

## Prevalence and risk factors of methotrexate hepatotoxicity in Asian patients with psoriasis

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Author contributions: Yeo CM and Yang WL conceived the idea of the study; Yeo CM collected that data; Chong VH and Earnest A analysed the data; Yeo CM and Chong VH wrote the manuscript; all authors read and approved the final manuscript; Yeo CM was the guarantor.

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Received: February 6, 2013 Revised: April 1, 2013

Accepted: May 7, 2013

Published online: May 27, 2013

### Abstract

**AIM:** To establish the prevalence of liver fibrosis and to evaluate the possible risk factors for fibrosis and progression in Asian with psoriasis treated with methotrexate (MTX) based on liver histology.

**METHODS:** Patients with psoriasis treated with MTX referred to the Department of Gastroenterology, Tan Tock Seng Hospital for liver biopsy were identified and retrospectively studied. Patient case notes and electronic records were retrieved from the hospital database and relevant data collated. Histological changes of liver biopsies were staged according to Roengik score. The factors assessed were age, gender, ethnicity, cumulative dose of MTX, presence of comorbid conditions such as diabetes, hypertension, hyperlipidemia, and ethanol use. We also assessed the histological change in those with multiple liver biopsies. Statistical analysis was performed using Stata V.9.2.

**RESULTS:** There were altogether 59 patients (median

age 50 years old, range 22-81 years old, male, 88%) with 98 biopsies liver biopsies; 6 normal [median cumulative dose (MCD), 2285 mg]; 62 grade I (MCD 2885 mg), 23 grade II (MCD 1800 mg) and 7 grade III (MCD 1500 mg). There was no grade IV or cirrhosis. The prevalence of liver fibrosis (grade III) was 12%. Of the factors assessed, diabetes ( $P = 0.001$ ) and hypertension ( $P = 0.003$ ) were significant for fibrosis on univariate analysis but not on multivariate analysis. Of the 26 patients who had more than one biopsy (median 2, range 2-6), 57.7% ( $n = 15$ ) were stable, 34.6% ( $n = 9$ ) had progression and 7.7% ( $n = 2$ ) had regression of histological grades. On univariate analysis, non-Chinese ethnicity ( $P = 0.031$ ), diabetes ( $P = 0.018$ ), and hyperlipidemia ( $P = 0.011$ ) were predictive of progression of grades, but these were not significant on multivariate analysis.

**CONCLUSION:** Liver fibrosis in Asian psoriatic population on MTX is comparable to the West. Cumulative dose was not associated with liver fibrosis. Metabolic syndrome is important factors.

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**Key words:** Hepatotoxicity; Liver fibrosis; Methotrexate; Risk factors; Cirrhosis

**Core tip:** Old studies have shown that the prevalence of methotrexate (MTX) associated liver fibrosis and cirrhosis to be as high as 50% and 26% respectively. Later studies have shown that the risk is much lower than previously reported. These studies have been based on western patients. To date, there is no study that had assessed MTX hepatotoxicity in Asian patient based on liver histology. This study showed that the risk of methotrexate hepatotoxicity in Asian patients with psoriasis is also low and progression is minimal. We showed that ethnicity and presence of diabetes and hyperlipidemia, part of the metabolic syndrome may be important factors.

Yeo CM, Chong VH, Earnest A, Yang WL. Prevalence and risk factors of methotrexate hepatotoxicity in Asian patients with psoriasis. *World J Hepatol* 2013; 5(5): 275-280 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v5/i5/275.htm> DOI: <http://dx.doi.org/10.4254/wjh.v5.i5.275>

## INTRODUCTION

Methotrexate (MTX) is used as immune-suppressive therapy for many conditions, and it remain the most commonly used systemic medical therapy for treating psoriasis even after the introduction of biologic therapy<sup>[1,2]</sup>. Hepatotoxicity associated with MTX in psoriatic patients is well recognised, and in some patients can lead to hepatic fibrosis and even cirrhosis<sup>[3]</sup>.

