

ORIGINAL ARTICLE

## Leflunomide or Methotrexate for Juvenile Rheumatoid Arthritis

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### ABSTRACT

#### BACKGROUND

We compared the safety and efficacy of leflunomide with that of methotrexate in the treatment of polyarticular juvenile rheumatoid arthritis in a multinational, randomized, controlled trial.

#### METHODS

Patients 3 to 17 years of age received leflunomide or methotrexate for 16 weeks in a double-dummy, blinded fashion, followed by a 32-week blinded extension. The rates of American College of Rheumatology Pediatric 30 percent responses (ACR Pedi 30) and the Percent Improvement Index were assessed at baseline and every 4 weeks for 16 weeks and every 8 weeks during the 32-week extension study.

#### RESULTS

Of 94 patients randomized, 86 completed 16 weeks of treatment, 70 of whom entered the extension study. At week 16, more patients in the methotrexate group than in the leflunomide group had an ACR Pedi 30 response (89 percent vs. 68 percent,  $P=0.02$ ), whereas the values for the Percent Improvement Index did not differ significantly ( $-52.87$  percent vs.  $-44.41$  percent,  $P=0.18$ ). In both groups, the improvements achieved at week 16 were maintained at week 48. The most common adverse events in both groups included gastrointestinal symptoms, headache, and nasopharyngeal symptoms. Aminotransferase elevations were more frequent with methotrexate than with leflunomide during the initial study and the extension study.

#### CONCLUSIONS

In patients with polyarticular juvenile rheumatoid arthritis, methotrexate and leflunomide both resulted in high rates of clinical improvement, but the rate was slightly greater for methotrexate. At the doses used in this study, methotrexate was more effective than leflunomide.

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JUVENILE RHEUMATOID ARTHRITIS, WITH an estimated prevalence of 0.07 to 4.01 per 1000 children,<sup>1</sup> has three major subtypes differentiated on the basis of onset: systemic, pauciarticular, and polyarticular (defined by the involvement of at least five joints). Treatments for juvenile rheumatoid arthritis include nonsteroidal antiinflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs).<sup>2-7</sup> DMARDs have been shown radiographically to inhibit progression in adults with rheumatoid arthritis.<sup>8</sup>

Methotrexate is the most commonly used DMARD for juvenile rheumatoid arthritis. In six-month trials, both methotrexate and sulfasalazine were more effective than placebo in children with juvenile rheumatoid arthritis and had acceptable short-term safety profiles.<sup>2,5</sup> In a randomized withdrawal trial, etanercept was effective in children with juvenile rheumatoid arthritis.<sup>3</sup> However, no randomized, controlled trials have compared these agents with methotrexate.

Leflunomide, an orally administered inhibitor of pyrimidine synthesis, has been shown to be a safe and effective long-term therapy for adults with rheumatoid arthritis.<sup>9-14</sup> In a pilot open-label study of children with polyarticular-course juvenile rheumatoid arthritis, 52 percent of those receiving leflunomide had a response, even though all patients either had had no response to or were intolerant of methotrexate.<sup>7</sup> To confirm these findings, we conducted a 16-week randomized, controlled comparison of leflunomide with methotrexate in children with active polyarticular-course juvenile rheumatoid arthritis. Those completing the initial 16-week study could enter a 32-week blinded extension study (total, 48 weeks).

## METHODS

### PATIENTS

Patients 3 to 17 years of age were recruited from 32 centers in 12 countries (listed in the Appendix) from March 2002 to January 2003. Patients met the American College of Rheumatology (ACR) criteria for juvenile rheumatoid arthritis,<sup>15</sup> had active polyarticular-course disease, and had not received methotrexate or leflunomide. Postpubertal and sexually active female patients had to have negative serum pregnancy tests throughout the study. Exclusion criteria included ACR functional class IV disease, active systemic symptoms within four weeks

before entry, persistent or severe infection within three months before entry, or current inflammatory disease other than juvenile rheumatoid arthritis or a history of such a disease.

