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Use of methotrexate in juvenile idiopathic arthritis

A V Ramanan, P Whitworth, E M Baildam

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Methotrexate (MTX) has transformed the outlook for children with juvenile idiopathic arthritis (JIA). Most of the evidence from uncontrolled clinical trials suggests that MTX is an effective agent for treating active JIA. Data from controlled clinical trials suggests that MTX has statistically significant effects on patient centred disability measures in JIA patients with active arthritis. Although we would like a much larger study directed evidence base for our use of the drug, the studies that have been done are sound and have been followed by a change in clinical expectations and advice that speak of qualitative evidence from clinical practice, confirming the scientifically acquired data. Randomised controlled multicentre trials using sufficient numbers of patients, including functional assessment and quality of life measures, are needed to confirm the long term efficacy and safety of MTX in JIA.

The aim of modern treatment for juvenile idiopathic arthritis (JIA) is for rapid induction of disease control to prevent joint damage, to maximise physical function, and to achieve a normal lifestyle for our patients. Weekly methotrexate (MTX) is an established treatment in paediatric rheumatology, with its efficacy shown by a randomised controlled trial in children with severe JIA and borne out in many years of subsequent clinical use.[1] JIA is one of the most common chronic disorders in childhood, with a UK incidence of 1/10 000 and a prevalence of 1/1000.[2] There has been too little awareness of the major role played by modern treatment regimes in JIA where MTX has transformed the outlook for most children with severe disease

There is clinical experience and data from adult studies of early arthritis to suggest that there may be a window of opportunity whereby early aggressive intervention may buy long term disease suppression. Thus the concept of a therapeutic pyramid, with gradual addition of more active treatments, has been reversed. Treatment regimes are individualised depending on the subtype of JIA and according to individual response, to achieve maximum regression of disease.

In polyarticular JIA, MTX is the mainstay of treatment and is used as a first line agent, either alone or with initial pulses of methylprednisolone and/or multiple intra-articular steroid injections to achieve rapid disease control. The use of etanercept, either instead of, or in addition to MTX has added another step in improving the lot of the most severely affected patients.[3–5] However, etanercept is a new drug and hence deserves the usual cautions for use in children, whereas MTX now has a 16 year track record of safe and effective use in JIA.[6]

MTX is also used in other rheumatic diseases such as juvenile dermatomyositis, localised scleroderma, sarcoidosis, Wegener's granulomatosis, and some cases of systemic lupus erythematosus.[7] There are no controlled trials of the use of MTX in these rarer disorders but experience in treating JIA successfully has encouraged the same treatment principles to be tried.

MECHANISM OF ACTION

MTX is a folate analogue with an amino group (NH_2), methyl group (CH_3), and a fully oxidised pteridine ring, rendering the molecule inactive as a cofactor.[8] MTX binds dihydrofolate reductase (DHFR) with high affinity. It may also inhibit thymidylate synthase and interferes with the metabolic transfer of single carbon units in methylation reaction, especially those involved in synthesis of thymidylate and purine deoxynucleosides, which are essential components of DNA.[9]

Once administered, MTX is delivered to cells in the same way as the parenteral folates; 3–12% is hydroxylated in the liver and circulates as 7-OH MTX.[10] Intracellular MTX and 7-hydroxy-MTX (7-OH-MTX) are metabolised to polyglutamtes (MTX-glu) in the same manner as naturally occurring folates.[11]

MTX may also interfere with de novo purine biosynthesis by inhibition of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase, an enzyme in the purine biosynthetic pathway. Because there is a latent period of weeks before the MTX effects are appreciated in children with JIA, it may be that the intracellular MTX-glu derivatives are the true active anti-inflammatory agents.[12]

MTX-glu binds DHFR and has fairly high affinity for enzymes that require folate cofactor, including thymidylate synthetase (TS) and AICAR transformylase. The inhibition of TS, induced by MTX, interferes with DNA synthesis in actively dividing cells, and the increase of AICAR enzyme system, which plays a key part in the purine metabolism of the cell, leads to enhanced release of adenosine into the blood.[13–15]

Although the primary mechanism of action of MTX in JIA, or adult RA is not clearly known, recent reviews suggest that the anti-inflammatory effects of MTX seem to be related to

