Tapering subcutaneous methotrexate causes more disease flares compared with tapering oral administration in established rheumatoid arthritis patients

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Letter to the Editor (Other)

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Rheumatology key message

- Tighter monitoring is advised, as more flares occur during tapering of s.c. versus oral methotrexate.

Dear Editor, Thanks to improved treatment strategies, disease remission in RA patients has become more common. As a result, current guidelines recommend to consider tapering DMARDs in patients who are in sustained remission, which may include MTX [1]. Previous research has shown that s.c. MTX may have a better bioavailability, efficacy and tolerability in active RA compared with oral MTX [2, 3]. However, the higher efficacy might be a disadvantage when tapering s.c. MTX is considered. Therefore the aim of this study is to compare the cumulative flare rates after 1 year between RA patients who taper oral and s.c. MTX.

Data from the TApering strategies in rheumatoid arthritis (TARA) trial were used [4]. In this trial, established RA patients with well-controlled disease, defined as DAS $\leq$2.4 and a 44-joint swollen joint count (SJC44) $\leq$1, using one or more conventional synthetic DMARD (csDMARD) and TNF inhibitor (TNFi) were included. Participants were randomized into two groups that gradually tapered their csDMARD first followed by the TNFi, or vice versa. The csDMARD was tapered by reducing the original dosage by one-half at baseline, to one-quarter at 3 months and was stopped at 6 months (Supplementary Fig. S1, available at *Rheumatology* online). Patients who tapered MTX were included in this analysis. If a disease flare (DAS >2.4 or SJC44 >1) occurred, the last effective therapy was restarted and intensified every 3 months until DAS $\leq$2.4 and SJC44 $\leq$1.

Following an intention-to-treat principle, flare rates were compared between patients who tapered s.c. and oral MTX using a χ^2 test. A linear mixed model was used to compare the SJC44 between both groups over time after a disease flare. Two sensitivity analyses were performed: 'complete cases only', in which we included patients with a complete follow-up, and 'worst case scenario', in which we assumed that patients developed a flare at the moment of dropout. Stata version 17 (StataCorp, College Station, TX, USA) was used and *P*-values $\leq$0.05 were considered statistically significant.

Baseline characteristics are presented in Supplementary Table S1, available at *Rheumatology* online. Respectively, 17 and 71 patients tapered s.c. and oral MTX. The median disease duration was 5.9 years and 70% were female. The median MTX dosage for both administration routes was 20 mg/week.

After 12 months, 53% of patients who tapered s.c. MTX developed a flare compared with 27% who tapered oral MTX [OR 3.1 (95% CI 1.0, 9.1), $P = 0.037$] (Fig. 1A). Respectively, 67% and 68% of the patients who developed a flare and were using s.c. and oral MTX had well-controlled disease 3 months after restarting their treatment ($P = 0.93$; Fig. 1A). Although a trend was seen in the SJC44 between both groups over 1 year after flare development (Fig. 1B), this was not significantly different ($P = 0.50$). Both sensitivity analyses showed similar results (Supplementary Table S2, available at *Rheumatology* online).