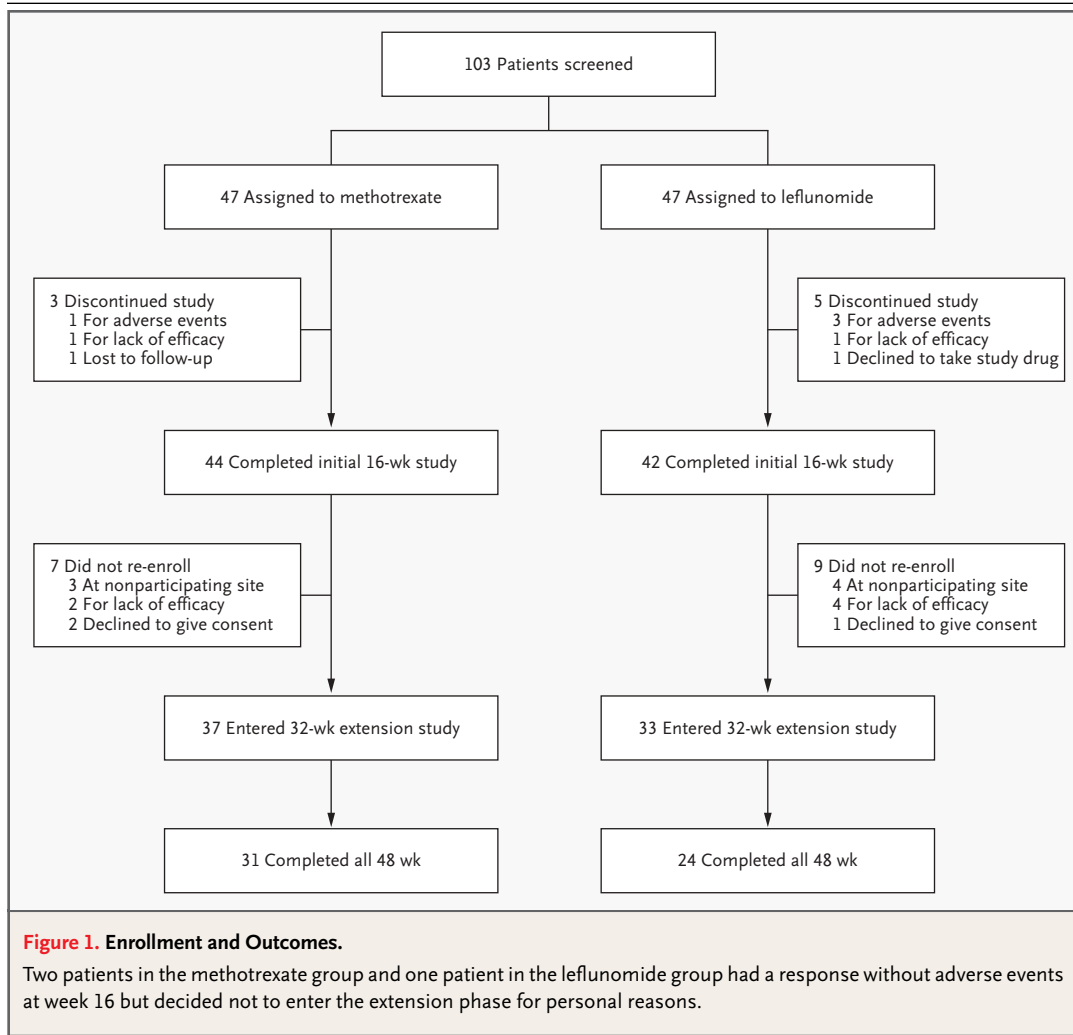
### STUDY DESIGN

This multinational, multicenter, randomized, controlled trial was approved by the ethics committee of each participating center and conducted in compliance with the Declaration of Helsinki. Concomitant treatment with NSAIDs and no more than 0.2 mg of prednisone or the equivalent per kilogram of body weight per day (maximum daily dose, 10 mg) was allowed, provided the dose remained unchanged beginning at least 2 weeks before enrollment and throughout the study; treatment with other DMARDs was to have been discontinued within 14 days before entry.

After the patients or their parents or guardians provided written informed consent, patients were randomly assigned to receive oral leflunomide (Arava, Sanofi-Aventis) or oral methotrexate and oral matching placebo. Randomization was centralized and used double-dummy blinding. Patients weighing less than 20 kg received 100 mg of leflunomide for one day followed by a maintenance dose of 10 mg every other day. Those weighing 20 to 40 kg received 100 mg of leflunomide for two days followed by a maintenance dose of 10 mg per day. Those weighing more than 40 kg received 100 mg of leflunomide for three days followed by a maintenance dose of 20 mg per day. The dose of methotrexate was 0.5 mg per kilogram per week (maximum, 25 mg per week). All patients received at least 5 mg of folate, in the form of folic acid or folinic acid, per week (maximum, 5 mg per day). During the study, patients could receive up to two intra-articular injections of corticosteroid (triamcinolone hexacetonide), with the dose left to the discretion of the investigator; the treated joint was considered active if it was evaluated within 28 days after an injection. Patients who completed the initial 16-week study were offered continued blinded treatment in a 32-week extension study.

### ASSESSMENTS

Efficacy was assessed at baseline and every four weeks in the initial study; the two primary end points were assessed at week 16. In the extension study, efficacy was assessed every eight weeks. The two primary outcome measures were the mean Percent Improvement Index and the percentage of pa-



tients with a 30 percent improvement from baseline in at least three of the six response variables included in the ACR Pediatric core set of disease-activity measures (ACR Pedi 30) in children with juvenile rheumatoid arthritis.<sup>3,16</sup> These measures consisted of a count of swollen joints (66 joints evaluated), a count of joints with active arthritis (68 joints evaluated), global assessment of disease activity by the patient or a parent or guardian on a visual-analogue scale ranging from 0 (disease inactive) to 100 (maximal disease activity), physician's global assessment of disease activity, assessment of physical function by the patient or a parent or guardian (by means of the Childhood Health Assessment Questionnaire Disability Index), and laboratory evaluation of acute-phase reactants (erythrocyte sedimentation rate).