See end of article for authors' affiliations

Correspondence to: Dr A V Ramanan, 508, 77 Elm Street, Toronto, Canada M5G 1H4; avramanan@hotmail.com

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Abbreviations: DHFR, dihydrofolate reductase; JIA, juvenile idiopathic arthritis; NSAID, non-steroidal anti-inflammatory drug; JRA, juvenile rheumatoid arthritis; MTX, methotrexate; RA, rheumatoid arthritis

the extracellular adenosine release and its interaction with specific cell surface receptors.[12 16]

EFFICACY OF MTX FOR JIA

The short to medium term efficacy of MTX in children with JIA is now well established. A recent review by the Cochrane Database of Systematic Reviews only identified two controlled clinical trials from the literature. The study by Giannini *et al* forms the basis of the current use of MTX in paediatric rheumatological practice.[1] This was a six month randomised, double blind controlled multicentre study of 127 children with resistant juvenile rheumatoid arthritis (JRA) (mean age 10.1 years, mean disease duration 5.1 years); 63% of the group, treated with 10 mg/m^2 of MTX, improved compared with only 32% of those treated with 5 mg/m^2, and 36% of the placebo group. The assessment of efficacy was based on a composite of clinical and laboratory parameters and subjective scores. Global assessment was by physician and parent but did not include any functional assessment or radiographic examinations.

A more recent randomised, controlled, double blind crossover, multicentre study by Woo *et al* looked at the effectiveness and safety of orally administered MTX in extended oligoarticular and systemic arthritis.[17] This study used a MTX dose of 15–20 mg/m^2. A significant improvement occurred in three of the five core variables (ESR, physician's and parent's global assessment of disease activity) for the extended oligoarthritis group. Neither trial included functional outcomes as there were no validated outcome tools at the time.

The role of MTX in systemic onset JIA is still unclear. Woo *et al* showed significant improvement in only two of the five core variables (physician's and parent's global assessment of disease activity).[17] The systemic feature score was not significantly different between MTX and the placebo group in their study.

Early treatment with MTX, before the appearance of radiographic changes, may influence the outcome in children with systemic onset JIA.[18] MTX may also slow the radiographic progression of disease in JIA, especially if commenced early in the disease course, although the data are not conclusive and most studies were uncontrolled.[19 20]

PRACTICAL ISSUES

Dose and route of administration

In general, for children with JIA, MTX therapy is started at a dose of 10–15 mg/m^2/week or 0.3–0.6 mg/kg/week. However, children seem to tolerate much higher doses than adults and some series describe using up to 20–25 mg/m^2/week in children with refractory disease, with relative safety in the short term.[6 7] At doses more than 15 mg/m^2/week the parenteral route may be better because of the decreased oral bioavailability of the drug at high doses. It has been shown that subcutaneous administration of MTX has a 10–12% increased absorption compared with oral preparations.[21]

At the standard dose regime, 60–75% of patients with JIA benefit significantly from MTX therapy, with the maximum therapeutic effect usually becoming apparent 4–6 months after the beginning of treatment.

The issue of whether MTX acts in a dose dependent manner in JIA is still unclear. A recent multinational, randomised controlled study coordinated by the Paediatric Rheumatology International Trials Organization (PRINTO) compared higher dose (30 mg/m^2/week) MTX with medium dose (15 mg/m^2/week) in children with polyarticular JIA who failed to improve significantly on the conventional dose regimen (8–12.5 mg/m^2). There was a high rate of response to the conventional dose, with 72% improving significantly, and there was a significant improvement in the non-responders when the dose was increased to 15 mg/m^2. However, there was no added benefit of the 30 mg/m^2 dose over the 15 mg/m^2 dose.[22]

Oral treatment is satisfactory in most patients as a single weekly dose. Occasionally the liquid preparation is needed, but there are issues around handling a liquid cytotoxic in the community where instructions for handling of spillage and disposal of empty containers need to be clear. Subcutaneous MTX may be required and provided in prefilled syringes to the home, for self administration. The time of adolescence can add compliance difficulties.