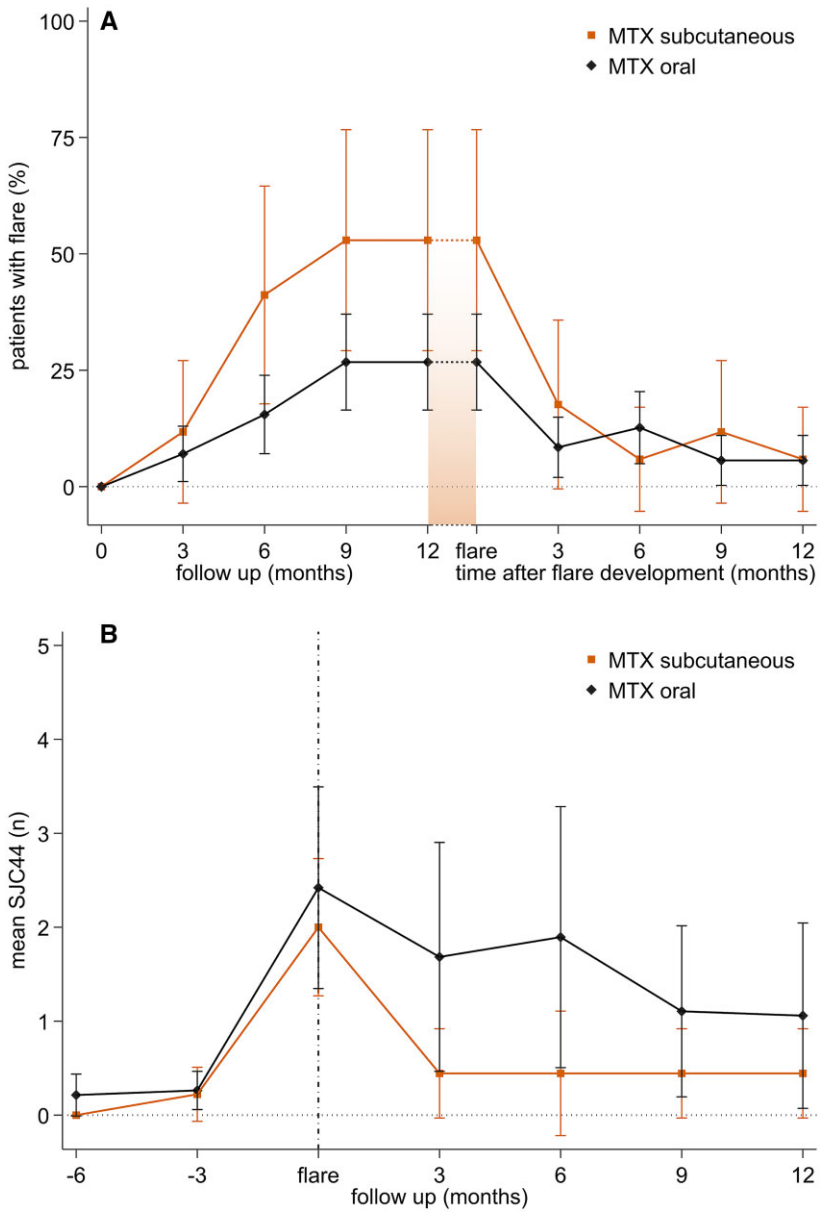
Our study shows that patients who tapered s.c. MTX have a higher risk of developing a disease flare compared with those who tapered oral MTX. This could be explained by a higher efficacy of s.c. MTX when similar dosages are used [5]. Alternatively, the better tolerability of s.c. MTX, especially regarding gastrointestinal side effects, may lead to a difference in adherence [3, 6].

A limitation is that patient groups were not randomized for administration route. However, patient characteristics and disease activity were similar for both groups, which may argue against relevant confounding by indication. Another limitation is that only a small number of patients used s.c. MTX. This is due to the fact that in the region where the TARA trial was conducted, patients commonly start with oral MTX and switch to s.c. MTX when they experience gastrointestinal complaints. Validation of the results is therefore needed. Strengths are the extensive data that were collected with a standardized medication tapering protocol and follow-up.

In conclusion, when deciding to taper MTX, the administration route should be taken into account. Because of the increased risk of flare after tapering s.c. MTX, these patients should be monitored more closely than those tapering oral MTX.

LETTER

Fig. 1 Flare and swollen joint development and resolution over time for different administration routes of MTX



(A) The first part on the *x*-axis illustrates the cumulative percentage of patients who develop a disease flare during follow-up. The second part illustrates the cumulative percentage of patients who still have active disease (DAS >2.4 and SJC44 >1) from the point of flare development and after restarting the last effective treatment. **(B)** Mean SJC44 before, during and after development of a disease flare.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials, available at *Rheumatology* online.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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