Leflunomide in juvenile idiopathic arthritis

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The gold standard of therapy for patients with juvenile idiopathic arthritis (JIA), previously referred to as juvenile rheumatoid arthritis (JRA), has been methotrexate and, if methotrexate fails, a biological agent. Leflunomide, an oral pyrimidine synthesis inhibitor, has been shown to be well tolerated and effective in both short-term and long-term studies of adult rheumatoid arthritis (RA). This article reviews the current state-of-the-art use of leflunomide in JIA. A Phase Ib study demonstrated that leflunomide is effective in patients who have either failed methotrexate or are intolerant of methotrexate (50% American College Rheumatology [ACR] Pedi 30). Following the encouraging results of this initial study, a large, multicentered comparator study of leflunomide versus methotrexate was performed. This study demonstrated that both drugs had excellent response rates (ACR Pedi 30 rates of 68 and 89%, respectively) although there was a statistically significant higher response rate for methotrexate.

Keywords: drug therapy, drug trials, inflammatory arthritis, juvenile idiopathic arthritis, juvenile rheumatoid arthritis, leflunomide, outcomes, pediatrics

future medicine

Leflunomide (Arava®) is an oral pyrimidine synthesis inhibitor that takes effect via its active metabolite. This metabolite inhibits both dihydroorotate dehydrogenase (DHODH) and tyrosine kinases. The major effect is via DHODH inhibition of *de novo* uridine monophosphate synthesis rather than tyrosine kinase inhibition. The inability to synthesize uridine ribonucleotides leads to arrest at the G_1 phase and decreased lymphocyte activation and proliferation [1]. In 1998, randomized controlled studies from both Europe and North America demonstrated that leflunomide decreased the number of tender and swollen joints, improved patient pain and physical function, and decreased x-ray progression in adult patients with rheumatoid arthritis (RA). These improved outcomes were equivalent to those observed with methotrexate and sulphasalazine, and superior to placebo [2–4]. Long-term treatment demonstrated that the efficacy and tolerability of leflunomide was maintained over 12 and 24 months with continued inhibition of radiographic progression [5–7]. A meta-analysis of six randomized controlled trials, totaling 2044 patients with RA, confirmed that leflunomide improved all clinical outcomes and delayed radiographic progression at both 6 and 12 months of RA, with an efficacy and safety profile at 2 years comparable to methotrexate and sulphasalazine [8]. Improvement in health-related quality of life (HRQOL) was demonstrated at 6 months and sustained over 2 years with improvements in both mental and physical domains of Medical Outcomes Survey Short Form-36 (SF-36) [9,10]. Most recently, data from a 5-year follow-up have demonstrated the durability of response and radiographic benefit with leflunomide [11].

Following these studies, an open-label series and subsequent randomized controlled trial confirmed the benefit of leflunomide in combination with methotrexate in patients with persistently active RA [12]. As methotrexate and leflunomide have similar adverse event profiles, there were concerns about increased liver toxicity (see section on adverse events), which were not confirmed. The response to combination therapy was superior to continued treatment with methotrexate alone. Similarly, studies with an increased dose to 40 mg/day from 20 mg/day was generally well tolerated without a significant increase in adverse events [13].

Based on the efficacy and safety profile of leflunomide, studies in juvenile idiopathic arthritis (JIA) were performed. These are the subject of this review.

Pilot study

The initial study was open-label and had a 26-week duration with a further 2-year extension phase to examine the safety and efficacy of leflunomide in polyarticular course JIA [14]. A total of 27 patients with long-standing polyarticular course JIA who had either failed methotrexate or were intolerant of methotrexate entered initial treatment and 17 proceeded into the extension phase. All 27 patients had active polyarticular course JIA (at least five active joints), with a mean disease duration at study entry of 6.9 years. The most common diagnoses

were rheumatoid factor (RF)-negative polyarticular JIA, found in 40% of patients, RF-positive polyarticular JIA in 30%, extended oligoarticular JIA in 22% and systemic JIA in 8%. Patients had received methotrexate for a mean of 36.0 months prior to study entry.

Following a loading dose, patients were initially started on a dose of 10 mg/1.73 m^2/day, which could be increased to 20 mg/1.73 m^2/day (maximum 20 mg/day) if tolerated in the event of poor responses. Two patients discontinued study treatment prior to dose escalation; 20 of the remaining 25 (80%) required a dose escalation.

