A Longterm Prospective Real-life Experience with Leflunomide in Juvenile Idiopathic Arthritis

Antonia Célia de Castro Alcântara, Christiane Araújo Chaves Leite, Ana Caroline Rocha Melo Leite, José Julio Costa Sidrim, Francisco Saraiva Silva Jr., and Francisco Airton Castro Rocha

ABSTRACT. Objective. To describe a clinical practice with leflunomide (LEF) in juvenile idiopathic arthritis (JIA).

Methods. Patients with JIA seen between May 2008 and May 2012 and considered nonresponsive to methotrexate (MTX) were given LEF and prospectively followed. Primary outcome was a 28-joint Disease Activity Score (DAS28) of low disease activity (< 3.2) in less than 6 months. Childhood Health Assessment Questionnaire (CHAQ) scores and safety data were recorded.

Results. Forty-three patients (33 female) were included with 25 (58.1%) polyarticular, 10 oligoarticular (7 extended; 3 persistent), 6 systemic, and 2 enthesitis-related. Ten (23.2%) were rheumatoid factor–positive and 7 (16.3%) had antinuclear antibodies. Prior drugs other than MTX: 11 (25.5%) chloroquine diphosphate + MTX and 2 (4.6%) sulfasalazine + MTX; mean prednisone dose was 6.4 ± 9.3 mg. The MTX dose prior to LEF was 14.5 ± 4.5 mg/m²/week. LEF dose and duration of therapy were 16.6 ± 5.2 mg/d and 3.6 ± 2.2 years, respectively. Nineteen patients (44.2%) interrupted LEF: 1 entered remission, 11 were nonresponsive, and 7 were intolerant (16.2%). Baseline DAS28 (5.57 ± 0.7) dropped to 3.7 ± 1.2 at final analysis (p < 0.001) and 16 patients (37.2%) had a low DAS28 (< 3.2; 12 (27.9%) while taking LEF + MTX and 4 (9.3%) while taking monotherapy]. At last followup, the number of patients with DAS28 > 5.1 dropped from 34 (79%) to 9 (20.9%) and CHAQ scores from 0.86 ± 0.7 to 0.44 ± 0.5 (p < 0.001).

Conclusion. LEF isolated or combined with MTX is effective and safe to treat JIA in patients refractory to MTX. (First Release Dec 15 2013; J Rheumatol 2014;41:338–44; doi:10.3899/jrheum.130294)

Key Indexing Terms: JUVENILE IDIOPATHIC ARTHRITIS LEFLUNOMIDE METHOTREXATE DISEASE ACTIVITY SCORE DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS

Juvenile idiopathic arthritis (JIA) is the most frequent chronic arthropathy in childhood, affecting 1 or more joints in children less than 16 years old. It is more common among girls. The prevalence of JIA in developing countries has not been extensively studied and differences in the clinical presentation, as well as response to treatment, may vary among patients with JIA worldwide. Methotrexate (MTX) is currently the first choice among disease-modifying antirheumatic drugs (DMARD) in JIA. Although we do not have written guidelines for the treatment of JIA in Brazil, the current practice among rheumatology centers is also to start with MTX. Leflunomide (LEF) is classified as a DMARD that effectively ameliorates signs and symptoms in patients with rheumatoid arthritis (RA). In addition, LEF can also be combined to the so-called biologic DMARD to treat patients who have RA that is nonresponsive or who are intolerant to MTX. In Brazil, a common practice in treating RA is to add LEF to MTX or to use it as monotherapy in those intolerant to MTX. This practice is also followed often in the treatment of JIA. However, concerns persist about less tolerability of LEF because of increased incidence of adverse events (mostly linked to hepatotoxicity). Few studies have focused on the efficacy of LEF in JIA. One of those studies compared the administration of either MTX or LEF to patients with JIA. The results showed a mild though significantly better response with MTX for a 16-week period, with acceptable tolerability for both compounds. A retrospective study of children with the polyarticular presentation of JIA who were not responsive to MTX or who could not tolerate it showed that LEF led to clinical improvement in up to 75% of the patients, including...
almost 30% who achieved remission with an acceptable safety profile.

