Use of Methotrexate in the Treatment of Juvenile Idiopathic Arthritis

MANIK KUMAR TALUKDER[1], SHAHANA A RAHMAN[2]

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood[1]. It is a significant cause of both short and long term disability. The aim of modern treatment for juvenile idiopathic arthritis is rapid induction of disease control to prevent joint damage, to maximize physical function and to achieve a normal lifestyle[2]. During the past years, remarkable advances in the treatment of JIA have been made with the advent of new disease modifying anti-rheumatic drugs (DMARDs). They work to decrease pain and inflammation, reduce or prevent joint damage, and preserve the structure and function of the joints[3]. There are clinical experiences and data from different studies, suggesting that early use of DMARDS may induce long term disease suppression. Thus the concept of a therapeutic pyramid, starting with non steroidal anti-inflammatory drugs (NSAIDS) with gradual addition of more active treatments, has been reversed.[2-4]

Commonly used DMARDS are Methotrexate (MTX), Sulfasalazine, Hydroxychlroquine and leflunomide. MTX has been recognized as the most effective disease modifying antirheumatic drug (DMARDs). Because it is given in low doses, there is less side effects, it is very effective and cheap[5]. Methotrexate can be used in all types of JIA but in polyarticular and systemic onset types, it is the first drug of choice.

MTX was synthesized in the 1940s as a specific antagonist of folic acid and designed to inhibit dihydrofolate reductase[3]. Since then MTX was been used primarily to treat malignancies including leukemia, lymphoma, osteosarcoma and choriocarcinoma. Since last few decades MTX in low weekly dose (5-30mg/m^2) has also been used to treat many rheumatic diseases like JIA, SLE, scleroderma, dermatomyositis etc. as well as many non-rheumatic conditions, including inflammatory bowel disease and uveitis.[6,7] Over the years of clinical use, MTX has transformed the outlook for children with JIA, and it is considered as the gold standard therapy for patients with JIA[2]. This review article is written with the aim to highlight different aspects of MTX in the treatment of JIA.

Mechanism of action of MTX in JIA:

MTX is a folate antagonist with an amino group (NH_2), methyl group (CH_3), and a fully oxidized pteridine ring, rendering the molecule inactive as a cofactor. In low doses (7.5-30mg/m2) MTX causes the following effects[2,3,8,9]:

1. Decrease in pro-inflammatory cellular signaling: It reduces the production of pro-inflammatory monocytic/macrophagic cytokines (IL1, IL6 and TNFα). This ultimately results in increased gene expression of anti-inflammatory Th2 cytokines (IL4 and IL10), and decreased gene expression of proinflammatory Th1 cytokines (IL2 and INFã), which in turn cause anti-inflammatory effects.
2. Immunosuppressive and lymphotoxic effects: MTX polyglutamase inhibit the enzyme 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) transformylase. As a result there is increased AICAR level which inhibits the degradation of adenosine-5-p and adenosine by the AMP deaminase and adenosine deaminase (ADA) respectively. As a result, there is increased accumulation of intra-acellular and extra-cellular adenosine-5-p and adenosine at the site of inflammation. Adenosine binds to adenosine surface receptor A_2 with resultant inhibition of neutrophil adherence to endothelial cells and fibroblast causing anti-inflammatory effects. This also increases intracellular cAMP. This cAMP in turn leads to immunosuppression by inhibition of phagocytosis, inhibition of secretion of TNF, IFNã, IL2 and many others.
3. MTX inhibits the neutral metalloproteinase and collaginase enzymes, thereby inhibiting the destruction of articular cartilages and synovial tissue.
4. Reduction of leukocyte proliferation: It binds more tightly to dihydrofolate reductase (DHFR) and

1. MD Final part student, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
2. Professor of Paediatrics, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
Correspondence: Dr. Manik Kumar Talukder

results in a marked reduction in the production of tetra hydrofolate. As a result production of DNA and RNA is decreased[9]. When high doses of MTX (500-80000 mg/m^2 per week) are used to treat malignancy, profound folate depletion halts the production of DNA and RNA causing cell death, particularly in rapidly dividing cells.