Initial 26 weeks

The primary outcome variable used was the American College of Rheumatology (ACR) Pedi 30. A patient meets the ACR Pedi 30 definition of response if at least three of the core set variables had at least 30% improvement (a percent change from baseline ≤ 30%), and no more than one core set measure worsened by 30% or more (percent change from baseline ≥ 30%). The core set variables are: number of active joints, number of joints with limited range of motion, physician global assessment, patient/parent global assessment, Childhood Health Assessment Questionnaire disability index (CHAQ/DI) and the erythrocyte sedimentation rate (ESR). Similarly, a patient met the ACR Pedi 50 and ACR Pedi 70 when the response rates have a minimum of 50% and 70% improvement, respectively.

Of the 27 patients, 17 (63%) completed 26 weeks treatment; in 14 of 17 (82%), ACR Pedi 30 response criteria were met. Using last observation carried forward (LOCF) analysis in the intend-to-treat population, 52% of the initial cohort were responders; 30% ACR Pedi 50 and 19% ACR Pedi 70 responders. Mean change in physician global assessment of disease activity was -2.14, with a mean decrease in active joints of 5 or 19%. There was a significant and clinically meaningful decrease in mean CHAQ scores from 1.33 to 1.07.

Extension phase

In total, 17 patients entered the extension phase; nine (53%) completed 30 months of study treatment. Five patients withdrew because of failure to maintain efficacy, one because of an adverse event and two withdrew their consent. Using an LOCF analysis, 65% patients met ACR Pedi 30 response criteria at 1 and 2 years, and 53% at study completion; 47% of the patients were ACR Pedi 50, and 24% were ACR Pedi 70 responders at 2 years. Mean changes in physician global assessment of disease activity was -2.1 and patient/parent global assessment was -1.3; the mean decrease in number of swollen joints was 6.9. Importantly, CHAQ scores decreased by an additional 0.36.

Overall, a response rate of 52% was observed after 26 weeks of treatment, which was durable as 53% of patients who entered into the extension phase were responders at the end of the study (30 months) [14].

Controlled, blinded pivotal trial

Following the results of the pilot study above, a multicenter, multinational, randomized active controlled trial was initiated to compare the safety and efficacy of leflunomide with methotrexate, as a placebo-controlled trial was not considered ethical. A total of 94 methotrexate and leflunomide naive patients with active polyarticular-course JIA were enrolled with 86 (91%) completing the initial 16 week trial.

Following a loading dose of 100 mg/day of leflunomide for 1, 2 or 3 days in patients weighing less than 20 kg, 20–40 kg, or greater than 40 kg, respectively, patients received daily maintenance doses of 10 mg every other day, 10 mg/day, or 20 mg/day, respectively. A single dose level of methotrexate (0.5mg/kg/week; maximum 25 mg per week) was selected, which was similar to or higher than utilized in previous trials in JIA.

Of the 47 patients randomized to receive leflunomide, 42 (89%) completed 16 weeks of treatment. At week 16, there were 68% ACR Pedi 30 responders, 60% ACR Pedi 50 responded and 43% ACR Pedi 70 responders. Mean decreases were 8.1 in the number of active joints (54% decrease), 5.2 in joints with limitation of motion (68%), 31.5 in physician global assessment of disease activity (60% decrease), 15.9 in patient/parent global assessment (44% decrease), and 6.5 in ESR (22%) (Table 1). Importantly, the CHAQ decreased by 0.44 from a mean baseline of 1.00 (44% decrease). The changes in the individual parameters of the ACR Pedi 30 were similar in the leflunomide and methotrexate groups.

Using the percent improvement index (PII), a continuous measure comprised of all the components of the ACR Pedi 30 criteria, there was a 44.4% improvement with leflunomide compared with 52.9% with methotrexate. This indicates that, on average, each patient improved by 44.4% in all of the parameters of the ACR Pedi response criteria with leflunomide treatment and

Table 1. Mean changes in core set variables at week 16.

