Journal of Advanced Medical and Dental Sciences Research

@Society of Scientific Research and Studies

Journal home page: www.jamdsr.com doi: 10.21276/jamdsr Index Copernicus value ICV = 82.06

(e) ISSN Online: 2321-9599; (p) ISSN Print: 2348-6805

Review Article

Toxicity Profile of Methotrexate in Patients on Treatment for Rheumatoid Arthritis- A Review

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ABSTRACT:
Methotrexate (MTX) is the cornerstone of treatment in rheumatoid arthritis (RA). It has already been used for over 40 years as an anchor treatment in a number of rheumatic diseases, thereby; it remains a gold standard of therapy for RA. The weekly low dose MTX provides a cost effective, efficacious and generally well tolerated treatment for RA. The physicians should be aware of the risks associated with MTX use and must monitor accordingly. The present review provides a concise discussion of the toxicity and safety of methotrexate in treatment of rheumatoid arthritis.
Key words: Rheumatoid arthritis, MTX toxicity, MTX treatment.

Received: 28 October, 2019 Revised: 25 December, 2019 Accepted: 27 December, 2019

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This article may be cited as: Rahman MM, Ahmad SJ, Shariff RC, Tiwari RVC, kumar S, Wasan B, Tiwari H. Toxicity Profile of Methotrexate in Patients on Treatment for Rheumatoid Arthritis- A Review. J Adv Med Dent Scie Res 2020;8(2):65-68.

INTRODUCTION:

Methotrexate (MTX) is an efficacious disease modifying antirheumatic drug (DMARD). The efficacy of MTX has been proved in placebo controlled trials as well as in comparison with the other DMARDs.[1] In RA patients, superior "drug survival rate" indicates a favorable tolerability with presumptive potency and the limited toxicity of MTX. Although, a drug with desirable effects on multiple organ systems must also has some undesirable effects as well. There are some adverse events which appear to be related with the antifolate activity of MTX and thereby mimic the symptoms of folate deficiency. There are relatively rare clinically relevant side effects. In the various prospective long-term studies in which patients were seen frequently as well as in the studies with i.v. application of higher MTX doses, approximately 60–85% of patients reported adverse events and about 10-30% of the patients discontinued MTX due to its toxicity. The predisposed adverse events related to

MTX are elevated creatinine serum levels, low folic acid levels and advanced age. However, generally the creatinine elevations are reversible when MTX is discontinued. In approximately 10% of patients, a post-dosing reaction characterized by the myalgias/arthralgias or malaise/fatigue or both is seen within hours after dosing. On a weekly dose MTX can be used for years and the use is mainly limited by its toxicity.[1] As far as toxicity of MTX is concerned, renal impairment and age are generally considered risk factors, although the studies have shown conflicting results. A rise in liver enzymes, particularly the transaminase occurs frequently during the MTX treatment. Obesity, dose, alcohol use as well as lack of the folate supplementation are considered to be associated with the hepatotoxicity.[1, 2] Moreover, gastrointestinal (GI) side effects have also often occur during MTX treatment. Although, folinic acid supplementation reduce the occurrence of GI side effects.[2] The overall toxicity scores, including both the GI side effects and hepatotoxicity have also reduced by addition of folic acid.13–15 However, the pulmonary toxicity is less common. The pre-existent pulmonary disease as well as the age has been shown to increase the risk of pulmonary side effects.[2] In elderly patients with mild renal insufficiency, pancytopenia was found commonly and to be related to the renal impairment and central nervous system toxicity.[3] The disease activity, disease duration, functional class, sex and prior DMARD use are suggested to be related to the treatment response. According to some studies, the supplementation with folates has raised the questions about the reduced efficacy of MTX, but most of the studies did not show a negative effect.[2, 3] There is a dose- response relation in MTX treatment, but the optimal dose is determined individually. It is important for the clinical practice to predict the toxicity, efficacy and final dose. The present review will provide a discussion in a concise way about the safety and toxicity of methotrexate in Rheumatoid Arthiritis.

