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ORIGINAL RESEARCH

Effect of Methotrexate Discontinuation on Psoriatic Patients with Significant Liver Fibrosis

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Background: Patients with psoriasis, particularly those receiving systemic therapies such as methotrexate (MTX), are at increased risk of developing significant liver fibrosis. Although MTX remains widely used, its hepatotoxic potential remains controversial. Transient elastography (TE) allows non-invasive monitoring of liver fibrosis; however, data on fibrosis regression after MTX discontinuation are limited.

Objective: To assess the incidence of liver fibrosis regression in psoriasis patients following MTX withdrawal and to identify clinical and laboratory factors associated with this outcome.

Methods: We conducted a pilot cross-sectional study involving 15 prospectively recruited psoriasis patients with significant liver fibrosis (liver stiffness measurement [LSM] ≥7.1 kPa) who had discontinued MTX for at least 6 months. Fibrosis regression was defined as a >30% reduction in LSM from baseline. Univariate logistic regression was used to evaluate associations between clinical variables and fibrosis regression.

Results: Fibrosis regression was observed in 5 patients (33.3%) who had remained MTX-free for a mean duration of 3.6 ± 3.1 years. MTX treatment duration >4 years was significantly associated with fibrosis regression (OR = 16.00, 95% CI: 1.09–234.25; p = 0.043). A cumulative MTX dose >2 grams showed a non-significant trend toward increased odds of fibrosis regression (OR = 6.00, 95% CI: 0.56–63.98; p = 0.138). Male gender (OR = 0.17, 95% CI: 0.02–1.78; p = 0.138) showed a non-significant trend toward reduced odds of fibrosis regression.

Conclusion: One-third of psoriasis patients with significant liver fibrosis showed regression after a mean MTX-free duration of 3.6 years, with MTX use duration of more than 4 years significantly associated with this outcome. Given the small sample size, these results should be interpreted with caution. Nonetheless, these findings suggest a potential benefit of MTX withdrawal in selected patients and warrant confirmation in larger, prospective studies.

Keywords: psoriasis, methotrexate, liver fibrosis, transient elastography, fibrosis regression, hepatotoxicity

Introduction

Liver disease accounts for approximately 2 million deaths annually, representing 4% of all deaths, with cirrhosis and hepatocellular carcinoma as leading causes.[1] Patients with psoriasis are more likely to have liver diseases than matched controls in the general population, particularly those who receive systemic treatment.[2] Notably, 10% of patients with psoriasis are at a high risk of developing advanced liver fibrosis, with elevated prevalence among those with a history of methotrexate (MTX) use.[3] Despite the availability of biologic therapies, MTX remains a widely prescribed treatment due to its accessibility, ease of administration, and relatively low cost.[4] As a result, many international guidelines recommend MTX as one of the first-line systemic treatments for moderate-to-severe psoriasis, a practice that is also followed in Thailand.

The hepatotoxic potential of MTX in patients with psoriasis remains controversial. Early reports of cirrhosis prompted routine liver biopsies after each cumulative MTX dose of 1500 mg.[5,6] However, subsequent studies have generally not found a clear association between cumulative MTX dose and histologic liver fibrosis grading.[6–8] One study

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did report an increased risk of advanced liver fibrosis at cumulative MTX doses exceeding 5000 mg.[6] It is now established that cumulative MTX doses up to 2 grams were less likely to cause clinically significant hepatotoxicity, nevertheless, the current AAD-NPF guideline recommends that gastroenterology consultation and liver biopsy be considered for patients who exceed cumulative MTX doses of 3.5 to 4 grams.[4]

The introduction of transient elastography (TE) has improved non-invasive monitoring of liver fibrosis in psoriatic patients treated with MTX, reducing reliance on liver biopsy.[4] A meta-analysis found no significant association between cumulative MTX dose and the risk of significant liver fibrosis when assessed by non-invasive tests.[3] Instead, risk factors such as age, obesity, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome were linked to liver fibrosis.[3] Similarly, recent studies using TE have confirmed that high BMI,[9,10] metabolic syndrome,[10] and diabetes[10,11] are significantly associated with liver fibrosis, while cumulative MTX dose has not shown a statistically significant relationship.[9–11]

Although several studies have explored risk factors for the development of liver fibrosis in patients with psoriasis, evidence regarding the potential for fibrosis regression following MTX discontinuation remains limited. This gap in knowledge is particularly notable given the common clinical practice of discontinuing MTX in patients diagnosed with significant liver fibrosis and the ongoing controversy surrounding MTX-induced hepatotoxicity. Therefore, the present study aims to assess the incidence of liver fibrosis regression after MTX discontinuation and to identify clinical and laboratory factors associated with this outcome.

