Evaluation of the benefits of sequential addition of leflunomide in patients with polyarticular course juvenile idiopathic arthritis failing standard dose methotrexate

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Abstract

Objective

To evaluate the benefits of the addition of leflunomide (LEF) in children with polyarticular course juvenile idiopathic arthritis (JIA), non-responsive to standard dose parenteral methotrexate (MTX).

Methods

In an observational study, 32 children with polyarticular course JIA failing standard dose MTX (up to 15 mg/m^2/week sc for at least 3 and up to 6 months) received additional LEF. Permitted concomitant drugs included pulse steroids for flares and/or low bridging dose of prednisolone, intra-articular steroids and non-steroidal anti-inflammatory drugs. No other DMARDs had been used before enrolment. Patients underwent 8–12 weekly assessment. At each visit, core set of outcome variables and laboratory parameters, viz. haemogram and liver enzymes were recorded. The primary efficacy outcome was the ACR Pedi 30 criteria. At the last follow up, Wallace's criteria were used to determine children achieving remission.

Results

25 of 32 children who followed up for at least 3 months were analysed. Mean follow up duration following addition of LEF was 1.61 years (range: 0.29 to 3.0 years). At 3 months, 68% of the patients met the ACR Pedi 30 response. 17 of the 20 children (85%) showed an ACR Pedi 30 response at 6 months and 16 out of 18 (88.8%) at 1 year. Of the 18 children followed up till the end of the study, 12 (66.6%) met the ACR Pedi 30 criteria and 9 (50%) were in clinical remission on medications (off steroids). Adverse effects were observed in 2 children (gastritis in one and elevated liver enzymes in the other).

Conclusion

Our findings support further study of the role of this combination in the management of polyarticular course JIA refractory to standard dose MTX, especially in resource challenged settings where biologicals are unaffordable. The open observational nature of the study is its limitation.

Key words

leflunomide, methotrexate, polyarticular course juvenile idiopathic arthritis

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Introduction

Methotrexate (MTX) is currently regarded as the disease-modifying anti-rheumatic drug (DMARD) of first choice in patients with polyarticular course JIA because of its excellent efficacy-toxicity profile (1). Methotrexate, an anti-folate agent, inhibits cytokine production and purine biosynthesis and also causes the release of adenosine, a potent anti-inflammatory agent (2). Long-term studies with MTX have shown that it is effective in 60–70% of JIA patients, with efficacy measured by the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30) improvement criteria (3, 4). A study by Ruperto *et al*. demonstrated that the plateau of efficacy of parenteral MTX in JIA is reached at a dosage of 15 mg/m^2/week, and that a further increase in dose is not associated with any additional therapeutic benefit (3).

As per the 2011 American College of Rheumatology (ACR) recommendations for the treatment of juvenile idiopathic arthritis, when MTX fails, the next step is to start biologicals (5). In resource-limited settings, this step is constrained by prohibitive cost and children failing MTX run the risk of poor disease control or steroid overuse. There is paucity of data on the use of other DMARDs (thalidomide, leflunomide, azathioprine, hydroxychloroquine, etc.) or their combinations in such children.

Leflunomide (LEF), a newer DMARD of the isoxazole class, acts by inhibiting dihydro-orotate dehydrogenase and preventing lymphocyte proliferation and differentiation. The active metabolite of leflunomide, A77 1726, inhibits dihydroorotate dehydrogenase, a critical enzyme for *de novo* production of pyrimidine (6-8). Since expansion of pyrimidine pools is required for mitogen induced T cell proliferation to proceed, the net effect of inhibition of pyrimidine synthesis is to halt this process, which is thought to be a key step in the pathogenesis of rheumatoid arthritis (RA) (9).

Given the high failure rate of RA monotherapy and the multi-factorial nature of pathogenesis of RA, an increasing emphasis is being placed on combinations of therapeutic agents which act to inhibit different pathophysiologic processes in the disease (10). The biochemical mechanisms of action of MTX and LEF in the treatment of JIA are quite different. The potentially complementary mechanisms of action of these two effective DMARDs should provide a rationale for their use in combination therapy for patients who do not respond adequately to methotrexate alone (2). This combination has been studied in adults (9, 11, 12) and their combined cost is a fraction of the cost of biologicals. As of now, a few studies involving the use of LEF in JIA have shown promising results (13-17). However, there is limited data (15) on the use of this combination in polyarticular course JIA.

Our objective was to evaluate the benefits of the *addition* of leflunomide to methotrexate in children with polyarticular course juvenile idiopathic arthritis who have suboptimal response to standard dose parenteral methotrexate.