Core set variables	Leflunomide			Methotrexate			p-value
	n	*Baseline mean (SD)*	*Change at week 16 mean (SD)*	*n*	*Baseline mean (SD)*	*Change at week 16 mean (SD)*	
Number of active joints	47	14.2 (1.45)	-8.1 (0.99)	47	14.2 (1.42)	-8.9 (0.96)	0.5671
Number of joints with limited ROM	47	7.6 (0.97)	-5.2 (0.81)	47	8.8 (0.94)	-5.3 (0.79)	0.9157
Physician global assessment (mm)	47	52.4 (2.82)	-31.5 (2.98)	47	47.2 (2.75)	-32.1 (2.94)	0.8884
Patient global assessment (mm)	47	36.5 (4.09)	-15.9 (2.97)	47	36.2 (3.99)	-22.0 (2.89)	0.1359
CHAQ DI	47	1.00 (0.114)	-0.44 (0.075)	47	1.11 (0.11)	-0.39 (0.73)	0.6060
ESR (mm/h)	43	29.5 (3.26)	-6.5 (1.28)	45	34.7 (3.08)	-7.2 (1.20)	0.6588

CHAQ DI: Childhood Health Assessment Questionnaire; ESR: Erythrocyte sedimentation rate; ROM: Range of movement; SD: Standard deviation.

52.9% with methotrexate. At week 16, 68% of patients were ACR Pedi 30 responders with leflunomide, 60% were ACR Pedi 50; and 43% were ACR Pedi 70; compared with 89, 77 and 60% with methotrexate, respectively.

Of the 42 patients who completed the initial 16 weeks, 33 (79%) entered into a 32-week extension phase. The major reason for failure to enter the extension phase was the inability of some centers to obtain Research Ethics Board Approval of the protocol prior to the end of the study. Of the 33 patients who entered the extension phase receiving leflunomide, ACR Pedi 30 responders were 79%, ACR Pedi 50 were 76% and ACR Pedi 70 were 70%; indicating that improvements achieved at week 16 were maintained at week 48. This was similarly true for methotrexate: 91% were ACR Pedi 30, 86% were ACR Pedi 50 and 83% were ACR Pedi 70. Using the PII, the average improvement in the leflunomide group was 55.4 and 65.5% in the methotrexate group.

Although PII and ACR Pedi responses were higher with methotrexate, these may be in part attributed to the leflunomide doses that were administered, which, following formal pharmacokinetic analysis of the open-label JIA trial, were demonstrated to be too low. This was further confirmed by increases in responses over time in the leflunomide treatment group compared with stabilization and/or decreased responses with methotrexate.

Leflunomide plus methotrexate

The first published article of the use leflunomide in combination with methotrexate in pediatric patients with JIA described 40 Chinese patients with active polyarthritis JIA; 21 received 0.2–0.4 mg/kg/day of leflunomide plus intravenous methotrexate every 2 weeks, while the other 19 received only methotrexate. The outcome used some of the components of ACR Pedi 30 as well as other measures. Specifically, they examined changes in:

- Number of tender and swollen joints
- Tender articular index
- Swollen articular index
- General articular function score
- Parent global assessment
- Physician global assessment
- Erythrocyte sedimentation rate
- C-reactive protein
- Rheumatoid factor

Outcome

Patients receiving combination therapy had response rates of 39.6 and 71.9% at weeks 12 and 24, respectively, which is statistically superior to methotrexate alone (27.5% and 49.5%; $p < 0.01$). Of note, 4.8 and 38.1% of patients treated with the combination had no active disease at 12 and 24 weeks, respectively, versus none of the methotrexate-treated group at either of these times. There was a trend for a higher rate of adverse events with combination therapy that was not statistically significantly different; 9.5% compared with 5.3% for methotrexate alone. The most common adverse events reported were leukopenia and elevated liver enzymes, which were mild and generally did not require any change in therapy [15]. However, it must be noted that the dose of methotrexate used in this study was lower than the convention dose of 0.3–0.5 mg/kg/week and there was no control arm of leflunomide alone.

Pharmacokinetics

Leflunomide is rapidly metabolized into an active metabolite, which is referred to as A77 1726 or M1. In adult patients with RA, the bioavailability of this metabolite shows a large variability, with a two-log range in adult patients receiving the same dose [16]. M1 has linear pharmacokinetics and a long half-life of approximately 10–14 days; approximately 90% of a single dose of leflunomide is eliminated after a single dose [17]. In patients with RA, lower serum concentrations were generally associated with poorer responses, but there were no clear correlations between blood levels and efficacy and/or adverse events [18].

