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# The Use of Methotrexate in Juvenile Idiopathic Arthritis: A Single Center Experience

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**Abstract** In the recent decade, an increasing number of disease-modifying anti-rheumatic drugs (DMARDs) have been developed for treatment in juvenile idiopathic arthritis (JIA). Currently, methotrexate (MTX) is the DMARD of first choice particularly in oligoarticular and polyarticular JIA, but its efficacy in systemic-onset JIA and enthesitis-related JIA was less satisfactory. A retrospective study on 40 patients followed up at Queen Mary Hospital for JIA was performed to review the treatment outcome and adverse effects associated with use of MTX. We concluded that MTX was safe and well tolerated in majority of patients, but treatment response varied with different JIA subtypes. Combination of MTX with other anti-inflammatory agents was often required to achieve disease remission in patients with more severe disease. Large, randomised controlled trials are needed to determine the efficacy of individual drug and their combination in each JIA subtype.

**Key words** Juvenile idiopathic arthritis; Methotrexate

## Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood. It is a clinical diagnosis made in a child less than 16 years of age with chronic arthritis for at least 6 weeks' duration after excluding other identifiable causes of arthritis.[1] In Western countries, the overall prevalence is approximately 30-150 per 100,000 children.[2] JIA is reported to be less common among Chinese children; a recent population-based epidemiologic study in Taiwan revealed that the prevalence was 3.8 per 100,000 children under the age of 15.[3] While approximately one-third of children with JIA achieve disease remission at the time of adolescence, it is estimated that up to 50% of all JIA patients continue to have debilitating joint damage and systemic disease that persist into adulthood.[4] Poor prognostic factors include polyarticular onset and disease course, systemic onset subtype and rheumatoid factor positivity. Current management guidelines for rheumatoid arthritis advocate that aggressive use of disease-modifying agents should be initiated early to minimise joint damage and slow down disease progression.[5]

Methotrexate (MTX) is a well established treatment for JIA. Its efficacy and safety has been demonstrated in randomised controlled trials in children with JIA.[6-8] Data on the use of MTX in Chinese children with JIA is scarce, and the experience among local paediatricians with MTX is limited. The aim of this study is to review the overall clinical characteristics, disease course and outcome of patients who received MTX for JIA in our unit.

## Study Setting

Queen Mary Hospital is the teaching hospital for The University of Hong Kong. The Department of Paediatrics and Adolescent Medicine is a tertiary-quaternary care center

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receiving referrals from other district hospitals and private practitioners. From November 1988 to March 2006, 109 children were seen in the Paediatric Rheumatology Clinic for rheumatic joint disease.

Since 1996, MTX has been administered to children with different subtypes of JIA that did not respond well to non-steroidal anti-inflammatory drugs (NSAIDs), as determined by symptoms (pain, joint stiffness), signs (joint effusion, range of movement and deformity) and level of inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and platelet count. In the earlier years systemic steroid was commonly prescribed to patients with severe persistent symptoms, and MTX was used as an add-on therapy in case of inadequate disease control. Before commencement of MTX, patients (if mature enough) and their parents are counseled on the potential side effects including gastrointestinal upset, liver toxicity and marrow failure. Abstinence from alcohol is emphasised, and in particular adolescent girls are counseled on the importance of contraception in view of the risk of fetal teratogenicity. Baseline complete blood count and liver function tests were obtained before starting MTX. Upon each follow-up at 4-12 weeks' interval, blood would be taken for ESR and CRP for monitoring of inflammatory activity, while complete blood count (CBC) and liver function test (LFT) would also be ordered for monitoring of toxicity. MTX would be increased up to around 20 mg/$m^2$/day or switched to subcutaneous route if satisfactory response is not obtained. All patients taking MTX receive folic acid supplementation.

