

# Therapeutic role of methotrexate in pediatric Crohn's disease

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## ABSTRACT

The main role of therapy in Crohn's disease (CD) is to achieve long-term clinical remission, and to allow for normal growth and development of children. The immunomodulatory drugs used for the maintenance of remission in CD include thiopurines (azathioprine and 6-mercaptopurine) and methotrexate (MTX). Development of hepatosplenic T-cell lymphoma in some patients with inflammatory bowel disease, treated with thiopurines only or in combination with anti-tumor necrosis factor agents, resulted in a growing interest in the therapeutic application of MTX in children suffering from CD. This review summarizes the literature on the therapeutic role of MTX in children with CD. MTX is often administered as a second-line immunomodulator, and 1-year clinical remission was reported in 25–69% of children with CD after excluding for the use of thiopurines. Initial data on MTX effectiveness in mucosal healing, and as a first-line immunomodulator in pediatric patients with CD, are promising. A definite conclusion, however, may only be made on the basis of additional research with a larger number of subjects.

KEY WORDS: Methotrexate; Crohn's disease; children; therapy; MTX; thiopurines; immunomodulator; remission

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## INTRODUCTION

Crohn's disease (CD) is an inflammatory disease of the gastrointestinal tract with a growing global incidence, ranging from 2.5 to 11.4 per 100,000 in the pediatric population [1]. CD is characterized by a spectrum of inflammatory lesions of the gastrointestinal tract mucosa, with mild aphthous ulcerations at one end, and severe deep serpiginous ulcers and cobblestoning at the other end of spectrum (Figure 1 and 2). More aggressive forms of CD are observed in children compared to adults. Furthermore, the course of the disease may vary between patients and it may significantly affect not only the quality of life, but also the growth and development of children.

Among immunomodulatory drugs, thiopurines (TPs) such as azathioprine (AZA) and 6-mercaptopurine (6MP) have been considered the first-line therapy for the maintenance of remission of CD in children. In patients without a response or with intolerance to TPs, methotrexate (MTX) has been used

as an alternative immunomodulatory agent. Moreover, in the last two decades, there was a significant increase in the use of MTX as a first-line immunomodulatory drug in the treatment of pediatric CD, due to occurrence of hepatosplenic T-cell lymphoma (HSTCL) in some young male patients treated with TPs, independently or in combination with anti-tumor necrosis factor (TNF) agents, as well as because of clinical experience that indicates effectiveness and a good safety profile of MTX [2-6]. Although in a smaller number of patients, recent studies indicated that MTX is effective for mucosal healing (MH) in children with CD and also in patients who underwent a combined treatment regimen with anti-TNF agents, resulting in a significantly extended durability of biological drug [7,8].

## METHOTREXATE MECHANISM

MTX is a competitive antagonist of folic acid which, at high doses, produces a cytotoxic and antiproliferative effect by inhibiting dihydrofolate reductase and thus blocking DNA and RNA synthesis. Due to this activity, MTX has been used since the 1950s in the treatment of patients with leukemia and different types of malignant tumors.

When given in small doses (5–25 mg, once a week), MTX acts as an immunomodulator and does not exhibit

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any cytotoxic or antiproliferative effects [9]. Although different mechanisms of action have been proposed for low-dose MTX, the exact mechanism of its anti-inflammatory effect is still not clear. One of the proposed modes of action is that MTX causes an increase in the intracellular and extracellular concentrations of adenosine via accumulation of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), and adenosine, in turn, leads to the reduced production of proinflammatory agents such as leukotriene B<sub>4</sub> (LTB<sub>4</sub>), TNF- $\alpha$ , interleukin-6 (IL-6) and IL-8, as well as increased synthesis of anti-inflammatory IL-10 and IL-1 receptor antagonists [10-14]. In addition, adenosine likely has an inhibitory effect on neutrophil chemotaxis and neutrophil adhesion to endothelial cells [9,14].

Low-dose MTX has been used for the treatment of many inflammatory diseases in children, including CD, juvenile rheumatoid arthritis, juvenile dermatomyositis, uveitis, and psoriasis [15].

## METHOTREXATE PHARMACODYNAMICS AND DOSAGE

MTX may be administered to CD patients perorally or parenterally (i.e. subcutaneously and intramuscularly). After peroral administration, MTX resorption is complete, reaching the maximum serum concentration after 30–60 minutes [16]. Studies in adult patients with stable CD indicated significant individual differences in drug absorption after peroral administration of MTX, with the average variability in oral MTX bioavailability of 73% of that of subcutaneous administration [16,17]. On the contrary, in a study on 11 pediatric patients with inflammatory bowel disease (IBD), bioavailability was not significantly different between oral and subcutaneous administration of MTX [18].