The long half-life of leflunomide enabled daily dosing, although longer intervals between doses may be warranted. All initial studies of leflunomide in adult RA utilized a loading dose of leflunomide, which may have resulted in a more rapid onset of efficacy, as early as 2 weeks. However, elimination of the loading dose was generally associated with a lower rate of adverse events and improved overall compliance without observable changes in efficacy [19]. The currently recommended adult dose of leflunomide is 20 mg/day. There has been one postmarketing study that examined the efficacy of once-weekly leflunomide at a dose of 100 mg/week. This study demonstrated similar efficacy as 20 mg/day without an increase in severe adverse events and better compliance [20–22]. Regardless of dosing schedule, most rheumatologists no longer use a loading dose.

As part of the initial North American pediatric study, formal pharmacokinetic data were obtained. Based on the initial evaluation of these data, the recommended dosing of leflunomide for the pivotal was determined to be 10 mg every other day for patients up to 20 kg; 10 mg/day for 20–30 kg; 10 mg/day alternating with 20 mg/day for 30–40 kg, and full adult dose of 20 mg/day for patients greater or equal to 40 kg. Using data from 674 samples of MI in 73 patients in the second study, a population pharmacokinetic (PPK) study indicated a one-compartment model with first-order kinetics [23]. Body weight correlated strongly with volume of distribution, but weakly with clearance. The mean steady-state concentration of M1 in patients greater than 40 kg was 38.9 µg/ml, which is comparable to levels in adults following administration of 20 mg/day. Mean levels decreased to 30.0 µg/ml in patients weighing 20–40 kg, and only 14.5 µg/ml in patients weighing less than 20 kg.

Of note, in our study, patients weighing less than 40 kg had the highest ACR Pedi 30 response rates, followed by those between 20–40 kg. Patients weighing greater than 20 kg had the lowest response rates. The overall model suggested that higher doses be administered to patients; 10 mg/day for patients between 10–20 kg, 15 mg/day for patients between 20–40 kg, and the adult dose of 20 mg/day for patients greater than 40 kg. However, similarly to studies in adults, there was a great variability in the bioavailability of M1 [23,24].

Dosing of leflunomide

- Less than 20 kg: 10 mg on alternative days
- 20–30 kg: 10 mg/day
- 30–40 kg: 10 mg alternating with 20 mg or 15 mg/day
- More than 40 kg: 20 mg/day

Leflunomide can be crushed and mixed with food for improved compliance in children who can not swallow tablets. Although a loading dose was initially advocated in order to decrease the time to respond, it was found to increase the gastrointestinal (GI) toxicity and, therefore, is generally not warranted. The pharmacokinetic data would suggest that higher doses may be more effective in patients weighing less than 30 kg, however, there is currently no safety data using a higher dose. Therefore, if a higher dose of leflunomide is used then vigilant screening for adverse events is warranted.

Adverse events

Overview of adult studies

In adult trials, the most common adverse events were GI complaints (diarrhea and nausea), skin rash, reversible alopecia, hematologic and liver function test (LFT; transaminase) elevations [2–4]. No evidence of new or increased toxicity was demonstrated by 2-year follow-up data [6]. Diarrhea, nausea and alopecia were less frequently observed with continued treatment [7]. Hypertension has also been reported, but is rare and has no effect on renal function [25].

An observational study reviewing 40,594 RA patients, with accumulated 83,143 patient-years follow-up, showed that the reported incidence rate of all adverse events was lower for leflunomide monotherapy than methotrexate, including a lower rate of hepatic events. Even in combination with methotrexate the adverse event rate with leflunomide administration was lower than or comparable to the rates seen with methotrexate

and other agents [26]. One report suggested that the risk of hepatotoxicity with leflunomide was related to CYP2C9 polymorphism [27]. In 2004, an expert panel considered the adverse events associated with leflunomide to be manageable and predictable and that they would diminish in severity with continued treatment [28]. Although it is likely that the safety and efficacy profile would be similar to that seen in RA, there is limited data on the safety and efficacy of use of combination methotrexate and leflunomide in JIA.