## Methodology

### *Subjects*

Of the 109 patients who were followed up in our clinic for rheumatic joint disease, 96 of them fulfilled the International League of Associations for Rheumatology (ILAR) diagnostic criteria for JIA. They have been followed up regularly at intervals of 4-12 weeks depending on disease severity. Nine patients were excluded from the study as their follow-up was closed more than 5 years ago. Three other patients were excluded because of defaulting follow-up. Out of the remaining 84 patients 46 were started on MTX. Data was incomplete in six of them, so ultimately 40 patients who have been treated with MTX for JIA were included for data analysis (Figure 1).

### *Data Collection*

The type of JIA and disease course of each subject was reviewed in detail to identify the indication of commencing MTX and any disease flare-up while on MTX. Information on the time elapsed from diagnosis of JIA to starting MTX, drug dosage, route of administration and side effects were collected. The types of add-on therapy in those who did not have satisfactory response to MTX were identified. Inflammatory markers including ESR, CRP as well as white cell count, haemoglobin and platelet counts before and at 3 months, 6 months and 12 months after commencement of MTX were recorded.

### *Statistical Analysis*

Descriptive statistics were used for reporting demographics, clinical characteristics, adverse effects and types of add-on therapy. The trends of ESR, CRP, haemoglobin, white cell and platelet count were expressed in box plots.

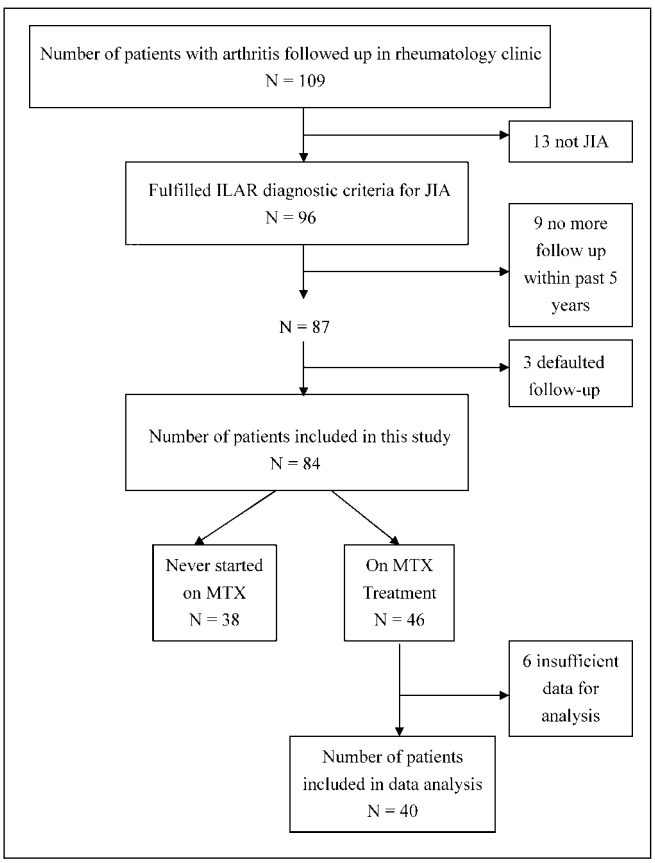


**Figure 1** Schematic diagram showing inclusion criteria for the present study (MTX, methotrexate; JIA, juvenile idiopathic arthritis).

## Results

### *Demographics*

Twenty-five males and 15 females who received MTX for treatment of JIA were analysed. Majority of the patients (95%) were Chinese, while 2 patients were Japanese. The mean age of onset of JIA was 9.35 years (range 1.16-15.84), and the mean duration of follow-up was 4.4 years (range 0.68-17.09).

### *JIA Subtypes and Disease Characteristics*

Fifteen patients had polyarticular JIA, 14 had enthesitis-related JIA, 7 had oligoarticular JIA and 4 had systemic-onset JIA (Table 1). Three patients with enthesitis-related JIA had uveitis.