Patients with an ACR Pedi 30 response could

also have worsening of 30 percent or more in no more than one of the six response variables. The Percent Improvement Index, a continuous variable, was calculated as the mean of the percent changes from baseline in each core set of disease-activity measures for juvenile rheumatoid arthritis, with negative values indicating improvement and positive values set to 0, indicating no improvement.

Secondary outcomes included the rates of ACR Pedi 50 and ACR Pedi 70 responses (50 percent and 70 percent improvement, respectively, according to the ACR criteria), the time to an ACR Pedi 30 response, area-under-the-curve analyses, the mean changes in each core set of disease-activity measures for juvenile rheumatoid arthritis,<sup>3,16-19</sup> and C-reactive protein concentrations.

Safety variables included adverse events, find-

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Leflunomide Group (N=47)	Methotrexate Group (N=47)
Age at enrollment		
Mean — yr	10.1±4.0	10.2±3.8
Median — yr	11	11
Range — yr	3–17	3–17
<12 yr — no. (%)	27 (57)	27 (57)
≥12 yr — no. (%)	20 (43)	20 (43)
Sex — no. (%)		
Female	35 (75)	34 (72)
Male	12 (26)	13 (28)
Race or ethnic group — no. (%)		
White	41 (87)	35 (74)
Black	1 (2)	2 (4)
Asian	1 (2)	0
Other†	4 (9)	10 (21)
Type of disease at onset — no. (%)		
Antinuclear antibody–positive	13 (28)	19 (40)
Pauciarticular	10 (21)	8 (17)
Polyarticular	36 (77)	39 (83)
Rheumatoid factor–positive	10 (21)	9 (19)
Systemic	1 (2)	0

ings on physical examination, and laboratory values. An independent data and safety monitoring board reviewed adverse events and laboratory data throughout the study. During the 16-week study, samples were collected at each visit for pharmacokinetic analysis. Plasma concentrations of M1 (A77-1726), the active metabolite of leflunomide, were quantified by means of high-performance liquid chromatography with ultraviolet detection. Methotrexate concentrations were not measured.

#### STATISTICAL ANALYSIS

All analyses of the initial 16-week study used the intention-to-treat population. Using a superiority design, we estimated that the enrollment of 37 patients per group would give the study a statistical power of 80 percent to detect an absolute difference between groups of 15 percent in the Percent Improvement Index at week 16, assuming a standard deviation of 23 percent and completion rates of 80 percent ( $\alpha=0.05$ ).

Analysis of variance was used to assess the mean Percent Improvement Index in the two groups as

well as in various subgroups, with treatment and pooled site as fixed effects. The Cochran–Mantel–Haenszel procedure controlling for pooled site in the analysis of the rates of response was performed. Logistic regression was used to analyze the rates of response in various subgroups. Analysis of covariance was used to assess individual variables in the core set of disease-activity measures and C-reactive protein concentrations, with treatment and pooled site as fixed effects and the corresponding baseline value as the covariate. Differences in values between visits for individual patients were assessed by means of analysis of variance, with visit and patient as fixed effects for continuous variables, and by means of McNemar’s test for the rates of response. All analyses were prespecified in the study protocol. Nonlinear mixed-effects models were used to analyze pharmacokinetic data on M1, the details of which have been published previously.<sup>20</sup>

The data were collected, held, and analyzed by Sanofi–Aventis. The principal investigator had access to the data and vouches for the accuracy of the data and data analysis.

Table 1. (Continued.)\*

Characteristic	Leflunomide Group (N=47)	Methotrexate Group (N=47)
Disease duration†‡		
Mean — yr	1.69±3.21	1.37±1.97
Median — yr	0.33	0.33
Range — yr	0–15.33	0–9.00
<1 yr — no. (%)	32 (68)	32 (68)
1 to <10 yr — no. (%)	13 (28)	15 (32)
≥10 yr — no. (%)	2 (4)	0
No. of active joints	14.4±7.9	14.0±9.9
No. of joints with limited range of motion	7.7±6.4	8.0±6.6
Global assessments — mm§		
Physician	55.1±18.3	47.3±19.3
Patient¶	39.6±28.1	36.5±23.8
CHAQ DI¶¶	1.03±0.71	1.11±0.74
Inflammatory markers		
Erythrocyte sedimentation rate — mm/hr	30.8±18.2	34.5±21.7
C-reactive protein — mg/liter	19.6±22.8	13.8±25.6
No history of DMARD therapy — no. (%)	45 (96)	43 (91)
Corticosteroid use at study entry — no. (%)	9 (19)	9 (19)

\* Plus-minus values are means ±SD.