Patients and methods

This study was carried out at the Paediatric Rheumatology Clinic, Jaslok Hospital & Research Centre, Mumbai, between April 2009 and May 2013.

For the purpose of this study, the term polyarticular-course juvenile idiopathic arthritis encompasses the International League of Associations for Rheumatology (ILAR) categories of extended oligoarthritis, rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarthritis, as well as patients with systemic onset juvenile idiopathic arthritis who have developed active arthritis in 5 or more joints in total during the course of their disease.

After obtaining due clearance from the hospital's ethics committee and informed consent from the parents, 32 children with polyarticular course JIA (systemic onset JIA – 30, polyarticular JIA-RF positive – 1, polyarticular JIA RF negative – 1 as per the ILAR criteria) with suboptimal response to methotrexate (up to 15 mg/m^2/week subcutaneously for at least 3 months) were enrolled on this study. All of them had been offered biologicals, but refused due to their prohibitive cost in a largely non-insured society with a low per

capita income. These children received additional leflunomide (per oral) as per their body weight. Patients weighing less than 20 kg received a loading dose of 100 mg of leflunomide for one day followed by a maintenance dose of 10 mg every other day. Those weighing between 20 and 40 kg received 100 mg of leflunomide for 2 days, followed by a maintenance dose of 10 mg per day. Those weighing more than 40 kg received 100 mg of leflunomide for 3 days, followed by a maintenance dose of 20 mg per day. The dosage of methotrexate was reduced to 10 mg/m^2/week s.c. at the time of addition of leflunomide in view of the potential hepatotoxicity of this combination. Concomitant folic acid supplement (1.25 mg daily) was administered to all patients to reduce toxicity associated with MTX therapy.

No other DMARDs were allowed during the study. Pulse steroids (methyl prednisolone), low dose bridge prednisolone, intra-articular steroids and non-steroidal anti-inflammatory drugs (NSAIDs) were allowed. The patients were assessed once every 8–12 weeks. The parameters recorded at baseline and each subsequent visit included the core set of outcome variables (physician global assessment of disease activity, parent/patient assessment of overall well-being, functional ability, number of joints with active arthritis, number of joints with limited range of motion and erythrocyte sedimentation rate). Adverse effects were monitored by clinical assessment for drug toxicity, haemogram and liver enzymes at each visit.

Outcome measures

Patients were evaluated for efficacy at 3 months, 6 months, 1 year from the point of addition of leflunomide and at the end of the study or follow-up. The primary efficacy outcome was the American College of Rheumatology (ACR) Pediatric 30 (Pedi 30) response. The ACR Pedi 30 criteria are defined as an improvement of ≥30% in at least 3 of 6 core variables and worsening of ≤30% in not more than one variable (4). At the end of follow-up, Wallace's criteria (18) were used to determine the percentage of children achieving remission.

Results

Patient characteristics

Thirty-two (17 male, 15 female) children with polyarticular course JIA, failing standard dose subcutaneous methotrexate (upto a maximum of 15 mg/m^2/week for at least 3 months) were enrolled on the study. The mean duration of disease at commencement of combination therapy was 3.6 years (range: 1.2–10 years) and mean duration of methotrexate therapy was 1.6 years (range: 0.5–6.2 years). The mean dosage of prednisolone (as maintenance therapy) was 0.275 mg/kg (range: 0–0.72 mg/kg).

Disease activity at commencement of combination therapy

The core set variables at the time of addition of leflunomide are summarised in Table I.

Pulse methyl prednisolone (30 mg/kg) was administered to 6 children at the time of initiation of the combination therapy, 2 of them receiving one additional pulse later during follow-up. These 6 children had systemic onset JIA with unremitting systemic features unresponsive to non-steroidal anti-inflammatory drugs and/or unrelenting polyarthritis with severe functional limitation. Four other children received pulse steroids during relapses while on combination therapy. Five children received at least one intra-articular (*i.a.*) injection (three received 2 *i.a.* injections) during the course of the study. However, no pulses or intra-articular injections were given within one month of the scheduled evaluation.

Efficacy

At the 3-month visit, 17 (68%) out of 25 children met the ACR Pedi 30 response. The mean follow-up duration for these 25 children with at least 3 months of combination therapy was 1.61 years (range: 0.29–3.0 years). As shown in the consort diagram (Fig. 1), seven children dropped out of the study in the first 3 months since the addition of leflunomide – 5 had irregular follow-up and 2 developed viral hepatitis-A.