### *Use of Methotrexate*

In majority of patients the indication for starting MTX was persistent or flare-up of systemic or joint symptoms and high levels of inflammatory markers despite optimal dose of NSAIDs. In 9 patients MTX was started as an add-on treatment to oral steroid because of suboptimal response. The mean time of commencing MTX from diagnosis was 16.6 months. For the 20 patients who were diagnosed with JIA after 2003, MTX was started much earlier at a mean time of 7.35 months from diagnosis, compared with 25.85 months for those who were diagnosed with JIA before 2003. The mean starting dose was 11.66±3.03 mg/m$^2$ (range 4.1-16.0 mg/m$^2$), and the mean peak dose was 16.77± 4.53 mg/m$^2$ (range 10.0-30.8 mg/m$^2$). Sixteen patients (40%) were switched to subcutaneous MTX because of inadequate response to oral MTX. The total duration of MTX use in the cohort was 103.33 patient-years (mean= 2.58±2.37 years).

**Table 1** Distribution of juvenile idiopathic arthritis subtypes in the methotrexate group and non-methotrexate group

| | Not on methotrexate (N=38) | On methotrexate (N=40) |
|---|---|---|
| Oligoarthritis | 14 | 7 |
| Persistent | 13 | 4 |
| Extended | 1 | 3 |
| Polyarticular | 9 | 15 |
| RF-positive | 0 | 3 |
| RF-negative | 9 | 12 |
| Enthesitis-related | 13 | 14 |
| Systemic-onset | 2 | 4 |
| Psoriatic | 0 | 0 |

RF, rheumatoid factor

### *Treatment Response to Methotrexate*

Thirteen patients showed good response to MTX in terms of symptomatic control and lowering of inflammatory markers without the need of additional DMARDs. Five of them were able to take off MTX after a mean duration of 32.2 months without disease relapse up to the last follow-up date. Twenty-seven patients showed only partial response to MTX judging from the degree of symptomatic relief and drop in inflammatory markers, and 24 of them required add-on treatment with other anti-inflammatory agents (Table 2). In the earlier years prednisolone, hydroxychloroquine and sulphasalazine were commonly used as add-on therapy to MTX, but in recent few years leflunomide, thalidomide and etanercept were used more frequently than the aforementioned agents. The mean time from commencement of MTX to addition of a third anti-inflammatory agent was 15.3 month (range 1.2-53.3 months). At the time of review, 15 patients were receiving leflunomide in addition to MTX for control of disease activity, and 5 of them also received thalidomide as the third DMARD. One patient with RF-negative polyarticular JIA and another with systemic-onset JIA underwent autologous stem cell transplant; the former patient remained in full remission over 5 years post-transplant without taking any medications, but the latter required combined leflunomide and thalidomide for disease control.

The trends of CRP, ESR, haemoglobin, platelet and white cell count, within the first 12 months of MTX treatment, in the group of patients with good response to MTX (n=13) and the group with only partial response requiring subsequent add-on therapy (n=27) are shown in Figure 2. The levels of all markers before starting MTX were not different between the two groups. An overall downward trend of CRP, ESR, platelet and white cell counts were seen in both groups. However, the group of patients who ultimately required other DMARDs in addition to MTX for disease control had only modest fall of these markers when compared with those who

had good MTX response. Maximal drop in CRP, ESR, platelet and WBC count could be observed in the first 3 months after starting MTX in both groups, with a more dramatic drop in the group with good MTX response. In particular, ESR was the marker which showed the greatest discrepancy between MTX responders and partial responders. Those with good MTX response also showed a rise of mean haemoglobin level over the first 12-month period compared with those with partial MTX response.

### *Side-effect Profile*

In general MTX was well tolerated by majority of patients. The most commonly seen side effect was gastrointestinal upset. Fifteen patients (37.5%) had nausea and two of them required the use of ondansetron for relief. Four patients had oral ulcers and 2 complained of dizziness after MTX use. Four patients had raised liver enzymes and as a result MTX was stopped in two of them. Poor compliance was seen in 2 patients and they stopped MTX because of severe nausea.

