–10.05, –7.15)	Fixed
Patient global assessment	6	WMD –0.64 points (–0.79, –0.49)	Fixed
	12	WMD –2.2 points (–2.84, –1.56)	Fixed
Physician global assessment	6	SMD –0.67 (–0.82, –0.52)	Random
	12	WMD –1.8 points (–2.41, –1.19)	Fixed
Pain (VAS)	6	SMD –0.92 (–1.45, –0.38)	Random
	12	WMD –18.0 mm (–24.04, –11.96)	Fixed
ESR	6	WMD –7.94 mm/h (–10.96, –4.92)	Fixed
	12	WMD –8.9 mm/h (–13.68, –4.12)	Fixed
HAQ	6	SMD –0.69 (–0.97, –0.42)	Random
	12	WMD –0.48 point (–0.6, –0.36)	Fixed
Total Sharp scores	6	WMD –4.65 points (–7.21, –2.09)	Fixed
	12	WMD –1.63 points (–2.78, –0.48)	Fixed

WMD: weighted mean difference, SMD: standardized mean difference, VAS: visual analog scale, HAQ: Health Assessment Questionnaire.

Adverse Events from Leflunomide Treatment

Table 3 summarizes the withdrawals from leflunomide compared to placebo and SSZ or MTX. Total withdrawals in the leflunomide group were significantly fewer than placebo (RR 0.70, 95% CI 0.59, 0.83) but not different from SSZ (RR 0.75, 95% CI 0.53, 1.07). However, the number of patients who discontinued leflunomide was significantly higher than for MTX (RR 1.26, 95% CI 1.08, 1.48). Withdrawals due to adverse events from leflunomide were significantly higher than for placebo (RR 2.73, 95% CI 1.67,

4.47) and MTX (RR 1.43, 95% CI 1.13, 1.83), but were not different from SSZ (RR 0.77, 95% CI 0.45, 1.33).

Major reported adverse events from leflunomide treatment included gastrointestinal (GI) symptoms [diarrhea (18–33.5%), dyspepsia (2.4–13.7%), nausea (11.2–20.9%), abdominal pain (5.6–13.7%), and oral ulcers (3–6%)], elevated liver function tests (2.7–14.8%), rash/allergic reactions (6.5–24.2%), alopecia (4.5–16.6%), infections (4.5–56.6%), weight loss (2%), and hypertension (11%). Significant heterogeneity was observed when pooling adverse events, so random effects models were used for this analysis.

GI symptoms (RR 1.61, 95% CI 1.18, 2.2), elevation of liver function tests more than 3 times upper normal values (RR 3.74, 95% CI 1.86, 7.54), mild allergic reactions (RR 1.59, 95% CI 1.07, 2.37), and reversible alopecia (RR 6.6, 95% CI 2.36, 18.44) were more likely to occur in the leflunomide group than with placebo. However, infection rates, significant weight loss, and hypertension were not significantly different between leflunomide and placebo. Most adverse events occurring in the leflunomide group were not significantly different from SSZ or MTX, except for GI symptoms (RR 1.25, 95% CI 1.11, 1.41), alopecia (RR 1.68, 95% CI 1.24, 2.26), and hypertension (RR 2.29, 95% CI 1.42, 3.69), which were found significantly more in the leflunomide group than in those treated with MTX. Elevated liver function tests, reported either as adverse events or number of withdrawals, were not significantly different for the leflunomide-treated group from those treated with MTX or SSZ (data not shown).

Sensitivity Analysis

No significant effect of the quality of blinding, number of patients receiving steroids, or withdrawal rate on the results of the ACR20 responder rate was observed. However, when comparing the efficacy of leflunomide to MTX, the patients with mean disease duration less than 5 years[18] responded better to MTX (RB 0.78, 95% CI 0.70, 0.87), while in the trial that included patients with mean disease duration of 5 years or more[16], there was a trend for leflunomide to be more effective (RB 1.13, 95% CI 0.91, 1.39), but it was not statistically significant.