Clinical presentation as well as response to treatment may vary worldwide among patients with JIA. Specifically with regard to LEF, there are reports on the possible difference in the prevalence of side effects among various populations, suggesting that the effects are worse in patients from East Asia. We live in a low latitude region, with a low-income population of about 8.5 million in the northeast of Brazil. Sanitary problems and the hot weather account for a high prevalence of both parasitic and infectious diseases so that helminthic infections are endemic. Therefore, we have special concerns about safety issues owing to opportunistic infections before prescribing biological DMARD for our patients.

Defining specific targets to treatment has been shown to improve outcome in patients with RA. Criteria for the definition of remission or inactive disease in JIA have been published, but the definition of minimal or low disease activity still needs to be determined. This is particularly important in JIA, because achieving a state of inactive disease has been shown to improve outcome concerning longterm joint damage.

Our aim was to prospectively evaluate the use of LEF in children with JIA who were considered nonresponsive or intolerant to MTX and seen at the outpatient clinics of the Hospital Universitário Walter Cantídio (HUWC) of the Faculty of Medicine of the Universidade Federal do Ceará. Because our study was designed in 2007, we used RA outcomes to evaluate our patients with JIA. To this purpose, low disease activity based on the 28-joint Disease Activity Score (DAS28) definition in RA was the primary outcome to be achieved within a maximum of 6 months.

MATERIALS AND METHODS
All patients with a diagnosis of JIA according to the International League of Associations for Rheumatology and seen at the rheumatology outpatient clinics of the HUWC, Fortaleza CE, Brazil, between May 2008 and May 2012 were prospectively evaluated. There were 43 children treated with LEF, with an age range from 1 to 16 years at study entry.

The clinical protocol was submitted and approved by our local Ethics Regulatory Committee, which follows the rules of the Brazilian National Ethics Committee on Clinical Research. All patients or their responsible relatives signed an informed consent form before any intervention. At the start of the protocol, all children were identified after a survey in the pharmaceutical division of the HUWC and had their clinical records evaluated to confirm diagnosis. The fact that LEF is prescribed under a strict regulatory control and is free of charge to the patient guarantees that helminthic infections are endemic. Therefore, we have special concerns about safety issues owing to opportunistic infections before prescribing biological DMARD for our patients.

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RESULTS
Figure 1 illustrates the number of patients included in each category and their outcomes. Table 1 shows the baseline demographics. Forty-three patients were included; 33 were female (76.7%). The polyarticular presentation was the most common category, representing 25 of the patients (58.1%), with a striking predominance of 23 girls (92%) within this category. Among the 10 cases (23.2%) with oligoarticular presentation, 3 (6.9%) remained as persistent and 7 (16.3%) turned into a polyarticular form, being classified as extended oligoarticular. Ten (23.2%) children were RF-positive, so that 9 (20.9%) of them were classified in the polyarticular category and 1 patient (2.3%) was classified as extended oligoarticular. Seven patients (16.3%) tested positive for the presence of antinuclear antibodies [4 (9.3%) polyarticular, 2 (4.6%) oligoarticular, and 1 (2.3%) systemic].

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The mean age at diagnosis was 10 ± 4 years, with 32 (74.4%) being older than 7 years at the time of diagnosis. The age of appearance of first symptoms was 8 ± 4 years and the time to definitive diagnosis ranged from 1 to 60 months (median = 12 mos). Eight patients (18.6%) had the diagnosis more than 2 years after the appearance of symptoms.

Ten patients (23.2%) had existing deformities at the time of diagnosis. Among these, 8 (80%) were in the polyarticular category. The other remaining children in this category were 1 (2.3%) in the enthesitis and the other in the systemic category. Although the difference did not reach statistical significance (p = 0.257), it was remarkable that 9 of the 33 girls and 1 of the 10 boys had deformities at the beginning of the protocol. At last followup, those numbers remained unchanged.