Nevertheless, head-to-head studies comparing the effectiveness of parenteral and subcutaneous administration of MTX are currently lacking. In retrospective analysis based on propensity score method, Turner et al. compared the effectiveness of oral versus subcutaneous MTX in children with CD [19]. Their results indicated that subcutaneous administration was not absolutely superior to peroral administration of the drug. Therefore, the authors suggested switching children to the oral therapy after complete remission is achieved with subcutaneous MTX, with regular monitoring of inflammatory markers and growth in children [19].

The recommended dose of MTX in the treatment of pediatric CD is 15 mg/m<sup>2</sup> once a week, which may be increased to a maximum dose of 25 mg MTX (administered subcutaneously or intramuscularly) [20]. In clinical remission for more than 3–6 months, the weekly dose of MTX should be reduced

to 10 mg/m<sup>2</sup> (maximum 15 mg). All patients should take folic acid in a daily oral dosage of 1 mg or 5 mg in one dosage during the period of 24–72 hours after MTX intake, to avoid the side effects of MTX, particularly those related to the digestive tract and leukopenia [21,22]. In addition to hospital administration of MTX, subcutaneous therapy of MTX was successfully administered to children with CD in their community setting, after nurse-led education of parents and children [23].

## METHOTREXATE EFFECTIVENESS

Up to date, 10 retrospective and 1 prospective study showed that MTX was effective in the maintenance of remission for 1 year, in 25–69% of TP-resistant and TP-intolerant pediatric patients with CD (Table 1) [6,7,19,24-32].

In a large multicenter study, 113 pediatric CD patients in remission, 7–17 years of age, were followed for at least 12 months while on MTX monotherapy [32]. Out of 113 patients, 75 patients (66%) did not show response to TPs, while 38 patients (34%) were TP-intolerant. After 12 months of MTX therapy, 52% of patients were still in stable clinical remission, however the percentage decreased to 29% after 24 months. A significant difference between TP-intolerant and TP-resistant patients was not observed. The authors concluded that MTX maintenance therapy should be considered before transition to anti-TNF agents [32].

In a retrospective longitudinal cohort study, Turner et al. examined 60 pediatric CD patients undergoing MTX therapy, in whom TP therapy had been stopped due to either ineffectiveness or undesired effects [28]. In 42% of the patients, treatment with MTX resulted in steroid-free remission lasting a year after the onset of the therapy. In 7 out of 11 patients with perianal fistula at baseline, the complete fistula closure was observed after 1 year of therapy. Also, good clinical response to MTX was associated with increased height velocity in children, possibly due to positive effect of MTX on MH [28].

According to the new European guidelines, MH is the ultimate goal of therapy in CD patients [20]. Early administration of immunomodulatory and biological drugs to pediatric CD patients may result in MH, changing the course of the disease, and leading to better long-term outcomes with minor complications, as well as allowing for normal growth and development of children with CD. In a recently published study by Santha et al. [33], MH estimated on the basis of a Simple Endoscopic Score for CD was achieved in 45% and histological healing (HH) in 46% out of 76 pediatric CD patients in clinical remission, using various therapeutic options [33].

Hojsak et al. published the first report on the efficacy of intramuscular administration of MTX to achieve MH in pediatric CD patients [7]. These authors followed 32 patients treated with MTX for  $\geq$ 12 months after failed AZA treatment.

