Methotrexate Toxicity and Associated Risk Factors in Filipino Patients with Rheumatoid Arthritis Included in the Rheumatoid Arthritis Database and Registry

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Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease that is severely debilitating with a prevalence in the Philippines of 0.17-0.4%. This study aims to determine rate of methotrexate (MTX) toxicity, identify risk factors and comorbid conditions predisposing to toxicity and describe management of MTX toxicity.

Methods: Rheumatoid arthritis (RA) cases from the Rheumatoid Arthritis Database and Registry (RADAR) diagnosed by the 1987 ACR criteria receiving MTX monotherapy or combination disease modifying anti-rheumatic drugs (DMARDs), with at least one dose of treatment, were included. Patients were grouped into those with and without adverse events (AE). Disease activity was measured using DAS 28-ESR. Baseline characteristics, duration of use, dose, concomitant drugs and all toxicities were listed. Management of AEs were described. Independent t-test and Mann-Whitney U test were used for numerical data and Chi-square and Fisher's exact test for continuous data.

Results: One hundred ninety four patients are included, with 95% females, age 35-64 years, disease duration of 0.2-10 years. Eighty three percent are on methotrexate monotherapy. Fifty cases (25.77%) all with dose of 8.75±2.5 had AEs: hepatotoxicity (52%), gastrointestinal (24%), hematologic (14%), dermatologic (8%), pulmonary (6%). Risk factors directly correlated with toxicity were older age (p=0.024), disease duration (p=0.024), dose (p<0.000), duration of use ($p \leq 0.001$), anemia (p=0.038) and osteoarthritis (p=0.011).Management included dose reduction (52%), dose retention with close monitoring (26%), addition of (24%) or shift to (22%) other DMARDS. Folate dose was increased in all cases.

Conclusion: Methotrexate (MTX) toxicity rate of RA patients from the RADAR is similar to those in literature. While dose reduction is the main management strategy, some patients' doses were maintained while others were shifted to other DMARDS.

Keywords: rheumatoid arthritis, methrotrexate toxicity, rheumatoid arthritis database and registry

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that causes debilitation and destruction of affected joints leading to disability and premature mortality. Philippine prevalence is 0.17-0.4%.[1] The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend methotrexate (MTX), a disease modifying anti-rheumatic drug (DMARD) as the first line therapy for patients with RA due to its efficacy and acceptable risk profile.[2-9] One of the most frequent reasons for terminating MTX treatment is development of toxicity to the drug.[10] Results from 21 prospective studies on long term treatment of MTX have shown 10-37% of patients discontinuing its use due to toxicity.[11-31] Adverse events to MTX reported are gastrointestinal (GI) and hepatotoxicity, renal toxicity, pneumonitis, neurologic and hematologic.[32,33] MTX affects tissues undergoing rapid cellular turnover which include the oral mucosa, gastrointestinal tract and bone marrow cells making these systems at risk for toxicity to the drug.[33,34,35] Prolonged exposure to MTX also depletes folate levels in hepatocytes due to competitive inhibition of MTX with dihydrofolate reductase, thus making hepatotoxicity one of the more common side effects observed in RA patients on long term treatment with MTX. Risk factors that were associated with MTX toxicity include older age, body mass index (BMI), female sex, and folic acid supplementation.[32,36,37]

The study aims to determine the prevalence of MTX toxicity in adult Filipino patients included in the Rheumatoid Arthritis Database and Registry (RADAR) of the Philippine General Hospital. Risk factors associated with the development of MTX toxicity will also be identified and current practice regarding management of MTX toxicity will be described.

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Methods

This case control study used the RADAR of the Philippine General Hospital. Charts of patients who developed MTX toxicity were retrieved for review. Patients who did not develop MTX toxicity served as the control group. Patients with known liver, renal, hematologic and neurologic disease prior to starting methotrexate treatment were excluded.

MTX toxicity is defined as any adverse event experienced by the patient attributed to the use of MTX. Hepatotoxicity as ALT/AST greater than normal. Gastrointestinal toxicity includes nausea, vomiting, diarrhea, and abdominal pain. Renal toxicity as creatinine clearance less than or equal to 50 ml/min. Hematologic toxicity as pancytopenia, thrombocytopenia and neurologic toxicity as headache, vertigo, dizziness, fatigue.