Longerterm postmarketing surveillance indicated peripheral neuropathy could be observed, which usually improved if leflunomide was stopped [29–33]. Cutaneous reactions, which included vasculitis, ulceration, erythema multiforme-like eruptions, exfoliative dermatitis, subacute cutaneous lupus erythematosus and alopecia areata were reported [34–42]. Development of interstitial lung disease was reported in Japanese patients with an incidence possibly as high as approximately 1.1% [43–46]. Of interest, the majority of these patients were male and smokers and most of whom had pre-existing interstitial lung disease. Similar adverse events have not been reported in JIA, but may be due to far fewer patient–years of therapy.

Although the adverse event rate, even in combination with methotrexate, has been reported to be comparable to those with methotrexate and other agents, careful monitoring of liver and hematologic parameters is required [19,26,47].

Liver function test abnormalities

One of the major concerns regarding the use of leflunomide is the development of LFT abnormalities; cirrhosis has not been documented and few cases of liver failure have been related to this therapy. In the uncontrolled open label extension study in JIA, one of the 27 patients stopped leflunomide as a result of elevated LFTs. In the controlled trial, involving JIA patients, LFT elevations greater than 1.2-times upper limit of normal (ULN) were seen in eight patients (14.9%) treated with leflunomide and 11 patients treated with methotrexate; all normalized without change in dosage. Similarly, LFT elevations 2–3-times ULN occurred in two patients treated with leflunomide and in three patients treated with methotrexate. All LFT elevations resolved without change in medication dose. Only one patient treated with leflunomide had LFT elevations that required treatment discontinuation (ALT >7 × ULN and AST 3.1 × ULN, while six patients treated with methotrexate had LFT elevations of >3 × ULN), which required temporary treatment discontinuation in three patients. The three remaining patients were withdrawn from the study.

Gastrointestinal

In adult trials, GI adverse events were generally mild. In the two pediatric studies, GI complaints were reported in approximately 50% of patients. Abdominal pain was usually mild-moderate, of at least 7 days duration and resolved in all but two patients despite continuing treatment. For the two patients in whom abdominal pain was accompanied by nausea and diarrhea, leflunomide administration was discontinued. Overall, diarrhea was the most common adverse event of leflunomide in the treatment of JRA (Table 2). However, cases were generally mild, self-limited, and the majority occurred within the first three months of therapy, with spontaneous improvement also observed in adult trials. Diarrhea was only occasionally related to the loading dose. Mild gastritis or gastroenteritis was reported in three patients, medication was held in only one and then restarted without recurrence. One patient suffered mild stomatitis while another developed mouth ulcerations, which resolved without change in study medication.

Abdominal pain was observed in seven patients treated with methotrexate and nausea in 23 patients. None of these patients required a permanent discontinuation of methotrexate. Diarrhea was seen in eight patients in the methotrexate group.

Although only occasionally observed in adults and not documented in the Phase III trials, weight loss (>10% of body weight) without diarrhea was seen in 7% (n = 3) of patients in the controlled trial [48]. It is not clear whether this weight loss is secondary to leflunomide or other factors. One patient was diagnosed with Crohn's disease instead of JIA at week 8. The only withdrawal in the extension phase was ulcerative colitis, which developed more than 1 year after starting leflunomide and 12 years after diagnosis of JIA. In adults, there was report of two patients who developed severe diarrhea 12 months after starting leflunomide. In both cases, the symptoms were caused by biopsy-proven colitis (one case of ulcerative and one nonspecific microscopic colitis) [49].

Hematologic

Thrombocytopenia, leukopenia and pancytopenia have rarely been reported in adults with RA following leflunomide administration. Of note, an Australian survey in 2004 reported 14 cases of

Table 2. Adverse events likely related to medication in the Comparator Study.