Absorption and kinetics

After administration, methotrexate has a relatively short half- life in plasma, 80-90% of the drug is cleared up by the kidney in less than 24 hours. Any decrease in glomerular filtration rate can prolong tissue exposure to MTX and increase the risk of toxicity[8].

Methotrexate rapidly enters cells and is polyglutamated by hepatocytes, red cells, fibroblast, bone marrow myeloid precursor, and possibly other cells. Although methotrexate is cleared rapidly by the kidneys, polyglutamated MTX accumulates intracellularly. The single weekly dose of MTX is found to be effective in children, i.e., 0.3-1.0mg/kg (10-30mg/m^2) are considerably higher than the weekly doses usually given for adult patients. Usually children can tolerate much higher doses of MTX than adults[1]. The route of administration is an important factor for children since at times much higher doses are required, which is not very well absorbed by oral route (>0.3 mg/kg, >10mg/m^2). The amount of MTX absorbed by children has a wide inter-patient variability as well[10]. After starting treatment with MTX, a minimum of 2 to 3 months are usually needed for getting adequate response.

Route of administration of MTX in JIA

At present there is no clear consensus about the route of administration of MTX in JIA patients. It differs between countries and rheumatologists according to the prevailing medico-social system and legislation. MTX may be given orally or parenterally. Most commonly used route is oral route. Several studies have demonstrated that children absorb methotrexate at different rates[10,11]. Absorption depends on variables such as the amount of food in the stomach (if given orally), dose and the route of adminstration[10].

Parenteral administration is more effective than oral because there is about 10% to 12% increased absorption and less side effects[12]. There is no significant difference of pharmacokinetics of MTX between intramuscular (IM) and subcutaneous (SC) route. Several studies had been done for comparing the efficacy and tolerance of SC and IM MTX[13,14]. These studies did not find any difference in efficacy between SC and IM route. But at the same time, it had been shown that SC was more convenient, less painful and easier to administer. Therefore, it is recommended by some author that all children currently receiving IM methotrexate should be switched to the SC route and in the future only SC route should be prescribed[14]. Quite low dose of MTX is used in JIA, so intravenous route is not recommended for it.

Subcutaneous MTX is administered by using an insulin syringe and it is very easy and safe to administer. So, parents/caretakers and older children themselves can take it at home if they are taught the technique properly. Till date no local side effects related to SC methotrexate is reported.

Advantages of home administration of subcutaneous MTX[14]:

- It is cost effective and the patient has a greater degree of independence.
- The advantage for children, young people and their families are:

1. Not missing school/work, no need to spend time traveling to and waiting for healthcare personnel.
2. Decrease fear that only health professional can administer SC methotraxate.
3. A more consistent approach to care**.**
4. Child or young person can self administer, thereby increasing independence and concordance.

Dose of methotrexate in JIA

Unlike adults, dose of MTX in children is usually calculated by body surface area (BSA) rather than weight alone because, this is a more accurate calculation in growing children[12]. It is widely acknowledged that, since MTX is cleared from the body more rapidly in children than in adults, children can tolerate much higher doses. Some reports show children receiving MTX at 20 to 25mg/m^2/week for refractory JIA cases[2]. There had been a multi-national randomized trial looking at the safety and efficacy of methotrexate in JIA in medium (15mg/m^2/week) versus high dose (up to 30mg/m^2/week) in polyarticular JIA, who failed to improve with the standard dose (10mg/m^2/week). This study showed that MTX efficacy platue was reached at 15mg/m^2/week, and further increase in the dose did not give any additional benefit[15].

Children therefore usually started MTX with doses between 10mg to 15mg/m^2/week.

Storage

Tablet MTX is usually available in 2.5 mg strength and it is yellow in colour. Injection MTX is a clear yellow solution that is usually available in 50 mg/2 ml strength. Both the tablet and injection should be stored at normal temperature but out of direct sunlight[12].