Table 2 displays the data concerning the drugs prescribed. All patients used other nonbiologic DMARD before starting LEF, as follows: all 43 used oral MTX; 2 patients (4.6%) used sulfasalazine associated with MTX, and 11 (25.5%) used chloroquine diphosphate along with MTX. Twenty-seven patients (62.7%) were using oral steroids at the start of the protocol, comprising 15 (34.9%), 6 (13.9%), 4 (9.3%), 1 (2.3%), 1 (2.3%) in the polyarticular, systemic, extended oligoarticular, persistent oligoarticular, and enthesitis categories, respectively. Thirty-one of the 43 patients had LEF added to MTX whereas 12 had LEF used as monotherapy. The mean daily dose of prednisone was 0.156 mg/kg. None of these patients received any biologic DMARD before starting LEF.

At the start of the protocol, 43 children evaluated were considered as having inadequately controlled disease, with 34 (79%) classified as having severe disease (DAS28 > 5.1). The mean MTX dose prior to changing to or adding LEF was 14.5 ± 4.5 mg/m²/week. The mean LEF dose during the protocol was 16.6 ± 5.2 mg/day (0.34 mg/kg/day), and the mean duration of LEF therapy was 3.6 ± 2.2 years.
At the end of followup (37 ± 8.9 mos), 19 patients (44.2%) had LEF interrupted. In one case the drug was stopped because the child achieved remission criteria (DAS28 < 2.6) after 2 years of uninterrupted treatment with LEF combined with MTX. That girl continued with MTX (5 mg/week) after withdrawal of LEF. For 11 patients (25.5%), LEF was considered to have failed, and 9 among those patients (20.9%) were taking concomitant MTX. Seven patients (16.2%) were considered intolerant of LEF. For 3 of them (6.9%) the intolerance was due to nausea and abdominal pain, and 4 (9.3%) had increased liver enzymes (> 2 × upper limit of normal). Two of the patients with an increase in liver enzymes were taking concomitant MTX (7.5 mg/week) + LEF (20 mg/d). After withdrawal of both compounds, liver enzymes returned to normal in 1 month. Two months later, 1 of those latter patients had reinstitution of LEF, which was maintained as the sole DMARD for 39 months until the end of the study without adverse events. There were no other clinically relevant laboratory changes during followup. Our patients were also followed in the pediatric outpatient clinic that gives us support in clinical control in about one-third of those MTX-nonresponsive patients with JIA, with an acceptable safety profile. As a whole, our data reveal that the clinical response achieved with LEF both as add-on therapy to MTX or monotherapy led to a sustained and significant clinical change from baseline as compared to the last followup. At the end of the protocol, 16 patients (37.2%) had a low DAS28 (< 3.2) including 12 (27.9%) taking LEF + MTX and 4 (9.3%) taking monotherapy with LEF; 18 patients (41.8%) had a DAS28 between 3.2 and 5.1 and 9 (20.9%) had a DAS28 higher than 5.1, indicating severe disease. There was also a significant change in the pain as judged by the patient (parent) at baseline as compared to the last followup, dropping from a mean of 3.79 ± 1.9 to 3.65 ± 2.0 (p < 0.001), respectively. Baseline mean CHAQ scores also significantly dropped from 0.86 ± 0.7 to 0.44 ± 0.5 (p < 0.001) at the end of followup. Although the low numbers when evaluating the clinical outcome according to disease subset do not permit a statistical analysis, patients from all subsets, when evaluated as a group, had a mean improvement at last followup, as compared to baseline. Also, there were dropouts in all groups, as shown in Table 4.

Table 3 shows the proportion of patients achieving ACR-Pedi responses. The majority of the patients [28 (65.1%)] achieved at least an ACR-Pedi30, including 12 (27.9%) who achieved at least an ACR-Pedi50 response. The number of children with joint deformities did not change at the end of followup as compared to baseline.

**DISCUSSION**

This is the first study, to our knowledge, on the use of LEF as a second-line effective DMARD therapy on JIA in patients from an equatorial area. Although not being a randomized controlled trial, we conducted a prospective longterm followup study on the use of LEF in JIA in a real-life situation following a clinical protocol with defined outcomes.