Adverse event	Initial phase (weeks 0–16)		Extension phase (weeks 16–32)	
	Leflunomide n = 47 (%)	*Methotrexate n = 47 (%)*	*Leflunomide n = 33 (%)*	*Methotrexate n = 37 (%)*
Gastrointestinal symptoms				
Abdominal pain	12 (25)	5 (11)	3 (9)	1 (3)
Diarrhea	7 (14.9)	8 (17.0)	2 (6.1)	1 (2.7)
Nausea	10 (21.3)	12 (25.5)	0	1 (2.7)
Alopecia	7 (15)	3 (6)	3 (9)	0
Acute liver injury elevation				
>1.2 × upper limit of normal	7 (15)	15 (32)	5 (15)	11 (30)
>3 × upper limit of normal	1 (2)	3 (6)	0	3 (8)
Cough	5 (10.6)	0	1 (3.0)	2 (5.4)
Dizziness	3 (6.4)	2 (4.3)	1 (3.0)	0
Fatigue	2 (4.3)	4 (8.5)	1 (3.0)	3 (8.1)

reversible pancytopenia in patients treated with leflunomide, ten of whom received combined treatment with methotrexate; as similarly reported by others [50–52].

As in the adult randomized controlled trials (RCTs), no cases of pancytopenia were reported. Anemia was the only common hematologic abnormality detected and, whether secondary to the disease process or its treatment, they generally resolved without change in leflunomide dose. Anemia was seen in two patients treated with methotrexate. One patient in each group had leukopenia, which spontaneously resolved without a change in leflunomide dose. Thrombocytosis and leukocytosis likely secondary to active JIA were also observed in both groups. None of the patient in the study developed thrombocytopenia.

Skin

Alopecia, a reported adverse event in adults, was observed in seven patients (14.9%) in the JIA study (Table 2). The alopecia was mild in six patients and moderate in one. However, the alopecia resolved in all cases without a change in leflunomide dose. Five of the seven cases of alopecia occurred in the first month. Three of the patients treated with methotrexate developed alopecia, which resolved without change in medication. Three patients (6.4%) had an unspecified rash and a further three had rashes that were described as exanthem, acne, dermatitis or vesiculobullous eruption. There was only one severe rash diagnosed as pityriasis lichenoides, which was felt to be either idiopathic or related to an infection. The leflunomide was stopped, but the rash continued, while in the other patients the rashes resolved while continuing on leflunomide. Three patients treated with methotrexate developed an unspecified rash, two patients had an exanthem, two patients had a papular rash, acne and dry skin, and erythema in one patient each.

Infection

In the JIA trials, infections were generally self-limited and resolved without stopping either leflunomide or methotrexate. However, there was one case of cellulitis requiring hospitalization and one case of herpes zoster requiring antiviral therapy in the leflunomide group. In both cases, leflunomide was temporarily stopped and treatment resumed without recurrence. One patient treated with methotrexate temporarily discontinued medication due to infection with Epstein–Barr virus (EBV).

Adverse events requiring treatment interruptions

In the initial study, leflunomide was temporarily stopped in 11 patients for adverse events and then estarted with no recurrence of the adverse event in the majority of patients. These events were rash, herpes zoster, flu-like illness, GI distress and anemia. In the controlled trial, leflunomide was temporarily stopped in five of 47 patients (10.6%); three patients as the result of an infection and in two patients for GI distress. All patients resumed leflunomide without recurrence. In the methotrexate group, three patients had temporary discontinuation due to elevated liver enzymes; one for GI distress, one for EBV infection and one for erythema of toes. All patients resumed methotrexate without recurrence.

Adverse events leading to study withdrawal

In the pilot study, one patient withdrew from the study due to hypertension, as has been reported in adults with RA [25]. In the pivotal study, there were three serious adverse events requiring treatment withdrawal; one abnormal LFT; one suspected infection; and one parapsoriasis. Two additional patients withdrew citing the development of colitis. In the methotrexate group, four patients discontinued treatment as a result of elevated liver enzymes, one for GI distress and one for infection. There were no withdrawals due to renal or hematologic abnormalities in either group.

Summary

The current data strongly suggest that leflunomide has an efficacy and safety profile in JIA that is similar to that observed in adult RA and has a role in the therapy of polyarticular-course JIA. The pivotal trial that compared leflunomide to methotrexate demonstrated that both drugs had excellent response rates in patients with early polyarticular course JIA. The response rates exceeded initial expectations. However, there was a statistically significantly higher percentage of patients who met the ACR Pedi 30 response criteria in the methotrexate group as compared with the leflunomide group, although the individual components of the Pedi 30 were not significantly different between the groups. The response to leflunomide was durable, as demonstrated in the extension phase. The safety profiles were similar, although patients on methotrexate tended to have more frequent LFT abnormalities.