In the west, the prevalence of MTX associated liver fibrosis and cirrhosis has been reported to be as high as 50% and 26% respectively<sup>[3]</sup>. Alcohol consumption, diabetes, obesity, chronic viral hepatitis and medications such as arsenic and vitamin A have been reported to be significant risk factors of MTX associated liver fibrosis<sup>[4-7]</sup>. Previous guidelines recommend that liver biopsy should be considered at intervals of 1500 mg cumulative MTX dose to assess for fibrosis and to decide on whether it is safe to continue MTX therapy<sup>[8]</sup>. However, recent reports have suggested that MTX may be less hepatotoxic and liver fibrosis may be less prevalent<sup>[9-12]</sup>. Therefore in 2009, the American Academy of Dermatology has updated their recommendation to consider liver biopsy only after a cumulative dose of 3500 to 4000 mg in patients without any risk factors for hepatotoxicity<sup>[13]</sup>. Most of these studies have been conducted on the Western population. Data remains scarce on Asian patients treated with MTX. This only study done on Asian patients had shown that MTX was safe based on fibroscan in Korean patients with rheumatoid arthritis<sup>[14]</sup>. A retrospective study from Malaysia showed that hepatotoxicity based on serum transaminases was uncommon<sup>[15]</sup>.

Fibroscan is now becoming widely used for the assessment liver fibrosis as it is non-invasive. However, fibroscan is user dependent and is not specific for grades II and III fibrosis. Therefore, liver histology assessment remains the gold standard. To date, there is no study that had used liver biopsy to assess impact of MTX treatment and hepatotoxicity in Asian patients. The aims of our study were to: (1) establish the prevalence of liver fibrosis based on liver biopsy in among multi-ethnic Asian patients with psoriasis treated with MTX; and (2) to evaluate the possible risk factors for fibrosis and progressions.

## MATERIALS AND METHODS

### Study

We retrospectively reviewed the medical records of all psoriatic patients on MTX referred to our institution for liver biopsy over a seven years period. Pre-biopsy evaluation included history taking, physical examination, basic

blood investigations and ultrasound scan of the hepatobiliary system.

### Setting

Tan Tock Seng Hospital, Singapore (1300 bedded hospital) is one of the biggest tertiary referral hospital with population catchment close to 1.5 million. It is also the centre that serves the National Skin Centre located close to the hospital where most of patients with psoriasis are treated.

### Data

We collected data on the patients' age, gender, ethnicity, cumulative MTX dose, presence of potential risk factors (diabetes, hypertension, alcohol consumption and hyperlipidemia), hepatitis B and C status and the liver biopsy results. There were a total of 101 liver biopsies of which three histological reports could not be traced leaving 98 available liver biopsy reports from 59 patients for the study. Histological slide preparation followed the standardised methods of assessment using hematoxylin and eosin stain and Masson trichrome stain for fibrosis. Histological changes were graded according to Roengik Classification as shown in Table 1.

### Statistical analysis

Statistical analysis was performed using Stata V.9.2 (Stata Corp, College Station, Tx, United States). For comparison, Fisher's Exact Test was used to evaluate the effect of gender, ethnicity (Chinese *vs* non-Chinese), diabetes, hypertension, hyperlipidemia and alcohol consumption on MTX associated liver fibrosis. Mann-Whitney test was applied to compare the effect of age and the distribution of the MCD between patients with and without fibrosis. The binary logistic regression model was subsequently used to assess whether any of the independent risk factors found to be significant on univariate analyses for liver fibrosis and progression of grades on repeat biopsies. For the assessment of the prevalence of fibrosis and the progression of Roengik histological grades, the latest biopsies results were taken as the end point of progressions.

This study was approved by the Research Ethics Committee of Singapore National Healthcare Group.

## RESULTS

### Demographics

Over the period, there were 59 patients who were referred and had at least one liver biopsy. The median age was 50 (range 22-81) with majority male (88%) and the ethnic breakdown consisting of Chinese ( $n = 39$ , 66%), Malays ( $n = 13$ , 22%), Indians ( $n = 6$ , 10%) and others ( $n = 1$ , 2%).

Thirty-four patients had no risk factor whereas 11 patients had one risk factor, 9 had 2 risk factors and 6 had 3 risk factors. Among the 59 patients, 15 (25.4%) had diabetes, 15 (25.4%) had hypertension, 9 (15.3%) had hyperlipidemia, and 5 (8.5%) were occasional light social drink-

**Table 1** Roenigk classification of liver damage

Grade	Fibrosis	Fatty infiltration	Nuclear variability	Portal inflammation
I	None	Mild	Mild	Mild
II	None	Moderate to severe	Moderate to severe	Portal expansion, lobular necrosis
III A	Mild (Septa extending into lobules)	Moderate to severe	Moderate to severe	Portal expansion, lobular necrosis
III B	Moderate to severe	Moderate to severe	Moderate to severe	Portal expansion, lobular necrosis
IV	Cirrhosis			

**Table 2** Distribution of the grades of the liver histology and the median cumulative dose

Histology grade	No.	Median MTX cumulative dose (mg)
Normal	6	2285
I	62	2885
II	23	1800
III	7	1500
IV	0	-
Total	98	2500

MTX: Methotrexate.

ers (less than one drink a week). None of our patients had hepatitis B or C infection. None of the patients had significantly impaired liver profiles especially the serum albumin and bilirubin.

