Methotrexate intolerance in psoriatic arthritis: prevalence and associated factors

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Methotrexate (MTX) remains one of the most widely used conventional synthetic disease-modifying anti-rheumatic drugs in the management of psoriatic arthritis (PsA), particularly for peripheral arthritis, and continues to play an important role in routine clinical practice and guideline recommendations (1, 2). Although MTX has been extensively evaluated in PsA and with respect to clinical outcomes and safety, MTX intolerance has received considerably less attention as a distinct clinical concept (3).

The Methotrexate Intolerance Severity Assessment (MISA) questionnaire is an adult-focused instrument developed to assess MTX intolerance and has been validated in patients with rheumatoid arthritis (RA) (4). We have previously validated the Turkish version of the MISA questionnaire in patients with RA, demonstrating good reliability and clinical applicability (5). However, evidence regarding MTX intolerance in PsA remains limited. Therefore, we aimed to evaluate the prevalence and clinical correlates of MTX intolerance in patients with PsA using the MISA and MISA-Cross Product (MISA-CP) instruments.

This multicentre cross-sectional study included adult patients with PsA followed at three rheumatology centres who had been receiving MTX for at least six months. PsA was diagnosed according to the CASPAR criteria. MTX intolerance was assessed using the MISA questionnaire, which evaluates gastrointestinal, behavioural, anticipatory and post-dose symptoms. A MISA score ≥1 defined MTX intolerance, while a MISA-CP score ≥4 indicated moderate-to-severe intolerance, in accordance with the original validation study of the MISA questionnaire (4). Analyses focused on comparisons according to MISA cut-offs, correlation analyses and multivariable logistic regression.

A total of 103 PsA patients receiving MTX were included (mean age 48 [SD 12] years; 73% female). Median PsA duration was 4 (IQR 8) years and median body mass index (BMI) was 28 (IQR 7) kg/m^2. MTX intolerance (MISA ≥1) was observed in 58 patients (56%), while moderate-to-severe intolerance (MISA-CP ≥4) was present in 23 patients (22%). MTX intolerance was reported by the treating physician in 38% of patients. Patients with MISA ≥1 had a lower BMI compared with those without intolerance (mean 28 [SD 5] *vs*. 30 [SD 5] kg/m^2, p=0.02). No other relevant differences were observed between groups. Patients with MISA-CP ≥4 were significantly younger than those with MISA-CP <4 (mean age 42 [SD 10] *vs*. 50 [SD 12] years, p=0.002), while other demographic, clinical and treatment-related characteristics were comparable (Supplementary Table S1).

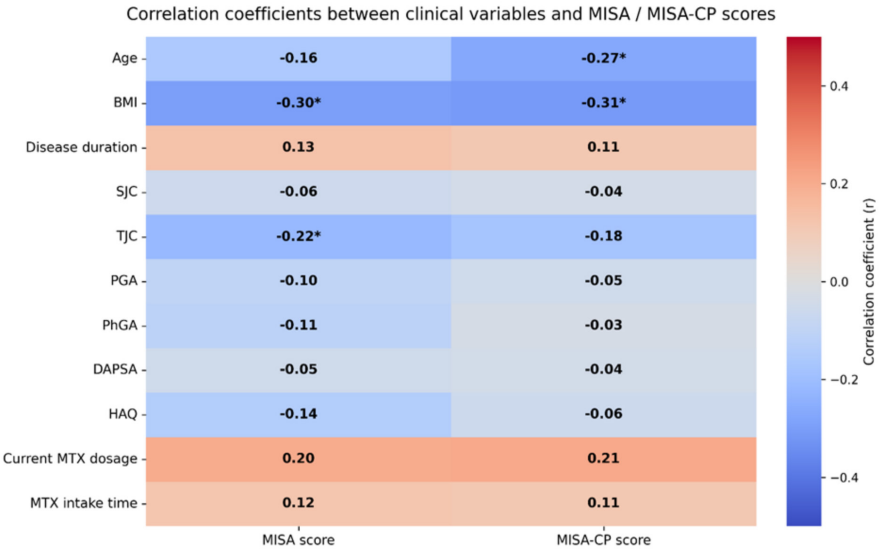

Fig. 1. Correlation coefficients between clinical variables and MISA/MISA-CP scores.
Correlation heatmap demonstrating the associations between clinical variables and MISA / MISA-CP scores. The colour scale reflects both the direction and magnitude of the correlation, with red shades indicating positive associations and blue shades indicating negative associations. Numerical values within the cells represent the corresponding correlation coefficients. Values marked with an asterisk (*) indicate statistical significance at p<0.05.
BMI: body mass index; DAPSA: Disease Activity in Psoriatic Arthritis score; HAQ: Health Assessment Questionnaire; MTX: methotrexate; PGA: patient global assessment; PhGA: physician global assessment; SJC: swollen joint count; TJC: tender joint count.

MISA scores were negatively correlated with BMI (r = -0.30, p=0.002) and tender joint count (r = -0.22, p=0.03), while MISA-CP scores showed weak negative correlations with age (r = -0.27, p=0.007) and BMI (r = -0.31, p=0.001), with no meaningful correlations observed with disease activity measures (Fig. 1). In multivariable logistic regression analyses, lower BMI remained independently associated with MTX intolerance (OR 0.90, 95% CI 0.82–0.99, p=0.04). For moderate-to-severe MTX intolerance, younger age was the only independent factor associated with the outcome (OR 0.94, 95% CI 0.89–0.99, p=0.02) (Suppl. Table S2).

Taken together, these findings indicate that MTX intolerance in PsA is largely independent of inflammatory disease burden. More than half of PsA patients receiving MTX experienced intolerance, and approximately one in five reported moderate-to-severe intolerance. Importantly, intolerance was not associated with disease activity indices, suggesting that it should not be interpreted as a marker of uncontrolled disease.

The discrepancy between MTX intolerance reported during routine clinical assessment and intolerance identified using the MISA questionnaire has important clinical implications, suggesting that intolerance may be under-recognised in daily practice when structured assessment tools are not routinely used. As a result, intolerance may remain unaddressed, potentially affecting treatment adherence and optimisation.

A key limitation of this study is its cross-sectional design, which precludes causal inference. As MTX intolerance and patient characteristics were assessed at a single time point, temporal relationships cannot be determined, and the observed associations should be interpreted as correlational. Another limitation is the demographic characteristics of the study population and its derivation from a Turkish cohort, which may affect the generalisability of the findings. Nevertheless, these data highlight MTX intolerance as a frequent and clinically relevant issue in PsA.

In conclusion, MTX intolerance is common in PsA and appears to be more closely associated with patient characteristics, particularly younger age and lower BMI, than to inflammatory disease activity.

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Competing interests: none declared.

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