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# The use of methotrexate in children with rheumatic diseases

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## ABSTRACT

*Methotrexate (MTX) is one of the most useful drugs for the treatment of various rheumatic diseases in children, mainly juvenile idiopathic arthritis (JIA), juvenile dermatomyositis (JDM), and localised scleroderma. MTX is considered the standard treatment of JIA, particularly of those subgroups with polyarticular course. JIA response and remission rates to MTX are the standard for comparison with other drug modifying anti-rheumatic drug (DMARD) and biologic agents in clinical trials. On the other hand, short and long-term data suggest that MTX is a safety drug in the paediatric population with rheumatic diseases. Not surprisingly, MTX is the DMARD of choice in JIA either as monotherapeutic drug or in combination with biologic agents.*

## Introduction

Juvenile idiopathic arthritis (JIA) comprises several subgroups of arthritis presenting before the age of 16 years of age and lasting at least 6 weeks (1) (Table I). Various JIA subgroups are clinically equivalent to specific adult onset diseases and their short and long-term consequences may resemble each other. In this context, it is not surprising that the management of JIA as a whole and each subgroup in particular were certainly similar to their adult onset counterparts.

The main objectives of treatment of JIA are remission of inflammatory disease activity and symptom control, prevention of joint and organ damage, preservation of physical function and avoidance of functional disability, and improvement of health-related quality of life (HRQoL). To achieve these goals, the paediatric rheumatologist and his team rely on patient and parent's education, family association network and support, medications, physical therapy, rehabilitation, psychological support, and surgical procedures.

In this review we focus on drug treat-

ment and specifically on methotrexate (MTX) as the standard treatment for most JIA subgroups. Our approach includes principally the clinical efficacy, safety, and recommendations for MTX use in JIA. We have added only some important information related with the pharmacologic properties and the mechanisms of action of MTX in children since in the present issue these topics are reviewed extensively.

## The use of MTX in paediatric rheumatic diseases

The use of weekly MTX is an established treatment in children with most subgroups of JIA (2-5), particularly those with prominent involvement of the joints and in patients with juvenile dermatomyositis (6-9). MTX has been also used with some success in children with localised scleroderma (10-13), Wegener's granulomatosis (14), Takayasu's arteritis (15), sarcoidosis (16), Behçet's disease (17, 18), chronic uveitis (19), and systemic lupus erythematosus (20-22). Evidence for the use of MTX in JIA comes from few double-blind, placebo controlled randomised trials and open studies whereas the evidence demonstrating the efficacy of MTX in other indications is less strong. Most rheumatic diseases in children are rare and the feasibility for studying the efficacy and safety of any form of therapy in a proper way is certainly little compared with adult onset diseases.

## Pharmacology

### *Mechanism of action*

MTX, a folate analogue, is a potent competitive inhibitor of several enzymes involved with *de novo* purine and pyrimidine biosynthesis, including dihydrofolate reductase, thymidylate synthase, and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase (23). AICAR inhibition by MTX polyglutamates derivatives increases the release of adenosine, which may be the primarily responsible for the

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**Table I.** ILAR / WHO\* classification of Juvenile Idiopathic Arthritis (ref. 1).

1. Systemic arthritis
2. Oligoarthritis
  - a. Persistent oligoarthritis
  - b. Extended oligoarthritis
3. Polyarthritis (rheumatoid factor negative)
4. Polyarthritis (rheumatoid factor positive)
5. Psoriatic arthritis
6. Enthesitis related arthritis
7. Undifferentiated arthritis

anti-inflammatory effect of the drug (23). However, the mean concentration of adenosine in the blood in children receiving MTX, untreated controls, responders, and non-responders is rather similar (24). Moreover, adenosine blood concentration does not correlate with MTX dose or MTX polyglutamate concentration in erythrocytes.

#### Pharmacokinetics

The dose-normalised area under the plasma concentration *versus* time-curve (AUC) of MTX increased with the age of the children and might explain that overall, children require higher MTX dose than adults to obtain a therapeutic effect (25).