† “Other” includes patients of other racial or ethnic groups or multiracial patients and patients who did not respond to the question on the questionnaire.

‡ The duration of disease was determined from the time of diagnosis. For patients who were enrolled during the same month in which juvenile rheumatoid arthritis was diagnosed, the duration of disease was 0 months.

§ A 100-mm visual-analogue scale was used in which higher scores meant more active disease.

¶ The patient or a parent or guardian made the assessment.

¶¶ Scores for the Childhood Health Assessment Questionnaire Disability Index (CHAQ DI) can range from 0 (best) to 3 (worst).

## RESULTS

Of 103 patients who were screened, 94 underwent randomization and 86 completed the 16-week treatment: 42 of 47 in the leflunomide group (89 percent) and 44 of 47 in the methotrexate group (94 percent). Reasons for withdrawal in each group are shown in Figure 1. Six patients received intraarticular injections of corticosteroid during the initial 16 weeks (four in the methotrexate group and two in the leflunomide group).

Of the 86 patients who completed the initial study, 70 entered the extension study (33 in the leflunomide group and 37 in the methotrexate group) (Fig. 1), with completion rates at week 32 (week 48 of treatment) of 73 percent in the leflunomide group and 84 percent in the methotrexate group.

Fifteen patients withdrew from the extension study (six in the methotrexate group and nine in the leflunomide group), five because of a lack of efficacy. Of the five patients who withdrew owing to a lack of efficacy, one had an ACR Pedi 70 response at that time, another had an ACR Pedi 30 response at that time, and a third entered a higher weight category without a dose adjustment. Eleven patients received intraarticular injections of corticosteroid during the extension phase (six in the methotrexate group and five in the leflunomide group).

### BASELINE CHARACTERISTICS

There were no significant differences between the groups in demographic or disease characteristics at baseline (Table 1) or in the extension phase (data not shown).

**PHARMACOKINETICS**

The mean ( $\pm$ SD) steady-state concentration of M1 was  $38.9 \pm 20.4$   $\mu$ g per milliliter (equivalent to the administration of a 20-mg dose in adults)<sup>21</sup> among patients weighing more than 40 kg,  $30.0 \pm 19.3$   $\mu$ g per milliliter among those weighing 20 to 40 kg, and  $14.5 \pm 7.2$   $\mu$ g per milliliter among those weighing less than 20 kg. These findings indicate that body size (calculated as weight or body-surface area) had a relatively weak influence on the clearance of M1 (i.e., clearance did not decrease significantly as body size decreased), as reported previously.<sup>20</sup> This effect resulted in lower concentrations of the active metabolite in patients weighing less than 40 kg.