### Liver histology

Of the 98 liver biopsy reports, 6 (5.9%) were normal, 62 (61.4%) had grade I histological changes, 23 (22.8%) had grade II changes, 7 (6.9%) had grade III changes and none showed grade IV cirrhotic change. The prevalence of MTX associated liver fibrosis (grade III) was 12%.

### Risk factors analysis

**MTX cumulative dose:** The MCD of MTX was 2500 mg with a range of 875-14433 mg. There was a liver biopsy done at the cumulative dose of 875 mg because of persistent abnormal liver profiles. Table 2 summarises the relationship between MCD and liver histology. There was no difference in the MCD of the patients with MTX associated liver fibrosis compared with those without liver fibrosis (1500 mg *vs* 2500 mg,  $P = 0.18$ ).

**Other risk factors:** There was no difference in the age of patient with or without fibrosis ( $50.9 \pm 10.2$  *vs*  $49.8 \pm 9.9$ ,  $P = 0.901$ ). On univariate analyses, diabetes and hypertension were risk factor for liver fibrosis whereas age, gender, ethnicity, hyperlipidemia and alcohol consumptions were not (Table 3). Seven of the 20 patients (35%) with either diabetes or hypertension had liver fibrosis with MCD of 1500 mg. None of the 40 patients without risk factor developed fibrosis with MCD of 3000 mg. Among the 7 patients without any history of alcohol consumption, all had either diabetes or hypertension. However, neither diabetes nor hypertension were significant on multivariate analyses.

### Histological changes

Among the 59 patients, 26 (43%) had more than one liver biopsy. There were no change in the grade reported in 57.7% ( $n = 15$ ), progression in 34.6% ( $n = 9$ ) and regression in 7.7% ( $n = 2$ ). On univariate analyses, non-Chinese ethnicity and the presence of diabetes and hyperlipidemia were significant predictors (Table 3) for progression of grades. However, these were no significant on multivariate analysis.

## DISCUSSION

Data on MTX in psoriatic patients is well reported in the Western population but data remains scarce on Asian population. The prevalence of liver fibrosis in our psoriatic patients was only 12%, and none of our patients had cirrhosis based on histology evaluation. Generally our findings are consistent with findings of recent studies from the West. Therefore, our findings also suggest that liver fibrosis may be less prevalent (fibrosis 16% and cirrhosis 2%) compared to older studies (fibrosis up to 50% and cirrhosis 26%)<sup>[7,8]</sup>.

Several factors have been reported to accelerate the fibrotic progression in patient treated with MTX, and these include alcohol consumption, presence of diabetes, obesity, chronic viral infections, and use of medications such as arsenic and vitamin A<sup>[5-8]</sup>. Our study also showed that diabetes and hypertension were significant risk factors, but not alcohol use or hyperlipidemia, age, gender or ethnicity. Correlations with diabetes have been shown but not hypertension. This is perhaps not unexpected considering that hypertension is part of metabolic syndrome, which have also been shown to be an important risk factor. However, further studies are required to assess this correlation.

Among our patients with reported alcohol consumption, none developed liver fibrosis compared to the 12.7% who did not give any history of alcohol consumption. However the latter patients had other risk factors, either diabetes or hypertension. An earlier study showed no association with alcohol consumption<sup>[16]</sup>.

