Review Article

Methotrexate in inflammatory bowel disease: A primer for gastroenterologists

Turki AlAmeel, Eman Al Sulais[1], Tim Raine[1]

Department of Medicine, King Fahad Specialist Hospital, Dammam, Saudi Arabia, [1]Division of Gastroenterology, Department of Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

Abstract

Methotrexate is an antineoplastic agent that is also used at lower doses for anti-inflammatory properties. Along with thiopurines (azathioprine and 6-mercaptopurine), it has historically been an important part of pharmacological treatment for patients with inflammatory bowel disease. Despite an increase in therapeutic options, these immunomodulators continue to play important roles in the management of inflammatory bowel disease, used either as a monotherapy in mild to moderate cases or in combination with monoclonal antibodies to prevent immunogenicity and maintain efficacy. In light of data linking the use of thiopurines with the risk of malignancies, methotrexate has regained attention as a potential alternative. In this article, we review data on the pharmacology, safety, and efficacy of methotrexate and discuss options for the positioning of methotrexate alone, or in combination, in therapeutic algorithms for Crohn's disease and ulcerative colitis.

Keywords: Crohn's disease, methotrexate, ulcerative colitis

Address for correspondence: Dr. Eman Al Sulais, Division of Gastroenterology, Department of Medicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, CB2 0QQ, UK.
E-mail: e.alslais@gmail.com
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INTRODUCTION

The medical management of inflammatory bowel disease (IBD) has evolved considerably over the past two decades since the arrival of tumor necrosis factor inhibitors (TNFi), bringing the possibility of unprecedented levels of disease control. Further, monoclonal antibodies and small molecules have since been approved, with others in late phase development for both ulcerative colitis (UC) and Crohn's disease (CD).[1]

Nonetheless, the use of conventional immunomodulatory therapy, in the form of either thiopurines and methotrexate (MTX), remains a key element of therapy, reflected in international recommendations[2] and real-world cohorts.[3] To some extent, this reflects the economic reality of access to advanced therapies, particularly for less severe cases and/or in cost-sensitive settings. However, the use of immunomodulators is supported by clinical trial data, both in the context of use as monotherapy,[4-6] as well as the recognition that co-prescription of a conventional immunomodulator alongside anti-TNF therapy can help to reduce problems associated with immunogenicity.[7] Although most gastroenterologists treating patients with IBD will be familiar with the respective arguments and clinical utilization of thiopurines in this context, the use of methotrexate is somewhat less common in many settings.[3] At the same time,

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ongoing concerns regarding the safety profile of thiopurine therapy have revitalized MTX as a potential alternative.[8,9]

Our objective in this article is to give the practicing gastroenterologists an overall review of MTX and its use in IBD. We have also discussed the practical aspects of prescribing the medication including safety, monitoring, and contraception.

Methotrexate: Mechanism of action

Drug Class: Antimetabolite (folate antagonist)

Routes of administration: Parenteral (IM or SC) and oral

Recommended dosage:

Induction dose: 25 mg/week for 16 weeks

Maintenance dose: 15 mg/week

*Concurrent folic acid supplementation (5 mg) 2–3 days apart from MTX is advisable

The native form of the drug is methotrexate monoglutamate, which has a short half-life of about 6 h and can only be detected in blood for 18 h after dosing. Within tissues, the drug undergoes a serial polyglutamation process that results in methotrexate polyglutamate formation by the addition of a varying number of molecules of glutamic acid.[10] Methotrexate polyglutamate, the active form of the drug, has a longer half-life as it is detectable in the serum for weeks.[10] In addition, it has a much higher potency (>2,000 times) than the naive form in terms of methotrexate polyglutamate, which inhibits a large number of enzymes including those involved in de novo purine and pyrimidine biosynthesis (e.g., dihydrofolate reductase (DHFR)).[10] This inhibits the nucleic acid synthesis and leads to toxicity particularly in rapidly proliferating cells, which was the basis for the early use of MTX in oncology. At doses typically 100-fold lower than those used in oncology, MTX still inhibits the cycling of proliferating lymphocytes and neutrophils during inflammatory response. The inhibition of other enzymes leads to a wide range of additional anti-inflammatory mechanisms, notably through effects on adenosine metabolism (increased intracellular adenosine concentrations lead to inhibition of a range of inflammatory pathways), alterations in reactive oxygen species production and increased sensitivity to apoptosis and inhibition of nuclear factor-κB (NF-κB) signaling.[11] Cumulatively, the wide cellular effects of MTX impact the biology of almost all cells involved in IBD pathogenesis, including T cells, neutrophils, monocytes/macrophages, endothelial cells, and fibroblasts.

