Methotrexate

31

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Introduction

The inflammatory bowel diseases (IBDs) are characterized by chronic gastrointestinal inflammation in association with ongoing and inappropriate activation of the mucosal immune system [1]. In the correct clinical setting, pharmacologic treatment can include locally acting anti-inflammatory therapies, immune-modifying agents and now, biologic therapies. The short-term goal of therapy remains the relief of clinical symptoms, while the long-term goal is to improve quality of life while changing the natural history of the disease by decreasing the incidence of adverse outcomes such as the need for hospitalization and surgical intervention. The long-term goals have undergone a paradigm shift over the last decade, embracing a model that emphasizes the induction and then maintenance of not only a clinical but a biologic remission marked by mucosal healing [2].

Glucocorticosteroids have both anti-inflammatory as well as immunomodulatory effects. As such, steroids are still the most commonly used immune-modifying agent and have the longest history of use as induction agents. At a year after diagnosis, more than 30% of pediatric Crohn's patients will remain dependant on glucocorticosteroids and almost 10% will already have undergone surgery, demonstrating steroids' inability to alter the course of Crohn's disease [3]. In addition to this lack of long-term efficacy, chronic corticosteroid use is associated with a legion of side effects mandating the identification of more effective, steroid-sparing agents. Concordantly, approximately 60% of pediatric Crohn's disease patients will be placed on immunomodulatory therapy within the first year of diagnosis [4].

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The thiopurines, 6-mercaptopurine (6MP) and azathioprine (AZA), have been shown to be efficacious as well as steroid sparing and are covered in more detail in Chap. 30. Using the Harvey-Bradshaw Index (HBI) as end-point, the prospective multicenter trial by Markowitz, et al., showed that 91% of pediatric Crohn's patients who underwent successful induction remain in remission on 6MP/AZA at 18 months [5]. With the subsequent advent and pediatric validation of the Pediatric Crohn's Disease Activity Index (PCDAI), more recent studies of thiopurines have demonstrated a lower long-term efficacy closer to 30–40% [6]. Additionally, pancreatitis and idiosyncratic reactions including gastrointestinal toxicity, fever and idiopathic pancreatitis are seen in 5–10% of patients. Increasing concerns related to potential toxicity from thiopurine therapy, especially with regard to hemophagocytic lymphohistiocytosis (HLH) and lymphoma, especially hepatosplenic T-cell lymphoma (HSTCL), have driven clinicians to look for other potential immune-modifying agents [7].

Methotrexate has emerged as an effective and overall well-tolerated alternative to the thiopurines [8]. Controlled trials have confirmed methotrexate as an effective agent in inducing as well as maintaining clinical remission in adult patients with Crohn's disease [9, 10]. While a prospective pediatric trial has not yet been performed, there is now ample published data regarding the efficacy of this agent in pediatric Crohn's disease [11].

Mechanism of Action

Methotrexate is a folic acid derivative originally designed as an analogue of dihydrofolic acid. As a competitive antagonist of folic acid, methotrexate inhibits folate-dependent enzymes such as dihydrofolate reductase (DHFR) which is critical to both purine and pyrimidine synthesis. In relatively high doses, methotrexate inhibits DNA production and exerts antiproliferative as well as cytotoxic effects [12].

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Table 31.1 Effects of adenosine-related pathways on adaptive immune response

Increased interleukin (IL)-10
Increased IL-2
Inhibition of neutrophil chemotaxis
Decreased leukotriene B_4 (LTB_4)
Decreased tumor necrosis factor alpha
Decreased IL-6
Decreased IL-8
Decreased selective adhesion molecules (SAM)

Table 31.2 Methotrexate (MTX):dosing and monitoring

Supplemental oral folic acid 1 mg/day to be given to all patients
Consider pretreatment with ondansetron for first 4–8 doses of MTX and then as needed
Dose (subcutaneous injection on a weekly basis)
15 mg/m^2 (body surface area) to a maximum dose of 25 mg once a week
Maintenance
Consider conversion to oral dosing if stable > 3 months
If clinical remission for > 3–6 months consider decreasing dose to 10 mg/m^2 to a maximum of 15 mg once a week
Patient Monitoring
Complete blood count with differential and platelets (CBC), erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP), Hepatic Function Panel weekly for the first month and then every 2–3 months if stable
The dose should be reduced by 50% for elevation in alanine aminotransferase (ALT) > twice baseline
The dose should be reduced by 50% for white blood count (WBC) <4000, absolute neutrophil count (ANC) <1500 or platelet <120,000 and held for 2 weeks for WBC <3000, ANC <1000 or platelets <100,000.

