A 2018 Approach to Combating Methotrexate Toxicity

Folic Acid and Beyond

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Abstract

Methotrexate (MTX) is the cornerstone to management across a variety of rheumatic diseases. Effective use and adherence to MTX treatment is dependent on toxicity prevention and management. The major deterrents to patient tolerability and adherence can include GI upset, hepatic transaminase elevation, stomatitis, hair loss, and CNS toxicity. Many rheumatologists are familiar with employing supplementation of folic acid and folinic acid, as well as a change from oral to subcutaneous (SC) MTX, to help combat MTX toxicity. There are, however, more potential strategies in a rheumatologist's armamentarium to ameliorate side effects and improve adherence, including vitamin A supplementation and dextromethorphan. Herein, we will provide a review of the literature (both rheumatologic and oncologic) and expert opinion in terms of managing methotrexate toxicity and improving adherence in rheumatic diseases.

First introduced in 1955 as a chemotherapeutic agent for the treatment of leukemia, the role and utilization of methotrexate (MTX) has greatly evolved in the recent past.[1,2] In 1986, it became FDA approved for the treatment of adults with severe rheumatoid arthritis (RA) and in children with active polyarticular juvenile RA.[1,2] It is now known as the first line treatment for these diseases and remains arguably the anchor drug in the armamentarium of the rheumatologist treating RA. Among the rapidly changing landscape in rheumatology therapies, MTX continues to be the gold-standard drug against which all other biologics and disease-modifying anti-rheumatic drugs (DMARDs) are compared. However, it is not without its complications, which can often be a deterrent for patients either in treatment initiation or adherence. The main MTX side effects include gastrointestinal (GI) toxicity (malabsorption, diarrhea, nausea, and vomiting), stomatitis, alopecia, elevated liver transaminases, and CNS toxicity.[1-3] Effective adherence to MTX treatment is largely based on toxicity prevention and management.

Several studies have been published in the recent past with suggested modalities for combating MTX toxicity. Classically, folic acid and folinic acid, as well as a change from oral to subcutaneous (SC) MTX are well known regimens. Alternative treatments such as vitamin A supplementation and dextromethorphan may be less well-known but still effective strategies for the rheumatology community. Herein, we will provide a review of the literature pertaining to MTX toxicity treatment for 2018 (Table 1). With suggestion that MTX may be underutilized in diseases such as RA, and in an era of increased payer scrutiny over treatment decisions, we hope you will find this a relevant review.[3]

Folic Acid and Folinic Acid: Combating GI Toxicity, Hepatic Transaminase Elevations, and Hair Loss

While pharmacologically it is classified as a folate depleting antimetabolite, MTX works by modulating adenosine in rheumatic diseases.[2,4] The human body needs folate to perform many functions, including cell division, growth, and hematopoiesis. Hence, due to lack of folate, many patients treated with MTX experience GI, hepatic, and hematologic toxicity. Supplementation with either folic acid or folinic acid during treatment with MTX has been shown to ameliorate many of these side effects.[5-11] Folinic acid (also known as its brand name Leucovorin) is the reduced and active form

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Table 1 List of MTX Toxicity Agents and Key Illustrative Studies