Material and Methods

Study Design and Ethical Consideration

A pilot cross-sectional study of patients with psoriasis, significant liver fibrosis and a history of methotrexate usage was conducted. The study was approved by the Institutional Review Boards of Mahidol University (COA. MURA2022/432) which are in full compliance with international guidelines for human research protection such as the Declaration of Helsinki. Informed consent was obtained from all participants prior to enrollment in the study.

Patient Selection Process

Medical records of all outpatients aged 18 years or over who were treated at Ramathibodi Hospital, Bangkok, Thailand, from January 1, 2008, to August 1, 2024, with an International Classification of Diseases, 10th revision (ICD-10) code of L40.0 (psoriasis vulgaris) and had at least one TE result were reviewed. Patients were prospectively recruited between April 2023 and November 2024. Significant liver fibrosis is indicated by a liver stiffness measurement (LSM) ≥7 kilopascals (kPa).[12]

Inclusion criteria were patients aged ≥18 years with a dermatologist-confirmed diagnosis of psoriasis vulgaris and a most recent LSM of ≥7.1 kPa, who had discontinued methotrexate treatment for a minimum of six months prior to recruitment. Exclusion criteria included current use of potentially hepatotoxic agents, hepatocellular carcinoma, chronic viral hepatitis, heavy alcohol consumption (>20 grams per day), and pregnancy or breastfeeding.

Data Collection

The patient's demographics, medical comorbidities, clinical presentations, laboratory results (HbA1c, triglyceride, HDL, LDL), type and dosage of systemic therapy (MTX, cyclosporine, acitretin, phototherapy, and biologic agents), reasons for MTX discontinuation, and psoriasis area and severity index (PASI) were extracted from the medical records on the day of each TE session.

Liver Stiffness Measurement Using Transient Elastography

LSM were obtained using TE (FibroScan, Echosens, Paris). TE was performed on the right lobe of the liver through an intercostal space with the patient in the dorsal decubitus position and the right arm fully abducted. All patients underwent TE after a minimum of 4 hours of fasting. The measured depth of the liver was between 25 and 65 mm. Ten validated measurements were taken. Only the LSM results with 10 validated measurements, a success rate of at least 60%, and an

interquartile range (IQR)/median of less than 30% were deemed acceptable. All TE procedures were performed by an experienced operator who was blinded to patient clinical data.

Statistical Analysis

Categorical variables were summarized as frequencies and percentages, while continuous variables were described using means and standard deviations. The primary outcome was the incidence of liver fibrosis regression, defined as a >30% reduction in LSM from baseline. This threshold was selected based on the FibroScan manufacturer's acceptable variability (up to 30% IQR relative to the median LSM in a reliable scan) and has been used in prior studies.[13–16]

The secondary objective was to identify factors associated with liver fibrosis regression. Univariate logistic regression was used to assess the association between clinical variables and fibrosis regression. Categorical thresholds for cumulative MTX dose (>2 grams) and treatment duration (>4 years) were selected based on existing guidelines and prior literature.[4,17] Multivariate analysis was not performed due to the limited sample size, in order to minimize the risk of overfitting. A p-value < 0.05 was considered statistically significant. All analyses were performed using STATA version 16.0 (StataCorp LLC, College Station, TX, USA).

Results

A total of 15 patients with psoriasis and significant liver fibrosis were included in the study. The mean age was 53.6 ± 13.9 years, and 10 patients (66.7%) were male. The mean BMI was 31.2 ± 6.1 kg/m². The mean baseline PASI score was 5.3 ± 6.1. Psoriatic arthritis was present in 6 patients (40%). Comorbidities included type 2 diabetes mellitus and obesity in 13 patients (86.7%), dyslipidemia in 10 (66.7%), and hypertension in 7 (46.7%).

All patients were diagnosed with significant liver fibrosis by TE while on MTX therapy or shortly after MTX discontinuation. Upon significant liver fibrosis diagnosis, MTX was promptly discontinued in all cases. Following MTX discontinuation, 5 patients (33.3%) received no additional systemic therapy or phototherapy, 8 (53.3%) received acitretin, 3 (20.0%) were treated with cyclosporine, 2 (13.3%) received phototherapy, and 2 (13.3%) were prescribed IL-17 inhibitors.

The mean duration of MTX use was 4.6 ± 2.9 years, with 6 patients (40.0%) using it for more than 4 years. The mean cumulative MTX dose was 2.0 ± 1.5 grams, with 5 patients (33.3%) received a cumulative dose exceeding 2 grams. The mean MTX-free duration prior to follow-up TE was 3.5 ± 2.2 years. Patient characteristics are summarized in Table 1.