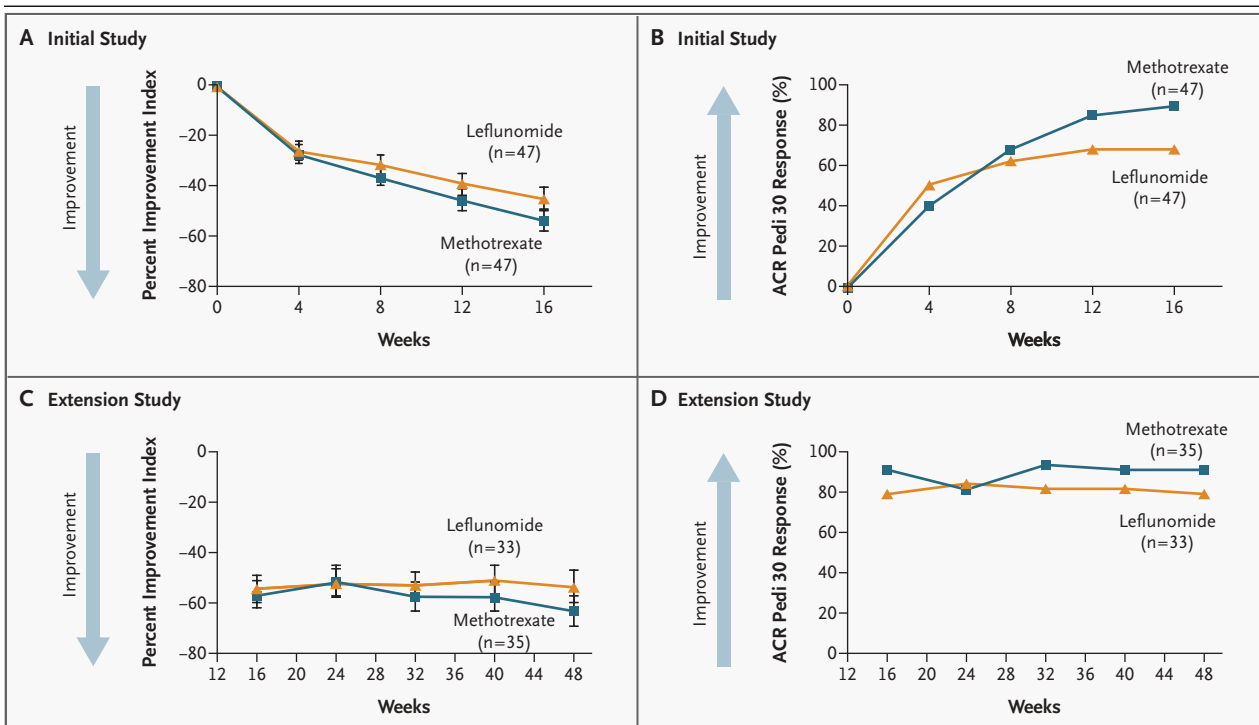
**EFFICACY**

*Initial Study*

After adjustment for an imbalance in the numbers of patients between groups and among sites, the mean ( $\pm$ SE) Percent Improvement Index was similar in the leflunomide group and the methotrex-

ate group at week 16 ( $-44.41 \pm 4.51$  percent and  $-52.87 \pm 4.40$  percent, respectively), and the adjusted mean difference between groups was not significant (8.46 percentage points; 95 percent confidence interval,  $-3.86$  to  $20.77$ ;  $P=0.18$ ) (Fig. 2A). However, the rate of ACR Pedi 30 responses was significantly higher in the methotrexate group than in the leflunomide group (89 percent vs. 68 percent; 95 percent confidence interval,  $-37$  to  $-5$ ;  $P=0.02$ ) (Fig. 2B).

At week 16, the rates of ACR Pedi 50 responses were 60 percent in the leflunomide group and 77 percent in the methotrexate group ( $P=0.10$ ), and the rates of ACR Pedi 70 responses were 43 percent and 60 percent, respectively ( $P=0.14$ ). The median time to an ACR Pedi 30 response was 52 days in the leflunomide group and 56 days in the methotrexate group. The mean ( $\pm$ SE) area under the curve for the ACR Pedi 30 response rates was  $1.86 \pm 0.17$  months in the leflunomide group and  $2.12 \pm 0.17$  months in the methotrexate group; the areas under the curve for the ACR Pedi 50 response rates



**Figure 2.** Mean ( $\pm$ SE) Changes in the Percent Improvement Index and Rates of ACR Pedi 30 Responses in the Initial 16-Week Study, According to the Intention to Treat (Panels A and B, Respectively), and in the Extension Study (Panels C and D, Respectively).

Results are from analyses between groups. Two patients in the methotrexate group were not included in the extension-study population because they withdrew before efficacy data could be obtained. For each analysis, the last observation was carried forward in the case of missing data.

were  $1.51 \pm 0.19$  and  $1.57 \pm 0.18$  months, respectively; and the areas under the curve for the ACR Pedi 70 response rates were  $0.88 \pm 0.17$  and  $0.92 \pm 0.17$  months, respectively, with no significant differences between the groups.

Mean changes from baseline in the core set of disease-activity variables included in the ACR Pedi 30 response did not differ clinically or significantly between the two groups (Table 2). At week 16, clinically meaningful decreases in scores for the Childhood Health Assessment Questionnaire Disability Index were reported:  $-0.44$  in the leflunomide group and  $-0.39$  in the methotrexate group ( $P=0.61$ ). Mean changes in the erythrocyte sedimentation rate at week 16 did not differ significantly between the leflunomide and methotrexate groups ( $-6.5$  and  $-7.2$  mm per hour, respectively), but the methotrexate group had a significantly larger decrease in C-reactive protein concentrations ( $-11.4$  mg per deciliter [95 percent confidence interval,  $-0.3$  to  $-14.9$ ], as compared with  $-3.9$  mg per deciliter;  $P=0.04$ ).

Logistic-regression analyses of Percent Improvement Index values and the rates of ACR Pedi 30 responses according to predefined weight subgroups revealed that weight was significantly associated with a response (Table 3). Patients weighing less than 20 kg had the greatest improvement

in the Percent Improvement Index with methotrexate treatment and showed the greatest differences in the rates of response between treatment groups. These differences were even more apparent in the analysis of the rates of ACR Pedi 30 responses: logistic regression demonstrated that body weight ( $\leq 40$  kg vs.  $>40$  kg,  $P$  for interaction =  $0.24$ ) influenced the treatment effect.

