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BRIEF REPORT

Methotrexate in a Real-World Psoriasis Treatment: Is It Really a Dangerous Medication for All?

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Dear Editor:

Introduced in 1958, methotrexate (MTX) is an effective medication that is commonly used in patients with moderate to severe psoriasis[1,2]. Despite its widespread use in psoriasis treatment, there is little evidence on the safety of MTX in psoriatic patients[3,4]. Although MTX has had a long history of use, there is insufficient data on cumulative MTX doses that result in early liver toxicity and the duration to develop such adverse events owing to the limited data on MTX safety. In this study, we focused on the common adverse effects caused by MTX and their risk factors in real-world use.

Data from psoriasis patients receiving MTX therapy between January 2009 and June 2014 were retrospectively collected. All patients were administered MTX exclusively for psoriasis management. Only those whose screening laboratory findings were normal commenced treatment with MTX with the exception of 2 patients who had chronic glomerulonephritis. The starting dose was 0.2～0.4 mg/kg/wk orally in a single dose along with folic acid 1 mg daily; after 2～3 months of treatment the dose was adjusted based on clinical efficacy. Routine laboratory tests were conducted 1 month after treatment and every 2 months thereafter. A Cox proportional hazards regression model was used to determine the clinical factors that could affect the development of adverse events among patients with psoriasis who were receiving MTX, by using SAS software (ver. 9.3; SAS Institute Inc., Cary, NC, USA). This study was approved by the institutional review board

Table 1. Clinical, demographic, and laboratory characteristics of patients (n=42)

Characteristic	Value
Age (yr)	44.10±16.81
Gender	
Female	11 (26.2)
Male	31 (73.8)
Duration of disease (mo)	143.08±164.83
PASI score	14.97±7.92
≤10	16 (38.1)
>10	26 (61.9)
Total medication period (d)	284.07±223.44
Cumulative dose (mg)	467.26±372.70
Underlying diseases	
None	26 (62.0)
Diabetes	5 (11.9)
Hypertension	11 (26.2)
Dyslipidemia	5 (11.9)
Liver disease	0 (0)
Kidney disease	2 (4.8)
Others*	5 (11.9)
Follow-up laboratory abnormality	11 (26.2)
CBC	0 (0)
AST/ALT	10 (23.8)
Uric acid	2 (4.8)
BUN/Cr	1 (2.4)
U/A	0 (0)

Values are presented as mean±standard deviation or number (%). PASI: psoriasis area and severity index, CBC: complete blood cell, AST: aspartate aminotransferase, ALT: alanine aminotransferase, BUN: blood urea nitrogen, Cr: creatinine, U/A: urinalysis. *Aortic dissection, autism, stroke, thyroid disease.

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Forty-two Korean psoriatic patients treated with MTX were included (Table 1). Eleven patients (26.2%) developed laboratory adverse effects over a mean medication period of 9.5 months; of these, 2 patients showed abnormalities in two kinds of blood tests. Liver enzyme elevations (range of aspartate aminotransferase: 42～90 IU/L; range of alanine aminotransferase: 41～115 IU/L) occurred most frequently in 10 (23.8%) patients; of these, 2 patients showed transaminase levels greater than twice the upper limit of normal (>2 ULN) and 8 patients displayed transaminase level ≤2 ULN. Most patients who showed transaminitis stopped MTX and were concomitantly administered silymarin 140 mg twice daily for hepatoprotection. In contrast to the frequent transaminase elevations, hyperuricemia and elevated blood urea nitrogen/creatinine appeared to be rare. No abnormalities were observed in complete blood cell count or urinalysis values. In the analysis of clinical factors associated with laboratory abnormalities, there were no statistically significant risk factors related to overall laboratory test abnormalities (Table 2).