Lipid disorders are common and are also a part of metabolic syndrome. Hence one would expect hyperlipidemia to be an important factor. A recent case series showed that non-alcoholic steatohepatitis (NASH) contribute to MTX hepatotoxicity in patients with psoriasis<sup>[17]</sup>. In fact NASH is a recognised and an important cause of liver cirrhosis<sup>[18,19]</sup>, in particular those catego-

**Table 3 Risk factors analysis for fibrosis and progression of Roenigk grades *n* (%)**

Risk factor	Proportion of patients with fibrosis	<i>P</i> value <sup>1</sup>	Proportion of patients with progression	<i>P</i> value <sup>1</sup>
Gender (male <i>vs</i> female)	4/42 (9.5) <i>vs</i> 3/17 (17.6)	0.382	5/9 (55.6) <i>vs</i> 4/17 (23.5)	0.102
Ethnicity (Chinese <i>vs</i> non-Chinese)	4/39 (10.3) <i>vs</i> 3/20 (15)	0.594	3/16 (18.8) <i>vs</i> 6/10 (60)	0.031
Diabetes mellitus (yes <i>vs</i> no)	5/15 (33) <i>vs</i> 2/44 (4.4)	0.008	4/5 (80) <i>vs</i> 5/21 (23.8)	0.018
Hyperlipidemia (yes <i>vs</i> no)	1/9 (11.1) <i>vs</i> 6/50 (11.7)	> 0.99	3/3 (100) <i>vs</i> 6/23 (26.1)	0.011
Hypertension (yes <i>vs</i> no)	5/15 (33) <i>vs</i> 2/44 (4.4)	0.008	4/6 (66.7) <i>vs</i> 5/20 (25)	0.060
Alcohol consumption (yes <i>vs</i> no)	0/5 (0) <i>vs</i> 7/54 (12.7)	> 0.99	0/2 (0) <i>vs</i> 9/24 (37.5)	0.284

<sup>1</sup>Comparison made with Fisher's Exact Test.

rised as cryptogenic cirrhosis. One reason to account for the lack of significance in our study was probably related to the fact that patients were already on treatment by the time they had their biopsy.

Recent studies have reported that MTX cumulative dose or duration of therapy was not correlated with liver toxicity<sup>[7]</sup>. Our present study also showed no such correlation. In fact, our patients with normal or grade I changes had higher MCD (2285 mg) compared to those with grade III changes (MCD, 1500 mg). This could be explained by the fact that the latter patients had other risk factor, namely diabetes. Among our 35% of patients with either risk factor, they developed liver fibrosis with a MCD of 1500 mg compared to MCD of 3000 mg for those without risk factors. Rosenberg *et al*<sup>[5]</sup> reported that 96% of their patients with at least one other risk factor (diabetes, being overweight, heavy alcohol consumption, chronic hepatitis B or C) developed liver fibrosis after MCD of 1500 mg. In contrast, 58% without risk factors developed liver fibrosis at a MCD of 2100 mg<sup>[6]</sup>.

Studies based on rheumatoid arthritis and inflammatory bowel diseases have also shown similar results<sup>[14,20-22]</sup>. A multicentre study looking at the effects of MTX in 46 patients with inflammatory bowel disease showed that advanced fibrosis was only encountered in 6.3% of patients based on elastography scan, with a MCD of 1242 ± 1349 mg. Gender, age, type of inflammatory bowel disorder, or MCD did not have any impact on liver stiffness<sup>[20,21]</sup>. Another study showed that body mass index (BMI) above 28 kg/m<sup>2</sup> and excess alcohol consumption were important factor but not the cumulative doses<sup>[21]</sup>. Studies on rheumatoid arthritis also reported low incidence of liver fibrosis and showed similar risk factors.

Majority of our patients who had more than one liver biopsy had stable grade. Progression of histology was seen in only 34.6%. Interestingly, two patients had regression of their histological grade. Non-Chinese ethnicity, diabetes and hyperlipidemia were significant factor for progressions on univariate analysis but not on multivariate analyses. Most progressions were increase of one grade, from grade I to grade II which basically indicated increase in the degree of steatosis, nuclear variability and expansion of the portal tract, changes which are also seen in non-alcoholic fatty liver disease. The significance of non-Chinese ethnicity is perhaps related to the higher incidence of overweight among our Malays and Indians population. The small sample size probably also ac-

counted for the non-significance on multivariate analysis. Other studies have also shown that fibrosis progressions among patients continuing on MTX therapy are actually uncommon and some may actually regress<sup>[23,24]</sup>.