Methotrexate monotherapy in CD

Two placebo-controlled trials addressed the efficacy of MTX in CD. The North American Crohn's Study Group published their results of induction and maintenance trials in 1995 and 2000, respectively.[12,13] The induction trial lasted for 16 weeks and randomized a total of 141 patients with steroid-dependent CD to receive MTX 25 mg administered intramuscularly (IM) weekly or placebo. The primary endpoint was steroid-free clinical remission using a Crohn's Disease Activity Index (CDAI) score of ≤150. This was achieved in 37/94 (39%) patients on MTX as compared to 9/47 (19.%) in the placebo group ($P = 0.025$). More patients in the MTX group stopped the study medication due to adverse events as compared to those in the placebo group 16/94 versus 1/47 (17% vs. 2%). The most reported adverse events with MTX were abnormal liver enzymes and nausea.[12]

Patients who were in remission at the end of 16 weeks of the induction phase were enrolled in the maintenance trial. Over 40 weeks, a total of 76 patients were re-randomized to either receive MTX 15 mg IM weekly or a placebo. Steroid-free clinical remission was achieved in a higher percentage of patients on MTX as compared to those on placebo, 26/40 versus 14/36, respectively (65% vs. 39%, $P = 0.04$).[13]

In a retrospective study performed at a single center, Hausmann *et al.* analyzed 63 patients with CD treated with MTX. The mean duration of the therapy was 100 weeks, with a mean cumulative dose of 2,130 mg; 79% of the patients treated with MTX achieved remission within 3 months of therapy. The cumulative probabilities of these patients remaining in remission were 95, 90, 71, and 63% at 6 months, 1, 2, and 3 years of treatment, respectively. Drug-related adverse effects leading to the withdrawal of therapy were reported in one-third of the patients.[14] A Cochrane review that included five studies with a total of 333 patients inferred that there is moderate-quality evidence to show that MTX at a dose of 15 mg IM is superior to placebo, in maintaining remission in CD.[15] An observational study found that the median clinical response time to MTX parenteral therapy in CD was 9 weeks and the time to clinical remission was 22 weeks.[16,17] These slow response times mean that the current guidelines recommend MTX as an option for the maintenance of remission but not as an induction agent.[18]

Methotrexate monotherapy and UC

In contrast to the data in CD, MTX has failed to show

evidence of efficacy in UC [Table 1]. Early negative studies included an Israeli multicenter double-blind controlled trial of oral MTX in 67 UC patients.[19] [Table 1], Another study from the same era included a total of 72 UC and CD patients who were steroid-dependent of the 34 patients with UC included in the study, those randomized to treatment with MTX failed to show a difference in either the induction or maintenance of remission compared to a placebo group.[20]

More recently, two randomized controlled trials have investigated the use of MTX in UC. The METEOR trial assessed MTX as an agent for the induction of remission. It was a double-blind placebo-controlled trial that evaluated the efficacy of MTX 25 mg IM or SC weekly, in steroid-dependent UC patients. One hundred and eleven patients were recruited from 26 European centers. The primary outcome of the study was a steroid-free clinical remission (defined as a Mayo score of ≤2 with no item of >1) at week 16. Endoscopic healing was evaluated as a secondary endpoint. At week 16, steroid-free remission was achieved in 19 of 60 patients administered MTX (31.7%) and 10 of 51 patients in the placebo arm (19.6%) ($P = 0.15$). Steroid-free endoscopic healing at week 16 was reported in 35% of the patients in the MTX group and 25.5% of the patients in the placebo group ($P = 0.28$).[21]

