

## INVESTIGATIVE REPORT

# Methotrexate Reduces the Occurrence of Cerebrovascular Events among Taiwanese Psoriatic Patients: A Nationwide Population-based Study

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**Psoriasis is a chronic inflammatory disease. The aim of this study was to evaluate the effects of methotrexate and retinoid on risks for developing cerebrovascular disease among psoriatic patients. A population-based nested case-control study was conducted using the Taiwanese National Health Insurance database. Cox proportional hazards models were adopted. The hazard ratio (HR) of newly developed cerebrovascular disease was 1.28 (95% confidence interval (CI)=1.162–1.413;  $p < 0.0001$ ) for psoriatic vs. non-psoriatic subjects. In terms of the effects of methotrexate or retinoid on the occurrence of cerebrovascular disease, a significant protection effect (HR=0.50; 95% CI=0.27–0.92;  $p = 0.0264$ ) was found for patients with methotrexate prescription. Retinoid prescription showed no protective effect. Further analyses revealed that a low cumulative methotrexate dose is associated with significant protective effect (HR = 0.53; 95% CI=0.28–1.00;  $p = 0.0486$ ) while a high cumulative dose is not (HR 0.80; 95% CI=0.11–5.68;  $p = 0.8214$ ). These results suggest that psoriatic patients receiving low-dose methotrexate treatment may have reduced risk for developing cerebrovascular disease. Further prospective study should be performed to validate the vasculoprotective effect of this treatment strategy. Key words: psoriasis; cerebrovascular disease; methotrexate.**

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Psoriasis is a chronic, inflammatory, immune-mediated disease affecting approximately 2–3% of the world's population, with some variations among different ethnic groups (1). Classic studies on psoriasis have focused on skin manifestations and joint complaints. As patient-centred care has evolved over the past years, it is now

recognized that psoriasis is associated with depression and a lower quality of life (2, 3). More recently, psoriasis has been considered as a systemic inflammatory condition with genetic and environmental factors playing important roles. From a pathogenic point of view, the disease progression of psoriasis is a classical Th-1, Th-17, and Th-22 inflammatory disease with dysregulated production of associated cytokines, including interferon- $\gamma$ , tumour necrosis factor (TNF), and various interleukins (4). Intriguingly, the pathogenesis of atherosclerosis, a major risk factor for severe vascular disease including cerebrovascular diseases (CVD), is also characterized by an inflammatory process driven by Th-1 cells and their associated cytokines (5). Therefore, the chronic systemic inflammatory milieu, which is frequently observed in psoriatic patients, provides a link between psoriasis and severe vascular complications. In fact, many studies from different parts of the world, which have focused on associations between psoriasis and vascular disease risk factors, have documented higher prevalence of hypertension, diabetes mellitus (DM), and dyslipidaemia among patients with psoriasis (6–9). When controlling for these major contributing factors, these studies still demonstrated significant association between psoriasis and vascular complications (7–9). Therefore, the use of appropriate systemic anti-inflammatory agents should not only reduce the disease burden of psoriasis in terms of skin and joint complaints, but should also decrease the risks of serious vascular complications. In support with this notion, the viewpoint of "psoriatic march" has been proposed. According to this concept, severe psoriasis is associated with systemic inflammation, which, in turn, may cause insulin resistance, an event that can trigger endothelial cell dysfunction and lead to atherosclerosis and ultimately vascular complications (10, 11). Boehncke et al. (12) have shown that effective systemic therapy may ameliorate the endothelial function of psoriatic patients. In addition, reduction of C-reactive protein and normalization of vascular elasticity, the biomarkers for cardiovascular risk, have been documented in patients who received TNF- $\alpha$  inhibitors (13, 14).

CVD frequently result in long-term disability. Many studies have documented the impacts of CVD on patients' lives, including reduced health-related quality of life and high levels of depression (15, 16). CVD is an important cause of morbidity and mortality (17) for psoriatic patients. In fact, it has previously been reported that there is an increased mortality from CVD for patients hospitalized for psoriasis (18). How different systemic treatment for psoriasis affects the risks for developing CVD is an intriguing issue. Using the National Health Insurance (NHI) database in Taiwan, the current study aimed to evaluate the effects of methotrexate (MTX) and retinoid, the two most commonly prescribed systemic treatment for psoriasis in Taiwan (7), on risks for developing CVD.

## MATERIALS AND METHODS

The NHI programme in Taiwan was launched in 1995. This programme covers all inpatient and outpatient medical services as well as the cost of prescription drugs, with various co-payment rates from the patients. In 2010, the coverage rate of the NHI programme was 99.5% of Taiwan's 22.96 million population.

A population-based nested case-control study was conducted based on the Longitudinal Health Insurance Database 2005 (LHID2005, years 1996–2006), which contains all the original inpatient and outpatient physician claims and prescription drug claims, as well as demographic information for 1,000,000 beneficiaries, randomly sampled from the year 2005 Registry for Beneficiaries (ID) of the NHI research database. The LHID 2005 and the original NHI database are not significantly different in terms of gender, age distribution or mean insured payroll-related amount between the patients. Confidentiality assurances were addressed by observing the data regulations of the Bureau of NHI.