As a whole, our data reveal that the clinical response achieved with LEF both as add-on therapy to MTX or monotherapy led to a sustained and significant clinical control in about one-third of those MTX-nonresponsive patients with JIA, with an acceptable safety profile. We have had access to biologics since 2006, provided regularly by our public service. Our choice of MTX as a first-line DMARD in RA and JIA is based on current guidelines used in RA and our longterm good clinical experience with this compound. Although we have to mention the economic influence on our decision to choose LEF as our
generally preferable as the first-choice DMARD, followed by a biologic agent in the case of refractoriness or intolerance. More recently, following a systematic literature review, the ACR did not recommend the routine use of LEF as a preferable second-choice DMARD option in patients refractory to MTX and a double-blinded trial comparing MTX to LEF also reported an acceptable safety profile with no increase in infections or gastrointestinal side effects.

A previous open-label study of patients with JIA refractory to MTX and a double-blinded trial comparing MTX to LEF also reported an acceptable safety profile with significant improvement in signs and symptoms. However, worldwide experience and/or recommendations regarding JIA treatment, including the specific issue of LEF use, are yet to be defined. More recently, following a systematic literature review, the ACR did not recommend the routine use of LEF as a preferable second-choice DMARD option in patients with JIA, as we currently adopted in our service. As a whole, the recommendations were that MTX was generally preferable as the first-choice DMARD, followed by a biologic agent in the case of refractoriness or intolerance to MTX.

Current treatment outcomes and evaluation in JIA have greatly improved. However, by the time we designed our protocol, there were no specific instruments to establish outcomes in JIA. Our strategy was to define a target of low disease activity status. Although this strategy is open to debate, a study has shown that the RA DAS28 scores performed similarly to the Juvenile Arthritis Disease Activity Score in patients with JIA. Trying to define goals as a treat-to-target approach, our patients were prospectively followed up, and closely monitored so that each patient that was not considered in low disease activity or remission according to the DAS28 score was seen monthly. Those who did not achieve the outcome in 6 months and used combined MTX and LEF were considered nonresponsive to treatment; LEF was discontinued and a biologic was then started. For those taking LEF monotherapy, a biologic could then be added.

The sustained good clinical response was also a very positive result in our cohort. After a mean period of more than 3 years of followup for the whole cohort, the number of patients with high disease activity dropped from 39 to 9. Therefore, the addition of LEF to these MTX-nonresponsive patients with JIA led to a relevant improvement in two-thirds of those with high disease activity. This is also reflected by the significant reduction in the pain component as judged by the patient (parent). Considering that CHAQ scores also significantly improved, we can also infer that functional impairment was lessened in these patients after the introduction of LEF. Moreover, the number of joints with deformities did not increase, even in those cases that did not achieve the defined outcome of low disease activity. It should be mentioned that at study entry, patients in the systemic category had only joint features.

Second-choice DMARD, the main reasons to postpone the introduction of biologic DMARD were safety issues related to our high prevalence of infectious and parasitic diseases such as tuberculosis, hanseniasis, and visceral leishmaniasis. It should be mentioned that at study entry, patients in the systemic category had only joint features.

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An ACR-Pedi30 response was achieved by 28 of our patients (65%). A previous longterm open-label trial with LEF in polyarticular patients with JIA produced a similar response. However, a response greater than ACR-Pedi50

<table>
<thead>
<tr>
<th>Category</th>
<th>n (%)</th>
<th>Baseline DAS28, mean ± SD</th>
<th>Final DAS28, mean ± SD</th>
<th>Discontinued LEF, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligoarticular persistent</td>
<td>3 (7)</td>
<td>5.46 ± 0.4</td>
<td>4.41 ± 1.1</td>
<td>2</td>
</tr>
<tr>
<td>Oligoarticular extended</td>
<td>7 (16)</td>
<td>5.67 ± 0.8</td>
<td>4.1 ± 1.4</td>
<td>4</td>
</tr>
<tr>
<td>Polyarticular RF+</td>
<td>15 (35)</td>
<td>5.46 ± 0.67</td>
<td>3.4 ± 0.96</td>
<td>4</td>
</tr>
<tr>
<td>Polyarticular RF–</td>
<td>10 (23)</td>
<td>5.73 ± 0.6</td>
<td>4.12 ± 1.1</td>
<td>7</td>
</tr>
<tr>
<td>Enthesitis-related</td>
<td>2 (5)</td>
<td>5.1 ± 0.2</td>
<td>3.1 ± 0.7</td>
<td>1</td>
</tr>
<tr>
<td>Systemic</td>
<td>6 (14)</td>
<td>5.71 ± 0.7</td>
<td>2.69 ± 1</td>
<td>1</td>
</tr>
</tbody>
</table>

DAS28: 28–joint Disease Activity Score; RF: rheumatoid factor.