MTX may be given orally, subcutaneously, or intramuscularly. The bioavailability of oral MTX is highly variable, but mostly corresponds to 70% of the intravenous dosing. MTX serum levels are higher in children with JIA when given in the fasting state than after meals (26). The bioavailability of MTX is 11% to 15% lower after oral administration than those of the intramuscular or subcutaneous administration; on the other hand, no differences between intramuscular and subcutaneous dosing exist (27). Factors such as sex, age, body weight, creatinine clearance, dose, and concomitant medications may also contribute to MTX variability.

In terms of efficacy and safety, there seems to be no significant differences between the oral and intramuscular administration of MTX in children with JIA (28). However, the recommended route MTX administration in children receiving around 15mg/m<sup>2</sup> is either the subcutaneous or intramuscular routes to achieve a significant clinical response (29, 30).

#### MTX indications in JIA

MTX is the standard DMARD treatment for JIA, but most of the information about efficacy and safety of this drug derives from its use in children in polyarticular onset and polyarticular course of the disease. Along with the effect of MTX in disease activity parameters, there is some evidence of reduced radiographic progression in children receiving MTX (31-33).

While there is little information regarding the effect upon systemic manifestations such as those seen in the systemic JIA subgroup, chronic iridocyclitis, organ involvement and other systemic manifestations in children with IgM rheumatoid factor (RF), and psoriatic arthritis, it seems that MTX is of no benefit in children in enthesitis related arthritis.

MTX is generally indicated in children with polyarticular disease, particularly those not responding to non-steroidal antiinflammatory drugs (NSAID) in less than eight weeks and/or local therapy with corticosteroids (34). Starting doses range from 10mg to 15mg/m<sup>2</sup>/week (30), but refractory cases may receive up to 20mg/m<sup>2</sup>/week (34). Response at six months is much better when MTX is given early in the course of the disease (35). The long-term response to MTX appears related to the magnitude of the response in the initial six months of treatment. Patients reaching an ACR-Ped-70 response have a significantly greater improvement in the number of active and motion-restricted joints and a significant increase in the proportion of patients with inactive disease when compared to patients that only achieved ACR-Ped-30 between baseline and the fifth year of treatment with MTX (36). Predictors of poor response to MTX after six months of treatment in children with polyarticular-course JIA are long disease duration; negative serum antinuclear antibodies (ANA); high disability level; and wrist involvement (37).

In some cases, the maximum efficacy of MTX is only achieved after nine to 15 months of continuous treatment (30, 34). However, that does not mean that treatment changes should wait for such a long time. In fact, the addition of biologic agents may be carried out within

three months of unsuccessful treatment with MTX.

Once complete remission is achieved, withdrawal of MTX is an option that should be considered (34). In this regard, there are some specific recommendations that might help the clinician in deciding when to stop MTX after disease remission, but they need to be validated. Some authors recommend the continuous use of the same MTX dose, every week for six months in children on remission and then start to taper the dose (spacing the administration of MTX to every other week for six additional months) until discontinuation (38). Regular visits after discontinuation should be programmed in order to identify relapses of disease as soon as possible.

Relapse occurs in 30% to 50% of the patients, particularly children aged <4.5 years within the first year of MTX discontinuation (39, 40). Recently, Foell *et al.* (41) found that the median relapse-free interval and the rate of relapses in children with clinical remission on-MTX showed no significant differences between patients who stopped MTX six months and 12 months after remission. The risk of relapse off-MTX is associated with high levels of the phagocyte activation marker myeloid-related proteins 8 and 14 heterocomplex (MRP8/14), which are considered markers of residual inflammation (41, 42).

#### Efficacy

Since the first report on the effect of MTX in children (43), several retrospective and uncontrolled clinical trials evaluating its efficacy, bioavailability, toxicity, dosage levels, and routes of administration have been published (27). Giannini *et al.* (44) compared the efficacy of MTX 10mg/mg/m<sup>2</sup>/week in 46 children with JIA and 41 children receiving placebo for six months. Differences between groups favoured the use of MTX in regards to the number of tender and swollen joints as well as joints with reduced mobility, physician global assessment of disease activity, and erythrocyte sedimentation rate (ESR) levels. Overall, 63% of children with MTX and only 32% in the placebo group improved after six months.