Agent (Dose) Toxicity Treated	Key Studies	Patient Population Disease/Age Group	Study Details	Duration (weeks)	Conclusions
Folic Acid (1 mg PO daily or 5 mg PO weekly) & Folinic Acid (5 mg PO for 2-3 doses) GI toxicity Hepatic transaminase elevation Homocysteine Stomatitis	Van Ede et al. 2001[7]	Rheumatoid arthritis (RA)/adult	Randomized Control Trial (RCT), double blind (DB), placebo	48	Both folic and folinic acid decrease liver enzyme levels.
	Van Ede et al. 2002[8]	RA/adult	RCT, DB, placebo	48	Both folic and folinic acid decrease homocysteine levels—potentially decreasing cardiovascular risk.
	Shea et al. 2013[9]	RA/adult	Meta-analysis	N/A	Both folic and folinic acid decrease GI and hepatic side effects. There is a trend toward reduction in stomatitis.
	Dhir et al. 2015[11]	RA/adult	RCT, DB, placebo	24	No additional benefit (or harm) associated with higher dose folic acid (30 mg per week) versus lower dose (10 mg per week total).
	Shiroky et al. 1993[14]	RA/adult	RCT, DB, placebo	52	Folinic acid 2.5 to 5 mg given 24 hours after MTX demonstrated decrease in GI toxicity, transaminase elevation and stomatitis without decreasing MTX efficacy.
	Morgan et al. 1994[34]	RA/adult	RCT, DB, placebo	52	Folic acid 5 mg per week given as weekly dosing lowers side effects (mainly GI toxicity, hepatic transaminase elevation, stomatitis) while not decreasing MTX efficacy.
Vitamin A (8000 IU) GI Toxicity Stomatitis	Dagdemir et al. 2004[19]	Leukemia and Lymphoma/ pediatric	RCT, not blinded	N/A	Vitamin A before high dose MTX may protect against D-xylose malabsorption—a marker of mucosal damage.
	RheumNow[1]	RA/adult	Expert opinion	N/A	Vitamin A decreases stomatitis and improves GI toxicity.
Dextromethorphan (20 to 50 mg PO weekly) CNS Toxicity	Bettachi et al. 1999[28]	RA/adult	Randomized survey	N/A	Pilot study showing CNS toxicity improvement with dextromethorphan.
	Afshar et al. 2014[27]	Oncologic disease/ pediatric	Retrospective study	N/A	Using dextromethorphan concomitantly with MTX has the potential to improve CNS toxicity. Earlier administration of dextromethorphan results in faster improvement of symptoms.
Subcutaneous MTX GI toxicity	Li et al. 2016[32]	RA/adult	Meta-analysis	N/A	Subcutaneous administration of MTX at high doses reduces GI upset.

of folic acid. Folinic acid is chemically different from folic acid and is naturally found in a number of different foods. In contrast, folic acid is a synthetic form of folate.

Multiple reports have shown that folate supplementation with either folic and folinic acid have resulted in statistically significant reductions in GI side effects, such as malabsorption, nausea, vomiting, diarrhea, and abdominal pain, as well as hepatic dysfunction by lowering elevated serum transaminase levels.[5-11] Folate supplementation can also help protect against MTX induced stomatitis, although these changes were not reported as statistically significant (below we will discuss another strategy to combat stomatitis).[6,9,10] A study by van Ede et al.[8] posits that folate supplementation may have the additional benefit of cardiovascular protection due to its ability to prevent MTX-induced hyperhomocysteinemia. Finally, expert opinion has also demonstrated the utility of folinic acid in combating hair loss.[1]

With regard to dosing and timing of initiation, the guidelines to date remain ambiguous. While some reports suggest that folic acid only be added to MTX in certain situations, the 2013 European League Against Rheumatism (EULAR) Guidelines recommend that folate supplementation be used as soon as MTX is initiated regardless of whether the patient is experiencing side effects.[12] Furthermore, accord-

ing to the FOLVARI study, a double blinded randomized controlled trial published in 2015 comparing "low dose" folic acid of 10 mg per week versus "high dose" folic acid of 30 mg per week, folic acid dosed to 10 mg per week is sufficient for the treatment of MTX induced side effects, and the higher folic acid dose does not offer any additional benefit (or harm)—of special note, this study included a number of patients with higher doses of MTX of approximately 22 mg per week.[11] The traditionally employed 5 to 10 mg per week folic acid dosing can come either in the form of daily dosing (which is currently the gold standard in the US) or weekly dosing. In the US, expert opinion demonstrated utility in daily folate supplementation with 1 mg per day equating to 7 mg per week, including the day of MTX administration.[13] In a recent study published by RHEUMNOW surveying US versus non-US rheumatologists, approximately 11% of physicians elect to hold the folic acid dose on the day of MTX dosing, the majority of which are non-US rheumatologists.[13] This practice, however, is not supported by expert opinion, nor is a weekly 5 mg dose, which is also favored among non-US rheumatologists. Given the heterogeneity in usage and the discrepancies between the research and clinical practice, further investigation with evidence-based studies is needed.

