Effectiveness of Leflunomide in Patients with Juvenile Idiopathic Arthritis in Clinical Practice

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ABSTRACT. ***Objective.*** To evaluate the effectiveness of leflunomide in children with juvenile idiopathic arthritis (JIA) as used in actual clinical practice.

Methods. We conducted a retrospective review of medical records of patients with JIA who initiated leflunomide treatment between April 2001 and October 2006. Data derived from these charts included patient baseline characteristics, reason for starting leflunomide, adverse events, joint outcomes, Childhood Health Assessment Questionnaire (CHAQ) scores, visual analog scale pain and well-being scores, and current treatment status.

Results. Fifty-eight patients (33 female, 25 male) were included in this study. Forty-eight patients were switched from methotrexate (MTX) to leflunomide, primarily because of MTX-related adverse events, and leflunomide was added to ongoing MTX in 10 patients. The mean duration of leflunomide therapy was 1.45 years. The mean swollen joint count decreased from 1.40 at treatment initiation to 0.60 at last followup, while the mean tender joint count decreased from 1.83 to 0.29. Improvements were also observed in CHAQ, pain, and well-being scores. At last followup, 44.8% of patients were continuing leflunomide therapy, 29.3% had discontinued because of remission, and the rest had discontinued treatment because of side effects (22.4%) or other reasons (3.4%).

Conclusion. Leflunomide treatment, as employed in actual clinical practice, was well tolerated and resulted in substantial improvements in joint and functional status outcomes in children with JIA. Approximately 30% of the patients attained remission during leflunomide therapy. Leflunomide is thus a safe and effective alternative for patients with JIA who cannot tolerate or do not respond to MTX monotherapy. (J Rheumatol First Release May 15 2010; doi:10.3899/jrheum.090874)

Key Indexing Terms:
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SAFETY REMISSION

Methotrexate (MTX) is the first-line disease-modifying antirheumatic drug (DMARD) for most cases of juvenile idiopathic arthritis (JIA)[1]. Although about 70% of children with JIA respond to standard oral MTX doses, 30% do not respond or must discontinue therapy because of side effects[2]. Recent studies indicate that some of these patients may be helped by higher doses of MTX[2] or by subcutaneous administration of this drug[3]. However, there remains a substantial proportion of children with JIA who require treatment alternatives because they do not tolerate or respond to MTX.

Leflunomide is an option for children with JIA, either as monotherapy for patients who respond to but cannot tolerate MTX or as combination therapy for patients with an insufficient response to MTX. Silverman, *et al* conducted a randomized clinical trial of leflunomide versus MTX in 94 patients with polyarticular juvenile rheumatoid arthritis, most of whom (94%) were DMARD-naive[4]. At 26 weeks, 68% of leflunomide-treated patients met American College of Rheumatology (ACR) Pediatric Criteria for 30% improvement (Pedi 30)[5] compared to 89% of MTX-treated patients[4]. Both treatment groups maintained improvements up to the final study visit at 48 weeks. Tolerability of the 2 drugs was comparable. Silverman, *et al* also examined the longterm efficacy of leflunomide in an open-label study of 27 children who had failed or could not tolerate MTX therapy[6]. At 26 weeks, 52% of these patients met ACR Pedi 30 response criteria. Seventeen children continued into a longterm extension phase; 65% met ACR Pedi 30 response criteria at 50 weeks and 53% met response criteria at the end of the observation period (130 weeks). Leflunomide was generally well tolerated throughout the study[6].

These Silverman, *et al* studies provide strong support for the use of leflunomide in children with JIA. However, data from clinical trials do not always correspond with outcomes observed in clinical practice[7,8], and there is little published information concerning the use of leflunomide to treat JIA in "real world" clinical situations. Although leflunomide is

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not approved by regulatory agencies in the United States or Europe for the treatment of JIA, it is frequently used off-label to treat children with this condition. To assess the effectiveness of leflunomide in JIA as used in actual clinical practice, we conducted a retrospective review of medical records from patients in our practice who had received leflunomide therapy for JIA between April 2001 and October 2006.