The potential role of MTX in maintaining steroid-free remission was also addressed in the MERIT UC trial. In this study, the participants received 16 weeks of open-label MTX. A total of 84 patients who were steroid-free respondents were randomized to either continue MTX 25 mg SC weekly or receive a placebo for 32 weeks in a blinded manner. The primary endpoint of the relapse-free survival without the need for additional therapies, such as steroids, further immunosuppressants, or biologics, as well as the remission at week 48, did not differ between the groups ($P = 0.86$). The study did not find any signal of potential efficacy in multiple subgroup analyses.[22] Despite the rigorous methodology followed in both METEOR and MERIT UC trials, several observations have been made on these trials.[23] Both studies had difficulties in recruiting patients leading to long completion times (6 years for METEOR, and 10 years for MERIT UC). Unlike the pivotal trial of MTX in CD, these trials included a significant percentage of patients with the previous failure to thiopurine and TNFi. In MERIT UC, for example, two-thirds of the patients had failed a thiopurine or biologics. This is in clear contrast to 5% of the patients who failed thiopurine treatment in the study by Feagan *et al.* investigating the effectiveness of MTX in the maintenance of remission in CD.[13] Additionally, in the METEOR trial, high placebo response rates may have blurred the study results, possibly attributable in part to the lack of central reading for endoscopy.[24,25] Nonetheless, taken together, the results of all of these studies demonstrate that MTX monotherapy has no role in the management of UC.

Methotrexate in combination with biological agents

Much recent focus on the role of immunosuppressants in the management of IBD has tended to focus on the potential for reduction in the immunogenicity of biologic therapies - a problem encountered in 23–46% of patients over time and associated with a loss of response to these agents.[26,27] In this regard, two landmark trials (SONIC and UC SUCCESS) have shown the positive impact of combining thiopurines with infliximab on treatment outcomes in patients with CD and UC,[28,29] findings which were associated with reduced immunogenicity of infliximab in patients receiving combination therapy in both studies.

More recently, the use of immunosuppression with either thiopurines or methotrexate was associated with decreased immunogenicity to both infliximab and adalimumab in patients with CD or UC, in a large UK observational

Table 1: Major Randomized Clinical Trials of MTX Monotherapy in IBD.

Trial	Study Design	IBD type	Disease Phase	Study protocol	Number of subjects enrolled	Primary endpoint	Results
Study by Feagan *et al* [17]	Double-blinded RCT	CD	Induction for 16 weeks	MTX 25 mg IM weekly	141	clinical remission at week 16	Clinical remission: MTX arm (39.4%) vs. (19.1%) placebo arm (P=0.025)
Study by Feagan *et al* [18]	Double-blinded RCT	CD	Maintenance over 40 weeks	MTX 15 mg weekly	76	Proportion of patients who remained in remission at week 40	65% of patients were in remission in the methotrexate group vs. 39% in the placebo group (P=0.04).
METEOR [28]	Double-blinded RCT	UC	Induction for 24 weeks	MTX 25 mg SC or IM weekly	111	Steroid-free clinical remission at week 16	Steroid-free remission: MTX arm (31.7%) vs. (19.6%) placebo arm (P=0.15).
MERIT-UC [29]	Double-blinded RCT	UC	Maintenance over 54 weeks	MTX 25 mg SC weekly	84	Relapse-free survival at week 48	Relapse-free survival: MTX group (27%) vs. (30%) placebo group (P=0.86)

study of 1,610 patients.[30] This effect appeared to be particularly relevant in patients carrying at least one copy of the HLA-DQA1*05 gene.[31] Similar real-world findings were reported from a large Canadian cohort study of 11,244 patients treated with anti-TNF therapy.[7] In this study, a combination of either infliximab or adalimumab with immunosuppression treatment was associated with decreased rates of treatment failure in both UC and CD. Interestingly, although the effect of azathioprine (AZA) and MTX appeared similar in this regard in patients with CD, for patients with UC, AZA showed superior outcomes when used as the immunomodulatory agent. In this context, major guidelines suggest that clinicians should combine an immunomodulator with TNFi to reduce the risk of immunogenicity.[2,18,32]

The findings of these studies need to be set against the results of the one prospective double-blinded trial specifically to assess the use of MTX in this context. The COMMIT trial recruited patients with CD who were receiving prednisone and received either infliximab monotherapy or infliximab in combination with MTX.[33] Methotrexate was administered subcutaneously (SC) at a dose of 10 mg weekly and increased to 25 mg by week 5. The study continued for 50 weeks. The primary outcome of the treatment failure, defined as a lack of steroid-free remission at week 14 or failure to maintain remission through week 50, was similar in both groups. There was no difference in the mean change in the CDAI and the median change in C-reactive protein (CRP) levels between the intervention and control arms. In contrast to the findings of COMMIT, two randomized trials in patients with rheumatoid arthritis have demonstrated a benefit for the combination of TNFi with MTX.[34,35]