#### 32-Week Extension Study

At week 48, there were no significant differences between the groups in the Percent Improvement Index and the rates of ACR Pedi 30 responses — the two primary outcome measures (Fig. 2C and 2D, respectively) — or in the rates of ACR Pedi 50 and ACR Pedi 70 responses and the mean changes from baseline in the core set of disease-activity variables or C-reactive protein concentrations. Although there was a trend toward a larger improvement between week 16 and 48 in the methotrexate group, there was no significant difference in Percent Improvement Index values at week 16 and week 48 in either the leflunomide group ( $-54.7$  percent vs.  $-55.4$  percent,  $P=0.88$ ) or the methotrexate group ( $-58.0$  percent vs.  $-65.5$  percent,  $P=0.06$ ). A similar analysis of the rates of ACR Pedi 30 responses did not show significant differences for either treatment (leflunomide group, 79 percent

**Table 2.** Change from Baseline in the Core Set of Disease-Activity Variables Included in the ACR Pedi 30 Response during the Initial 16-Week Study.\*

Variable	Leflunomide Group (N=47)		Methotrexate Group (N=47)	
	Baseline	Change at Wk 16	Baseline	Change at Wk 16
	<i>mean ± SE</i>			
No. of active joints	14.2±1.5	-8.1±1.0	14.2±1.4	-8.9±1.0
No. of joints with limited range of motion	7.6±1.0	-5.2±0.8	8.8±0.9	-5.3±0.8
Global assessment (mm)†				
Physician	52.4±2.8	-31.5±3.0	47.2±2.8	-32.1±2.9
Patient‡	36.5±4.1	-15.9±3.0	36.2±4.0	-22.0±2.9
CHAQ DI§	1.0±0.1	-0.44±0.08	1.11±0.1	-0.39±0.1
Erythrocyte sedimentation rate (mm/hr)¶	29.5±3.3	-6.5±1.3	34.7±3.1	-7.2±1.2

\* There were no significant differences between groups at week 16. Values were adjusted for an imbalance in the numbers of patients between groups and among sites.

† A 100-mm visual-analogue scale was used in which higher scores indicated more active disease.

‡ The patient or a parent or guardian made the assessment.

§ Scores for the Childhood Health Assessment Questionnaire Disability Index (CHAQ DI) can range from 0 (best) to 3 (worst).

¶ Data were not available for four patients in the leflunomide group and two in the methotrexate group.

**Table 3. Effects of Treatment at Week 16 in the Various Weight Subgroups.\***

Variable	Leflunomide Group	Methotrexate Group	Difference within Subgroups		P Value for Interaction
			Mean or Odds Ratio (95% CI)	P Value	
Percent Improvement Index — %					0.66
Weight <20 kg	-46.3±11.6	-66.9±10.6	20.63 (-10.3 to 51.5)	0.19	
Weight 20–40 kg	-41.8±7.1	-49.5±8.3	7.63 (-14.5 to 29.8)	0.49	
Weight >40 kg	-46.3±6.9	-50.9±6.1	4.61 (12.7 to 22.0)	0.60	
ACR Pedi 30 response — no. (%)					0.24
Weight <20 kg	5 (62)	8 (100)			
Weight 20–40 kg	11 (58)	11 (85)	0.24 (0.02 to 2.60)†		
Weight >40 kg	16 (80)	23 (88)			

\* Values were adjusted for an imbalance in the numbers of patients between groups and among sites. The numbers of patients in each weight category were as follows: less than 20 kg, 8 patients in each group; 20 to 40 kg, 19 in the leflunomide group and 13 in the methotrexate group; and more than 40 kg, 20 and 26, respectively.

† In the logistic-regression analysis of weight subgroups for the ACR Pedi 30 response, the subgroup weighing less than 20 kg and the subgroup weighing 20 to 40 kg were combined to calculate the odds ratio, because all eight patients in the methotrexate group who weighed less than 20 kg had a response (100 percent), thereby creating a noncalculable odds ratio for that subgroup. In the combined leflunomide group, 16 of 27 patients who weighed 40 kg or less had a response (59 percent), and in the combined methotrexate group, 19 of 21 patients who weighed 40 kg or less had a response (90 percent).

at both 16 and 48 weeks;  $P=1.00$ ; methotrexate group, 91 percent at both 16 and 48 weeks;  $P=1.00$ ). These results demonstrate the durability of the treatment benefit. The rates of ACR Pedi 50 responses were also maintained (leflunomide group, 73 percent at 16 weeks and 76 percent at 48 weeks;  $P=0.74$ ; methotrexate group, 86 percent at both 16 and 48 weeks;  $P=1.00$ ), and a trend toward a higher rate of ACR Pedi 70 responses at week 48 than at week 16 was apparent in both groups (leflunomide group, 55 percent vs. 70 percent;  $P=0.10$ ; methotrexate group, 66 percent vs. 83 percent;  $P=0.06$ ). There were no significant differences between groups in the mean changes from baseline in the core set of disease-activity variables and C-reactive protein concentrations.

#### SAFETY

##### Initial Study

Four patients withdrew because of adverse events during the initial 16 weeks of the study: one patient in each group had liver-function abnormalities, one patient in the leflunomide group had parapsoriasis (lichenoid pityriasis), and one patient in the leflunomide group had Crohn's disease, which was judged to be unrelated to the study treatment.

Serious treatment-related adverse events were reported in three patients taking leflunomide (6 percent) — suspected salmonellosis, an abnormal liver-function test, and parapsoriasis — two of which, described above, resulted in the discontinuation of treatment. No serious adverse events were reported in the methotrexate group.