Table 1 Baseline Characteristics

Characteristics	Patients (N = 15)
Age, years; mean (SD)	53.6 (13.9)
Male; n (%)	10 (66.7)
BMI; mean (SD)	31.2 (6.1)
PASI; mean (SD)	5.3 (6.1)
Psoriatic arthritis; n (%)	6 (40.0)
Medical comorbidity; n (%)	
- Type 2 diabetes mellitus	13 (86.7)
- Obesity	13 (86.7)
- Dyslipidemia	10 (66.7)
- Essential hypertension	7 (46.7)
- Cardiovascular disease	1 (6.7)
- Cerebrovascular disease	1 (6.7)

(*Continued*)

Table 1 (Continued).

Characteristics	Patients (N = 15)
Other systemic treatment use, n (%)	
- None	5 (33.3)
- Acitretin	8 (53.3)
- Cyclosporine	3 (20.0)
- Phototherapy	2 (13.3)
- IL-17 inhibitors	2 (13.3)
MTX-free duration, years	3.5 (2.2)
MTX use history	
- Duration, years; mean (SD)	4.6 (2.9)
- Duration >4 years	6 (40.0)
- Cumulative dose, g; mean (SD)	2.0 (1.5)
- Cumulative dose >2 grams	5 (33.3)

Abbreviations: BMI, body mass index; IL-17, interleukin-17; MTX, methotrexate; PASI, psoriasis area and severity index; SD, standard deviation.

Liver fibrosis regression was observed in 5 patients (33.3%) following MTX discontinuation. These patients had a mean MTX use duration of 6.6 ± 3.2 years, a mean cumulative dose of 3.0 ± 2.2 grams, and had remained MTX-free for 3.6 ± 3.1 years before the follow-up TE.

In univariate analysis, duration of MTX use for >4 years was significantly associated with higher odds of regression (OR = 16.00, 95% CI: 1.09–234.25; p = 0.043). Non-significant trends toward increased odds of regression were also observed with longer MTX duration as a continuous variable (OR = 1.55, 95% CI: 0.92–2.63; p = 0.100), cumulative MTX dose (OR = 2.25, 95% CI: 0.74–6.85; p = 0.150), and cumulative MTX doses >2 grams (OR = 6.00, 95% CI: 0.56–63.98; p = 0.138). In contrast, male gender was associated with lower odds of fibrosis regression (OR = 0.17, 95% CI: 0.02–1.78; p = 0.138), although this association was not statistically significant.

Other variables, including age, BMI, HbA1c, PASI, BMI decrease of 1 kg/m^2, HbA1c decrease of 1%, triglyceride decrease of 10 mg/dL, HDL increase of 10 mg/dL, LDL decrease of 10 mg/dL, acitretin use, diabetes, dyslipidemia, hypertension, and MTX-free duration were not significantly associated with liver fibrosis regression. The results of the univariate analysis are presented in Table 2.

Table 2 Univariate Analysis of Potential Prognostic Factors for Liver Fibrosis Regression

Factor	Odds Ratio (95% CI)	P-value
Age, years	1.02 (0.94–1.11)	0.627
Male gender	0.17 (0.02–1.78)	0.138†
BMI, kg/m^2	0.90 (0.72–1.13)	0.384
HbA1c	1.33 (0.63–2.80)	0.448
PASI	1.09 (0.90–1.32)	0.378
BMI decrease, 1 kg/m^2	0.75 (0.33–1.73)	0.508

(*Continued*)

Table 2 (Continued).

Factor	Odds Ratio (95% CI)	P-value
HbA1c decrease, 1%	1.57 (0.46–5.25)	0.466
Triglyceride decrease, 10 mg/dL	2.19 (0.44–10.98)	0.341
HDL increase, 10 mg/dL	2.13 (0.03–166.28)	0.735
LDL decrease, 10 mg/dL	1.23 (0.81–1.86)	0.330
Acitretin usage	1.50 (0.17–13.23)	0.715
Cyclosporine	–	–
Phototherapy	–	–
IL-17 inhibitors	–	–
Diabetes	0.44 (0.02–9.03)	0.598
Dyslipidemia	2.67 (0.21–33.49)	0.447
Hypertension	2.25 (0.25–20.13)	0.468
Obesity	–	–
Cardiovascular disease	–	–
Cerebrovascular disease	–	–
MTX-free duration, years	1.01 (0.61–1.69)	0.956
MTX use duration, years	1.55 (0.92–2.63)	0.100†
MTX use duration >4 years	16.00 (1.09–234.25)	**0.043**
MTX cumulative dose, grams	2.25 (0.74–6.85)	0.150†
MTX cumulative dose >2 grams	6.00 (0.56–63.98)	0.138†

Note: "–" indicates that the odds ratio could not be estimated due to zero events in one or more groups. Variables with p-values < 0.05 are indicated by the bold font. † Variables with p-values <0.2.