Can we reconcile the negative findings of the COMMIT trial with the real-world observational studies showing apparent benefit to combination therapy with MTX, and with prior findings of the efficacy of MTX as monotherapy in CD? COMMIT did have some noteworthy study design features.[36] First, there was no minimum required CDAI score to be enrolled in the trial. In fact, just below one-third of the patients in each arm had CDAI scores of <150. These patients were less likely to achieve the primary endpoint of treatment failure, defined as a CDAI score of >150 and may have contributed to a high observed placebo response rate. Similarly, endoscopically active disease was not a prerequisite for study enrollment—in this regard it is notable that patients without endoscopic disease activity did not benefit from combining AZA and infliximab in the SONIC trial.[28] Finally, the use of steroids in this trial both as an induction treatment and given as intravenous therapy alongside each infliximab infusion may have further obscured any potential differences in therapeutic interventions.

While these studies may have set out to address the point of combining immunomodulators with TNFi in IBD, subjects enrolled in these trials may not represent some phenotypes and situations encountered in clinical practice. It has been shown that less than a third of IBD patients seen in a tertiary care center would qualify to participate in a clinical trial.[37] Patients with stricturing CD, stoma patients, and those with steroid-refractory IBD tend to be under-represented in the industry-sponsored clinical trials.[38] The decision on combination therapy should take into consideration the individual patient profile including previously failed therapy, intolerance to thiopurines, and immunogenicity toward one or more TNFi. In an open-label, investigator-initiated clinical trial, Roblin *et al.* randomized IBD patients with immunogenic failure to one TNFi to either a second TNFi with AZA or a second TNFi alone. Combining AZA to the second TNFi, be it adalimumab or infliximab, was associated with a significantly lower risk of developing anti-drug antibodies and low-drug concentration. Clinical failure based on clinical indices and objective parameters was more likely in the monotherapy group compared to the combination therapy group (78% vs. 23%, HR 6.29; 95% CI 2.98–13.26; log-rank test $P < 0.001$).[39] Although the investigators used AZA as their immunomodulator in this trial, it seems plausible that similar results would be achieved using MTX in CD patients who are intolerant or unwilling to take thiopurines. Patients receiving either adalimumab or infliximab are at risk of secondary failure due to the formation of anti-drug antibodies. Nonetheless, data from clinical trials and observational studies indicate that the risk of immunogenicity is higher with infliximab.[30] Clinical guidelines stress the importance of using combination therapy in patients receiving infliximab and suggest weighing the benefits and risks in adalimumab-treated individuals.[18]

More recently, licensed, non-anti-TNF biologics appear to have lower rates of immunogenicity, raising questions about the utility, if any, of combination therapy with these agents. A multicenter retrospective cohort study evaluated the impact of immunomodulator combination therapy on outcomes in 363 patients on ustekinumab and 263 on vedolizumab. The primary outcome was clinical remission or response at week 14, using the Harvey Bradshaw index for CD or simple clinical colitis index or partial Mayo score for UC. Secondary outcomes were clinical parameters at week 30 and week 52, endoscopic remission, and therapeutic failure. Among 131 patients who were in the combination arm, 53/131 (40.5%) received combination therapy with

methotrexate. After a follow-up period of 1 year, combination immunomodulatory treatment with ustekinumab or vedolizumab had no impact on the clinical response or remission, endoscopic remission, and durability of therapy compared to the patients on biologic monotherapy alone.[40,41]

Likewise, the *post hoc* analysis of UNITI trials suggested that there is no additional benefit from adding an immunomodulator (thiopurines or methotrexate) to ustekinumab, as it showed low immunogenicity behavior (incidence of ustekinumab antibodies formation at 1 year was 2.3%). Comparing the rate of antibodies formation among patients who received combination therapy versus ustekinumab monotherapy was 20/779 (2.6%) and 7/375 (1.9%), respectively.[40]

Looking at the totality of the evidence, MTX monotherapy is an acceptable option for maintenance in patients with CD. Notwithstanding the limitations of the COMMIT trial, MTX is an option to consider for combination with TNFi, particularly in groups of patients at higher risk of complications from thiopurines [Figure 1].