**Table 2** Response to methotrexate and requirement of add-on therapy in different juvenile idiopathic arthritis subtypes

| | Oligoarthritis | Polyarticular RF-positive | Polyarticular RF-negative | Enthesitis-related | Systemic onset |
|---|---|---|---|---|---|
| No. of patients | 7 | 3 | 12 | 14 | 4 |
| - Boys | 5 | 0 | 5 | 13 | 2 |
| - Girls | 2 | 3 | 7 | 1 | 2 |
| Drug treatment other than NSAIDs used in the past | 0 | 1 | 6 | 0 | 2 |
| - Prednisolone | | 1 | 6 | | 2 |
| - IVIG | | 0 | 2 | | 0 |
| - Penicillamine | | 0 | 0 | | 1 |
| - Azathioprine | | 0 | 1 | | 0 |
| Number of patients put on subcutaneous MTX | 1 | 3 | 2 | 6 | 4 |
| Number of patients with satisfactory response to MTX as the only 2nd line agent | 4 | 0 | 6 | 3 | 0 |
| Number of patients receiving MTX combined with systemic steroid or another DMARD | 3 | 3 | 4 | 10 | 4 |
| Type of add-on therapy in respective patients | 1,2: Leflunomide<br>3: Sulphasalazine | 1,2: Leflunomide<br>3: Leflunomide + cyclosporine A + prednisolone + etanercept + thalidomide | 1: Prednisolone<br>2: Prednisolone + cyclophosphamide<br>3: Myclophenolate mofetil<br>4: Cyclophosphamide, then underwent atuologous stem cell transplant with remission | 1-5: Leflunomide<br>6: Etanercept<br>7: Thalidomide<br>8: Prednisolone + leflunomide + thalidomide<br>9: Sulphasalazine + leflunomide + thalidomide<br>10: Hydroxychloroquine + sulphasalazine, switched to cyclosporine + leflunomide + thalidomide | 1: Prednisolone<br>2: Prednisolone + leflunomide<br>3: Prednisolone + thalidomide<br>4: Prednisolone + cyclosporine A + clophosphamide; then underwent autologous stem cell transplant but relapsed, in remission after taking leflunomide + thalidomide |

RF, rheumatoid factor; IVIG, intravenous immunoglobulin; MTX, methotrexate; DMARD, disease-modifying anti-rheumatic drug