Data on adverse events reported in at least three patients, regardless of the treatment assignment, are provided in Table 4. Treatment-related adverse events were less frequent among patients weighing 40 kg or less. In the leflunomide group, treatment-related adverse events occurred in 4 of 8 patients weighing less than 20 kg (50 percent), 11 of 19 weighing 20 to 40 kg (58 percent), and 15 of 20 weighing more than 40 kg (75 percent); the respective values in the methotrexate group were 2 of 8 (25 percent), 6 of 13 (46 percent), and 13 of 26 (50 percent).

Elevations in alanine aminotransferase concentrations were more than 1.2 times the upper limit of the normal range in 7 patients in the leflunomide group (15 percent) and 15 patients in the methotrexate group (32 percent) (Table 4). Elevations in alanine aminotransferase concentrations were more than 3.0 times the upper limit of the normal

**Table 4. Adverse Events during the Initial Study and the Extension Study.**

Adverse Event	Initial Study (Wk 0–16)		Extension Study (Wk 16–48)	
	Leflunomide Group (N=47)	Methotrexate Group (N=47)	Leflunomide Group (N=33)	Methotrexate Group (N=37)
	<i>number (percent)</i>			
<b>Highest ALT elevation (with or without AST elevation)*</b>				
>1.2 to ≤2.0×ULN	4 (9)	11 (23)	5 (15)	6 (16)
>2.0 to ≤3.0×ULN	2 (4)	1 (2)	0	2 (5)
>3.0×ULN	1 (2)	3 (6)	0	3 (8)
Any adverse event	43 (91)	38 (81)	29 (88)	31 (84)
<b>Adverse event reported in ≥3 patients</b>				
Headache	18 (38)	11 (23)	7 (21)	5 (14)
Nasopharyngeal symptoms†	15 (32)	11 (23)	8 (24)	6 (16)
Abdominal pain	12 (26)	5 (11)	5 (15)	2 (5)
Nausea, vomiting, or both	13 (28)	16 (34)	4 (12)	7 (19)
Diarrhea	7 (15)	8 (17)	4 (12)	1 (3)
Alopecia	7 (15)	3 (6)	3 (9)	0
Viral infection	6 (13)	2 (4)	2 (6)	2 (5)
Cough	5 (11)	0	1 (3)	5 (14)
Increased aminotransferase concentrations‡	4 (9)	4 (9)	1 (3)	4 (11)
Pyrexia	4 (9)	1 (2)	1 (3)	6 (16)
Upper respiratory tract infection	3 (6)	6 (13)	3 (9)	6 (16)
Overdose§	3 (6)¶	3 (6)¶	0	0
Rash	3 (6)	3 (6)	0	2 (5)
Arthralgia	3 (6)	2 (4)	3 (9)	3 (8)
Conjunctivitis	3 (6)	2 (4)	0	2 (5)
Dizziness	3 (6)	2 (4)	1 (3)	0
Gastroenteritis	3 (6)	1 (2)	2 (6)	3 (8)
Worsening juvenile rheumatoid arthritis	3 (6)	0	2 (6)	1 (3)
Upper abdominal pain	2 (4)	6 (13)	0	2 (5)
Rhinitis, rhinorrhea, or both	3 (6)	5 (11)	5 (15)	3 (8)
Fatigue	2 (4)	4 (9)	1 (3)	3 (8)
Sinusitis	0	3 (6)	0	0
<b>Serious adverse events possibly related to treatment</b>	3 (6)	0	1 (3)	4 (11)

\* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of the normal range.

† This category includes nasopharyngitis, pharyngitis (due to infection or an unspecified cause), pharyngolaryngeal pain, and pharyngeal discomfort.

‡ This category includes increased concentrations of ALT, AST, and  $\gamma$ -glutamyltransferase.

§ All overdoses of study drug are reported.

¶ One patient took 10 mg of leflunomide per day instead of 10 mg every other day for 28 days, with no problem; one patient took a loading dose of 100 mg of placebo for three days instead of one day.

|| One patient took 22.5 mg of methotrexate one day after taking 25.0 mg of methotrexate. The patient had no symptoms; however, the ALT value was 1.7 times the ULN for several days after the overdose. Twelve days after the overdose, the ALT was 1.3 times the ULN, and it remained at this level one month after the overdose, but the event was considered resolved.

range in three patients in the methotrexate group, all of whom weighed 40 kg or less (one weighing less than 20 kg and two weighing 20 to 40 kg), and one patient who was in the highest weight subgroup in the leflunomide group. Neither treatment was associated with a clinically significant change in renal function, neutropenia (fewer than 500 neutrophils per cubic millimeter), or thrombocytopenia (fewer than 100,000 platelets per cubic millimeter). One patient in each group had leukopenia (fewer than 3000 leukocytes per cubic millimeter), which resolved during continued treatment.