Table 3. Relative risk and 95% CI of total withdrawals and withdrawals due to adverse events (AE) of leflunomide.

Comparators	Relative Risk (95% CI)
Leflunomide vs placebo	
Total withdrawals	0.70 (0.59, 0.83)
Withdrawals due to AE	2.73 (1.67, 4.47)
Leflunomide vs SSZ	
Total withdrawals	0.75 (0.53, 1.07)
Withdrawals due to AE	0.77 (0.45, 1.33)
Leflunomide vs MTX	
Total withdrawals	1.26 (1.08, 1.48)
Withdrawals due to AE	1.43 (1.13, 1.83)

SSZ: sulfasalazine, MTX: methotrexate.

Number Needed to Treat (NNT) and Number Needed to Harm (NNH)

The NNT and NNH were calculated from the inverse of pooled risk differences of the dichotomous outcomes, the ACR20 response rate, and the number of withdrawals due to adverse events. The NNT for leflunomide-treated patients compared to placebo to achieve one ACR20 responder was 3.6 (95% CI 2.9, 4.8) at 6 months and 3.9 (95% CI 2.7, 6.7) at 12 months. The NNT for one ACR20 responder in the leflunomide group compared to MTX or SSZ was high (20–100) with infinite 95% CI, which indicated that there was no benefit of leflunomide over MTX or SSZ. The exception was the NNT to achieve one ACR responder for leflunomide compared with SSZ at 24 months of treatment, which was 4.5 with a finite 95% CI (2.6, 16.7).

The NNH for the withdrawal rate due to adverse events from leflunomide compared to placebo was 10 (95% CI 6.7, 16.7). When compared to MTX or SSZ, the NNH for leflunomide was also high (14.3–50) with infinite 95% CI. Thus, we cannot conclude that leflunomide caused more harm than MTX or SSZ. The NNT and NNH for leflunomide efficacy and toxicity are shown in Table 4.

Funnel Plots

Figure 3 shows the funnel plots of the relative benefit of the patients who met the ACR20 response criteria against the number of subjects in each trial. Since there were only 6 trials included in this review, the funnel plots showed a significant asymmetry. Trials with a small number of subjects and trials with small or no treatment effects were absent. This strongly suggested publication bias.

DISCUSSION

Leflunomide is a novel DMARD with a different structure and mechanism of action from other DMARD. It is an isoxazole derivative that, once ingested, is converted to the active form, A77 1726. The primary mode of action is to inhibit the enzyme dihydroorotate dehydrogenase, which activates the rate-limiting step in the pathway for de novo synthesis of pyrimidines[6,25,26]. Pyrimidine nucleotides are required for the proliferation of T lymphocytes. The autoreactive T lymphocytes are more sensitive to the depletion of pyrimidine pools than other types of lymphocytes and cells in the body[6]. This leads to a suppression of autoimmune T cell proliferation with a minimal effect on the other cells. Since most cells that infiltrate the RA synovium are activated CD4+ T cells, leflunomide can reduce the inflammation of synovium in patients with RA, with consequent improvement in clinical symptoms[6,25,26].

Leflunomide was approved by the US Food and Drug Administration in August 1998 for the treatment of adult

Table 4. Number needed to treat (NNT) and number needed to harm (NNH) for leflunomide treatment of active RA.

Criteria	Timepoint, mo	Comparator	Absolute Risk Difference, % (95% CI)	NNT/NNH (95% CI)
NNT				
ACR20 response rate	6	Placebo	28 (21 to 35)	3.6 (2.9 to 4.8)
	12	Placebo	26 (15 to 37)	3.9 (2.7 to 6.7)
	6	SSZ	1 (–13 to 11)	100*
	12	SSZ	2 (–17 to 13)	50*
	24	SSZ	22 (6 to 38)	4.5 (2.6 to 16.7)
	6	MTX	4 (–6 to 15)	25*
	12	MTX	5 (–25 to 15)	20*
	24	MTX	4 (–21 to 12)	25*
NNH				
Withdrawals due to AE	6–12	Placebo	10 (6 to 15)	10 (6.7 to 16.7)
	6	SSZ	4 (–5 to 13)	25*
	12	SSZ	4 (–2 to 11)	25*
	12	MTX	7 (0 to 15)	14.3*
	24	MTX	2 (–2 to 6)	50*

SSZ: sulfasalazine, MTX: methotrexate. * Cannot calculate 95% CI because it is infinite. This means leflunomide has no benefit or causes harm when compared with SSZ or MTX.