The education and organisation of parents, children, and health professionals is essential to facilitate adherence, optimise efficacy, and monitor MTX safety. The reasons for using MTX, potential side effects, and the justification for monitoring, along with the precautions and safety mechanisms to deal with problem all form part of informed consent. The concerns of parents and children regarding efficacy and long term side effects are usually reassured by the lack of evidence for long term complications, with reversibility on cessation of treatment or dosage reduction of the short term side effects. Drug interactions are rarely significant at the low doses used in rheumatology, and non-steroidal anti-inflammatory drugs (NSAIDs) can be safely used together with MTX.

Guidelines on immunisation in the immunocompromised child should be followed. In particular, the use of live attenuated vaccines should be avoided and use of live polio vaccines in family members avoided. Children who are varicella zoster non-immune may be at risk of severe chickenpox infection and may require zoster immune globulin if in close contact, or treatment with oral or intravenous acyclovir if they acquire an infection with the virus.

MTX is not licensed in the UK for use in JIA, other connective tissue diseases, and vasculitis, but this is not an uncommon situation with drug treatments in children.

Folic acid supplementation

Although it is standard practice by most paediatric rheumatologists to use folic acid or folinic acid along with MTX, there is little consensus on the regime and even less evidence supporting the use of folate supplementation in children with JIA on MTX. A recent multicentre randomised, double blind placebo controlled study on the effect of folate supplementation in adult rheumatoid arthritis shows that it reduced the incidence of increased liver enzyme levels during MTX therapy and as a consequence, MTX was discontinued less frequently.[23] However, this study showed that folate supplementation had no effect on the incidence, severity, and duration of other adverse effects, including gastrointestinal and mucosal side effects.

One approach to folate supplementation is to prescribe 1 mg tablets of folic acid daily, for all children begun on oral or subcutaneous MTX. Other combinations used include: (1) not giving folate at all unless the patient develops side effects such as oral ulcers; (2) skipping folic acid on the day before and/or after MTX administration; and (3) giving 2.5–5.0 mg of folic acid once a week two days after MTX administration. There are no clinical trials in childhood to support either regime, and the least frequent dosing is often used for reasons of patient compliance. Children are more likely than adults to have an adequate intake of folic acid in their diet, through enriched foods such as breakfast cereals or vitamin supplements.

When to discontinue MTX

The question of when, how, and by what criteria to attempt withdrawal of MTX therapy in JIA is still more a clinical art than a science. "Remission" is a controversial concept in JIA. The criteria for "remission" or "relapse" have never been operationally defined and then prospectively tested in JIA. In literature on JIA, the cited criteria for remission are often subjective and have not included long term physical and

Table 1 Reported adverse effects in children treated with MTX

	Reference								
	6	7	31	32	33	34	1	35	Total
Patients	19	23	12	19	30	62	86	26	277
Therapy duration									
Mean (months)	10.5	19.2	6	18.5		27	6		
Range (months)	4–10	6–52	6	8–39	6–30	19–65		6–72	4–72
MTX dose									
mg/m^2/wk	4–17		8–25	5–15		5–20	5 or 10	10–15	
mg/kg/wk		0.1–0.6			0.4–0.8				
Adverse effects									
Gastrointestinal symptoms	2	0	1	2	6	14	8	0	33 (11.91)
Peptic ulcer	0	0	ND	0	0	4	0	1	5 (1.80)
Stomatitis	1	0	ND	1	0	0	2	1	5 (1.80)
Mouth ulcers	1	0	1	0	2	0	1	0	4 (1.44)
Rashes	0	0	ND	0	ND	0	1	0	1 (0.36)
Alopecia	ND	0	ND	0	ND	2	0	0	2 (0.72)
Jaundice	0	0	ND	0	ND	ND	0	1	1 (0.36)
Bacterial infections	0	0	ND	ND	ND	4	0	ND	4 (1.44)
Herpes zoster	1	0	0	0	1	1	0	ND	3 (1.08)
Mood changes	0	ND	1	ND	ND	ND	0	ND	1 (0.36)
Liver function test elevations	3	10	1	1	3	9	1	4	25 (9.03)
Haematuria	0	0	0	0	0	0	0	0	0 (0.00)
Leucopenia	0	0	0	0	1	0	0	0	1 (0.36)
Anaemia	0	0	0	0	0	1	0	0	1 (0.36)
Proteinuria	3	0	0	0	0	0	0	0	3 (1.08)

Modified from Singsen *et al*.[36]
*ND, not determined.