Between 3 and 6 months, another 5 discontinued the study – 2 owing to lack of efficacy, one each due to lack of adherence and viral hepatitis A, while one patient developed macrophage activation syndrome (MAS) temporally related to the introduction of leflunomide. Seventeen (85%) of the 20 children who completed 6 months of combination therapy showed an ACR Pedi 30 response.

Eighteen children completed one year of combination therapy, one patient having dropped out of the study between 6 months and one year due to lack of efficacy, while another showing ACR Pedi 90 improvement had completed only 9 months of follow-up till the end of the study. At one year, the percentage of ACR Pedi 30 response was 88.8% with good response rates seen using the ACR Pedi 50 (83.3%), ACR Pedi 70 (61.1%) and ACR Pedi 90 (50%) criteria.

Of the 18 children who continued to the end of the study (follow-up duration more than 1 year), 12 (66.6%) met the ACR Pedi 30 criteria. These 12 children also met the ACR Pedi 50 and ACR Pedi 70 response criteria. ACR Pedi 90 response was seen in 11 (61.1%) children, who were also in clinical remission on medications as per Wallace's criteria. Steroids were discontinued in 9 of these 11 patients. Comparison of core set variables at commencement of the combination therapy and end of follow-up is shown

Table I. Core set variables at the commencement of combination therapy (n=32).

	Median (range)	Mean
Physician global assessment of disease activity (VAS 0-10)	5 (2-9)	5.26
Parent/patient assessment of overall wellbeing (VAS 0-10)	5 (0-9)	5.34
Functional ability (CHAQ)	0.562 (0-2.625)	0.76
Number of joints with active arthritis	3.5 (1-15)	4.47
Number of joints with limited range of motion	0 (0-14)	1.09
ESR (mm/1hr)	66 (16-125)	73.9

in Figure 2. The response rates to the combination therapy are represented graphically in Figure 3.

Of the 6 children with severe systemic onset JIA who had received pulse steroids at the commencement of combination therapy, 2 responded initially (at least ACR Pedi 30 response) but had a flare at the end of the study, 2 failed to show optimal response to the therapy, one patient developed viral hepatitis A necessitating discontinuation of the therapy and one patient was lost to follow-up.

Among the 13 patients who discontinued the study due to various reasons, 2 patients were switched to a combination of MTX with thalidomide, two received MTX with tocilizumab, two patients (including one who had developed viral hepatitis A) were restarted on MTX- LEF combination and 5 were lost to follow up. Of the other 2 patients in whom the combination was withdrawn due to viral hepatitis A, one succumbed to fulminant hepatic failure (as a complication of viral hepatitis), while the other patient died of macrophage activation syndrome a few months later.

Adverse effects

One child with systemic onset JIA developed macrophage activation syndrome 5 months after the addition of leflunomide. Minor adverse effects were observed in two children (one with gastritis and the other with elevated liver enzymes).