**TABLE 1.** Effectiveness of methotrexate in pediatric Crohn's disease

Reference	Number of centers/ Number of patients	Previous IS treatment	MTX treatment	Primary outcome	Remission rate
Mack et al. [25]	1/14	6MP	sc, qw	PCDAI $\leq$ 10	50% at 3 mo
Uhlen et al. [26]	3/61	AZA	im (n=51), sc (n=10), qw	HBI $\leq$ 4 CS-free Fistula closure	39% at 3 mo 49% at 6 mo 45% at 12 mo
Ravikumara et al. [27]	1/10	AZA	sc or im (n=9), po (n=1), qw	Symptom-free Normal IM	7 (70%) achieved remission
Turner et al. [28]	4/60	6MP/AZA	sc (n=43), po (n=5), sc $\rightarrow$ po (n=12), qw	PCDAI $\leq$ 10 CS-free	42% at both 6 and 12 mo
Weiss et al. [29]	5/25	6MP/AZA (n=25) IFX (n=14, stopped in 11)	sc (n=19), po (n=6), qw	HBI $\leq$ 4, CS-free No escalation of therapy (IFX)	16 (64%) achieved remission
Boyle et al. [30]	1/27	6MP/AZA	sc (n=26), po (n=1), qw	PGA CS-and IFX-free	48% at 6 mo 33% at 12 mo
Willot et al. [31]	1/63	6MP (n=61) IFX (n=16)	sc (n=61), im (n=1), po (n=1), qw	HBI $<$ 4, CS-free Fistula closure	29% at 3 mo 37% at 6 mo 25% at 12 mo
Sunseri et al. [6]	19/172	6MP/AZA (n=91) Without immunomodulators (n=81)	qw, mean dose 12.7 mg/m <sup>2</sup> (in remission), 12.4 mg/m <sup>2</sup> (not in remission)	PGA I, CS-, TP-, anti-TNF-free or surgery-free for $>$ 1 year	31% had sustained clinical remission
Turner et al. [19]	10/226	6MP/AZA (n=200) Without immunomodulators (n=26)	po (n=38), sc (n=90), qw sc $\rightarrow$ po (n=98)	PCDAI $\leq$ 10 No fistula discharge at 6 and 12 mo No need for: CS, anti-TNF and surgery	34% had sustained CS-free remission
Haisma et al. [32]	10/131	6MP/AZA	sc (n=105), po (n=8), qw	PCDAI $\leq$ 10 No need for CS, anti-TNF or EEN	52% at 12 mo
Hojsak et al. [7]	1/32	AZA	im, qw	PCDAI $\leq$ 10 CS- and EEN-free MH (SES-CD: 0)	69% at 12 mo, 14 (44%) during whole follow-up (1–4.8 years), MH 8/14 (57%)

MTX: Methotrexate; 6MP: 6-mercaptopurine; AZA: Azathioprine; anti-TNF: Anti-tumor necrosis factor agent; IFX: Infliximab; po: Peroral; sc: Subcutaneous; im: Intramuscular; qw: Once weekly; MH: Mucosal healing; PCDAI: Pediatric Crohn's disease activity index; CS: Corticosteroid; EEN: Exclusive enteral nutrition; TP: Thiopurines; HBI: Harvey-Bradshaw index; PGA: Physician Global Assessment; IM: Inflammatory markers; mo: Months; IS: Immunosuppressive; SES-CD: Simple endoscopic score for Crohn's disease

Out of the total number of patients, 22 (68.7%) were in stable clinical remission after a 12-month period, while in 14 patients (43.8%) no clinical relapse was noted during the entire follow-up period, lasting from 1 to 4.8 years. At the end of follow-up period, endoscopy was performed in 8 (57%) out of 14 patients in stable clinical remission. Complete endoscopic MH was demonstrated in all 8 patients, while HH was detected in 7/8 patients.

The growing clinical experience on the effectiveness and safety of MTX monotherapy, as well as the observed association of HSTCL with TP therapy, resulted in a significant increase in MTX application at several medical centers, during the last two decades [6].

To date, there are no head-to-head comparative studies on MTX and TP effectiveness as first-line immunomodulators in pediatric CD remission maintenance. In different studies, TPs showed significant effectiveness as a first-line therapy in remission maintenance and relapse prevention in children with CD. For instance, Riello et al. reported that 60% of patients with CD in their group successfully maintained remission after 6 months of AZA therapy. However, after 12 months, this number was reduced to 40% [34].

On the other hand, data on the effectiveness of MTX as a first-line immunomodulator are still insufficient. The Pediatric