Side of effects of MTX

Gastrointestinal toxicity is the most common adverse effect and occurs in 13% of the patients.[1] Additional side effects include hepatotoxicity, oral mucosal ulcerations, immuno-suppression, pancytopania, pulmonary disease and increased risk of lympho-proliferative malignancies. The toxicity of MTX is related more to the length of exposure than to the dose given[6]. Liver enzyme (ALT) level may be increased about two to three times of upper limit than normal. But in the majority, that is transient and usually becomes normal within two to three weeks.

Hepatotoxicity is one of the greatest worries with the long term use of MTX. But fortunately, cirrhosis has not been reported in children using MTX for rheumatic diseases. Several small studies did not reveal any significant liver biopsy abnormalities in children with JIA after 2.3-6.0 years of treatment with MTX[6,8].

Gonadal function and reproduction are not altered by MTX. However, both males and females should wait for 3 months after discontinuing MTX before trying to conceive because MTX is a powerful teratogen[8].

Contraindications of methotrexate[2,12]

Renal or liver failure

Blood report abnormalities:

- White cell count $<3.5\times10^9$/L
- Neutrophil count $<1.5\times10^9$/L
- Platelet count $<150\times10^9$/L
- ALT level >2 times above upper level of normal range
- Immunodeficiency state
- Child coming in contact with chicken pox or develops chicken pox

Monitoring of treatment

Before starting treatment with MTX, base line investigations like complete blood count (CBC) including Haemoglobin estimation, total WBC count (TC), differential count (DC), platelet count, ESR, liver enzyme (ALT), serum creatinine and urine for routine examination should be done. After that patients should be monitored initially after 4 weeks and then every 4-6weekly[1]. In every follow up visit investigations like CBC, ESR, ALT, Serum creatinine and Urine for routine examination should be monitored. Other investigations like urine for C/S, chest X-ray, blood culture, etc. should be monitored if indicated.

Folic acid supplementation

Methotrexate is a folic acid antagonist that decreases folic acid uptake at cell level. As folate deficiency has been thought to play an important role in the development of methotrexate related side effects, folic acid supplementation is used as a standard practice by most paediatric rheumatologist to reduce the side effects. Supplementation with folic acid has been shown to lessen the gastrointestinal and mucocutaneous side effects without altering the therapeutic effects of MTX.

However, there remain some differing opinions about the dose and frequency of folate supplementation necessary to reduce adverse effects, and the possible impact this might have on methotrexate efficacy[16]. One approach to folate supplementation is to prescribe folic acid daily, for all children begun with oral or subcutaneous MTX. Other opinions are: (1) not giving folate at all unless the patient develops side effects such as oral ulcer; (2) skipping folic acid on the day/ or after MTX administration; and (3) giving 2.5 to 5 mg of folic acid once a week two days after MTX administration. There are no clinical trial done in childhood to support either regime, and least frequent dosing is often used for patient compliance point of view.

Discontinuation of MTX

The optimal time for discontinuing MTX in children with JIA who have achieved complete control is not yet well established. However it is well recognized that methotrexate should be continued for many months to years after a remission has been achieved. Remission is a controversial term in JIA. It is often subjective and does not include long term physical and functional outcomes. MTX withdrawal may result in disease flare in more than 30% to 50% of patients[17-20]. One study found that there was no difference in the number of relapses between patients with prolonged or early discontinued MTX treatment. Longer duration of MTX treatment after induction of remission does not generally improve the status of remission in patients with JIA. Ultimately it is the residual synovial

inflammation which seems to influence the rate of relapses after discontinuation of MTX treatment[21]. Another study recommended that patients maintaining remission for 1 year can gradually discontinue MTX to reduce potential long term toxicities[22].

Conclusion:

Methotrexate is a unique and versatile drug for the treatment of JIA. It is cheap, available and a very effective drug. More over, as because it needs only once weekly dosing, there is chance of better compliance. It has minimum short -term and long – term side effects than any other drugs with similar efficacy. So, its use should be maximized. Early use of appropriate dose of MTX in JIA patients result slowing or inhibiting joint damage and thereby improve the quality of life. Subcutaneous (parenteral) route of MTX is more effective because of more bioavailability and less side effects.

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