Oral versus parenteral administration

Most clinical trials of MTX in IBD have used parenteral routes of administration. The two forms of the parenteral route (SC or IM) appear to be bioequivalent, although SC administration is more convenient and less painful for patients.[42] Although commonly prescribed in clinical practice for reasons of practicality and patient convenience, oral MTX has an average bioavailability of 73% compared to SC administration in patients with CD and shows marked inter-individual variation.[43] Similar results have been reported in patients with RA,[44] indicating that the differences in bioavailability are not solely related to small-bowel inflammation in CD. The difference appears to be particularly significant with higher MTX doses of >15 mg/week.[45]

Two randomized controlled trials have investigated the effectiveness of oral MTX in CD: both failed to show a statistically significant benefit of MTX but both were underpowered to detect clinically relevant effect sizes. Oren *et al.* included 84 patients with CD and randomized 26 of them to oral MTX (12.5 mg/week). After 9 months, the rates of clinical remission did not differ from the patients randomized to 6 MP or placebo. In the second study, a total of 33 patients with CD were maintained on oral MTX (15 mg/week) or placebo for a year, again without significant benefit for MTX in terms of clinical remission.[46,47]

The use of low-dose oral MTX (12.5–15 mg/week) in combination with anti-TNF therapy has been suggested by some experts to reduce the risk of immunogenicity.[2] However, this is largely extrapolated from the rheumatology literature[48] with no similar data published in IBD. Similarly, other current guidelines support the use of oral MTX in the maintenance phase of therapy.[32] Nonetheless, parenteral treatment remains the preferred method to ensure efficacy and adequate bioavailability.[42]

Methotrexate: Monitoring and safety

Although methotrexate has a relatively short half-life and is undetectable in the serum after 18 h,[49] the active polyglutamated forms remain detectable in tissues for many days. Excretion of methotrexate is largely by the kidneys, but the impact of MTX on the liver is one of the main concerns for clinicians.[42] Methotrexate-induced hepatotoxicity is thought to be secondary to excess homocysteine. The inhibitory effect of MTX on MTHFR (methylene-tetrahydro folate reductase) reduces the generation of methionine from homocysteine. The excess in homocysteine can contribute to oxidative stress and also induce endoplasmic reticulum stress, causing dysregulation of cholesterol and biosynthetic pathways, leading to fatty infiltration of the liver.[50] The risk of hepatotoxicity with MTX therapy in the IBD population is lower than that seen in rheumatological and dermatological diseases, possibly reflecting the lower comorbidities of this patient group.[51] In a meta-analysis of 13 trials, the pooled incidence of a two-fold increase in hepatic transaminases in IBD patients treated with MTX was 1.4 per 100 person-months. The rate of withdrawal of the drug due to hepatotoxicity was 0.8 per 100 person-months.[52] Weekly dosing is safer than smaller daily doses of the drug.[53]

A case-control study involving 518 patients receiving MTX for different indications found no correlation between cumulative MTX and severe liver fibrosis on non-invasive testing. On multivariable analysis, alcohol consumption (>14 drinks per week) and high BMI (>28 kg/m^2) were associated with increased risks of abnormal liver elastography results.[54] Some previous guidelines recommended scheduled liver biopsy in patients with psoriasis, receiving MTX after a cumulative dose of 1000–1500 mg if they have underlying risk factors for non-alcoholic fatty liver disease (NAFLD), and 3500–4000 mg in those without risk factors. Nonetheless, scheduled liver biopsy is not recommended for patients with IBD.[42] Any potential benefits from routine liver biopsies are outweighed by the invasiveness and risks associated with the procedure. Transient elastography can be considered in patients with underlying risk factors such as excessive ethanol use or obesity. In cases of suspected fibrosis based on non-invasive testing, liver biopsy is warranted.[42]

Lung injury is an uncommon complication that can occur after prolonged treatment with MTX for weeks or months. It has an incidence of around 1% in RA patients receiving MTX.[55] Advanced age, hypoalbuminemia, and preexisting lung diseases are the main risk factors for lung-related toxicity.[56] Acute interstitial pneumonitis is a rare but potentially serious complication of MTX-based therapy. Fortunately, the incidence of these adverse events has been decreasing lately, and it tends to be reversible after the withdrawal of MTX.[42]

The current guidelines recommend obtaining a chest X-ray and liver function test along with a complete blood count and renal profile before commencing therapy with MTX. The liver function tests should be repeated at weeks 2, 4, 8, and 12, and then, on a 3-monthly basis. This should be performed in addition to the clinical assessment of the patient for possible adverse effects[32] [Table 2].