MTX should be held for 2 weeks for nonproductive cough >1 week, and discontinued for pneumonitis or serious infections

When given for immune mediated diseases, low-dose methotrexate is used. At these doses, methotrexate does not exert such a profound antimetabolite effect. This is an important clinical distinction since at low dose, there is a relative absence of otherwise common side effects such as hair loss and folate supplementation may decrease the toxicity but not the apparent of efficacy of low-dose methotrexate [13].

The mechanism of action of low-dose methotrexate still needs to be fully elaborated. While not antiproliferative, low-dose methotrexate may induce T-cell apoptosis [14, 15], although there are studies that do not agree with this finding [16]. Other potential mechanisms of action include methotrexate's effect on intracellular and extracellular concentrations of adenosine and the effects of adenosine on the adaptive immune response [17] (see Table 31.1). Methotrexate has also been shown to have a more direct effect on a variety of regulatory cytokines [18, 19].

Improved understanding of methotrexate's mechanism of action and pharmacokinetics may also affect the recommended dosing. As has become appreciated with the thiopurines, metabolites of the parent drug may be the more clinically important compounds. There is now evidence that intracellular methotrexate polyglutamates are the active immune-modifying compounds [20] and that there are genetic polymorphisms that have been shown to affect intracellular methotrexate polyglutamate levels. Therefore, pharmacokinetics and pharmacogenetics may play a large role in the efficacy and potential toxicity of methotrexate in any individual [21]. The importance of methotrexate polyglutamate levels in IBD patients has not yet been studied. Such studies may lead to dosing recommendations based upon pharmacogenomics rather than weight-based dosing. For now, however, dosing is based upon weight or body surface area measurements (see Table 31.2).

Efficacy

In 1995, Feagan et al. published their 16-week induction study demonstrating that 25 mg of intramuscular methotrexate delivered weekly is an effective, steroid-sparing, induction strategy in adult patients with active Crohn's disease [9]. This study of 141 patients showed that 39% were in a steroid-free remission at 16 weeks compared to 19% of placebo patients. Those who achieved remission with methotrexate were then offered enrollment in a 40-week double-blind placebo-controlled maintenance trial of 15 mg of methotrexate administered intramuscularly on a weekly basis. Seventy-six patients participated and demonstrated a methotrexate remission rate of 65% compared to 39% with placebo. No serious adverse events were noted [10]. In addition, there have been head-to-head trials suggesting that the effect of methotrexate is similar to that seen with thiopurines [22, 23]. Data on the use of methotrexate to treat ulcerative colitis has been variable [24, 25]. Two prospective studies are nearing completion which will hopefully help further knowledge on this question.

There is now a fairly robust published experience with methotrexate in pediatric IBD, especially Crohn's disease [26–35]. Mack et al. [28] first reported on 14 patients with a mean age of 10.6 years who had active Crohn's disease and were intolerant or unresponsive to 6-mercaptopurine. Subcutaneous (SQ) administration of methotrexate was used and 64% of the patients showed clinical improvement by as early as 4 weeks. Steroid sparing was also demonstrated.

Another single center experience [30] demonstrated a 12-month steroid-free remission rate of about 33% which is similar to that seen in reports of adult patients with Crohn's disease. Good tolerance of the methotrexate therapy was reported. Two larger, multicenter retrospective reports [27, 29] demonstrated a 40–45% 1-year steroid-free remission rate

with methotrexate as a second line immune modulator in pediatric Crohn's disease patients. No difference in effect was seen whether the indication for the methotrexate was lack of thiopurine efficacy or intolerance. Again, overall good drug tolerance was demonstrated as were a steroid-sparing effect and a positive effect on linear growth [27]. Similar retrospective reports have been published from several European countries showing a 12-month remission rate of 25–52% and these studies are well summarized elsewhere [11]. Along with this growing evidence of the efficacy of methotrexate as monotherapy in treating pediatric Crohn's disease, there has been an increasing level of concern regarding the potential toxicities of thiopurine therapy, especially in the pediatric population. These two effects have likely led to a much higher rate of methotrexate use in this setting. In fact, a multicenter report from the Pediatric IBD Collaborative Research Group demonstrated that the number of patients exposed to methotrexate quadrupled from 2002 to 2010 (14–60%) [34].