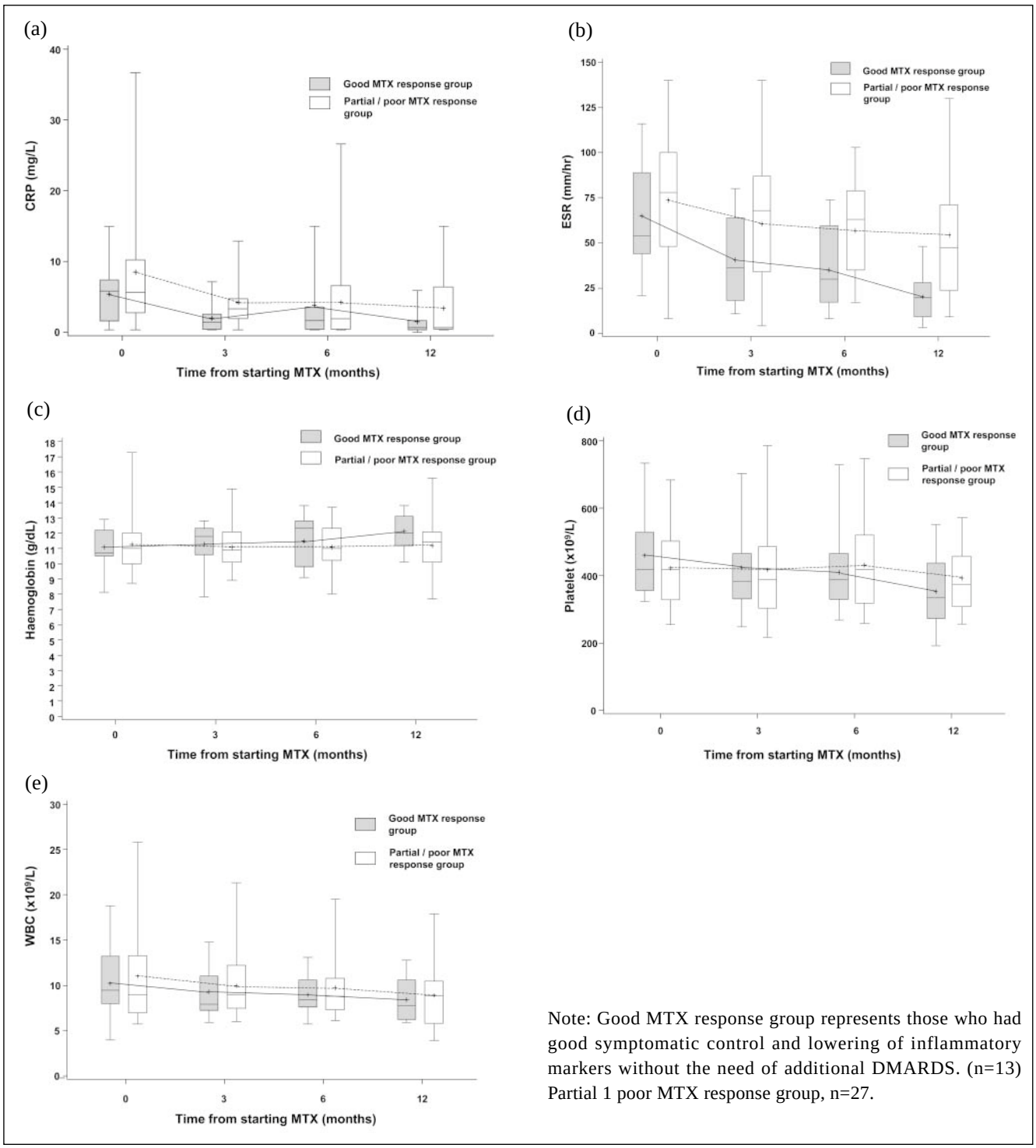


**Figure 2** Box plots showing the trends of CRP (a), ESR (b), haemoglobin (c), platelet (d) and white cell count (e) before and 3 months, 6 months and 12 months after commencement of methotrexate (MTX).

## Discussion

Since 1980, methotrexate has been widely used in all subtypes of JIA. It is regarded as the second-line agent of choice in managing children who have JIA unresponsive to NSAID. The first multi-center clinical trial on the use of MTX in JIA was conducted by the Pediatric Rheumatology Collaborative Study Group in the United States and the former Soviet Union.[6] It was a prospective, randomised placebo-controlled double-blind study on 114 children with systemic-onset, polyarticular and oligoarticular forms of JIA. In this 6-month trial, a dose-response relationship was observed with MTX at 10 mg/m$^2$/day being significantly more effective when compared to a lower dose at 5 mg/m$^2$/day and placebo. The most recent trial of MTX in JIA was conducted by the Pediatric Rheumatology International Trials Organization (PRINTO).[8] This study contained the largest cohort of JIA patients who were treated with MTX, consisting of 325 patients with polyarthritis (54%), 183 patients with extended oligoarthritis (31%) and 87 patients with systemic-onset arthritis (15%). The outcome was measured by American College of Rheumatology (ACR) Pediatric 30, which is a validated index indicating a 30 percent improvement from baseline in at least three of the six response variables included in the ACR Pediatric core set of disease activity measures: 1) physician global assessment of disease activity; 2) parent/patient assessment of overall well-being; 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; and 6) erythrocyte sedimentation rate.[9] Four hundred and thirty out of 595 patients (72%) had clinical improvement measured by ACR Pediatric 30 after taking MTX at standard dose of 8-12.5 mg/m$^2$/week by oral, subcutaneous or intramuscular route for a 6-month period. Approximately 50% of patients who were not responsive to the standard dose showed significant clinical improvement after switching to parenteral administration of MTX at 15 mg/m$^2$/week for an additional 6 months. However, further increase in dose up to 30 mg/m$^2$/week did not yield additional therapeutic advantage. No significant difference in response rate was observed between subtypes.