The most frequently encountered adverse effect is nausea. It occurs in up to 25% of the patients. This can be mitigated by administering an antiemetic agent, such as ondansetron, just before the MTX injection and 12–24 h after the dose.[42] Patients may experience stomatitis, hair loss, and leukopenia as a result of the antifolate mechanism of action of the drug, which in turn can inhibit cell proliferation. The use of folic acid is also strongly recommended to mitigate these and other adverse effects. It reduces gastrointestinal and liver toxicity of MTX without impacting its anti-inflammatory properties.[57] Weekly oral administration of 5 mg of folic acid and daily 1 mg are two acceptable options. Weekly dosing of folic acid can be administered on the day of MTX dose or delayed for 24–48 h.[42] Some prescribers recommend omitting the daily dose of folic acid on the day MTX is given. This is based on the theoretical concern that folic acid supplementation may reduce the efficacy of MTX by competing for the same transporter for cellular uptake. Although this presumed negative impact has not been proven in clinical settings, it remains a widely held belief.[58]

Although data were limited in IBD, weekly small doses of MTX do not appear to increase the risk of serious or opportunistic infections. A recent systematic review found that the use of MTX is associated with an increased risk of infection in RA but not in other immune-mediated diseases.[59] More specifically, the risk of pulmonary infection did not increase in a meta-analysis of randomized controlled trials investigating the use of MTX in non-RA immune-mediated conditions, including IBD.[60] The most recent guidelines from the Infectious Disease Society of America consider patients receiving MTX, at doses given for IBD, as having a low risk for immunosuppression.[61] As with low-dose steroids and thiopurines used in IBD, patients on MTX may receive live vaccines. However, the medication impairs the humoral response to both pneumococcal and influenza vaccines.[62] This led some experts to suggest holding MTX for 2 weeks after receiving these vaccines to improve the antibody response.[63]

In light of the safety profile of MTX and the relatively short half-life, patients with IBD scheduled for surgery may safely continue on this agent.[64,65] Methotrexate can be continued post-operatively as soon as the patient has resumed oral intake with no nausea and when there are no signs of sepsis or deranged renal or liver function tests.[66]

Methotrexate and teratogenicity

Most of the data on MTX use and pregnancy come from rheumatology literature. A systematic review evaluated patients receiving low-dose MTX (5–25 mg/week) from conception to the end of the first trimester. Around 100 pregnancies were included in the study. The pooled outcomes, excluding elective termination, were as follows: miscarriage in 23%, live pregnancy in 66%, and minor malformations in 5% of the pregnancies. Abortion was induced in 18% of the cases.[67] In a prospective European study examining 188 pregnancies with post-conception exposure to MTX, the incidence of spontaneous abortion was 42.5%. This was significantly higher than that in a disease-matched cohort and a control group of women without underlying autoimmune disorders. The risk of major birth defects was 6.6%, which was significantly higher than that in both control groups. The study included 136 pregnancies with exposure to MTX prior to conception.

Table 2: Recommended tests before and during MTX therapy.

Factors associated with toxicity	Clinical assessment	Biochemical assessment	Radiographic assessment	Suggested monitoring during the treatment course
Preexisting liver disease Impaired kidney function Low serum albumin Low serum folate levels Excess alcohol intake	Pre-existing liver disease Obesity Excessive alcohol consumption	CBC Liver enzymes: ALT and AST. albumin Creatinine	Chest x-ray: to rule out interstitial lung disease	CBC Liver enzymes: ALT and AST. albumin Creatinine *Induction phase: at week 2,4 and 8. * Maintenance phase Q 4-12 weeks. *Liver biopsy and liver elastography are not routinely recommended.

The risk of spontaneous abortion or major birth defects did not increase in this cohort.[68]

On this basis, female patients receiving MTX are advised to use effective contraception if they are of childbearing age. In clinical practice, a highly effective method of contraception is recommended. In case pregnancy is contemplated, the drug should be stopped at least 3 months prior to conception.[69] If an unintended pregnancy occurs while a female patient is receiving MTX, the drug should be stopped immediately and folic acid supplements (5 mg/day) should be initiated.[70] An obstetrician with experience in feto-maternal medicine should be consulted for further advice on the management of the pregnancy.[71,72]

The amount of MTX excreted in breast milk is limited. This is mainly due to the lipid insolubility of the drug at physiological pH. Nonetheless, due to limited data, breastfeeding should be avoided in patients receiving MTX.[69,73]