MATERIALS AND METHODS

Study design. Our study involved a retrospective review of patient records. Because of the noninterventional, observational design, ethics approval and patient consent were not required by German law. We identified patients diagnosed with JIA who had initiated leflunomide therapy between April 2001 and October 2006. In our practice, leflunomide was started without a loading dose and the daily dose was adjusted to body weight as described by Silverman, *et al*[6]. Patients with a body weight < 20 kg received 10 mg leflunomide every second day; patients with weight > 20 kg and < 40 kg received 10 mg leflunomide/day, and patients weighing > 40 kg received 20 mg leflunomide/day. All sexually active patients practiced birth control. The major indication to initiate leflunomide was MTX intolerance. In a smaller group of patients, leflunomide was added to MTX if there was an inadequate response to MTX monotherapy and the patient/parents refused etanercept therapy. All patients were considered by their clinician to require ongoing systemic therapy.

Diagnostic criteria for JIA utilized the International League of Associations for Rheumatology (ILAR) criteria at the time of inclusion[9,10]. A retrospective chart review was conducted on the medical records of all patients who met these entry criteria. Most patients had undergone clinical visits every 4 to 12 weeks, including physical examinations, full joint counts, evaluations of adverse events, and laboratory tests as needed.

Study endpoints and statistical analyses. Charts were reviewed for relevant variables, including patient demographic characteristics, the reason for starting leflunomide, adverse events, outcome data, and treatment status. Evaluations were conducted on 75 joints and included assessments of the number of swollen joints, the number of tender joints, and the number of joints with limited range of motion. Functional status was assessed by parent responses to the German version of the Childhood Health Assessment Questionnaire (CHAQ) disability index (0 = no limitation, 3 = severe limitation), which has been validated in JIA[11]. Pain and well-being were evaluated by use of 10-cm visual analog scales (VAS; 0 = no pain/very well; 10 = severe pain/very poor), components of the CHAQ.

All patients with JIA who received leflunomide therapy were included in the analyses (intention to treat). Descriptive statistics were used to summarize demographic and outcome data.

RESULTS

Patients. Fifty-eight patients, 33 female and 25 male, were included in this chart review (Table 1). The mean age at disease onset was 8.78 years and the mean age at initiation of leflunomide was 12.72 years (median 11 yrs; range 4.18–18.12 yrs). Seven patients were 16 years of age or older at the time of initiation of leflunomide treatment. Several different JIA subsets, as classified by ILAR criteria[9,10], were represented in our study; the most common were enthesitis-related (27.6%) and oligoarticular (25.9%) arthritis (Table 1). All patients had at least 1 involved joint at the time of initiation of leflunomide treatment (swollen, tender, or limited range of motion).

Table 1. Characteristics of patients with juvenile idiopathic arthritis (JIA).

Characteristic	Value
Sex, n (%)	
Male	25 (43.1)
Female	33 (56.9)
JIA subset, n (%)	
Oligoarticular	15 (25.9)
Oligoarticular, extended	5 (8.6)
Polyarticular	12 (20.7)
Enthesitis-related	16 (27.6)
Psoriatic	7 (12.1)
Systemic	3 (5.2)
Mean disease duration, yrs (range)	4.00 (0.08–15.09)
Mean age at onset, yrs (range)	8.78 (0.73–17.85)
Mean age at initiation of leflunomide, yrs (range)	12.72 (4.18–18.12)
Mean age at last followup, yrs (range)	17.43 (6–22)

Leflunomide therapy. All patients had received MTX treatment. Fifteen patients received prior treatment with additional DMARD or biologicals, including abatacept (n = 2), adalimumab (n = 2), anakinra (n = 1), azathioprine (n = 1), cyclosporine (n = 5), etanercept (n = 6), hydroxychloroquine (n = 1), infliximab (n = 1), and sulfasalazine (n = 2); some patients were treated with more than 1 of these.

The most common reason for initiating leflunomide therapy was MTX-associated side effects [47 patients (81%)], primarily nausea (39 patients). Most (n = 46) of the patients with side effects discontinued MTX and switched to leflunomide, but 1 patient with minor hair loss during MTX treatment continued MTX therapy at the same dose in combination with leflunomide. For the remaining 11 patients (19%), the primary reason for initiating leflunomide was insufficient therapeutic response to MTX. Leflunomide was added to MTX for 9 of these patients, and the other 2 patients discontinued MTX and switched to leflunomide. Accordingly, in the group as a whole, 48 patients switched from MTX to leflunomide, while 10 had leflunomide added to ongoing MTX therapy. In this latter group, leflunomide was chosen as additional therapy because the patients/parents did not wish to take etanercept.