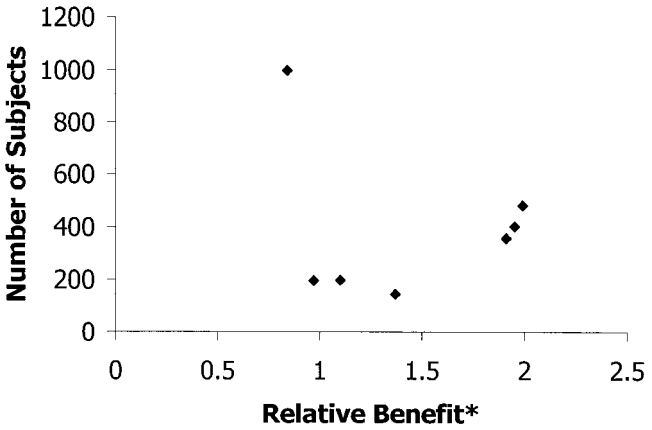

Figure 3. Funnel plots of leflunomide trials. *Relative benefit for the patients to meet the ACR20 response criteria.

RA. In 2000, a systematic review of leflunomide treatment in RA was published[27]. This systematic review was conducted for the UK Development and Evaluation Committee to provide decision makers with information on the efficacy, safety, and costs of leflunomide for RA treatment. Although this systematic review was based on a methodology similar to our review, there are a number of differences. For the inclusion criteria, the review by Hewitson, *et al* was limited to RCT and English language studies. Therefore, only 3 RCT were included in the review[15-17]: no information on the quality of the included trials was given; the results on the efficacy and safety of leflunomide were reported as percentage changes from baseline for each endpoint and percentage of patients that reported adverse events in each arm, respectively[27]; a meta-analysis was not performed and pooled estimates were not calculated. The costs of leflunomide calculated in this review consisted of the drug cost and monitoring costs compared to those of SSZ and MTX in one year. No cost-effectiveness analysis was performed.

For this metaanalysis, the 6 trials included had similar objectives and recruited RA patients with active disease. The pooled estimates of clinical efficacy of leflunomide showed it to be significantly better than placebo at both 6 and 12 months in all clinical outcomes. At 6 months, the clinical benefit from leflunomide was not significantly different from SSZ, except for the HAQ disability index, for which leflunomide was significantly better than SSZ. At 24 months, a significant reduction in the number of tender joints and swollen joints was observed in the leflunomide group compared to SSZ. For the comparison of leflunomide and MTX, the efficacy of leflunomide was not significantly different from MTX for most of the outcomes, except that the patient global assessment of disease activity at 6 months improved significantly in the leflunomide group.

For functional ability and health status, leflunomide improved these measures in almost every domain and was better than placebo. Only the mental component of the SF-36 showed no significant difference compared to placebo. This was also observed when leflunomide was compared to MTX. This might be because the improvement of mental status requires a sustained and clinically significant improvement of the patient's physical status, which might not be observable within a short duration study (data available at 6 and 12 months).