GIT- In many prospective studies, malaise, nausea and vomiting were observed in 10- 50% of the patients starting 1-8 hours after the medication and continuing for a few hours up to one week. Some of the patients are unable to work after the dosing and thereby take MTX only on the weekends. There is accumulation of MTX polyglutamate in the cells of intestinal mucosa, which may explain the gastrointestinal side effects in some of the patients. The healing of the peptic ulcers caused by the concomitant NSAID medication may be delayed.[4] Thereby, an active peptic ulcer must be regarded as a relative contraindication for MTX.

Skin & mucous membranes- The stomatitis has also been observed in the long term studies in about 12-37% of the patients and the same was the reason for discontinuation in about 6% of the patients. In upto 27%, mild alopecia occurs, but the prompted discontinuation in only 4%.[5] Small vessel vasculitis, urticaria and granulomatous vasculitis are rarely observed.

Hematopoetic system- The hematologic complications of weekly treatment of MTX for RA are infrequently seen. In the short term studies, they occurred in 2-3% in some reports even with the higher doses. In the long term studies, the bone marrow side effects have also been occurred in up to 24% of the patients. Mild to moderate leucopenia is the most frequent abnormality. According to one long-term follow up, it was observed that mild leucopenia occurred in only 8 while mild thrombocytopenia in 7 out of 271 RA patients.[5] The pancytopenia occurred in 7 of 511 patients (1.4%) included in prospective trials.[6] Due to cytopenias, the number of withdrawals ranged from 0 to 5.9%.[7] The risk factors that have been identified for the bone marrow toxicity are folic acid depletion, impaired renal function, advanced age, multiple co-medication, current infection and treatment with the trimetoprim-sulfamethoxazol. Within 2 weeks after the withdrawal of MTX, the blood counts are usually normalized, but some of the patients may require the supplementation with folic acid or even the treatment with colony stimulating factors.

Central nervous system-In some long term studies, the disturbances related to central nervous like dizziness, vertigo, headaches, lightheadedness and the mood alterations were reported in about 36% of the patients.[8] Moreover, the elevated serum creatinine and advanced age are also the predisposing risk factors. In two patients with a history of epilepsy, the seizures reappeared within 6 weeks of starting the MTX treatment and disappeared when MTX was discontinued.

Respiratory system- The MTX-induced lung disease is rare, but it is potentially life-threatening complication, and it is crucial to the rapid evaluate the pulmonary symptoms in patients receiving MTX. Subacute development of dyspnea, dry non-productive cough and fever along with malaise, headache, hypoxemia, cyanosis and restrictive pulmonary function changes are the predominant symptoms of MTX pulmonitis.[9] On the physical examination, rales may be present while the interstitial infiltrates may be seen on the chest radiographs. Lung biopsy may also reveal the hypersensitivity pneumonitis which has been

characterized by the massive interstitial and the alveolar infiltration with the inflammatory cells, predominantly the lymphocytes as well as the granuloma formation with giant cells.[10] Before establishing the diagnosis of MTX-induced pneumonitis, the other causes of pulmonary disease, e.g. nosocomial infections must be excluded. The pre-existing lung disease does not seem to pre-dispose to MTX pulmonary adverse events. Moreover, there is no evidence to suggest that the low-dose MTX is associated with the chronic interstitial lung disease.

Hepatic toxicity-Among the patients with liver fibrosis, psoriasis and cirrhosis developed with the increasing cumulative doses in up to 24% of patients treated with the daily MTX. In addition to daily dosing, the risk factors for liver toxicity included are obesity, high alcohol consumption, and diabetes. The weekly dosing was found to be better tolerated than the daily dosing. There should be awareness of potential liver side effects in the long-term treatment with MTX, although in patients with RA, the hepatotoxicity has not been a substantial problem with weekly low-dose MTX.[11] In a study, slight transient elevations were observed in the liver enzymes in about 48% of patients and in 53% in a more recent study. [11, 12] After reduction of the doses, these elevated levels returned to normal. Frequent elevations of the aminotransferases indicate the structural liver abnormalities and were correlated significantly with the liver biopsy grades. A comparative liver biopsy studies did not show differences in a number of histologic parameters, such as "necrosis", "fibrosis" and "inflammation" between the biopsies taken before and during the MTX treatment, even in cumulative doses of up to 8,400 mg. [13]Only 5 of 25 liver biopsies demonstrated the minor fibrosis in the patients who received MTX for more than 10 years.[14] According to the several overviews, the frequency of fibrosis among the MTX treated RA patients was estimated to be between 3% and 11%. The incidence of cirrhosis among RA patients treated with MTX for more than 5 years was estimated to be around 1:1000.