The mean MTX dose prior to changing to or adding leflunomide was 14.89 mg/m^2/week. The mean leflunomide dose during therapy was 16.64 mg/day (0.34 mg/kg/day), and the mean duration of leflunomide therapy was 1.45 years (range 0.04 to 5.28). There was no loading dose. The daily dose was adjusted to body weight as described by Silverman, *et al*[6].

Of the 10 patients who were treated with leflunomide plus MTX, 1 also took etanercept and 1 took additional cyclosporine and anakinra for part of the treatment period. Twelve other patients took DMARD in combination with leflunomide for at least part of the study period, including etanercept (n = 6), infliximab (n = 1), cyclosporine (n = 1), cyclosporine followed by etanercept (n = 1), sulfasalazine (n = 1), hydroxychloroquine (n = 1), and multiple biologic ther-

apies (adalimumab, etanercept, and rituximab; n = 1). Ten patients took concomitant therapy with oral corticosteroids as bridging therapy until the therapeutic effect of leflunomide was apparent. None of the patients was treated with intraarticular corticosteroids during the observation period.

Response to leflunomide therapy. Swollen and tender joint counts were available for all patients. Substantial reductions were observed in mean joint counts during leflunomide treatment (Figure 1). The number of joints with a limited range of motion showed more modest changes, with reductions from a mean of 3.50 (range 0–30) at the initiation of leflunomide therapy to 3.31 (range 0–30) at 3 months and 3.36 (range 0–30) at last followup. Further analysis of swollen joint counts revealed that 29 patients had no change (17 of these had 0 swollen joints at baseline), 23 showed improvement (range 1 to 13 fewer swollen joints), and 6 had an increased number of swollen joints (range 1 to 2 more swollen joints) at last followup. Analysis of tender joint counts revealed similar results: 23 had no change (17 of these had 0 tender joints at baseline), 33 showed improvement (range 1 to 14 fewer swollen joints), and 2 patients had an increased number of tender joints at last followup (both with an increase of 1 joint). As with mean joint counts, joints with a limited range of motion showed the least therapeutic effect: 41 patients had no change (3 had 0 limited joints at baseline), 10 patients showed improvement (range 1 to 4 fewer joints), and 7 had an increased number of limited joints at last followup (range 1 to 4 more joints).

Functional status, pain, and well-being scores were available for 25 patients at initiation of leflunomide therapy and for 35 patients at last followup. At treatment initiation, the mean CHAQ score was 0.53, the mean VAS pain score was 0.88, and the mean VAS well-being score was 0.94. At last followup, these values were 0.19, 0.41, and 0.48, respectively. Table 2 shows changes in these measurements in the 20 patients who had data at both treatment initiation and last followup. At study initiation, 7 of 25 patients (28.0%) had a CHAQ score of 0, indicating no functional limitations, compared to 22 of 35 patients (62.9%) with a CHAQ score of 0 at last followup. Of the 20 patients with scores recorded at both treatment initiation and last followup, scores increased in 3 (15%), stayed the same in 5 (25%; all of these patients had a CHAQ score of 0 at both treatment initiation and last followup), and decreased (improved) in 12 (60%). Of the 12 patients with improved scores, 11 had improvements of at least 0.13 point.

Treatment status at last followup is shown in Table 3. About half (26; 44.8%) of the patients continued leflunomide treatment and 29% discontinued because of remission (defined as no active joints, no elevated C-reactive protein or erythrocyte sedimentation rate, and CHAQ of 0 for 6 months, analogous to the Wallace criteria for remission on medication[12]). The highest remission rates were observed in patients receiving leflunomide monotherapy (38.9%). Side effects were the primary reason for discontinuation for about 22% of patients. Discontinuation because of remission was most common in patients in the psoriatic JIA subset, followed by enthesitis-associated and polyarticular disease (Table 4).

