Therapeutic Drug Monitoring in Predicting Methotrexate-induced Adverse Reactions in Patients with Rheumatoid Arthritis – Indicated or Not?

NMRR-18-3819-41652

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Introduction

Weekly oral low-dose methotrexate (MTX) therapy is widely used to treat rheumatoid arthritis (RA) due to its high efficacy. However, MTX is associated with some life threatening adverse drug reactions (ADR), namely hematological toxicity, hepatotoxicity and pneumonia. It is well known that the plasma MTX concentration is related to the efficacy and safety of MTX in high-dose therapy for malignancy. The role of therapeutic drug monitoring (TDM) to predict development of MTX ADR in RA patients remains a subject of debate. Hereby, we conducted a review to evaluate the relationship between MTX concentration and incidence of ADR in adult RA patients.

Methodology

Systematic review performed following PRISMA guidelines. The available literature search was from 1985 (the year of first study published on the efficacy of MTX in relieving symptoms in RA patients) up to April 2019. Search terms included ‘Methotrexate’, ‘Rheumatoid Arthritis’, ‘Concentration’ and ‘Adverse’.

Inclusion criteria: All articles that include MTX concentration measured and MTX ADR in adult RA patients.

Exclusion criteria: Index, glossary, appendices, editorials, book chapter, proceedings of conference and duplicate papers were excluded.

The quality of the observational studies was assessed using Murad’s 8-questions tool for evaluating the methodological quality of case reports and case series. The information was checked and verified by all the authors.

Results

Mean age of all the subjects is 50.6 years with median disease duration of 10 years. The mean dose of MTX is 10mg/week with mean cumulative dose of 775mg. Table 1 summarizes the characteristics of all the selected literatures.

Out of total 430 subjects, 161 (37%) reported MTX-related ADR. 80 (50%) subjects suffered from hepatotoxicity, 56 (35%) hematological toxicity, 7 (4%) pneumonia and 18 (11%) others. Among the 25 subjects where the outcome of ADR management reported, 8 (32%) died even after leucovorin rescue. Pancypopenia was present in all the patients who died.

Both Shoda and Gilani reported that MTX Cmax correlated with ADR (p<0.001). The receiver operating characteristic (ROC) curve analysis showed minimum toxic concentration of MTX = 0.16µmol/L (Sensitivity 81%, specificity 67%) and 0.71µmol/L (Sensitivity 71%, specificity 76%) respectively. 2, 3 While Sandhu and Takahashi reported that MTX-glu associated with ADR (p<0.05), with the cut off point for toxicity = 131nmol/L. 4, 5 However, study by Kivity did not show significant correlation between C≥24 and cytopenia (0.09 ± 0.15 µmol/L, p=0.10). 6

The quality assessment scores for the case reports or case series ranged from 4 to 8 (out of 8) while for observational studies ranged from 10 to 12 (out of 14).

Discussion

MTX Cmax was achieved 1-2 hours after the intake of MTX dose. MTX-glu, as a MTX metabolite, retained within the cells for some time after the elimination phase from plasma, while the plasma MTX concentrations fall below therapeutic levels rapidly. Therefore, it is believed that MTX-glu concentration and Cmax are more reliable for predicting MTX toxicity compared to C24 where the concentration sometimes are below detectable limit.

Regarding the other factors that may affect the MTX ADR, the baseline body mass index (BMI), serum albumin level, maintenance MTX dose and concomitant steroid administration were found to be statistically significant. In contrast, age, renal function, duration of MTX treatment were not found to be significant in all the literatures.

Conclusion

MTX and MTX-glu concentration can be useful in predicting ADR in adult RA patients. MTX dose as low as 7.5mg/week may result in ADR, where pancytopenia was the most severe, and can be fatal. In order to identify the accurate toxic MTX concentration in predicting the incidence of ADR, more randomized controlled studies are needed and other risk factors need to be adjusted in the analysis. Genetic polymorphism data may be required too to explain the interindividual variations of the MTX concentration in related to ADR.

References