The benefit of subcutaneous MTX for those who did not respond to standard dose of oral MTX was shown in a study by Alsufyani et al.[10] Seventy-seven percent of those who switched to subcutaneous MTX showed improvement, which could be explained by better bioavailability and improved compliance due to less gastrointestinal upset such as nausea. Pharmacokinetic study demonstrated that oral MTX absorption reduces at doses above 12 mg/m$^2$.[11] In our experience, subcutaneous MTX was well tolerated in majority of patients, and the technique of injection could be mastered satisfactorily after a few sessions of supervision by specialist nurses.

Majority of JIA patients receive NSAIDs as the initial therapeutic agent. However, NSAIDs only provide symptomatic relief for pain and stiffness and do not modify disease progression. Only approximately one-third of patients, mainly those with oligoarthritis, achieved adequate disease control with NSAIDs. At present there is no consensus on the exact time point of initiating MTX treatment, but it is advocated that MTX should be started if 6-8 weeks of NSAIDs and/or intra-articular steroid has not led to clinical remission.[12] In patients with very active disease or a poor prognosis, it may even be advisable to use MTX as the initial DMARD.

In our cohort, the groups with oligoarticular and RF-negative polyarticular JIA showed better response to MTX. Around 50% of patients in these two groups were in remission while on MTX without the need for further add-on therapy. All patients with RF-positive polyarticular JIA and systemic-onset JIA, and majority of enthesitis-related JIA required combination treatment with other DMARDs. To date there is no clinical trial comparing the efficacy of MTX in different subtypes of JIA and the predictors for MTX response. A randomised placebo-controlled crossover trial demonstrated that MTX, at 15-20 mg/m$^2$/day, produced significant overall improvement in children with extended oligoarticular JIA, but the clinical efficacy was less prominent in systemic JIA.[7]

Since 2003, we began to introduce leflunomide as an add-on therapy to JIA patients who had suboptimal response to MTX alone. Leflunomide has been shown to be a safe and effective drug for polyarticular JIA in a 2-year open label study.[13] Combination of DMARDs has not been well studied in JIA, but a number of studies have been published demonstrating the safety and efficacy of combination treatment in adult patients with rheumatoid arthritis.[14] As leflunomide and MTX are both anti-metabolic agents, combination of these 2 drugs is believed to have the potential for biochemical synergy. In a randomised, double-blind placebo-controlled trial, combination of MTX with leflunomide has been shown to produce significantly more clinical benefit in adult patients with active rheumatoid arthritis which had inadequate response to long-term MTX alone.[15] Elevation of liver enzymes was more common in

the combined treatment group, but majority had spontaneous resolution subsequently and the discontinuation rate was not different from the group receiving MTX alone.

In our experience, leflunomide plus MTX was well tolerated in most patients, and no significant liver toxicity was seen. Although the observation period was relatively short, majority of the patients showed good initial response with improved control of disease activity after addition of leflunomide. Apart from leflunomide, we also introduced cyclosporine A and thalidomide as add-on therapy to those with aggressive disease. In particular, we observed that patients with enthesitis-related JIA often had suboptimal response to MTX alone and required combination of DMARDs to improve disease control. At present, effective therapies for juvenile spondyloarthropathy are lacking. Sulfasalazine was not found to be significantly better than placebo in a randomised controlled trial.[16] NSAIDs and systemic steroids may provide symptomatic improvement but do not alter disease progression. Neither was MTX shown to have disease-modifying effect on the natural course of juvenile spondyloarthropathy. A recent retrospective study showed that anti-TNFα blockade with either infliximab or etanercept resulted in significant improvement in all 10 subjects with refractory juvenile spondyloarthropathy.[17] From our study, leflunomide and thalidomide as an add-on therapy to MTX induced almost complete clinical remission in 3 patients with the most severe enthesitis-related JIA. Leflunomide combined with MTX also induced remission in 4 other patients who had suboptimal MTX response initially. The efficacy and safety of combination treatment in different subtypes of JIA, in particular enthesitis-related JIA, has to be studied in larger randomised clinical trials.