The results of the 3 trials comparing the efficacy of leflunomide with MTX showed a significant heterogeneity. At one year, the improvement of the tender joint counts, swollen joint counts, and patient and physician global

assessment in the study by Emery, *et al* was significantly better for MTX treatment[18]. In contrast, improvement of all outcome measures from the study by Strand, *et al* favored leflunomide[16]. The discrepancy of the results in the 2 studies could be explained by the differences of subjects recruited and the use of folate supplement. The RA patients in the study by Strand, *et al* had longer disease duration than those in the study by Emery, *et al* (mean disease duration of 6.5–7.0 vs 3.7–3.8 yrs, respectively). The study by Emery, *et al* was conducted in Europe, in which the population is mainly Caucasian, while the study by Strand, *et al* was conducted in North America, in which the patients could be Caucasians, African-Americans, or Hispanics. This ethnic diversity might also determine the responsiveness to leflunomide and MTX. Regarding folate supplement, in the study by Strand, *et al*, folate supplement was obligatory, while it was taken by less than 10% of the patients in the study by Emery, *et al*. As shown in the study by van Ede, *et al*, mean dose of MTX required to achieve the same degree of clinical efficacy was higher in patients prescribed folic acid than in patients receiving MTX alone[28]. Folate supplement may decrease the efficacy as well as toxicity from MTX. However, at 2 years of study, the differences in the outcomes observed at Year 1 were lost. Most of the outcomes from the study by Emery, *et al* were not significantly different from those in the study by Cohen, *et al*.

Progression of radiographic changes was also significantly slower in the leflunomide-treated group than the placebo group. No differences were observed when compared to SSZ or MTX at 6 and 12 months. The results from the study by Strand, *et al*[16,22] tended to favor leflunomide over MTX, while the results from the study by Emery, *et al* favored MTX[18,22], but there was no significant difference. For the comparison between leflunomide and SSZ at 24 months, leflunomide delayed joint erosions at a significant rate compared to SSZ[24].

Adverse events in the leflunomide-treated group that were significantly increased compared to placebo included alopecia, GI symptoms, and elevated liver function tests. However, infections, hypertension, and weight loss were not significantly different. Adverse events were similar when comparing leflunomide and SSZ. Alopecia, GI symptoms, allergic reactions, and hypertension were significantly higher in the leflunomide group compared to MTX. The rates of elevated liver function tests, infection, and weight loss were not significantly different between the patients treated with leflunomide and MTX.

As expected, the number of withdrawals due to adverse events in the leflunomide group was significantly higher than in the placebo group. However, the total withdrawal rate was lower for patients receiving leflunomide, since the withdrawals due to lack of efficacy were higher in the placebo group. The total withdrawal rate was not different between leflunomide and SSZ, but was significantly higher for leflunomide than for MTX. No differences in withdrawals due to adverse events were observed between leflunomide and SSZ or MTX. This might be caused by different results from the 2 RCT comparing leflunomide and MTX[16,18]. Withdrawals due to lack of MTX efficacy were higher in the study by Strand, *et al*, while withdrawals due to lack of leflunomide efficacy were higher in the study by Emery, *et al*.

A followup study that extended from the trial by Mladenovic, *et al* has confirmed the efficacy and tolerability of leflunomide at 18 months of treatment[29]. Preliminary studies on the efficacy of combined leflunomide and MTX compared to MTX alone in the treatment of active RA at 24 weeks have shown that combined leflunomide and MTX was more efficacious in the ACR20 response rate[30] and functional ability[31]. More data on other outcomes and adverse events are required to include in this metaanalysis.

Conclusions

Leflunomide was shown to be efficacious and well tolerated in the treatment of active RA up to 2 years. Its efficacy was comparable to those of SSZ and MTX and was shown to be better than SSZ at 24 months of treatment. Leflunomide is considered a choice of DMARD therapy in the patients with active RA who do not respond to SSZ or MTX, or cannot tolerate these drugs. However, longer followup periods are needed to evaluate the longterm effectiveness and toxicity of leflunomide, especially its effect on delaying bone erosions and joint destruction from RA. The cost of this drug, together with its monitoring cost and the cost of its adverse events, should also be taken into consideration. Full economic evaluations should be conducted to determine the cost-effectiveness of leflunomide over the currently used DMARD, particularly MTX and SSZ.

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