Although MTX has been used in the treatment of moderate to severe psoriasis for the last 60 years, a close evaluation of adverse effects and related risk factors of MTX therapy has not been performed. In spite of growing concerns about cumulative toxicity, there are no detailed data for

Table 2. Univariate analysis results of all laboratory tests and liver transaminase levels (n=42)

	Normal group	Abnormal group	HR (95% CI)	*p*-value
All laboratory tests*				
Age (yr)	43.77±15.29	45.00±21.34	1.008 (0.969～1.045)	0.669
Gender				
Male	21 (67.8)	10 (90.9)	0.311 (0.017～1.654)	0.268
Female	10 (32.3)	1 (9.1)		
Duration of disease (mo)	131.20±131.65	176.55±240.28	1.002 (0.998～1.005)	0.213
PASI score				
≤10	13 (41.9)	3 (27.3)	1.058 (0.977～1.148)	0.163
>10	18 (58.1)	8 (72.7)		
Total medication period (d)	282.13±228.65	289.55±218.65	0.998 (0.994～1.002)	0.401
Cumulative dose (mg)	458.16±375.20	492.92±382.35	0.999 (0.997～1.001)	0.497
Underlying diseases				
Diabetes	4	1	1.315 (0.247～24.253)	0.795
Hypertension	8	3	0.663 (0.183～3.090)	0.553
Dyslipidemia	4	1	1.388 (0.254～25.875)	0.758
Kidney disease	1	1	0.437 (0.080～8.106)	0.435
Others†	4	1	1.152 (0.216～21.259)	0.893
Liver transaminase levels*				
Age (yr)	44.97±16.49	41.30±18.41	0.988 (0.943～1.028)	0.569
Gender				
Male	22 (68.8)	9 (90.0)	0.355 (0.019～1.935)	0.329
Female	10 (31.3)	1 (10.0)		
Duration of disease (mo)	149.60±166.15	122.20±167.50	1.000 (0.995～1.004)	0.994
PASI score				
≤10	13 (40.6)	3 (30.0)	1.040 (0.952～1.136)	0.379
>10	19 (59.4)	7 (70.0)		
Total medication period (d)	275.94±227.64	310.10±218.99	0.997 (0.992～1.001)	0.230
Cumulative dose (mg)	444.78±376.78	539.21±369.11	0.999 (0.996～1.001)	0.344
Underlying diseases				
Diabetes	4	1	1.413 (0.256～26.348)	0.746
Hypertension	9	2	0.933 (0.223～6.306)	0.932
Dyslipidemia	4	1	1.412 (0.250～26.599)	0.748
Kidney disease‡	2	0	0.785 (0.095～101.885)	0.877
Others†,‡	5	0	2.435 (0.309～314.260)	0.561

Values are presented as mean±standard deviation, number (%), or number only. HR: hazard ratio, CI: confidence interval, PASI: psoriasis area and severity index. *All laboratory tests: normal group, n=31; abnormal group, n=11; liver transaminase levels: normal group, n=32, abnormal group: n=10. †Aortic dissection, autism, stroke, thyroid disease. ‡Firth's correction was applied.

complications associated with an increased cumulative dose of MTX. In this study, we examined the laboratory adverse effects and clinical risk factors including cumulative dose or treatment duration related to laboratory test abnormalities in psoriasis patients treated with MTX in daily practice.

Elevated transaminases were found in about 20%～30% of patients treated with a typical dose of MTX, which was consistent with former studies[3,5,6], but signs of myelosuppression such as pancytopenia, which are well-recognized adverse effects of MTX, were not observed. We presume that hematologic toxicity can be prevented in certain psoriasis patients without significant risk factors, particularly renal impairment, lack of folate supplementation, and medication errors[7].

Our data illustrated that if patients continued MTX therapy for approximately 1 year, which could be a part of the rotational psoriasis therapy[8] for moderate to severe psoriasis, the mean cumulative dose was approximately 0.5 g. According to our findings, the use of MTX for up to 1 year in clinical practice does not require liver biopsy for hepatotoxicity monitoring[7,9].

Overall, our study suggests no statistically significant risk factors for laboratory abnormalities in psoriatic patients treated with MTX (Table 2). Interestingly, our results suggest no significant association between cumulative MTX dose and transaminitis (Table 2). Treatment duration was also not associated with increased liver enzymes. These findings corroborate previous reports[10]. In addition, advanced age, duration of psoriasis, and comorbidities were not clinical risk factors for the development of adverse events.

Although MTX therapy is considered relatively safe in laboratory controlled psoriatic patients, our study provides evidence that typical MTX therapy can result in clinically significant liver enzyme abnormalities independent of cumulative dose and treatment duration. Therefore, when using MTX, thorough and regular monitoring for identifying MTX-related toxicity should be performed for every patient, regardless of health status.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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