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Dr. Katchamart replies

WANRUCHADA KATCHAMART

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To the Editor:

We thank Dr. Yamazaki and colleagues for their comments related to our article[1]. According to Recommendation 1: Drug interaction, it was recommended that "Trimethoprim and sulfamethoxazole (TMP-SMX) should be avoided in patients treated with MTX." This recommendation is based on a systematic review by Bourré-Tessier, *et al*[2]. The review showed that TMP-SMX was a risk factor for developing bone marrow suppression in one retrospective case-control study and in 17 case reports. In these case reports, TMP-SMX was used mostly for the treatment of cystitis, for which the dose is usually higher than that for *P. jiroveci* prophylaxis. There was no reported case of interaction with the use of 3 times weekly TMP-SMX for *P. jiroveci* prophylaxis. The duration of antibiotic treatment before the discovery of cytopenia was between 2 days and 2 months, most of the time in the first 2 weeks. The MTX dose was usually low, between 5 and 15 mg per week. Folic acid was either not used or not mentioned in these reports.

We were unaware of Japanese experience of combination of MTX and TMP-SMX as data were unpublished. In Canada, the prevalence of pneumocystis pneumonia (PCP) in patients with rheumatoid arthritis (RA) is quite low. Most PCP cases in RA patients receiving biologics are treated, and no prohylaxis is required afterwards. In addition, the dose of MTX used for RA treatment in Japan is relatively low (maximum 8 mg/week) as compared to doses used in North America (15–25 mg/week), which may explain the low toxicity of MTX in combination with TMP-SMX in Japan. The risk of bone marrow suppression caused by MTX + TMP-SMX combination may be higher with the higher dose of MTX used in Canada. Our committee therefore suggested "TMP-SMX should be avoided in patients treated with MTX."

However, we agree that these 2 clinical settings should be separately considered. As there is no case report of cytopenia from TMP-SMX for *P. jiroveci* prophylaxis, it should be safe if used as proposed, but with a caution. Folate supplementation should be prescribed, and monitoring of bone marrow suppression including complete blood counts should be performed regularly, especially in the first 2 months.

WANRUCHADA KATCHAMART, MD, Department of Rheumatology, Mount Sinai Hospital, University of Toronto, 60 Murray Street, Toronto Ontario M5G 1X5, Canada. Address correspondence to Dr. Katchamart; E-mail: wanda.katchamart@utoronto.ca

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