When comparing folic acid versus folinic acid, a 2013 Cochrane review found no statistically significant difference in efficacy between the two agents. Folinic acid was also shown to be significantly more expensive than folic acid.[9,10] With regard to dosing of folinic acid, despite lack of clear evidence for superiority over folic acid in the literature, it has been utilized as a second line supplement by many rheumatologists when folic acid has failed (including the authors of this review). Contrasting from dosing in oncologic use in cases of MTX overdose (wherein the dosing is recommended at 15 mg taken every 6 hours for up to 8 doses[11]), folinic acid when employed by rheumatologists is typically given as 5 mg for 2 to 3 doses 12 hours apart and starting 12 hours after the MTX dose.[14-17]

A few studies have been published cautioning providers that folic and folinic acid supplementation may in turn decrease MTX efficacy. These post hoc analyses suggest that dietary folate supplementation plus folic and folinic acid supplementation may ultimately increase MTX dosage requirements.[18] These analyses, however, represent minority viewpoints in the literature.[18] In fact, folic acid should not directly affect MTX efficacy as it does not compete for the same reduced folate carrier (RFC) that takes up MTX. Conversely, folinic acid is taken up by the same RFC as MTX and may have a more direct effect on MTX efficacy compared to folic acid (Fig. 1).[18] At low doses and when folinic acid is given 10 to 12 hours after MTX administration, no changes in MTX efficacy are appreciated. However at higher oncologic doses, as mentioned previously, it is this direct competition of folinic acid against methotrexate transport that allows it to be useful in the setting of MTX overdose.[18]

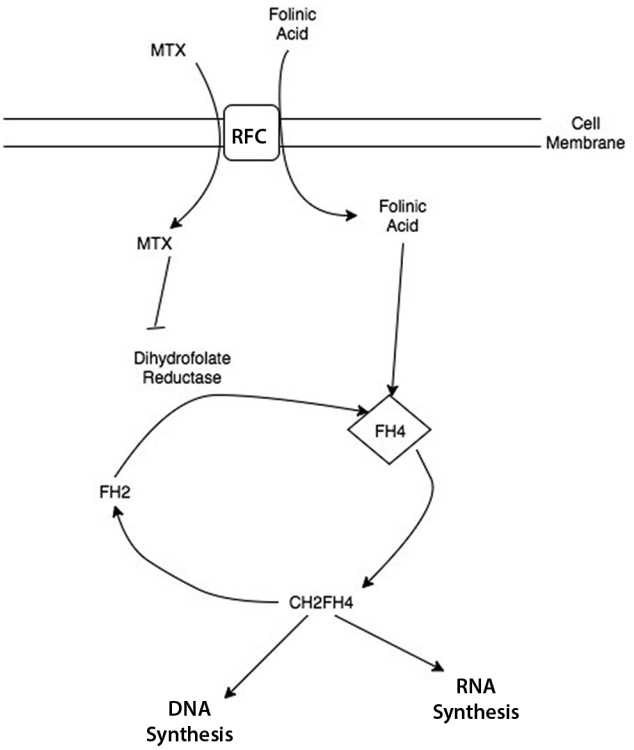

Figure 1 Schematic detailing the mechanism of action of folinic acid as a non-competitive antagonist of MTX. Folinic acid is taken up by the same reduced folate carrier (RFC) as MTX. (This figure is an adaptation of "Methotrexate Mechanism" by Vtvu licensed under Creative Commons Attribution-Share Alike 3.0 Unported license and accessed at https://commons.wikimedia.org/wiki/File:Methotrexate_Mechanism.jpg.)

As important as folate supplementation is to combating individual side effects of MTX, perhaps most importantly, folate supplementation with MTX has also been shown to significantly increase patient adherence to therapy. The 2013 Cochrane review demonstrated a statistically significant decrease in MTX withdrawal numbers between patients taking MTX in conjunction with folate supplementation and patients taking MTX alone. As a result, a higher persistence to MTX and less medication switching may ultimately reduce health care utilization and excess medication costs.[9,10]

Vitamin A: Combating GI Toxicity and Stomatitis

Some MTX experts recommend the use of vitamin A to combat recalcitrant GI toxicity and stomatitis. Much of what is known about vitamin A comes from expert opinion and common practice, and there remains a paucity of peer-reviewed studies validating its utility. Regarding GI toxicity, there is only one human study (published in the pediatric oncologic literature) and several basic science rat studies investigating the potential protective effect of vitamin A in alleviating nausea and small intestine malabsorption.[19-23] With regard to combating stomatitis, expert opinion and

common practice have demonstrated that vitamin A appears to decrease the intensity of oral ulcers more than folic acid.[1]

However, vitamin A dosing from a rheumatologic standpoint remains ambiguous. In the oncologic literature, 180,000 IU of vitamin A was used to combat MTX side effects without causing secondary vitamin A toxicity side effects (such as skin or vision changes).[19] From a rheumatology standpoint 8,000 to 10,000 IU has been used with success to combat GI toxicity and stomatitis.[1] Additional higher level of evidence investigations are needed to clarify vitamin A's mechanism of action, its utility in ameliorating MTX-induced toxicity, and optimal dosing modalities.