The International Classification of Diseases, revision 9 (ICD9) codes (Table SI; available from: <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1283>) were used to identify medical conditions from the database of outpatient physician claims during 1996 to 2006, as described previously (7, 8). Patients born between 1930 and 1990 were included in the analysis. To ensure no prior history of psoriasis for at least one year, those with date of first diagnosis during 1996 were excluded. The dates of first psoriasis diagnosis were taken as the index date for patients in the case group. Each psoriasis patient was matched by 20 controls of the same gender and with date of birth within 5 years of their birth year. The index date of each psoriasis patient was assigned to their matched controls as the index dates.

The primary endpoint of the event was the occurrence of CVD (ICD9 codes in supplementary file) documented by the physician claims. The duration of follow-up for patients with cerebrovascular event was the time between the index date and the date of first CVD diagnosis recorded in either inpatient or outpatient records, and the censored time of patients without cerebrovascular event was from the index date to the end of 2006 or to the date of withdrawing from the NHI programme. Prescriptions for MTX, retinoid (acitretin), and phototherapy were identified from the database of "Details of ambulatory care orders", and the indicator variables of users vs. non-users were constructed in the statistical analysis. For the stratified analyses for MTX, psoriatic patients with cumulative MTX dose  $\geq 1.56$  g ( $\geq 24$  months of full-dose and when liver biopsy is contemplated) were considered as patients who had received high cumulative MTX treatment, while those with cumulative dose  $< 1.56$  g were considered as patients who had received low-dose MTX therapy. Additional covariates also included physician

claims of hypertension, DM and dyslipidaemia (ICD9 codes) as well as age and gender. The descriptive data were presented as frequencies and percentages observed. The Pearson  $\chi^2$  tests were performed to compare the prevalence of hypertension, DM, dyslipidaemia and CVD between the psoriatic patients and matched controls. To investigate the risk of CVD for psoriatic patients, the Cox proportional hazards models were adopted to analyse the time to CVD diagnosis while excluding any persons with CVD diagnosis in the year before index dates. A  $p$ -value  $< 0.05$  was considered statistically significant.

## RESULTS

The basic characteristics of psoriasis patients and matched control are shown in Table SII (available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1283>). The prevalence rates of hypertension, DM, dyslipidaemia and CVD were significantly higher in the psoriatic group as compared to control group, as demonstrated in Table I. We further excluded subjects with prior history of CVD in the year before the index date. From the Cox-regression analyses, we obtained the hazard ratio of newly developing CVD to be 1.28 (95% CI=1.162–1.413;  $p < 0.0001$ ) for psoriatic patients vs. non-psoriatic patients. The patients who had received phototherapy were more likely to develop CVD compared with those who had not received phototherapy (HR 1.35; 95% CI=1.02–1.78;  $p = 0.0343$ ). In terms of the effects of systemic MTX or retinoid on the occurrence of CVD, Cox regression analysis on psoriatic patients showed a significant protection effect (HR 0.50; 95% CI=0.27–0.92;  $p = 0.0264$ ) for patients with a prescription of MTX only, while no significant protection effect was found for patients with a prescription of retinoid only (Table II). To determine the dose-response effect of MTX, further stratified analysis was performed. As demonstrated in Table III, a low cumulative MTX dose is associated with borderline protective effect (HR 0.53; 95% CI=0.28–1.00;  $p = 0.0486$ ), while high cumulative dose is not associated with protective effect (HR 0.80; 95% CI=0.11–5.68;  $p = 0.8214$ ). However, it should be noted that only low number of patients was included in this group.

## DISCUSSION

This study revealed several important issues regarding the associations between psoriasis, CVD, and systemic drugs (MTX and retinoids). First of all, after adjusting

Table I. Comparison of hypertension, diabetes mellitus (DM), dyslipidaemia and cerebrovascular disease between the psoriatic patients and matched control ( $p$ -value  $< 0.0001$ )

	Psoriatic patients <i>n</i> (%)	Matched controls <i>n</i> (%)
Hypertension	1,600 (19.6)	25,644 (15.7)
DM	894 (10.9)	12,590 (7.7)
Dyslipidaemia	1,054 (12.9)	15,184 (9.3)
Cerebrovascular disease	399 (4.9)	6,015 (3.7)

Table II. Effects of phototherapy, methotrexate (MTX) or retinoid on development of cerebrovascular disease (CVD)

	HR	95% CI	p-value
Phototherapy			
No (7,158)	1.00		
Yes (719)	1.35	1.02–1.78	0.0343
Medication used			
No MTX and no retinoid (7,426) <sup>a</sup>	1.00		
MTX only (258) <sup>b</sup>	0.50	0.27–0.92	0.0264
Retinoid only (193) <sup>c</sup>	0.70	0.39–1.23	0.2153

<sup>a</sup>M:F 3,940:3,486, <sup>b</sup>M:F 151:107 and <sup>c</sup>M:F 144:49.