The data from the pilot study of patients who were either intolerant of methotrexate or had an unsatisfactory response to methotrexate demonstrated a good response to leflunomide in approximately half of the patients. These patients tended to have a long duration of JIA. Lastly, a small study using the combination of methotrexate and leflunomide demonstrated that patients treated with both medications had a better response than patients treated with methotrexate alone. As observed in studies of adult RA, the side-effect profiles were similar between the two therapies, but this was a small, short-term study and the safety data must be taken within this context.

Conclusion

Overall the data would suggest that leflunomide is a well tolerated and efficacious drug in children with polyarticular-course JIA. The current recommendation would be to use leflunomide in patients with polyarticular-course JIA who are either intolerant to methotrexate or who do not have a satisfactory response to methotrexate. It should be considered prior to the use of a biologic agent. As clinicians become more familiar with the safety and efficacy profile of leflunomide, it is likely that this drug will gain a wider usage in JIA. However, it must be remembered that leflunomide currently does not have regulatory approval for the treatment of JIA and therefore its use in pediatrics must be considered off label.

The preliminary data suggest that a combination of leflunomide and methotrexate is superior to methotrexate alone and does not significantly increase the rate of adverse events. However, patients treated with the combination of the two drugs should be carefully monitored for liver enzyme and hematological abnormalities, and a large study of the combination of these drugs is required prior to advocating the routine use of the combination prior to the use of a biologic agent.

Finally, there is very little safety or efficacy data in patients with systemic JIA who have polyarthritis. It should be used with caution in patients who are systemically active as these patients tend to have a higher rate of, and more severe forms of, adverse events than patients with other JIA subtypes.

Future perspective

It was less than 20 years ago, in the premethotrexate era, that there was no disease-modifying drug that worked in JIA. However, in the past 5–10 years, the number of potential therapies for the treatment of patients with JIA has significantly increased. The current state is such that methotrexate still remains the first disease-modifying drug that clinicians should use in the treatment of JIA. However, safety and efficacy profile of leflunomide suggests that it should be used prior to the use of biologic agents. There are no data on the pediatric safety of leflunomide when used in combination with biologic agents. The overall future is very bright for the treatment of JIA and the goal of many clinicians is complete disease remission. However, the treatment of patients with systemic JIA still remains a challenge.

Disclosure

During the course of the pilot study in JIA and the leflunomide versus methotrexate study in JIA, Earl Silverman was a consultant to Aventis Pharmaceuticals. Vibeke Strand has also served as consultant to Sanofi-Aventis and many other pharmaceutical companies.

Executive summary

Mechanism of action

- Major effect by inhibition of dihydroorotate dehydrogenase.
- Arrest in G_1 phase and decreased lymphocyte activation.

Clinical efficacy

- Active comparator study demonstrated a 68% American College of Rheumatology (ACR) Pedi 30 response; 60% ACR Pedi 50 response and 43% ACR Pedi 70 response.
- Efficacy was durable in the extension phase with a 79% ACR Pedi 30 response, a 76% ACR Pedi 50 response and a 70% ACR Pedi 70 response.
- In the initial trial, 50% of patients unresponsive or intolerant of methotrexate responded to leflunomide.

Safety

- Common toxicities are diarrhea, gastrointestinal distress and alopecia. In the majority of cases, the adverse events resolved either spontaneously or following dose reduction.
- Major laboratory toxicity is elevation of liver function tests, although hematological abnormalities have been reported in adult studies.

Dosing

- For those weighing less than 20 kg: 10 mg on alternative days.
- For those weighing 20–30 kg: 10 mg/day.
- For those weighing 30–40 kg: 10 mg alternating with 20 or 15 mg/day.
- For those weighing greater than 40 kg: 20 mg/day.
- Generally, a loading dose is not warranted.

Recommendation

- Use leflunomide in patients intolerant of methotrexate.
- Use leflunomide in patients who have an inadequate response to methotrexate.
- Use leflunomide prior to the use of a biologic agents.
- Use leflunomide with caution in patients with systemic juvenile idiopathic arthritis who have active systemic features.

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