Dextromethorphan: Combating Central Nervous System (CNS) Toxicity

Methotrexate-induced CNS toxicity is a frequent complication of MTX therapy. In fact up to one third of patients experience CNS symptoms ranging from mild, such as mood disturbances, malaise, and somnolence, to severe, such as focal neurologic symptoms.[24-29] The pathogenesis of MTX-induced CNS toxicity is multifactorial and not completely understood. Several hypotheses have been proposed, such as altered folate homeostasis and N-methyl d-aspartate (NMDA) receptor activation by homocysteine.[24] With regard to the latter hypothesis, dextromethorphan, a cough suppressant and weak non-competitive NMDA antagonist, has been proposed as a potential therapy for MTX neurotoxicity.

In the recent past, several studies from the oncologic literature have investigated the utility of dextromethorphan in successfully treating MTX-induced CNS toxicity in patients with malignancy.[25-27] However, there is a paucity of data investigating the appropriate use and dosing of dextromethorphan for MTX toxicity in the rheumatologic setting. An abstract published by Bettachi et al.[28] remains one of the few studies detailing the utility of dextromethorphan in RA patients. Based on this pilot study as well as expert opinion, 20 to 50 mg of dextromethorphan administered weekly, first at the time of MTX administration and then again 8 to 12 hours later, is recommended to combat CNS toxicity.[28] One strategy in the neurology literature for increasing systemic dextromethorphan concentration is by the co-administration of quinidine, although we are unaware of any specific study of this in the rheumatologic setting.[29] Future studies are needed to better understand the pathogenesis of MTX induced CNS toxicity, the underlying mechanism of how dextromethorphan works to ameliorate CNS side effects, as well as proper dosing.

Subcutaneous MTX: Combating GI Toxicity

Switching from oral MTX to subcutaneous (SC) MTX in order to mitigate the effects of MTX toxicity continues to be a confusing and controversial topic. In general, SC MTX has a higher bioavailability than oral forms, which ultimately increases the body's absorption of the drug.[26-29] Methotrexate toxicity is positively correlated to its absorption. Thus, SC MTX is usually associated with increased toxicity side effects due to increased absorption and availability. However, several experts have demonstrated that switching to SC MTX can actually help decrease GI specific side effects including: nausea, vomiting, diarrhea, and dyspepsia.[30-33] Given the increased bioavailability of SC MTX, switching to a low dose SC MTX may be beneficial in patients requiring higher doses of oral MTX in order to maintain higher absorption with decreased GI toxicity.[29,33]

Patient Risk Education: Increasing MTX Adherence

Patient awareness of potential toxicity associated with MTX as well as risk education play an important role in overall reducing toxicity effects.[1] Generally, it is observed that when patients have a clear idea of the potential side effects, coupled with known treatment modalities for side effect management, they will be more likely to continue taking the MTX instead of self-discontinuing it.[1] Risk communication and developing a toxicity treatment plan prior to MTX initiation will help tremendously with treatment adherence.

Conclusion

Methotrexate continues to be the standard of care for the treatment of RA against which many of the new biologic agents are measured. However, it is associated with several debilitating toxicity side effects, which in turn decreases patient medication tolerability and adherence. Today there are only a handful of treatment modalities in the armamentarium of the rheumatologist to combat MTX induced toxicity. While there is ample literature on the classically used agents, folic acid and folinic acid, much of what is known about vitamin A and dextromethorphan come from basic science investigations and expert opinion. Gastrointestinal toxicity, which is the most common side effect described by patients, can also be alleviated by switching to subcutaneous MTX. Finally, patient risk education and a toxicity treatment plan should be discussed prior to MTX initiation in order to improve patient medication adherence.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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