Baseline characteristics (age, gender, BMI, disease duration, baseline disease activity and disease activity at the time of MTX toxicity, smoking history, alcohol intake, concomitant DMARD use, dose of MTX and folate supplementation) were obtained. Disease Activity Score 28 based on erythrocyte sedimentation rate (DAS 28) was used to define disease activity. Gastrointestinal, hepatic, renal, pulmonary, neurologic and hematologic adverse events were noted. Corresponding management after detection of adverse events were also described.

A sample size of 50 (25 cases of MTX toxicity and 25 non-toxicity) achieves 80% power and 95% confidence for detecting a MTX toxicity incidence of 27% among low-dose (2.5 to 10 mg) MTX recipients[37] and 66.64% MTX toxicity incidence among high-dose (12.5 to 25 mg) MTX recipients.[38] In this study, 50 patients who developed MTX toxicity and 144 patients without toxicity were used in data analysis.

For descriptive purposes, categorical data were presented as frequencies and proportions (percents) while numerical data were described using mean+standard deviation when the normality assumption was met and using median+interquartile range when the normality assumption was not met. Normality was tested using Shapiro Wilk test.

Moreover, independent t-test was used to compare numerical data between groups (with or without MTX toxicity) when the normality assumption was met. Mann-Whitney U test was used to compare numerical data which failed to satisfy the normality assumption. Chi-square and Fisher's exact tests were used to compare categorical data between the said groups.

P-values less than 0.05 were considered significant. All statistical calculations were performed using Stata IC version 13. The study has been approved by the UP-PGH Ethics Review Board. Patients' confidentiality was ensured.

Results

Baseline characteristics are summarized in Table I. One hundred ninety four patients are included, with 95% females, age 35-64 years, and disease duration of 0.2–10 years. Eighty three percent are on methotrexate monotherapy. Fifty cases (26%) have toxicity with a mean dose of 8.75 ± 2.5, 144 cases (74%) without. Risk factors directly correlated with toxicity were older age (p=0.024), disease duration (p<0.000), dose (p=0.003), and duration of use ($p \leq 0.001$).

Comorbidities associated with MTX toxicity include anemia (p=0.038) and osteoarthritis (p=0.011). Adverse events include: hepatotoxicity (52%), GI (24)%, hematologic (14%), dermatologic (8%), pulmonary (6%). (Table II)

Subgroup analysis for GI toxicity shows association with combination DMARD use (p=0.007); hepatotoxicity with disease duration (p=0.009) and duration of MTX use (p=0.039). Management of toxicity (Table III) includes dose reduction (52%), retaining dose with close monitoring (26%), adding of or shifting to other DMARDs (22%), and discontinuation of MTX (22%). Folate dose is increased in all cases.

Discussion

Among 194 patients given MTX for rheumatoid arthritis, 50 (26%) developed toxicity at a mean dose of 8.75±2.5 mg/week. This is comparable to data from recent literature reporting a range of 10-37% of patients with MTX toxicity leading to discontinuation at a mean dose of 8.8 mg/week.[4-31,32,36,37]

Risk factors for MTX toxicity reported include older age, sex, BMI, and presence of folate supplementation.[32,36,39] Long term safety studies on MTX monotherapy with a mean duration of 36.5 months at dose range of 10-25 mg/week have at least 73% of patients developing one adverse event.[10,28, 40-42] This cohort also presented similar results as older age, higher MTX dose and longer duration of MTX intake were associated with MTX toxicity. Other risk factors noted in this cohort included longer duration of disease, presence of anemia and osteoarthritis. The role of BMI and folate supplementation was not significant in this cohort of patients and could be due to limited sample size.

Majority of adverse events to MTX in this cohort are due to hepatotoxicity (13%) and gastrointestinal toxicity (6%). Most literature on adverse events related to MTX show the same results with elevation of liver enzymes in 13% and gastrointestinal events in up to 65% of patients.[10,31,43,44] After doing a subgroup analysis, MTX dose (p=0.001) and combination DMARD use (p=0.007) was associated with GI toxicity to MTX. MTX tends to accumulate in the cells of the intestinal mucosa causing GI irritation at higher doses.[33,35] A

Table I. Comparison of baseline disease characteristics of RA patients with MTX toxicity and RA patients without MTX toxicity