Tolerability. Leflunomide was generally well tolerated. A transient increase in liver transaminases occurred in 9 patients (15.5%), but none of these patients required discontinuation of therapy. In these patients, leflunomide doses were temporarily decreased until transaminase levels normalized. In the 13 patients (22.4%) who discontinued leflunomide because of adverse events, 5 discontinued

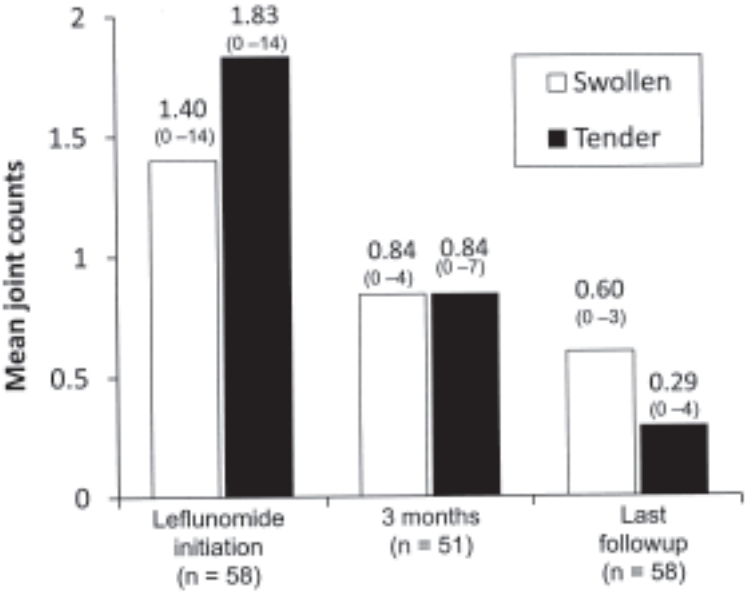

Figure 1. Mean swollen and tender joint counts during leflunomide therapy in 58 children with JIA.

Table 2. Functional status, pain, and well-being in 20 leflunomide-treated children with JIA. Data are derived from 20 patients with both treatment initiation and last followup values available. Functional status was assessed by CHAQ disability index (0 = no limitation; 3 = severe limitation), pain by 10-cm VAS (0 = no pain; 10 = severe pain), and well-being by 10-cm VAS (0 = very well; 10 = very poor). Negative changes indicate improvement.

Assessment	Leflunomide Treatment Initiation, mean (range)	Last Followup, mean (range)	Change During Treatment, mean (range)
CHAQ	0.48 (0 to 2.25)	0.30 (0 to 2.00)	–0.18 (–1.88 to 0.5)
VAS pain	0.88 (0 to 2.70)	0.51 (0 to 2.16)	–0.37 (–2.70 to 1.41)
VAS well-being	0.86 (0 to 2.40)	0.63 (0 to 1.92)	–0.26 (–2.34 to 1.32)

CHAQ: Childhood Health Assessment Questionnaire; VAS: visual analog scale.

Table 3. Treatment outcome at last followup.

Treatment Group	N	Continued Therapy, n (%)	Discontinued Therapy, n (%)*			
			Remission	Side Effects	Lack of Response	Lost to Followup
All patients	58	26 (44.8)	17 (29.3)	13 (22.4)	1 (1.7)	1 (1.7)
LEF monotherapy	36	14 (38.9)	14 (38.9)	8 (22.2)	—	—
LEF + MTX	10	3 (30)	1 (10)	4 (40)	1 (10)	1 (10)
LEF + etanercept	6	4 (66.7)	1 (16.7)	1 (16.7)	—	—
LEF + other DMARD	6	5 (83.3)	1 (16.7)	—	—	—

* Calculated as percentage of patients in that treatment group. LEF: leflunomide; MTX: methotrexate; DMARD: disease-modifying antirheumatic drug.

Table 4. Patients discontinuing leflunomide because of remission.

JIA Subset	N	Discontinuations Because of Remission, n (%)
Oligoarticular	15	4 (20.0)
Oligoarticular, extended	5	0 (0)
Polyarticular	12	3 (25.0)
Enthesitis-related	16	6 (37.5)
Psoriatic	7	4 (57.1)
Systemic	3	0 (0)

because of diarrhea, 4 because of abdominal pain or nausea, 2 because of headache, and 1 each because of fatigue and arterial hypertension. The patient with arterial hypertension received combination therapy with leflunomide and MTX. Although the numbers were small, tolerability appeared to be worse in patients receiving leflunomide in combination with MTX than in the overall study population or in patients receiving leflunomide in combination with other DMARD (Table 3).