A metanalysis comparing MTX (5mg and 10mg/m<sup>2</sup>/week doses) with penicillamine, hydroxychloroquine, oral gold, and placebo showed significant differences in the improvement between MTX (higher dose) and placebo, but not between other DMARD and placebo (45).

A randomised, controlled, double-blind, crossover, multicentre study comparing MTX and placebo for 4 months by Woo *et al.* (46) in children with systemic and oligoarticular extended JIA forms showed a significant improvement in physician and parent global assessments and ESR in the extended oligoarthritis subgroup and in physician and parent global assessments in the systemic subgroup. Regarding ACR-Ped-30 response, only the extended oligoarticular arthritis group reached a significant proportion of responders to MTX. Nevertheless, when data from both disease subgroups were combined, clinical improvement with MTX was significant.

The Pediatric Rheumatology International Trials Organization (PRINTO) conducted a multinational, randomised, open-label, double phase, standard-of-care trial in children with polyarticular course JIA naïve to MTX (30). Patients received standard doses of MTX (8mg to 12.5mg /m<sup>2</sup>/week) for 6 months. Results showed that 430 of them (72%) improved at the level of ACR-Ped-30, 360 (61%) at ACR-Ped-50, and 225 (38%) at ACR-Ped-70. Sixty-nine children (12%) met the definition of complete disease control. There were 80 non-responders in the study that were then randomised to receive either an intermediate dose (15mg/m<sup>2</sup>/week) or a higher dose (30mg/m<sup>2</sup>/week) of MTX for 12 months. The efficacy of intermediate and high doses were relatively similar as measured by ACR-Ped-30, 50 and 70 rates suggesting that there is no additional benefit in increasing the dose of MTX above 15mg/m<sup>2</sup>/week.

The efficacy of MTX in children with JIA has been also demonstrated by evaluating HRQoL. In a subanalysis of the study mentioned above (47), a statistically significant improvement in HRQoL, particularly the physical component was observed after six months

of MTX treatment. Similar improvements were observed in children who did not respond to a standard dose of MTX and were subsequently randomised to a higher dose.

Silverman *et al.* (48) compared the efficacy of leflunomide (dose according to weight) with that of MTX (0.5mg/kg/week; maximum dose: 25mg/week) in polyarticular course JIA for 16 weeks in a double-dummy, blinded fashion, followed by a 32-week blinded extension. The results of the study showed more patients in the MTX group (89%) having an ACR-Ped-30 response than in the leflunomide (68%) group. Such improvements were maintained up to week 48.

#### *MTX and biologic agents as combination therapy*

Patients not responding to MTX standard therapy may be eligible for biologic therapy, including tumor necrosis factor alpha (TNF) blockers and anti-interleukin 1 and 6 receptors (rIL-1 and rIL-6). The efficacy and safety of such biologic agents have been determined in a number of clinical trials in which the placebo arm has consisted of the administration of MTX at stable doses. Most studies include an open-label extension in which patients receive both MTX and the biologic agent. These studies suggest that MTX is less efficacious than most biologic agents, but it also suggest that the combination of MTX and biologic agents may be effective in treating JIA. Currently, however, there is only one study in which the combination of a TNF blocker (adalimumab) and MTX was compared with adalimumab monotherapy. Adult rheumatoid arthritis patient studies suggest that the combination of MTX and biologic agents are more efficacious than monotherapy with each of such agents in the long-term. In fact, concurrent treatment with MTX appears to enhance the therapeutic response to biologic agents (49-51).

Regarding etanercept, several studies (52-56) have demonstrated significant improvement in patients with active polyarticular JIA who did not tolerate or had an inadequate response to MTX. However, Schmeling *et al.* (57) found

a beneficial effect of etanercept and MTX in seven children with refractory JIA. The addition of MTX (10 mg to 20mg/m<sup>2</sup>/week) may have contributed to the sustained improvement seen in JRA patients treated with etanercept for up to four years (55).

Two recent studies (58, 59) addressed the issue of effectiveness of etanercept as monotherapy or in combination with MTX. In the first study (58), a total of 594 JIA polyarticular course patients were assigned to received MTX, etanercept, or etanercept *plus* MTX for three years in an open-label, non-randomised clinical trial. Scores for physician's global assessment and total active joints improved from baseline in a trend, which was similar in the three groups of treatment. In another study (59) -an open, non-randomised trial- the rates of ACR-Ped-30, 50, and 70 responders receiving combined therapy with etanercept and MTX were higher than etanercept monotherapy. In fact, combined therapy increased the likelihood of achieve an ACR-Ped-70 response to 2.1 (95% CI 1.2 to 3.5).

