Can pretreatment serum calcium level predict the efficacy of methotrexate in the treatment of severe plaque psoriasis?

Zhifang Zhai, MD, PhD,[a] Ling Chen, MD,[b] Huan Yang, MD,[c] Jun Yan, PhD,[d] Chunyou Wang, MD,[a] Jinxin Yang, BA,[a] Wenying Liu, MS,[a] and Zhu Shen, MD, PhD[a]
Chongqing, China

Background: The efficacy of methotrexate (MTX) varies in the treatment of psoriasis.

Objective: We sought to identify an indicator from routine pretreatment tests to predict MTX efficacy in the treatment of psoriasis.

Methods: In a retrospective analysis of 77 psoriatic patients, the correlation between MTX efficacy and pretreatment routine test results was analyzed with Spearman correlation. The potential risks were further evaluated with a linear regression model. Receiver operating characteristic analysis was performed to examine the effectiveness of serum total calcium (tCa) to predict the effect of MTX on psoriasis. The highest Youden index was used to determine the cutoff point, with which the positive and negative predictive values were calculated. Synergistic effects of MTX and calcium on keratinocyte growth and psoriasis-like mouse model were also investigated.

Results: The pretreatment tCa level exhibited the closest association with MTX efficacy. The relative psoriasis improvement with tCa was 61.07% (95% confidence interval, 42.85-79.29; $P < .001$) and better improvements were observed in patients with higher tCa ($r = 0.588$; $P < .002$). MTX inhibited keratinocyte growth, which was enhanced synergistically by calcium. In a psoriasis-like mouse model, MTX strongly inhibited epidermis proliferation in the high-calcium group.

Limitations: One limitation of our study is the relatively small sample size.

Conclusion: Pretreatment tCa level has the highest correlation with MTX efficacy, which might be useful in predicting beneficial treatment results in psoriasis. Larger studies are required to confirm our findings. (J Am Acad Dermatol 2015;73:991-7.)

Key words: calcium; keratinocyte; methotrexate; predictor; psoriasis; treatment efficacy.

INTRODUCTION

Since it was introduced about half a century ago, methotrexate (MTX) has remained one of the important choices for severe psoriasis worldwide.[1] In clinical trials measuring the efficacy of new biologic agents, MTX has always been used as a control of traditional therapy.[2,3] However, the varied treatment efficacy and adverse effects limit its application, with bone marrow suppression and hepatotoxicity being of the greatest concern.[4] Few patients are willing to take the unnecessary risk of the toxicities of MTX, especially when the treatment efficacy is uncertain. Both physicians and psoriatic patients hope to find a pretreatment indicator to

From the Departments of Dermatology at Southwest Hospital[a] and Daping Hospital,[b] the Institute of Toxicology,[c] and the State Key Laboratory of Trauma, Burns and Combined Injury, Research Institute of Surgery, Daping Hospital,[d] Third Military Medical University, Chongqing.

Supported in part by National Natural Science Foundation of China (no. 81373237) and Clinical Innovative Project of Third Military Medical University (SWH2012LC13).
Conflicts of interest: None declared.

Accepted for publication August 15, 2015.
Correspondence to: Zhu Shen, MD, PhD, Dermatology Department, Southwest Hospital, Third Military Medical University, No 30 Gaotanyan Main Street, Shapingba District, Chongqing, 400038 China. E-mail: zhushencq@hotmail.com.
Published online September 24, 2015.
0190-9622/$36.00

http://dx.doi.org/10.1016/j.jaad.2015.08.036

predict the efficacy of MTX in the treatment of psoriasis.

METHODS

Patients

This study was retrospectively performed at Southwest Hospital and Daping Hospital, Third Military Medical University (Chongqing, China), between July 2012 and June 2014. It was approved by the Ethics Committee of Southwest Hospital. Seventy-seven patients of severe plaque-type psoriasis had been treated with MTX for 2 weeks (0.3 mg/kg/week, twice weekly). Demographic details and baseline disease characteristics are listed in Table I. The exclusion criteria were as follows: (1) patients who had been prescribed another biologic agent, MTX, or other systemic treatments in the previous 4 weeks; (2) patients who had accepted topical corticosteroid therapy, vitamin D_3 derivatives, or narrowband ultraviolet B light phototherapy in the previous 2 weeks; (3) patients who had been suffering from any digestive diseases affecting calcium uptake or use; (4) patients who had been taking medications affecting calcium phosphorus metabolism; (5) patients with special dietary needs of high or low calcium or phosphorus diets; (6) patients who had received a diagnosis of parathyroid gland tumors or other tumors affecting calcium phosphorus metabolism; and (7) patients who were pregnant or nursing. Pretreatment routine laboratory tests included a complete blood cell count, routine urinalysis, a liver function test, a renal function test, blood biochemical examination, and a lipid profile. A baseline Psoriasis Area and Severity Index (PASI) score was taken as 100%, and the improvement after MTX was expressed as the percentage of this baseline score.

CAPSULE SUMMARY

- Methotrexate has mixed results in the treatment of psoriasis.
- Pretreatment serum total calcium exhibited the closest association with methotrexate efficacy in psoriasis treatment.
- Pretreatment serum total calcium could serve as an indicator of methotrexate treatment efficacy in psoriasis.

Statistical analysis

PASI score percentage was tested for normality, and the Student *t* test was used to evaluate the distribution of psoriasis improvement between sexes. The Spearman correlation was applied to assess the relationship between psoriasis improvement and baseline data of renal function or lipid profile. By introducing the Bonferroni correction, $P < .002$ was considered to be statistically significant in univariate analysis. PASI score percentage was considered dependent in a linear regression model. All potential risk factors ($P < .002$) of renal function or lipid profile were included in this model, and the stepwise method was performed to evaluate the effects in the final model. By defining the threshold of marked response to MTX as 60% improvement, receiver operating characteristic (ROC) analysis was performed to examine the effectiveness of tCa to predict the effect of MTX on psoriasis. The area under the curve (AUC) of ROC was used to assess the effectiveness of the models. The Youden index was calculated to identify the tCa concentration cutoff for effectively predicting the response to MTX. The positive predictive value (PPV) and negative predictive value (NPV) were calculated by comparing the actual response rates and the predicted response rates with this cutoff. $P < .05$ was considered statistically significant in multivariate and ROC analyses. These analyses were performed using STATA software (version 11.0; StataCorp LP, College Station, TX).

Keratinocyte growth assay

Keratinocytes were cultured in keratinocyte–serum free medium (Appendix A; available online at www.jaad.org). Fourth passage cells were exposed to MTX ranging from 4×10^{-7} mol/L to 4×10^{-5} mol/L for 24 hours, washed, and were then placed in fresh medium (no MTX) with or without calcium (0.2 mmol/L). Keratinocyte growth was assessed counting the cells with a hemocytometer.

In vivo study in a psoriasis-like mouse model

Male C57BL/6 mice (4 weeks old) were fed a low- (0.5% Ca) or high-calcium diet (1.2% Ca) for 8 weeks. The psoriasis-like model was established by injection of recombinant mouse interleukin-23 (1 μg) into the dorsal skin for 4 days.[5] Epidermal psoriasiform hyperplasia was confirmed by histopathologic staining. MTX was then subcutaneously injected (0.75 mg/kg) into the psoriasis-like lesions 3 times at 12-hour intervals. To verify the synergistic effects of MTX and calcium on psoriatic lesion in vivo, histopathologic changes of the lesions before and after MTX injection were analyzed. The study was approved by the institutional ethics committee and conformed to the Guide for the Care and Use of Laboratory Animals.