Abbreviations: CI, confidence interval; BMI, body mass index; IL-17, interleukin-17; HbA1c, hemoglobin A1c; HDL, High-Density Lipoprotein; MTX, methotrexate.

Discussion

In this pilot cross-sectional study, we observed that one-third of psoriasis patients with significant liver fibrosis showed evidence of fibrosis regression following MTX discontinuation, which suggests potential reversibility of MTX-associated liver fibrosis. Notably, patients who had used MTX for more than 4 years had significantly greater odds of liver fibrosis regression (OR = 16, p = 0.043). However, given the small sample size, this high OR may be influenced by selection bias. While previous studies have reported no clear association between cumulative MTX dose and liver fibrosis,[3,9–11] we observed a non-significant trend toward fibrosis regression in patients who discontinued MTX after a cumulative MTX dose exceeding 2 grams (OR = 6, p = 0.138). We hypothesize that among patients with significant liver fibrosis and prior exposure to MTX, only a subset may have developed fibrosis primarily due to MTX toxicity. MTX has been postulated to contribute to liver fibrosis through folate depletion, Nrf2 suppression, and mitochondrial dysfunction, leading to oxidative stress and hepatic inflammation.[18] These patients, especially those with extended MTX usage, showed a higher likelihood of fibrosis regression following to MTX cessation. These observations highlight the potential role of MTX withdrawal in liver fibrosis management.

Interestingly, liver fibrosis regression was not significantly associated with MTX-free duration (p = 0.956). This finding suggests that the possibility of regression does not simply increase with time following MTX withdrawal. It also implies that if regression is not observed in a certain amount of time, other reasons for liver fibrosis should be looked into, and further interventions may be needed. In terms of clinical practice, this underscores the need for structured TE monitoring at predefined intervals rather than relying solely on time since withdrawal. Prospective studies are needed to define the significance of MTX-free duration in fibrosis regression and to inform guideline recommendations on TE monitoring schedules and potential MTX discontinuation thresholds.

Given the shared pathophysiology between metabolic-associated steatotic liver disease (MASLD) and psoriasis,[19] weight loss, an established strategy for fibrosis regression in MASLD,[20] might be expected to have similar effects in our cohort. Obesity is a known risk factor for liver fibrosis in psoriasis[3,9,10] and MTX-related liver injury.[8] However, our study did not find a significant association between a 1 kg/m^2 decrease in BMI and fibrosis regression (OR = 0.75, p = 0.508). This suggests that weight loss may not be sufficient to reverse fibrosis in this specific patient population, though larger studies are needed to confirm this.

We also observed a non-significant trend suggesting that male gender (OR = 0.17, p = 0.138) was associated with lower odds of fibrosis regression. Although this finding did not reach statistical significance, it may indicate that fibrosis regression is less likely in male patients. This raises the possibility that gender-related differences or non-MTX-related mechanisms could contribute to persistent liver fibrosis in certain subgroups.

Our study has limitations. As a pilot study with a small sample size, the statistical power to detect associations was limited, and multivariate analysis could not be performed, leaving results vulnerable to unadjusted confounding. It may also have introduced selection bias. Additionally, our cohort consisted predominantly of patients with known risk factors for MTX-induced hepatotoxicity, such as obesity, diabetes, and dyslipidemia. However, as metabolic comorbidities are common in psoriasis and are part of the psoriatic march,[21] their presence in our cohort likely reflects the typical clinical profile of psoriasis patients rather than merely acting as confounding factors. Nevertheless, the generalizability of our findings to lower-risk psoriasis populations may still be limited. Future prospective studies involving larger, more diverse cohorts are warranted to validate our findings and further explore the predictors and reversibility of liver fibrosis in psoriasis patients treated with MTX.

Conclusion

One-third of psoriasis patients with significant liver fibrosis experienced regression following MTX discontinuation for a mean duration of 3.6 years. MTX use duration >4 years was significantly associated with fibrosis regression. These findings suggest potential benefits of MTX withdrawal in selected patients with significant liver fibrosis. However, given the small sample size, these results should be interpreted with caution. Larger, prospective studies are warranted to validate these preliminary findings, determine the optimal timing of follow-up TE, and further clarify factors influencing fibrosis regression.

Data Sharing Statement

The data sets used to support the findings of this study are available from the corresponding author upon request.

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The authors declare that this manuscript was prepared in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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