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Methotrexate toxicity in patients with rheumatic diseases: A 10-year evaluation of manifestations, risk factors, and mortality

Saeedeh Shenavandeh[1], Mohammad Haghighat[2*], Amir Hossein Hassani[2]

[1]Division of Rheumatology, Department of Internal Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. [2]School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Methotrexate (MTX) is a commonly used medication in the treatment of rheumatic diseases. MTX toxicity is a serious and at times fatal complication. In this 10-year cohort, we retrospectively evaluated the cases of MTX toxicity among rheumatic patients to identify demographic, clinical, and laboratory characteristics and risk factors of mortality. Through 10 years, patients older than 17 years with a rheumatic disease and at least one major manifestation of MTX toxicity (mucositis, myelosuppression, pneumonitis) were enrolled in the study. Demographic, clinical, and laboratory data were collected. Comparisons were made between patients who recovered and those who passed away. Of the 66 patients, most had rheumatoid arthritis, followed by systemic lupus erythematous. Most patients were females, and their mean age was 63.3±12.4 years. The most common comorbidity was hypertension followed by diabetes mellitus. Most patients were on polypharmacy and were taking MTX incorrectly. Other potential risk factors of toxicity were hypoalbuminemia, decreased renal function, and infection. The outcome of six patients was death and the predictors of mortality were severe leukopenia at admission, infection, especially sepsis, and severe renal impairment. In this study, we observed some potential risk factors for toxicity, namely incorrect MTX use, polypharmacy, renal impairment, hypoalbuminemia, infection, and comorbid conditions such as diabetes mellitus, hypertension, and ischemic heart disease. We also identified the risk factors of mortality, including infection, sepsis, severe leukopenia, high creatinine levels, and severe renal impairment.

Keyword: methotrexate; methotrexate toxicity; risk factor; mortality

Introduction

Methotrexate (MTX), a disease-modifying antirheumatic drug (DMARD), was initially used for treating rheumatoid arthritis (RA) in 1951 [1]. Today, MTX is an essential component of the initial treatment regimen for RA, a disease with a global prevalence of 460 per 100,000 population [2,3]. Beyond RA, low-dose MTX is a primary DMARD for various rheumatic conditions such as juvenile idiopathic arthritis and psoriasis. It also plays a role in treating inflammatory bowel diseases, vasculitis, and systemic lupus erythematosus (SLE) [4,5].

While the precise mechanism through which MTX alleviates RA is not fully elucidated, hypotheses include folate antagonism, polyamine inhibition, cytokine profile alteration, reduced adhesion of inflammatory cells, generation of reactive oxygen species, and adenosine signaling, with the latter currently being widely accepted [6].

MTX use is associated with hematological,

*Corresponding author: Mohammad Haghighat, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.
Tel: +98-9359235088, E-mail: mammadht@gmail.com

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while AST levels were slightly higher in our study. Most patients in Bhargava's study received intravenous antibiotics and G-CSF; the former is also true for our study, while less than half of the evaluated patients had received G-CS in our study.

Although the patients were 10 years younger on average, the mortality was about 3 times that of Bhargava's study as compared to ours. The higher mortality reported by Bhargava and colleagues may be explained by several factors, including greater average severity of baseline myelosuppression and hypoalbuminemia [14]. Another factor that may have potentially affected the mortality rates, however, is the significantly higher average dose of folinic acid recorded in our study, a discrepancy which certainly merits further research. The importance of investigating this potential benefit is further supported by the lower mortality rate in our study compared to several other previous studies [8,12,15,16,22].

Limitations of our study, given its retrospective nature, included a lack of adequate data for evaluating some potential risk factors of MTX toxicity, namely regular folic acid intake and regular follow-up, as well as the lack of laboratory parameters of renal function before the development of toxicity. A similar limitation was present in identifying the cases of pneumonitis, as many patients had not undergone CT imaging. Another limitation was the limited number of cases, and the risk factors for mortality identified in our study need further evaluation in larger cohorts or possibly systematic reviews.

Future studies with a larger pool of patients are needed to solidify the findings of our study, especially regarding predictors of mortality in cases of MTX toxicity. Prospective long-term cohort studies on patients taking low-dose MTX are suggested, to identify the patients who develop toxicity and compare their characteristics with patients who did not develop toxicity. Such prospective studies can help evaluate the potential risk factors of MTX toxicity presented in our study more accurately.

Conclusion

While MTX remains a frequently prescribed drug for the treatment of various rheumatic diseases, cases of MTX toxicity are likely to occur. In this study, we observed several potential risk factors for toxicity, the most frequent one being incorrect MTX use. Others included renal impairment, polypharmacy, hypoalbuminemia, infection, and comorbid conditions such as diabetes mellitus, hypertension, and ischemic heart disease. We also identified several risk factors for mortality, including infection, sepsis, severe leukopenia, high creatinine levels/lower GFRs, and severe renal impairment. We hope these findings will promote safer MTX prescriptions in rheumatic patients, guide management decisions in cases of toxicity, and serve as an encouragement for further research.

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Conflict of Interest

Saeedeh Shenavandeh, Mohammad Haghighat, and Amir Hossein Hassani declare that they have no conflict of interest.

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