Table 5. American College of Rheumatology Pediatric response (ACR-Pedi) in 43 patients with juvenile idiopathic arthritis treated with leflunomide.

<table>
<thead>
<tr>
<th>Categories</th>
<th>n</th>
<th>ACR-Pedi &lt; 30</th>
<th>ACR-Pedi30</th>
<th>ACR-Pedi50</th>
<th>ACR-Pedi70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Polyarticular RF+</td>
<td>10</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Polyarticular RF–</td>
<td>15</td>
<td>6</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Oligoarticular persistent</td>
<td>3</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Oligoarticular extended</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Enthesitis-related</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>43</td>
<td>15</td>
<td>16</td>
<td>8</td>
<td>4</td>
</tr>
</tbody>
</table>

RF: rheumatoid factor.
was seen in only 29.7% of our patients, as compared to 47% in that trial. We cannot exclude the possibility that persistence with LEF could have resulted in further improvement in those who achieved a partial response in the first 6 months.

Notwithstanding the clinical response, the safety profile was excellent. It has to be stressed that most of our patients used LEF concomitant to MTX and that only 6 of them, regardless of whether they used LEF as an add-on or monotherapy, had to definitively discontinue LEF because of adverse events. In addition, we had no hospitalizations or deaths during the protocol. Laboratory alterations were also not relevant, meaning that there were no significant changes in blood cell counts or routine biochemistry. Liver enzymes elevations were mild and led to definitive discontinuation in only 3 of the 43 exposed patients. As mentioned, those patients were under close surveillance both by a pediatrician and a rheumatologist. Therefore, the possibility of uncheckered serious infections, malignancies, or other serious adverse events was low. What probably accounted for these safety data were avoiding the use of an LEF loading dose, adherence to dosage using a previously suggested protocol and close surveillance, and using the treat-to-target monthly approach to aim for low disease activity. We had no pregnancies during the study period. However, it is necessary to collect longterm data on our patients who received LEF, with special attention to girls, aiming to detect a possible negative effect on pregnancy outcomes in the future.

Biologic therapy is a mainstay in the treatment of RA and also in patients with JIA refractory to MTX, providing an ACR-Pedi response in clinical trials over 70%. A trial using an antinterleukin 6 antibody in patients with systemic JIA reported that 80% achieved at least 70% improvement. Therefore, our results with LEF seem modest, especially for a higher ACR-Pedi response. However, a possible increased risk of the incidence of adverse events, with special concern about infections, malignancies, and induction of autoimmune phenomena, still requires attention when using biologics.

Using DAS28 can be seen as a limitation of our study, as discussed. Being an open-label trial may also have influenced clinical evaluation. One major limitation, however, could be achievement of an ambitious primary outcome in the first 6 months. This strategy may have prematurely excluded patients with a partial response to LEF who could have improved later. However, current experience with LEF in JIA is scant. Therefore, despite limitations, our data reflect a real-life experience, adding support to an acceptable safety profile with the longterm use of LEF, under close scrutiny, in patients with JIA.

This is the first report, to our knowledge, on the prospective evaluation of LEF use in patients with an equatorial nonwhite ancestry. Moreover, to our knowledge, this is the largest and longest clinical protocol of LEF use in JIA. In addition to showing a statistically significant response, based on the baseline and final DAS28 scores, we believe that our results are clinically relevant. The reasons for this are both the improvement obtained and a documentation of an acceptable safety profile. When evaluating our experience (including our unpublished observations) with the treatment of patients with JIA, after combining the number of patients achieving a low DAS28 or clinical remission, our conservative estimate is that around two-thirds of our patients have a clinically manageable disease with the use of LEF, either alone or combined with MTX and low-dose steroids. LEF is an effective and safe option that appears worthwhile for patients with JIA who are considered unresponsive or intolerant of MTX prior to starting biologics.

REFERENCES