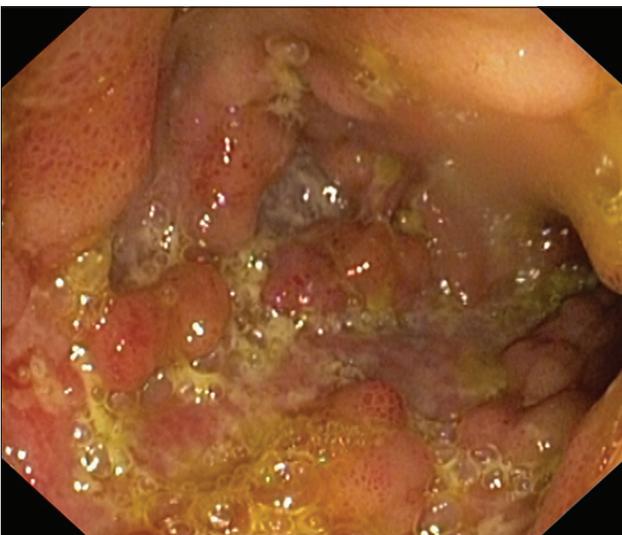
IBD Collaborative Research Group retrospectively investigated the effectiveness of MTX as a first- and second-choice immunomodulator in remission maintenance in children with CD [6]. Out of 81 patients in whom MTX was administered as a first-line immunomodulatory drug, 22 patients (27%) achieved stable clinical remission that lasted at least 12 months. In 91 patients, MTX was administered as a second-line immunomodulator after TP therapy. One-year remission was recorded in 32 (35%) patients. There was no significant difference in the MTX effectiveness between those two groups of patients [6].

MTX can be administered in a combination with anti-TNF agents to prevent the production of anti-drug antibodies and, consequently, to increase the durability of biological drug. In a recent pediatric study, males demonstrated higher durability of infliximab therapy when administered together with MTX over a 6-month period, compared to patients administered with MTX for a shorter period or those who were not treated with MTX [8]. Moreover, MTX was more effective in achieving extended durability of infliximab therapy compared to TPs.

There has been an ongoing debate regarding the optimal MTX dose and the route of administration for its concomitant use with anti-TNF agents. For example, a low oral MTX dose



**FIGURE 1.** Endoscopic appearance of Crohn's disease (aphthous ulcers) in the descending colon of a 14-year-old male.



**FIGURE 2.** Endoscopic appearance of severe Crohn's disease (deep serpiginous ulcers and cobblestoning) in the terminal ileum of a 16-year-old male.

of <10 mg once a week had no effect in reducing infliximab immunogenicity in pediatric patients with CD [35]. However, additional studies are needed to estimate the effects of higher MTX doses in these patients.

## METHOTREXATE SAFETY AND SIDE EFFECTS

Due to its teratogenic effect, MTX is contraindicated during pregnancy and in the lactation period. Also, live vaccines should not be administered to MTX-treated children, due to immunosuppression. Vaccination with live vaccines should be performed at 3 weeks before initiating therapy or 3 months after the termination of immunomodulatory therapy [36].

In children with CD, low-dose MTX therapy usually shows no serious side effects. If these effects occur, they

typically elapse after dose is reduced or therapy is discontinued. The most common side effects of MTX include nausea, vomiting, and an increase of transaminases. Nausea occurs in 9–26% of CD children on therapy [29,30] and is one of the most frequent reasons for therapy discontinuation. In some children, this side effect may present as so-called anticipatory nausea. Preventive peroral administration of ondansetron at 30–60 minutes before subcutaneous administration of MTX, for 4–8 weeks, may successfully prevent nausea in a majority of patients [37].

In a meta-analysis, Valentino et al. [38] analyzed the results of 12 studies on the hepatotoxic effect of MTX in children with IBD, and found that hepatotoxicity developed in approximately 10% out of 457 cases. MTX-associated hepatotoxicity was the reason for dose reduction in 6.4% and therapy discontinuation in 4.5% of the cases [38]. Significant liver fibrosis is rarely found in adult patients with IBD or rheumatoid arthritis who were treated with MTX, but is more frequently observed in psoriatic patients [39–41]. Liver biochemical tests should be conducted on a weekly basis in the first 4 weeks of therapy, and then, once every 2–3 months [21].

Other complications of MTX administration include myelosuppression, rash, diarrhea, stomatitis, headache, fatigue, and hypersensitivity pneumonitis. The drugs that may intensify the toxic effects of MTX, if used simultaneously, include trimethoprim-sulfamethoxazole (folate antagonist), acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, penicillin, and probenecid [9].

## CONCLUSION

MTX is an inexpensive drug with a good safety profile, and it demonstrates high effectiveness as a second-line immunomodulator in children with CD after TP discontinuation. Although the initial experiences are encouraging, future prospective studies with a larger number of patients are needed to generate a definite conclusion, both on MTX effectiveness as a first-line immunomodulator as well as on its efficacy in MH. Further studies should also clarify the optimal MTX dose and the route of administration in the case of concomitant use of MTX with anti-TNF agents in children.

## DECLARATION OF INTERESTS

The authors declare no conflict of interests.

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