Infliximab (3mg/kg) and MTX (10mg to 30mg/m<sup>2</sup>/week) led to a significant improvement in the number of active joints, pain as well as patient's and physician's global assessments of disease, ESR and CRP in a open study that included 24 patients with JIA (60). Fifty-four percent to 86.7% of patients met ACR-20 improvement criteria and 37.5% to 63.6% had "good response" according to Disease Activity Score in 28 joints (DAS-28). Thus, the combination of MTX and infliximab improved the clinical markers of disease activity of polyarticular JIA.

However, the results of a larger study were somewhat different (61). Specifically, the efficacy of placebo/methotrexate (oral or parenteral: 10-15mg/m<sup>2</sup>/week) was compared with infliximab (3mg/kg plus MTX) in a randomised, placebo-controlled, double-blind study for 14 weeks (61). This phase was followed by an all-active treatment extension through 44 weeks in which 122 children with persistent polyarticular JRA despite prior MTX therapy received infliximab at doses of 3mg/kg or 6mg/kg every eighth weeks. Interesting-

ly, there were no significant differences at the end of the double-blind phase between infliximab and placebo/MTX in the primary outcome measure because of the high reponse rate in the placebo/MTX arm. In the open label phase, the combination of infliximab and MTX showed that 44%, 40%, 33%, 24%, and 13% of the patients had reached ACR-Pedi-30, 50, 70, 90 response, and inactive disease status, respectively at week 204 (62).

Regarding adalimumab, the efficacy and safety of this TNF-blocker as monotherapy and combined therapy with MTX were compared with placebo/MTX in a randomised, double-blind, stratified, placebo-controlled, multicenter, medication-withdrawal study with a 16-week open-label lead-in phase, a 32-week double-blind withdrawal phase, and an open-label extension phase (63). Seventy-four percent of the patients who did not receive MTX and 94% of those MTX who received it had an ACR-Pedi-30 response at week 16. Furthermore, a higher rate of MTX-treated patients with adalimumab had an ACR-Pedi-30, 50, 70, and 90 responses in comparison with the group with adalimumab monotherapy throughout the open extension phase of the study.

## Safety

### *Monitoring of toxicity*

MTX is generally safe and well tolerated in children with JIA. MTX is seldom discontinued because of adverse events and its administration is rarely associated with serious adverse events (27). Nevertheless, MTX safety and tolerance should be closely evaluated. MTX monitoring includes some investigations before the start of the drug to exclude possible contraindications and pre-existing organ dysfunction. Investigations throughout the treatment are intended to monitor efficacy and identify potential adverse effects.

Clinical data and laboratory investigations before starting MTX therapy include height, weight, and body surface area, blood counts, CRP, ESR, liver enzyme and function tests (AST, ALT, alkaline phosphatase,  $\gamma$ -glutamyl-transferase, lactic dehydrogenase, bilirubin and proteins), hepatitis serology (B and

C virus), varicella-zoster virus serology (even if there is a history of chickenpox), renal function tests, urine analysis and tuberculin test. Laboratory examinations throughout treatment include blood cell counts, CRP, ESR, liver enzyme and function, renal function tests, and urine analysis. (34). Despite these suggestions -derived from literature review- there is no consensus on which and how often such clinical and laboratory should be actually performed. For example, two recent studies agree that routine blood tests every four to eight weeks in children with JIA are unnecessary since viral infections rather than MTX are most frequently involved in the development of significant abnormal blood tests (64, 65).

Routine invasive liver biopsies are not necessary since several studies have shown no long-term adverse effects or liver fibrosis in patients treated for a mean of 3.5 to 5 years (66). Liver biopsy is only indicated if pre-existing or a recently acquired liver disease is found (34).

MTX does not seem to affect the lung in children with JIA and therefore, pulmonary function tests are usually not necessary (67).