Limited data on paternal exposure to MTX do not suggest an increase in negative outcomes. In a prospective study, Weber-Schoendorfer *et al.* included 113 pregnancies with paternal low-dose MTX exposure and compared them to 412 non-exposed pregnancies. The risk of spontaneous abortion and major birth defects did not increase in the exposed group.[74] Similar reassuring results were exhibited in a Danish nationwide study that included 864 pregnancies with paternal exposure to MTX.[75] Therefore, the American College of Rheumatology made a conditional recommendation to continue MTX by men who are planning to father children.[71]

Choice of immunomodulator: Methotrexate versus thiopurines

The majority of patients with CD requiring immunomodulatory therapy receive thiopurines. In the Epi-IBD study, a European population-based study evaluating CD, 95% of the patients receiving an immunomodulator received a thiopurine.[3] This can be attributed to the ease of administering an oral medication over a parenteral injection, and that a larger proportion of experienced gastroenterologists prefer thiopurines over MTX. However, approximately 27–50% of the patients are intolerant or refractory to AZA or 6-MP.[76]

Recent concerns over the safety profile of thiopurines have reignited the interest in MTX. Thiopurine use has been associated with an increased risk of lymphoma in IBD patients.[9,77]

Post-mononucleosis and hepatosplenic T-cell lymphomas have been reported almost exclusively in young men who are Epstein–Barr virus (EBV) seronegative and receive thiopurine therapy. Although the absolute risk of developing these types of lymphomas in the CESAME population is relatively small, 3/1000 patient-years and 0.1/1000 patient-years, respectively,[78,79] the potentially fatal outcome makes MTX a more appealing alternative in this particular demographic. Older patients are another group of patients where MTX ought to be considered. In a meta-analysis of multiple population-based studies, the thiopurine-treated patients above the age of 50 had the highest absolute risk of getting any form of lymphoma [2.6/1000 patient-years].[80]

There is no known association between MTX use and lymphoma in patients with IBD. Although this might reflect lower power to detect an association given the less widespread usage of the drug, data from other indications are reassuring. In patients with RA, reversible EBV-associated lymphoproliferative changes have been reported without any increased risk of lymphoma.[81,82] These studies may earn more confidence in patients and clinicians favoring MTX over thiopurine as an immunomodulator [Figure 2].

A recently published retrospective study used a cohort of 782 patients[83] to compare the tolerability of AZA and MTX (oral and SC forms) in patients with IBD. The rate of discontinuation due to adverse events was significantly higher in the MTX arm 97/244 (40%) than that in the thiopurine arm 102/538 (19%; $P < 0.001$). Headache (4% vs. 2%), nausea (15% vs. 3%), fatigue (8% vs 2%), and hepatotoxicity (7% vs. 3%) (each $P < 0.05$), were the common adverse events reported in the MTX and thiopurine arms. On the other hand, the thiopurine arm experienced more acute pancreatitis events (2% vs. 0%, $P = 0.036$), as well as leukopenia and neutropenia (each, $P < 0.001$). However, the rates of serious infections, hospitalizations secondary to adverse events, and deaths (1% vs. 0%) were comparable between the groups (all $P > 0.05$). In addition, the authors looked at the rate of discontinuation of both agents due to the adverse events. Overall, MTX discontinuation occurred at rates twice that of thiopurine. On multivariate analysis, the likelihood of MTX discontinuation due to adverse events was significantly higher than that of thiopurine (hazard ratio, 2.36; $P = 0.003$). Moreover, they noticed that discontinuation occurred later in patients who were on MTX than in those who were on thiopurines (median 7 vs. 5 months, $P = 0.08$). The study was limited by methodological imperfections, and further prospective studies are needed to establish causality.