#### Extension Study

During the extension study, five patients in the methotrexate group withdrew because of adverse events (a gastrointestinal disorder in one, a viral infection in one, and liver-function abnormalities in three), as did one patient with colitis in the leflunomide group (histologic findings were consistent with the presence of ulcerative colitis). Serious treatment-related adverse events were reported in one patient in the leflunomide group (the one with colitis) and four patients in the methotrexate group (iritidocyclitis in one, a gastrointestinal disorder in one, liver-function abnormalities in one, and liver-function abnormalities, nausea, and vomiting in one). Data on adverse events reported in at least three patients are provided in Table 4.

The incidence of treatment-related adverse events was similar in the leflunomide group (12 of 33 patients, or 36 percent) and the methotrexate group (15 of 37 patients, or 41 percent). Elevations in alanine aminotransferase concentrations were more than 1.2 times the upper limit of the normal range in 5 patients in the leflunomide group (15 percent) and 11 patients in the methotrexate group (30 percent) (Table 4). Elevations in alanine aminotransferase concentrations were more than 3.0 times the upper limit of the normal range in three patients in the methotrexate group (8 percent) (Table 4).

## DISCUSSION

In this randomized, controlled trial comparing methotrexate with leflunomide in patients with juvenile rheumatoid arthritis, the rates of response at 16 weeks were higher than expected in both groups. More patients in the methotrexate group than in the leflunomide group had an ACR Pedi 30 response (89 percent vs. 68 percent,  $P=0.02$ ). Re-

sponse rates in both groups compare favorably with previously published rates of ACR Pedi 30 responses of 48 percent with methotrexate,<sup>6</sup> 44 percent with sulfasalazine,<sup>5</sup> and 74 percent after three months of open-label etanercept. Eighty percent of the patients in the open-label etanercept study maintained their response at seven months in the placebo-controlled withdrawal phase.<sup>3</sup>

We did not observe a significant difference between the methotrexate and leflunomide groups in the other primary outcome variable, the Percent Improvement Index, a continuous variable composed of the same core set of six measures as in the ACR Pedi response. There were no significant differences between groups in the mean changes in the components of the ACR Pedi 30, the ACR Pedi 50, or the ACR Pedi 70 responses. The two treatments resulted in similar and clinically meaningful improvements in physical function, since the mean changes from baseline for both treatments far exceeded the minimal clinically important improvement as reflected by the scores for the Childhood Health Assessment Questionnaire Disability Index.<sup>17</sup> Data from the extension study demonstrated that the responses were durable and that after 48 weeks of treatment there were no significant differences in clinical responses between treatment groups with respect to the primary or secondary outcome measures or mean changes from baseline in the core set of disease-activity measures.

The higher-than-expected rates of responses in both treatment groups may in part be attributed to the early stage of disease (median duration of four months) in this population, presumably because patients could not previously have received methotrexate or leflunomide. Specifically, an aggressive dosing regimen was chosen for methotrexate (0.5 mg per kilogram per week, similar to that used by Woo et al.<sup>6</sup>) because the 16-week end point was judged insufficient to accommodate dose titration.

Although the dose of methotrexate per kilogram was the same for all patients, the dose of leflunomide was based on three weight categories. Among patients weighing 40 kg or less, as compared with those weighing more than 40 kg (57 percent of those in the leflunomide group and 45 percent of those in the methotrexate group), the rates of responses with methotrexate differed more from those with leflunomide. This difference was more striking in the subgroup weighing less than 20 kg than in the subgroup weighing 20 to 40 kg. The

pharmacokinetic analysis suggested that the doses of leflunomide in the lower-weight patients may have been too conservative, since patients weighing 40 kg or less who were treated with leflunomide had mean M1 concentrations that were lower than those associated with clinical responses in adults with rheumatoid arthritis. Although each weight subgroup was small, the trends in clinical responses and M1 concentrations suggested that in patients weighing 40 kg or less, the true therapeutic benefit of leflunomide may have been underestimated.

Overall, the safety profile with both DMARDs was consistent with their known profiles of adverse events and results in adults with rheumatoid arthritis and children with polyarticular-course juvenile rheumatoid arthritis. Methotrexate had a better safety profile than leflunomide during the initial 16 weeks of treatment, although not during the subsequent 32-week extension. The exception to this observation was that liver-function abnormalities in both the initial and extension studies were more frequent with methotrexate, including elevations in alanine aminotransferase that were more than 3.0 times the upper limit of the normal

range; such elevations were reversible on discontinuation of study medication.

Our patients with juvenile rheumatoid arthritis had high rates of responses to both methotrexate and leflunomide, but our findings suggest that methotrexate is more effective than leflunomide for polyarticular-course juvenile rheumatoid arthritis at the doses we used. Improvements were maintained in both groups over a total of 48 weeks of treatment. As has been true for other medications for juvenile rheumatoid arthritis, additional studies may be required to determine the response to leflunomide in the various subgroups of patients with polyarticular-course juvenile rheumatoid arthritis.

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#### APPENDIX

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