DISCUSSION

About 30% of children with JIA do not respond to or cannot tolerate oral MTX at conventional dosages[2]. These patients require therapeutic alternatives to improve function and health-related quality of life. Effective DMARD treatment may have longterm benefits as well. For patients with adult rheumatoid arthritis, early aggressive DMARD therapy results in sustained benefits (reviewed by Machold, *et al*[13]), and there is evidence that this may also be true for JIA[14]. Leflunomide has shown efficacy in a randomized clinical trial in patients with JIA and in a longterm open-label study[4,6]. On the basis of these data, we conducted a retrospective chart review to assess the longterm effectiveness of leflunomide in the treatment of JIA as used in actual clinical practice.

Our study evaluated the medical records of 58 MTX-treated patients with JIA who had initiated leflunomide therapy. Most of the patients had switched from MTX to leflunomide because of MTX-related adverse events. Although the randomized clinical trial of leflunomide versus MTX conducted by Silverman, *et al* involved patients who were mostly DMARD-naive[4], in clinical practice leflunomide is primarily used as a second-line or third-line agent. This is due in part to the fact that JIA is an off-label indication for this drug in Europe and the United States. In most cases, leflunomide is offered to patients who respond to MTX, but cannot tolerate the drug because of side effects. It is thus important to characterize the response of patients to leflunomide as used in actual clinical practice.

Because the patients in our study had been receiving MTX prior to leflunomide therapy, joint involvement at baseline was generally modest (mean of 1.40 swollen joints and 1.83 tender joints at the initiation of therapy) and most patients were mildly to moderately disabled, as indicated by a mean baseline CHAQ of 0.53[15]. From the time of initiation of leflunomide treatment to last followup, mean swollen joint counts decreased by 57% (from 1.40 to 0.60) and tender joints were reduced by 84% (from 1.83 to 0.29; Figure 1). Mean CHAQ, pain, and well-being scores also showed

marked improvement in patients with values available from both treatment initiation and last followup (Table 2). We observed a mean reduction of 0.18 points in CHAQ scores in this patient subset; the minimal clinically important difference for improvement has been reported as a reduction of 0.13 point by Dempster, *et al*[15] and as a reduction of 0.18 point by Brunner, *et al*[16]. The mean pain and well-being scores also decreased (improved) in these patients by 0.37 cm and 0.26 cm, respectively. We were unable to evaluate the rate of ACR Pedi 30 responses in our study because we did not perform all the outcome measures required by these criteria during routine clinical treatment.

Improvements observed during leflunomide therapy were sustained. At the last followup, 17 patients (29.3%) had discontinued treatment because of remission, while 15 (22.4%) discontinued because of side effects, primarily gastrointestinal symptoms. Only 1 patient (1.7%) discontinued because of lack of response. On the basis of remission rates, leflunomide monotherapy was as effective as combination therapy in this study. However, patients chosen to receive leflunomide monotherapy had less severe disease at baseline. Although the numbers in our study are small, leflunomide appeared to be particularly effective in patients with psoriatic or enthesitis-associated arthritis. In adults, leflunomide is an effective therapy for both the joint and psoriatic manifestations associated with psoriatic arthritis[17,18].

Leflunomide was generally well tolerated. Transient increases in transaminase levels were observed in 9 children (15.5%), but these patients were able to successfully continue therapy after a temporary reduction of the leflunomide dose. Diarrhea and abdominal pain were the most common causes of treatment discontinuation. Silverman, *et al* also found a high frequency of gastrointestinal events in their longterm open-label study of leflunomide in JIA. These events usually occurred during the first 3 months of therapy and were of mild intensity[6]. Reduction of the daily dose helps to reduce gastrointestinal side effects.

Our findings support the use of leflunomide to treat children with JIA who cannot tolerate or do not respond to MTX. Under "real world" clinical conditions, leflunomide therapy was associated with substantial improvements in joint outcomes and functional status. Most adverse events were manageable without treatment discontinuation, and only 1 patient discontinued because of lack of response. We conclude that leflunomide is a safe and effective treatment option for children with JIA as used in actual clinical practice.

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