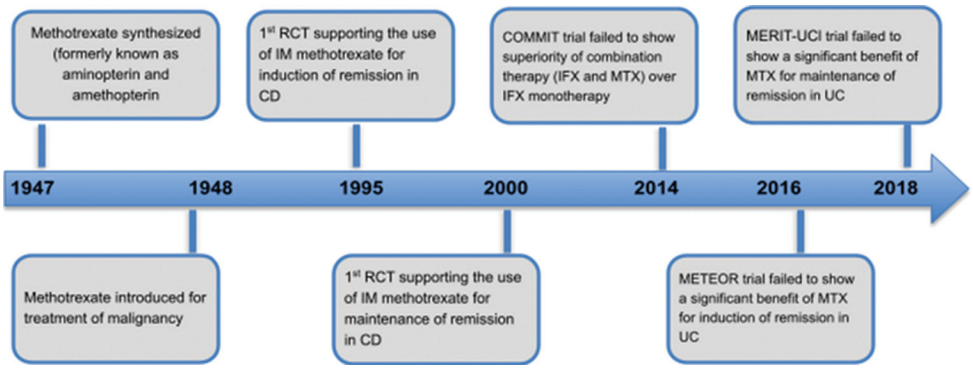

Figure 1: Methotrexate development and major trials in IBD. RCT: Randomized controlled trial, IFX: Infliximab, MTX: Methotrexate, CD: Crohn's disease, UC: Ulcerative colitis, IBD: Inflammatory bowel disease

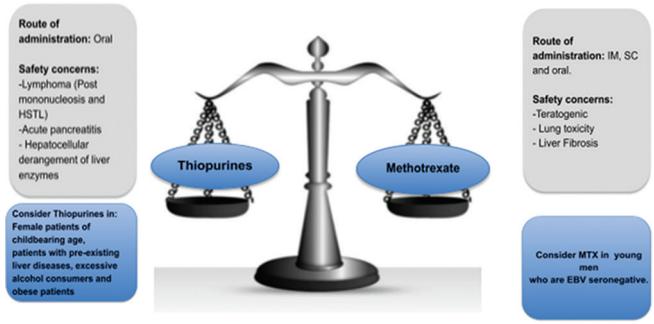

Figure 2: A proposed approach for considering methotrexate or thiopurines in patients with Crohn's disease. MTX: Methotrexate, IM: Intramuscular, SC: Subcutaneous, EBV: Epstein–Barr virus, HSTL: Hepatosplenic T-cell lymphoma

Methotrexate: The future?

While the identification of safety concerns and suboptimal disease outcomes continue to refocus efforts on the optimal use of all existing therapeutics, a rich developmental pipeline of novel agents in IBD has recently started to produce newly licensed therapies. However, even the most effective of these agents have not exceeded a remission rate of 50% by the end of 1 year of treatment, leading to much discussion around the safety and appropriateness of combination therapies, with multiple different mechanisms of action.[84]

EXPLORER is a phase 4 open-label trial looking at a combination of vedolizumab, adalimumab, and MTX as initial therapy in newly diagnosed patients with CD who are predicted to have a high risk of complications, with the subsequent withdrawal of adalimumab and MTX to leave patients on open-label vedolizumab. The primary outcome is endoscopic remission at week 26, with follow-up of patients to week 102 for key secondary endpoints, including the safety of this aggressive approach.[85] Although there is no comparator arm, post-marketing data will serve as a benchmark for the safety of combining these agents in patients with CD and the expectation would be that clinical outcomes would have to be markedly different from prior expectations in order to justify further exploration of such a radical approach.[84]

MTX is also under investigation in another important phase 4 trial. In the pediatric REDUCE RISK (NCT02852694) study, patients with CD, who are considered at low risk, will receive either SC MTX weekly or oral thiopurine once daily. In the high-risk population, MTX will be compared with adalimumab. The primary outcome of the study is steroid-free/exclusive enteral nutrition-free remission at 12 months. The estimated study completion date is July 2022.[86]

CONCLUSION

Methotrexate remains a valuable option for managing patients with CD, both as a steroid-sparing agent and as part of a combination regimen with an anti-TNF agent. However, it shows no efficacy as a monotherapy in UC, while any potential use as a combination agent in UC may be limited to patients with a clear contraindication to a thiopurine and in whom there is significant concern around immunogenicity either due to patient- or drug-related factors. As with all drugs, safety concerns will be paramount, and particular consideration must be given to family planning wishes of female patients of childbearing potential, as well as monitoring for hepatotoxicity. Nevertheless, the available safety and efficacy data for MTX suggest an agent that will continue to have a role in future IBD management algorithms.

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Conflicts of interest

TA received speaker's honorarium and has been on advisory boards for Janssen, AbbVie, Takeda, Pfizer and Amgen. ES declares no conflicts of interest related to this paper. TR has received research/educational grants and/or speaker/consultation fees from Abbvie, Arena, AstraZeneca, BMS, Celgene, Ferring, Galapagos, Gilead, GSK, Heptares, LabGenius, Janssen, Mylan, MSD, Novartis, Pfizer, Sandoz, Takeda and UCB.

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