### *Gastrointestinal complications*

Gastrointestinal complaints, mainly nausea and epigastric pain are rare, but their intensity may require the withdrawal of MTX. The addition of folic acid may lessen such symptoms (34). Despite most children become tolerant to MTX or adapt to such complaints, some of them develop psychological adverse events, presenting as anticipatory nausea and behavioral distress induced by MTX. Van der Meer *et al.* (68) documented 29 JIA cases with these side effects and treatment with behavioural therapy adapted to age and systemic desensitisation (distraction in a positive atmosphere) or cognitive behavioural therapy (relaxation and overruling negative thoughts by positive ones) could be of help for these symptoms.

### *Liver toxicity*

MTX is associated with the potential for both acute and chronic hepatotoxicity (69). Cirrhosis of the liver has not

been reported in children with rheumatic diseases under MTX treatment and several studies (66, 70-73) reported liver biopsy findings as normal, even after long periods of MTX treatment (2.3 to 10 years) and with accumulated dose of 750mg to 5,300mg. However, the interpretation of these data deserves special attention because the small population studied (statistical type II error), the possibility of selection bias and the lack of control biopsies to distinguish the effects of the disease or concomitant medications on liver histology in MTX treated patients. Hashkes and coworkers (74) found 82% of biopsies classified as Roenigk grade I, 12% as grade II and 6% as grade IIIA, which suggest the need for long-term, prospective studies to define more accurately the risk of MTX-related liver fibrosis or cirrhosis.

### *Infectious complications*

Severe infections are very uncommon with low-dose MTX therapy and leukopenia is exceptionally rare (27). However, in the case of varicella infection, treatment with aciclovir is recommended. If exposure to varicella is documented and there is no immunity against the virus, prophylaxis with varicella hyperimmunoglobulin within 72 hours or treatment with aciclovir in the second week after incubation (*e.g.* days 7-9 after exposure) is recommended. Active varicella immunisation of susceptible children and family members may need to be considered before initiation of MTX therapy (75). Family members of MTX-treated patients who require polio immunisation should receive inactivated vaccine (75). There is lack of systematic studies addressing the question if MTX therapy can be continued during acute infections. Currently it is recommended to interrupt MTX therapy during anti-infective therapy (34).

### *Haematologic toxicity*

MTX therapy should be interrupted if leukocyte counts are  $<3000/\mu\text{L}$ , neutrophils counts are  $<1500/\mu\text{L}$ , or platelet counts are  $<100,000/\mu\text{L}$ . If there is persistent haematotoxicity, a lower dose of MTX (minimal dose  $10\text{mg}/\text{m}^2$



week) with supplementation of folic acid should be tried. If hematopoietic toxicity recurs, MTX therapy should be stopped (27, 34).

#### Teratogenicity and fertility

MTX is a powerful teratogen. Advice for contraception for sexually active teenage girls receiving MTX is required emphasising the need for planning pregnancies in order to discontinue MTX prior to conception. MTX is excreted in breast milk in low concentrations and is unknown whether this affects the newborn. Therefore women taking MTX should be advised not to breast-feed. There have not been any reports of azoospermia in JRA patients treated with low-dose MTX (34).

#### Folic acid supplementation

The anti-inflammatory effect of MTX is mediated by adenosine and it is independent of folic acid administration (27). Therefore, the concomitant use of MTX and folic acid may not reduce the efficacy of the former but may help to avoid the adverse events of MTX due to folate depletion.

One meta-analysis in adults patients (76) demonstrated that the administration of 1 to 5mg of folic acid, led to a significant reduction in adverse effects while preserving the efficacy of MTX therapy. In children, Hunt and collaborators (77) demonstrated in a small double-blind, placebo-controlled, crossover study that supplementation with folic acid (1mg/day) has no effect over MTX's anti-inflammatory efficacy. Therefore, in patients with minor adverse effects with MTX the use of folic acid at a dosage of 1 mg/day is feasible.

#### Concluding remarks

The use of MTX in children with JIA is supported by results of clinical trials and clinical experience throughout more than 20 years. Likewise, MTX has been an efficacious and safe in the short and long-term use. Some recent studies suggest that the combination of MTX and biologic agents could provide some more benefit to children with JIA than monotherapy with each of such drugs, but more trials are needed to confirm these observations.

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