	No toxicity (N = 144)	MTX toxicity (N = 50)	*p*-value
	n (%)		
Gender (n = 194)			
Female	137 (95.14%)	49 (98.00%)	0.343[F]
Male	7 (4.86%)	1 (2.00%)	
Smoking history			
Ever smoked (n= 148)	8 (7.21%)	2 (5.41%)	0.523[F]
Never smoked (n = 149)	75 (67.57%)	35 (92.11%)	0.002*[F]
Present smoker (n = 150)	5 (4.46%)	1 (2.63%)	0.524[F]
Alcohol intake			
Never took alcohol (n = 113)	63 (84.00%)	36 (94.74%)	0.087[F]
Currently with alcohol intake (n = 113)	10 (13.33%)	2 (5.26%)	0.161[F]
Combination DMARD use (n = 194)	22 (15.28%)	11 (22.00%)	0.190[F]
Folic acid supplementation (n = 182)	93 (69.92%)	31 (63.27%)	0.473[F]
Moderate disease activity	42 (49.41%)	10 (50.00%)	0.579[F]
High disease activity	43 (50.59%)	10 (50.00%)	
	mean ± SD		
Age in years (n = 194)	47.02 ± 12.97	51.9 ± 13.23	0.024*[t]
Age at onset in years (n = 194)	43.79 ± 12.55	45.92 ± 12.59	0.303[t]
Disease activity at time of MTX intolerance (n = 25)	N/A	4.00 ± 1.33	N/A
	median ± IQR		
BMI (n = 59)	23.50 ± 3.70	24.30 ± 2.80	0.845[M]
Baseline disease activity (DAS 28) (n = 105)	5.19 ± 1.62	5.09 ± 1.72	0.385[M]
DAS at last follow up (n = 68)	4.49 ± 1.59	3.2 ± 1.69	0.005*[M]
Duration of MTX intake in years (n = 193)	1.00 ± 1.67	2.38 ± 4.00	0.000*[M]
MTX dose (n = 183)	7.5 ± 2.5	8.75 ± 2.5	0.003*[M]
2.5 – 10 mg (n,%)	113 (84.96%)	38 (76.00%)	0.128[F]
12.5 – 20 mg (n,%)	20 (15.04%)	11 (22.00%)	
> 20 mg (n,%)	0 (0.00%)	1 (2.00%)	

** p<0.05; SD – standard deviation; IQR – interquartile range; F – Fisher's exact test; t – independent samples t-test; M – Mann Whitney U test*

Table II. Frequency of patients with MTX toxicity, n=50 (26%)

Hepatic	26 (52%)
GI	12 (24%)
Hematologic	7 (14%)
Dermatologic	4 (8%)
Pulmonary	3 (6%)

Table III. Management of MTX toxicity, n=50 (26%)

Folate supplementation	50 (100%)
Decreased MTX dose	26 (52%)
Retained MTX dose with close monitoring	13 (26%)
Added or shifted to other DMARDs	12 (24%)
Discontinue MTX	11 (22%)

study by Kremer of RA patients with MTX toxicity at a mean dose range of 12.4-14.6 mg/week reported 65% rate of GI toxicity.[31, 40-42] Combination DMARD use also show increased incidence of adverse events compared to monotherapy with MTX. Diarrhea was increased by 22% in patients with MTX combined with Leflunomide therapy.[45,46] Hepatotoxicity was associated with duration of disease (p=0.009) and duration of MTX intake (p=0.039) in this cohort. A study by Bologna in 1997 also reported that RA patients on long term MTX treatment showed an increasing trend of elevated liver enzymes >2x of normal in 69-88% of patients after the first four years of MTX intake.[47]

Management of adverse events for MTX in current practice usually involves folic acid supplementation, close monitoring and discontinuation of the drug.[48] Folic acid supplementation has been reported to decrease the incidence of GI toxicity by nine percent and hepatic toxicity by 16%. It also decreases the discontinuation rate of MTX by 15%.[49-55] All patients with MTX toxicity in this cohort were given folate supplementation. The discontinuation rate of MTX for this cohort of patients was 22%.

Limitations of the study included the small sample size which did not permit a multivariate analysis for association of risk factors for hematologic, dermatologic, pulmonary, renal and neurologic events.

Conclusion

MTX toxicity rate of RA patients from the RADAR is similar to those in literature. While dose reduction is the main management strategy, some patients' doses were maintained while others were shifted to other DMARDS.

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