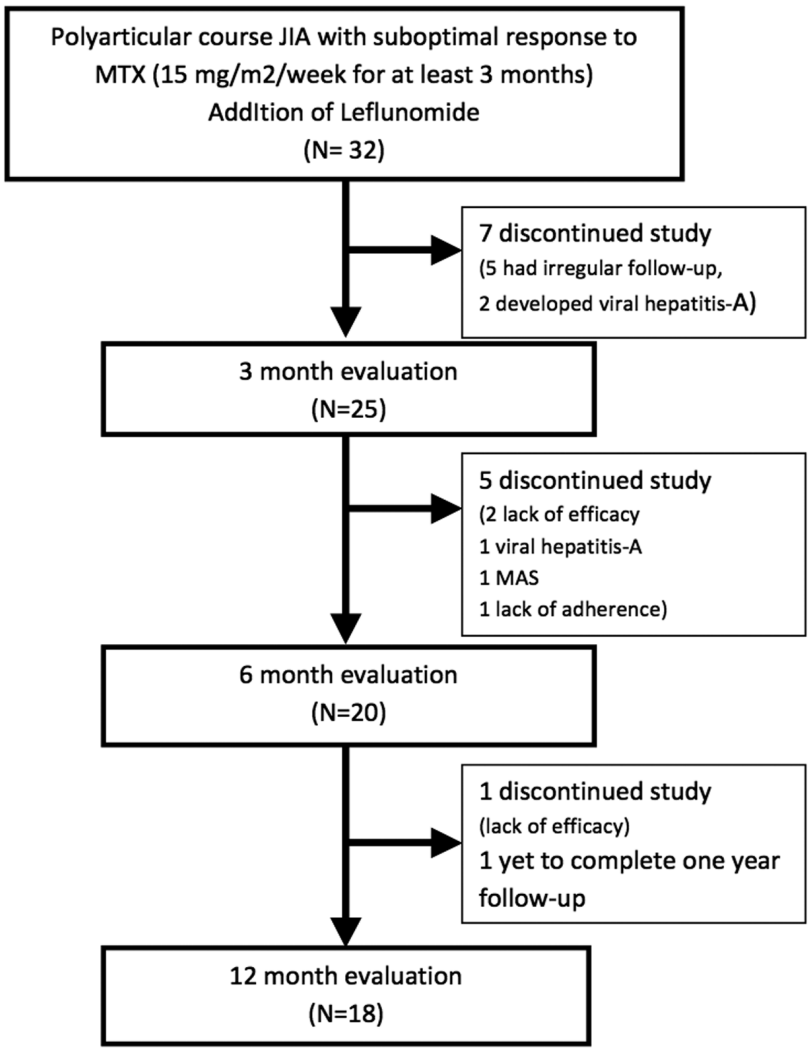

Fig. 1. CONSORT Diagram. Thirty-two patients failing MTX received additional LEF. The chart depicts the CONSORT diagram and status at 3, 6 and 12 months. (MTX: methotrexate; LEF: leflunomide; MAS: macrophage activation syndrome).

Discussion

Methotrexate (MTX), the most commonly used DMARD in JIA, is effective in about 60-70% of the patients when used at the standard dose (10-15 mg/m^2/week), with the maximum therapeutic effect usually becoming apparent 4 to 6 months after the initiation of therapy (19). The observation that a significant proportion of patients with polyarticular course JIA do not respond adequately to MTX monotherapy has led clinicians to resort to a combination of drugs, particularly MTX plus another DMARD, for the treatment of refractory disease. This is particularly relevant in resource – challenged settings, where the options are limited owing to the unaffordability of biologicals.

DMARDs used in combination therapy should have complementary mechanisms of action, non-additive toxicity, an acceptable dosing schedule, a rapid onset of action and should be cost-effective. While leflunomide inhibits pyrimidine biosynthesis, MTX primarily inhibits purine biosynthesis. Therefore, the rationale of combination therapy of these two DMARDs is based on their complementary mechanisms of action (9).

To date, few studies involving the use of LEF in JIA have been reported. Silverman *et al*., conducted a randomised clinical trial comparing LEF versus MTX in 94 patients with polyarticular juvenile rheumatoid arthritis (JRA) (13). At 26 weeks, 68% of the LEF-treated patients met the ACR Pedi 30 criteria compared to 89% of the MTX-treated patients. Both treatment groups maintained improvements up to the final study visit at 48 weeks. Tolerability of the two drugs was comparable. Silverman *et al*., also assessed the long-term safety and efficacy of LEF in an open-label study of 27 children with polyarticular course JRA who had failed or could not tolerate MTX (14). At 26 weeks, 52% of these patients satisfied the ACR Pedi 30 response criteria. Seventeen children continued into a long-term extension phase. 65% met the ACR Pedi 30 response criteria at 50 weeks and 53% of the patients entering

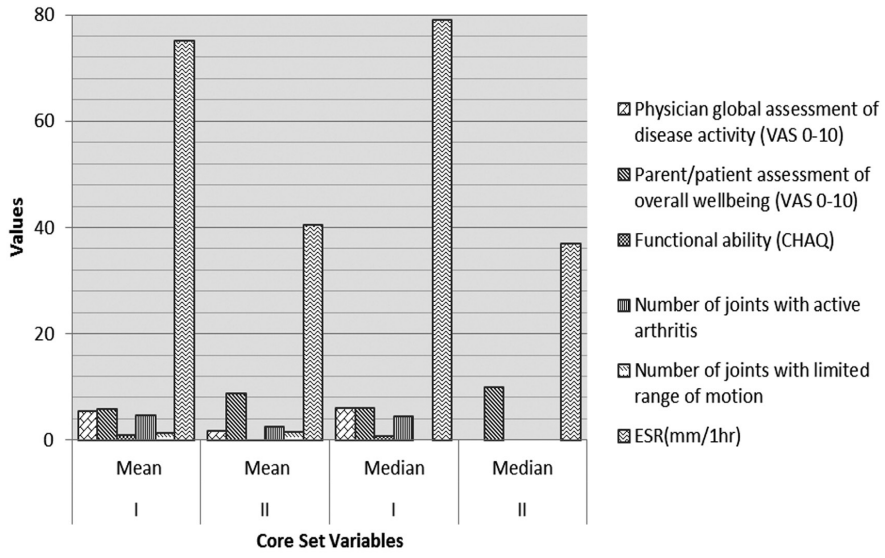

Fig. 2. Comparison of the core set variables (means and medians) at the commencement of combination therapy and at the end of the study in 18 patients who followed up through the length of the study. (I and II represent the status at the commencement of the combination therapy and at the end of the follow-up, respectively).