In addition to its use as monotherapy, there is a growing experience of using methotrexate in combination with monoclonal antibodies directed against tumor necrosis factor alpha (TNF). While the prospective COMMIT trial did not show improved efficacy of infliximab dosed in combination with methotrexate compared to infliximab monotherapy in adults with Crohn's disease [36], many factors including high rates of corticosteroid use at baseline may have been critically confounding [37]. More recently, retrospective data from the Pediatric IBD Collaborative Research Group demonstrated improved infliximab durability when administered in combination with methotrexate [38]. It has been shown that the methotrexate dose may be critical to fully achieve this effect and a weekly dose of 12.5–15 mg weekly may be optimal when methotrexate is used as a concomitant agent [39, 40].

Dose and Administration

Methotrexate is administered once a week. The route of administration can be parenteral (subcutaneous or intramuscular) or oral. Since there are no head-to-head prospective trials comparing the efficacy of oral and parenteral methotrexate for IBD, it remains controversial whether there is a preferred route of administration. Retrospective reports have provided some data relative to this question. Two uncontrolled, observational studies published within a year of each other differed in their conclusions with one showing no difference between oral and parenteral methotrexate [41] and the other showing clear advantage to the parenteral route [42].

Pharmacokinetic studies have been performed to see if there is a clinically significant difference in absorption between the two routes as it is recognized that oral absorption is individually variable and subject to a saturation effect with decreasing rates of absorption at higher doses [43].

In IBD, studies of adult [41] as well as pediatric patients [42] have demonstrated a wide individual range of methotrexate bioavailability. Interestingly, a study in adult patients showed the oral route to provide about 73% of the bioavailability that was seen with the parenteral route, while no such difference was seen in the pediatric study. Both of these pharmacokinetic studies were performed on subjects who were clinically stable on methotrexate maintenance therapy. Therefore, neither provides bioavailability data on patients being induced with methotrexate and there is retrospective data to suggest the parenteral route may induce a more rapid remission [26]. Additionally, it has recently been pointed out that any difference in bioavailability between these two routes of administration still falls within the FDA's definition of bioequivalence [44].

The question as to whether there is a clinically important difference in efficacy based upon the route of administration was investigated in a more direct, albeit retrospective manner, in the 2015 study by Turner et al. who used a propensity score analysis to look at outcomes in pediatric CD patients treated with oral vs. parenteral (subcutaneous) methotrexate [27]. This study demonstrated that any superiority of SQ over an oral route of administration was quite modest and the authors suggest that a change to oral MTX can be considered in those patients successfully induced with parenteral MTX. It is notable that a recent meta-analysis of the use of MTX in rheumatoid arthritis patients offered a different approach. This study demonstrated that efficacy and toxicity are related to an individual's absorbed dose rather than route of administration and the authors concluded that it is best to start patients on a relatively high oral dose and convert to the parenteral route in those who fail to respond [45].

In addition to the ongoing questions with regard to the optimal route of administration, the actual ideal dose of methotrexate for pediatric IBD patients has not been studied. The usual recommended dose is 15 mg/m^2 once weekly to a maximum weekly dose of 25 mg [46]. All patients are supplemented daily with folic acid 1 mg orally to avoid the development of medication-related nausea and subsequent anticipatory intolerance [47]. It has also been shown to be beneficial to recommend oral ondansetron as premedication before each of the first eight doses to prevent drug-associated nausea [48].

Toxicity and Monitoring

In patients with inflammatory bowel disease, low-dose methotrexate has been shown to be a well-tolerated agent with more than 90% of clinical trial patients able to complete study drug [19, 49]. Reported side effects are usually transient or respond to dose reduction and, less commonly, drug withdrawal (the potential side effects of low-dose methotrexate are summarized in Table 31.3).