Infections- The infections occur more often in the patients treated with MTX than with the other DMARDs, especially in the patients with severe RA and also during the first years of treatment. In some prospective studies, it was observed in up to 25% of patients. Increased frequency of herpes zoster, opportunistic infections, serious fungal infections as well as re-activation of hepatitis B and tuberculosis has been reported. Due to recurrent infections, some patients must discontinue MTX permanently, mostly affecting the urinary tract and small airways. The perioperative complications, like wound healing disturbances or wound infections were increased after the orthopedic surgery in some of the studies, but in others they were not. Some of the authors withhold the MTX for 2 weeks prior to surgery, but others continue treatment through a surgical intervention.

Kidneys and reproductive system-Excretion of the MTX and its metabolites is delayed in the patients with impaired renal function, leading to potentially increased toxicity. MTX treatment may also impair the renal function, especially in the elderly patient. According to one study, the tubular excretion and glomerular filtration rate was reduced by about 10% during the oral 15 mg weekly MTX treatment without any co-medication.[15] The creatinine clearance and MTX clearance also decreased with a stable MTX dose of 7.5 mg/week. Henceforth, these observations emphasize the need to monitor the creatinine levels during the MTX treatment. Impotence, oligospermia and gynecomastia have also been reported with the MTX. There were no malformations detected among 10 pregnancies during the low-dose MTX treatment in RA patients. [15]After the mother had been treated with weekly low-dose MTX during the first trimester of pregnancy; however a case with multiple congenital abnormalities has been described. Moreover, the malformations have also been reported after the MTX was used to induce abortion.

Oncogenicity-The larger number of studies of cancer and psoriasis did not establish an association between the MTX and malignancy. However, RA patients have disease-related increased risk for developing certain lymphoid malignancies. The cases of Hodgkin's disease and leukemia have been reported in the RA patients treated with the MTX. The majority of the cases with malignancy were having non-Hodgkin-lymphomas, most of which were associated with the Epstein-Barr-virus (EBV) infection. However, it is unclear that whether MTX plays a role in the development of lymphoma in RA patients. The patients with RA are known to have a defect in the HBV-directed suppressor T-cell-function. However, it is not clearly established that MTX augments this T-cell-suppressor defect or not, although the opportunistic infections are clearly associated with the MTX use, perhaps in the patients with severe RA. While taking the MTX, the risk for RA patients to develop lymphoma is increased in those with severe disease activity, genetic predisposition, intense immunosuppression and latent infections with EBV virus. Although, some lymphomas associated with EBV infection suspended after the discontinuation of MTX or with the treatment with rituximab.

Bone-The active RA has been associated with osteoporosis, especially in the patients taking corticosteroids. In the experiments where rats treated with MTX, bone formation was reduced markedly, the osteoid volume decreased significantly as well as significant osteopenia developed due to the suppression of osteoblast activity. However, in the RA patients, there was no difference in the bone mineral density between those treated with and those not treated with MTX. Although, when the patients who were taking prednisone in the doses >5 mg/day were additionally treated with MTX, they showed significant bone loss in comparison to those patients treated with a similar dose of prednisone without MTX.

CONCLUSION: MTX is still very much at the centre of all the therapeutic strategies for RA and other rheumatic diseases. The physicians must be aware of the risks and toxicity associated with its use and monitor accordingly.

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