In general MTX is well tolerated in children. Compared with treatment for leukaemia and other malignancies, the dose used for treating JIA is relatively low (10-20 mg/m$^2$/week compared with 200-3000 mg/m$^2$/week in the former). A summary of reported side effects from MTX in 3 large clinical trials is shown in Table 3. The most common side effect is gastrointestinal upset, followed by oral ulcers and abnormal liver enzymes. A similar pattern is also observed in our cohort. Only 2 patients stopped MTX because of intolerance. The toxicity of MTX is partly related to folate deficiency; folic acid supplementation significantly reduces gastrointestinal adverse effects. Situations under which MTX should be withheld include a three-fold rise in liver transaminase, leucocytes count below 3,000/μL, neutrophil count below 1,500/μL or platelet count below 100,000/μL.[15] MTX therapy should be stopped if there is recurrent hepatotoxicity or haematopoietic toxicity. Pulmonary toxicity is very rare in children, and severe irreversible liver

**Table 3** Adverse effects from methotrexate reported in large clinical trials on juvenile idiopathic arthritis

| | **Giannini et al (1992)[6]** | **Woo et al (2000)[7]** | **Ruperto et al (2004)[8]** |
|---|---|---|---|
| Number of subjects | 127 | 91 | 80 |
| Dose of methotrexate | 5-10 mg/m$^2$/week | 15-20 mg/m$^2$/week | 8-30 mg/m$^2$/week |
| Side effects reported | | | |
| - Gastrointestinal | 7 (5.5%) | 26 (23.1%)<br>Vomiting 9 = (11.1%) | Nausea = 17 (21.0%) |
| - Mucosal ulceration | 3 (2.4%) | 19 (20.9%) | 8 (9.9%) |
| - Headache | 3 (2.4%) | Not mentioned | Not mentioned |
| - Hair loss | Not mentioned | 8 (8.8%) | 4 (5.0%) |
| - Mood change | Not mentioned | 20 (22.0%) | Malaise = 4 (5.0%) |
| - Pneumonitis | Not mentioned | 1 (1.1%) | 0 (0%) |
| - Leukopenis | Not mentioned | 0 (0%) | 4 (5.0%) |
| - Abnormal AST | Not mentioned | 20 (22.0%) | 4 (5.0%) |
| - Abnormal alkaline phosphatase | Not mentioned | 12 (13.2%) | Not mentioned |
| - Abnormal bilirubin | Not mentioned | 2 (2.2%) | Not mentioned |
| Drop-outs as a result of side-effects | 3 (2.4%) | 1 (1.1%) | 0 (0%) |

AST, aspartate transaminase

fibrosis has not been reported. Current data do not suggest that children receiving MTX for JIA have higher risk of malignancy than in the general paediatric population.

As a referral center our cohort represents a biased sample, with majority of patients having the most severe spectrum of JIA. The greatest drawback of this study is that objective assessment of clinical response towards MTX was not possible due to the retrospective nature of the review. Standard outcome measures such as physician's global assessment of disease activity, parent's global assessment of overall well-being, and disability index of Child Health Assessment Questionnaire (CHAQ) are validated tools for measuring disease activity and improvement from baseline after a treatment has been administered. Prospective collection of such data will facilitate evaluation of new drug or combination regimen in the future.

## Summary

In contrary to the traditional pyramid approach, the treatment for JIA has been revolutionised by the early use of DMARDs, with methotrexate being the agent of choice. While previous studies on polyarticular and oligoarticular JIA have demonstrated satisfactory short-term improvement of outcome measures, our study showed that MTX, in combination with other DMARDs such as leflunomide and thalidomide, are required for disease control in some JIA subtypes such as enthesitis-related JIA and systemic-onset JIA. Well designed multi-centered trials are required to evaluate the efficacy of combination treatment in various JIA subtypes, and longer term studies are needed to assess whether the new DMARDs can improve the remission rate and functional outcome of children with JIA.

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