Table 31.3 Side effects and toxicities of low-dose methotrexate

Teratogenicity
Contraindicated in women of child-bearing potential
Contraindicated in breastfeeding women
Gastrointestinal—folate related
Nausea and behavioral/anticipatory intolerance—most common
Abdominal pain, diarrhea
Stomatitis including esophagitis
Bone Marrow Suppression
Monitor with CBC (Table 31.2 for schedule)
Increased with trimethoprim-sulfamethoxazole
Hepatic
Monitor with routine liver chemistries (Table 31.2 for schedule)
Increased risk with obesity, concomitant hepatotoxic medications
Routine liver biopsy not recommended
Possible role for elastography
Infections
Upper respiratory most common
Rarely herpetic as well
Rarely clinically serious
Pneumonitis
Immune-mediated
Rare
Suspect if prolonged nonproductive cough
Preliminary evaluation = chest radiograph and pulmonary function tests
Dermatologic
Hypersensitivity reactions

There were early reports from the rheumatology literature that pediatric patients may have fewer methotrexate-induced side effects compared to adult patients [50]. An exception to this may be the development of learned associations and anticipatory intolerance to the medication [47]. Nausea has been correlated with inhibition of folate-dependant enzymes. As a result, folic acid supplementation may help limit this side effect, which has been reported in more than 20% of the adult patients who participated in clinical IBD trials [51]. Use of ondansetron as a premedication for the first 4–8 weeks can effectively mitigate against the development of nausea [48]. Other gastrointestinal side effects include abdominal pain, diarrhea and stomatitis that may even evolve into mucositis involving the esophagus [52].

In light of the potential for hepatic toxicity with high-dose methotrexate, liver-related complications have been well studied with low-dose methotrexate. There may be a disease-related rate of liver complications following therapy with low-dose methotrexate. Patients with psoriasis were shown to have a 7% rate of hepatic fibrosis [53] as compared to the 1% rate in rheumatoid arthritis [54]. The low rate of hepatic fibrosis and cirrhosis in RA has led to the official recommendation of the American College of Rheumatology that routine, surveillance liver biopsies not be performed [54]. Studies in juvenile idiopathic arthritis (JIA) patients have shown at least as good hepatic tolerance [55]. Similarly, negligible rates of drug-related hepatotoxicity have been seen in adult IBD patients treated with prolonged low-dose methotrexate [56]. This may actually occur at a higher rate in pediatric patients with a meta-analysis demonstrating a rate of elevated liver chemistries as high as 10% with 6% requiring dose reduction [57].

Rather than biopsy, routine liver chemistry monitoring should be performed as shown in Table 31.2. Elastography is a promising tool to noninvasively monitor for drug-induced hepatic fibrosis and it may be more sensitive than measuring liver chemistries [58].

Bone marrow suppression leading to leukopenia or thrombocytopenia occurs in about 1% of low-dose methotrexate treated patients [19]. This is usually transient and responds to dose reduction or holding of the drug. Routine monitoring of complete blood counts should be performed to look for bone marrow suppression (Table 31.2). Concomitant medications, especially antifolate agents such as trimethoprim-sulfamethoxazole should be avoided with methotrexate therapy as these can exacerbate potential bone marrow suppression. Theoretically, this may be true of sulfasalazine as well although the combination of low-dose methotrexate and sulfasalazine has been utilized without increased toxicity [59].

An immunologically mediated pneumonitis can also rarely be seen with methotrexate therapy. Screening asymptomatic pediatric patients does not seem warranted [50] and in fact, the rarity of this condition when methotrexate is used for inflammatory disease has recently been further characterized [60]. Clinically, a persistent cough or other symptoms should prompt a chest radiograph and pulmonary function studies with suspension of methotrexate therapy until clarification of the clinical picture is achieved.

The most important toxicity of methotrexate is related to its teratogenicity. Methotrexate is completely contraindicated in pregnancy as well as during breastfeeding. All patients and their families must be educated about this prior to starting methotrexate therapy.

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