HR: hazard ratio of developing CVD; CI: confidence interval.

for relevant covariates, including hypertension, DM, dyslipidemia, age, and gender, the psoriatic patients in Taiwan were still 1.28 times more likely to have CVD as compared to control. Another result derived from this study is that psoriatic patients who had received systemic MTX treatment are associated with a decreased incidence of CVD, while systemic retinoid treatment did not provide similar protective effect.

Chronic inflammatory systemic diseases including psoriasis are characterized by long-term inflammation with a dysregulated inflammatory cytokine environment. Previous epidemiological research has shown that patients with one chronic inflammatory systemic disease are more likely to have another chronic inflammatory condition (19). Lesions of psoriasis and atherosclerosis plaques both contain an increased number of activated T cells and share similar inflammatory milieu (5, 20–22). These similarities provided the theoretical bases for the association between psoriasis and severe vascular complications in different studies (7–9). Using the Taiwanese NHI database, we showed that psoriatic patients who had received MTX treatment are less likely to have CVD than those who did not. Previously, it has been shown that MTX use is associated with reduced risk of cardiovascular complications in patients with rheumatoid arthritis (23). In addition, Prodanovich et al. (24) showed that MTX treatment is associated with reduced incidence of vascular diseases in patients with psoriasis or rheumatoid arthritis. The same study also showed that

Table III. Relationship between different cumulative methotrexate (MTX) doses and development of cerebrovascular disease (CVD) in patients with psoriasis

Medication used	HR	95% CI	p-value
No MTX and no retinoid	1		
Low cumulative MTX doses (n=239)	0.53	0.28–1.00	0.0486
High cumulative MTX doses (n=19)	0.80	0.11–5.68	0.8214

\*The cumulative MTX dose was categorized by an arbitrary cut-off point as follows: those received  $\geq 1.56$  g ( $\geq 24$  months of full-dose and when liver biopsy is contemplated) were considered as patients who had received high cumulative MTX treatment, while those with cumulative dose  $< 1.56$  g were considered as patients who had received low-dose MTX therapy.

HR: hazard ratio of developing CVD; CI: confidence interval.

low cumulative doses of MTX appeared to have greater vasculoprotective effects compared with high cumulative doses (24). Our results corroborated with their findings. However, since only limited number of patients received high cumulative MTX dose was included, further studies are needed to confirm this finding.

The reasons for the apparent vasculoprotective effect of MTX include: (i) reduction of C-reactive protein, an acute phase reactant found to significantly predict cerebrovascular events (25, 26). It should be noted that psoriatic condition is associated with elevated plasma levels of C-reactive protein (18, 27); (ii) medications that reduce inflammation have been demonstrated to have favourable effect on vascular diseases (28); and (iii) MTX upregulates the expressions of anti-atherogenic proteins, including ATP-binding cassette transporter-A1 (ABCA1) and 27-hydroxylase (HY27), which facilitate cellular cholesterol efflux (29). Moreover, the peripheral blood mononuclear cells obtained from patients with rheumatoid arthritis who had received low-dose MTX therapy showed increased gene expressions of ABCA1 and HY27 (30). Therefore enhanced expression of anti-atherogenic proteins after MTX treatment is another possible mechanism for the vasculoprotective effect of MTX.

In this study, psoriatic patients who had received systemic MTX or retinoid were not associated with higher risks for developing CVD. We speculate that in Taiwan, there may be a “physician selection bias,” which may result in prescription of systemic MTX/retinoids to psoriatic patients in good health condition. On the other hand, in Taiwan, psoriatic patients who required phototherapy, presumably those with a relatively larger body surface area involvement, were associated with higher risks for developing CVD. Further research into this intriguing issue is warranted.

Several important points should be noted regarding the design of this study. First, since the data records span over a decade, the temporal relationship between psoriasis and CVD was addressed in this study. In addition, since this study used ICD-9 codes to determine the presence of a health condition, it is difficult to validate whether the coding was both accurate and comprehensive. However, since this is a population-based study consisting of large cohort, it is unlikely that significant differences in coding accuracy exist between psoriatic patients and normal controls. Thirdly, the possibility of disease misclassification should be considered. It was found that the prevalence rate for psoriasis in Taiwan was 0.19%, which is much lower than that for Caucasians (7). One of the reasons may be that the medical services in Taiwan are easily accessible and that those with less severe disease may visit the pharmacy without obtaining prescriptions from the physicians first. Another possibility is that many people in Taiwan seek medical remedies from traditional herbal medicine providers. These records were often not included in the NHI database. Therefore, it is likely that our psoriatic



cohort tend to include patients with more severe disease. However, it should be noted that a previous report from China on 670,000 persons has shown that the prevalence of psoriasis is approximately 0.3% (31); a figure which is fairly similar to our result. Other intrinsic limitations of this study include inadequate documentation of lifestyle factors, including smoking and drinking habits, and we were not able to adjust for height, body mass index, or circulating levels of inflammatory markers for our studied subjects. Nevertheless, since this is a case-control study, the impact of these confounding factors should affect both the case and control cohorts equally.

In summary, our study suggests that judicious use of MTX may reduce incidence of CVD in psoriatic patients. Further studies are warranted to validate this therapeutic strategy.

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