Our findings suggest that the interval of repeat biopsy can be prolonged following what have been recommended in the West. The most recent guidelines from the West have recommended liver biopsy only after a cumulative dose of 3500-4000 mg in patients without any risk factors<sup>[11,13,25]</sup>. Therefore, based on our findings, this recommending can be adapted to the Asian population. In our practice, we also follow the latest recommendations<sup>[13,25]</sup> and only subject patients to liver biopsies if they have achieved cumulative doses of between 3500 and 4000 mg or those with risk factors such chronic viral hepatitis and disorders (*i.e.*, diabetes, hypertension, obesity) that are part of the metabolic syndrome. However, for patients who are not willing to undergo liver biopsy, we use fibroscan to assess the fibrosis score to decide if patient should go for a liver biopsy. Patients found to have high score or in the grey zone, we will further discuss with patients on the need for liver biopsy.

Currently, it remains uncertain whether use of non-invasive tests can replace liver histology. Based on currently available evidence, use of non-invasive tests such as fibroscan, fibrotest and procollagen III N-terminal propeptide (P<sub>III</sub>NP) are not sensitive enough to predict severity of fibrosis<sup>[26-28]</sup>. Fibrotest have been reported to predict presence of fibrosis whereas fibroscan to predict the absence of fibrosis. Use of serial P<sub>III</sub>NP following the Manchester protocol compared to the American Academy of Dermatology guidelines have been reported to lead to avoidance of liver biopsy with a factor of seven fold, without compromising patient care<sup>[26]</sup>. Use of P<sub>III</sub>NP has been shown to provide misleading results in patients with psoriatic arthropathy<sup>[23]</sup>. Whether this can be generalised to patient without arthropathy is unknown. In our setting, we currently do not recommend non-invasive tests as an alternative to liver biopsy as data on Asian patients with psoriasis treated with MTX is lacking.

There are several limitations with our study. First, the sample size was small and may account for the non-significant findings on multivariate analyses. Second, due to its retrospective nature, there were missing or incomplete data, and in our case, incomplete data on patients height made it not possible to assess of the impact of BMI. Despite these limitations, our findings are

consistent with what have been reported in the literatures on MTX and liver fibrosis. The main strength of our study is the use of liver histology which remains the gold standard compared to the available non-invasive tests which all have limitations in terms of sensitivity and specificity.

In conclusion, the prevalence of liver fibrosis in our multi-ethnic Asian patients with psoriasis on MTX is comparable to the rates reported recently which are much lower than the rates reported in older studies. Disorders associated with metabolic syndrome may be important risk factors for fibrosis and progression. Further studies with larger sample sizes will be required to assess the association. Inclusion of non-invasive tests such as fibroscan, fibrotest or PIII NP to liver histology assessment will also help to assess the reliability of these tests compared to the gold standard.

## COMMENTS

### Background

Psoriasis is a common chronic skin disorder that is commonly treated with methotrexate (MTX) which is associated with many side effects including hepatotoxicity. Previous studies have reported high prevalence of liver fibrosis and cirrhosis. However, later studies have shown that the risk is much lower than previously reported. These studies have been based on western patients. To date, there have only been few studies on the hepatotoxic effects of MTX in Asian patients.

### Research frontiers

This study looked at the prevalence of hepatotoxicity and progression in a multi-ethnic Asian population with psoriasis treated with MTX by using the liver histology, which is the gold standard.

### Innovations and breakthroughs

This study showed that significant liver histology is uncommon and the presence of diabetes and hypertension were significant for fibrosis on univariate analysis but not on multivariate analysis. This study also showed that progression is uncommon with most having only change of one grade which indicate increase in steatosis among patients who continued treatment with MTX. A small proportion actually had histology regressions. Non-Chinese ethnicity and the presence of diabetes and hyperlipidemia were predictive of progression of grades, but only on univariate analysis. However, study with larger sample size is required.

### Applications

Interval assessment can be delayed in Asian patients treated with MTX until a higher cumulative dose following the recommendations based on Western patients.

### Terminology

MTX hepatotoxicity is liver damage secondary to the effect of long term treatment with MTX. Histological assessment can be made using the Roengik Classification which categorise changes in five grades; I, II, IIIA, IIIB and IV (cirrhosis); Mean cumulative dose is the mean accumulated dose of MTX taken over a period of time and is a factor in deciding when to repeat a liver assessment.

### Peer review

This study showed that the risk of MTX hepatotoxicity in Asian patients with psoriasis is low and progression is minimal based on assessment of liver histology. Ethnicity, presence of diabetes and hyperlipidemia, part of the metabolic syndrome may be important factors. Based on the findings of this study, repeat liver biopsy assessment can be delayed to higher cumulative dose following updated recommendations.

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