Table 2 Baseline information to be obtained before commencing MTX

Height, weight, and body surface area
Full blood count and differential white cell count
ESR +/– C reactive protein
Transaminases
Renal function tests
Urinalysis
Varicella titre, even if there is a history of chickenpox*
MMR titres, if none or primary dose only has been given*

*If the child proves to be negative to any of the above, ideally vaccination should be offered prior to commencing MTX.

functional outcomes. MTX withdrawal may result in disease flare in more than 50% of patients as shown by Ravelli *et al*, a feature also noted by others.[24 25] The ease with which remission is achieved when MTX is re-established is still unclear. Reported rates of "remission" in JIA treated with MTX vary from 6.9 to 45%; the average duration of MTX treatment until "remission" is around one year at a weekly dose of 10–15 mg/m.[26]

Side effects

Nausea is infrequent and may be lessened by the use of folic acid, splitting the dose over 12–24 hours, parenteral dosing, or the use of antiemetics such as ondansetron. Consideration needs to be given to the psychological support of children/young persons on MTX, in whom habitual nausea may sometimes occur. Table 1 shows the reported list of adverse events seen in children treated with MTX from various trials.

Although in vitro studies have shown that MTX has mutagenic and carcinogenic potential, in vivo studies in animal models have failed to show any carcinogenicity. To date, there are only five case reports of lymphoma seen in children treated with MTX.[27] Long term prospective studies with appropriate controls are needed to define the risk of malignancies in MTX treated children.

High doses of MTX as used in cancer chemotherapy have been shown to be teratogenic ("fetal aminopterin syndrome").[28] The effect of low dose weekly MTX on fetal development is not clear. Based on case reports from the 1950s, the suggested critical dose by one report is >10 mg weekly.[29 30] The 6–8 week period of gestation is thought to be the critical period according to some reports.[30] On current evidence, the best practice would be to counsel all youngsters of child bearing age to practice effective contraception during the course of treatment. They often confuse the reduction in fertility which occurs while taking the drug with a safe contraceptive alternative and this needs to specifically addressed in all cases. Other lifestyle issues include advice to limit the use of alcohol while on MTX in order to minimise the risk of liver enzyme disturbance.

Monitoring MTX

Table 2 lists the baseline information to be obtained before commencing MTX. Full blood count and liver function monitoring is required fortnightly until a stable dose is achieved. Thereafter monthly monitoring for six months, increasing to six weekly is the usual practise. Urea and electrolytes and creatinine should be checked six monthly. The responsibility for initiating this monitoring rests with the initiating centre but can be shared with their district consultants or general practitioners with appropriate shared care guidelines. The use of parent/patient held shared care monitoring booklets can prove invaluable in this situation.

Children generally tolerate MTX well. Haematological abnormalities are rare. Intercurrent infections may cause transient dips in white cell count and/or neutrophils. Transient elevations of liver function enzymes, often with concurrent infections, usually settle without any action. A small percentage of children/young people develop persistent or frequently raised liver function tests. This is often a dose dependent phenomenon. Current guidelines allow the transaminases to be raised up to twice the upper limit of normal. If transaminitis persists or increases further, MTX is discontinued for two doses or the dose reduced, after which the liver enzymes are rechecked. If levels have returned to normal, MTX can be recommenced at the current dose; if further elevations occur, the MTX dose should then be reduced by 20%. Although these precautions are taken there is still little evidence of significant long term toxicity or liver damage caused by MTX.

Monitoring guidelines

- AST (or ALT) >2 times above upper level of the normal range
- Full blood count
  - Platelets $<150 \times 10^9$/l
  - White cell count $<3.5 \times 10^9$/l
  - Neutrophils $<1.5 \times 10^9$/l
- Rash or severe oral ulcers, new or increasing dyspnoea or cough

Action: For any of the above, withhold dose and discuss with paediatric rheumatologist.

Authors' affiliations
A V Ramanan, E M Baildam, Department of Paediatric Rheumatology, Royal Manchester Children's Hospitals, Charlestown Road, Manchester, UK
P Whitworth, Department of Paediatric Rheumatology, Birmingham Children's Hospital, Birmingham, UK

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