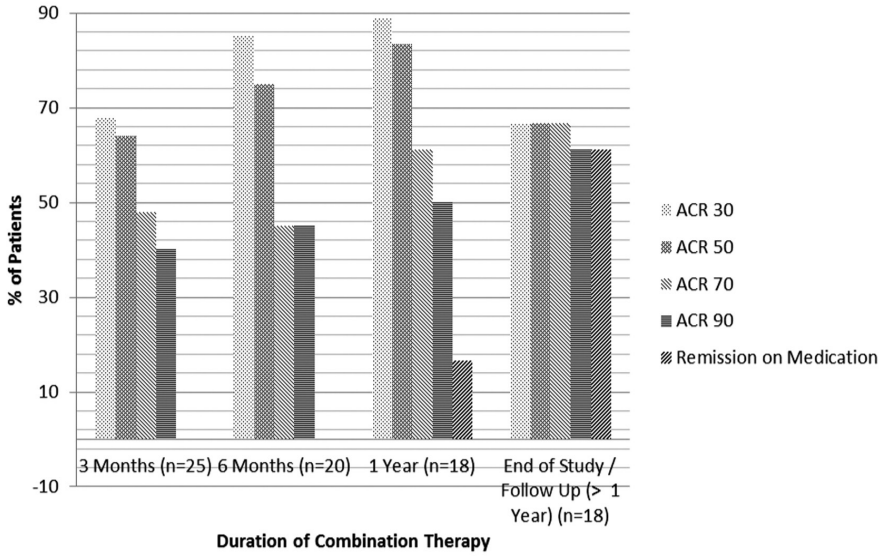

Fig. 3. Efficacy of MTX-LEF combination in our patients. (Response rates in terms of ACR Pedi 30, 50, 70 and 90 responses and remission on medications).

into the extension phase (maximum 30 months) met the response criteria at the end of this phase. The most frequently reported adverse events included headache, infections (mostly mild upper respiratory tract infections) and gastrointestinal symptoms (abdominal pain, nausea and diarrhoea).

In a study by Foeldvari *et al*. (15), involving a retrospective review of medical records of 58 patients with JIA who received LEF, it was added to ongoing MTX in a subset of 10 patients who refused etanercept. Among those who received the combination, 3 continued therapy, one achieved remission, 4 dropped out due to side effects, one discontinued due to lack of response, while one was lost to follow up. Diarrhoea and abdominal pain were the most common causes of treatment discontinuation. Although the numbers were small, tolerability appeared to be worse in patients receiving the combination of LEF with MTX than in the overall study population or in patients receiving LEF in combination with other DMARDs.

Jahan *et al*., have reported their experience using LEF in 4 children with systemic onset JIA (17). They found the clinical response to LEF to be good, which facilitated the withdrawal of other DMARDs and prednisolone. The response time ranged from 2 to 3 months. The side effects encountered were mild such as lower respiratory tract infections and diarrhoea.

Our study showed that combination therapy with methotrexate and leflunomide in patients with polyarticular course JIA with inadequate response to MTX monotherapy, appeared to be efficacious, well-tolerated and the response was durable in a significant proportion of our patients. In our study, adverse events were encountered in 3 patients (one had MAS, one gastritis and the other elevated liver enzymes).The lower incidence of adverse effects in our patients as compared to the other studies involving the use of LEF, as monotherapy or in combination with MTX could be due to the parenteral (subcutaneous) route of administration of MTX, lowering the risk of gastro-intestinal toxicity, reduction of MTX dose to 10 mg/m^2/week at the commencement of combination therapy thereby reducing the risk of hepatotoxicity and folate supplementation.

The observation that 11 out of 32 children enrolled on our study were in clinical remission on drugs at the end of the study suggests that this combination could reduce the need for biologicals in about a third of patients failing methotrexate therapy.

Our study had limitations in that it was an open observational study with a small sample size and involved concomitant use of steroids in some patients. This and such other combinations need further evaluation in the treatment of polyarticular-course JIA in resource-challenged settings.

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