Distinct clinical profiles of methotrexate intolerance and hepatotoxicity in psoriatic arthritis

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ABSTRACT

Introduction: Methotrexate (MTX) is the most widely used conventional DMARD for psoriatic arthritis (PsA), but intolerance and hepatotoxicity often limit its long-term use. This study aimed to describe the prevalence and clinical correlates of MTX intolerance and hepatotoxicity in PsA patients.

Methods: We conducted a retrospective study on adults with PsA who were exposed to MTX. Demographic, clinical, and treatment data were retrieved from electronic medical records. Intolerance was defined as discontinuation or dose reduction due to adverse effects, while hepatotoxicity was defined as discontinuation or dose reduction due to persistent liver enzyme elevation (≥2 times the upper limit of normal). Independent associations were explored using multivariable logistic regression.

Results: Among the 341 patients included, MTX intolerance occurred in 26.7% and hepatotoxicity in 10.3%. Bivariate analysis showed that intolerance was associated with female sex, shorter psoriasis–arthritis delay, enthesitis, higher use of csDMARDs and ts/bDMARDs, and lower persistence of TNF and IL-17 inhibitors. No independent predictors of intolerance were identified. Hepatotoxicity was linked to male sex, dactylitis, hypertension, hyperuricemia, and treatment-refractory PsA. In multivariable analysis, hepatotoxicity was independently associated with arterial hypertension (OR 4.40; *p* 0.007) and treatment-refractory PsA (OR 6.23; *p* 0.016) and inversely associated with intolerance (OR 0.09; *p* 0.023).

Conclusion: MTX intolerance and hepatotoxicity in PsA were associated with distinct clinical patterns: intolerance predominates in women and is associated with frequent therapeutic modifications, whereas hepatotoxicity is more common in men with metabolic comorbidities and treatment-refractory disease. Recognizing these patterns may help optimize MTX safety, guide therapeutic decisions, and enhance treatment persistence.

Keywords: Psoriatic arthritis; Psoriasis; Methotrexate; Drug-related side effects; Adverse reactions; Liver diseases.

KEY MESSAGES

1. MTX intolerance and hepatotoxicity represent distinct clinical profiles in psoriatic arthritis.
2. Hepatotoxicity clusters with metabolic comorbidities and treatment-refractory disease, suggesting risk beyond cumulative methotrexate dose.
3. Separating intolerance from hepatotoxicity improves clinical interpretation of MTX discontinuation in routine practice.

INTRODUCTION

Methotrexate (MTX) is a folic acid antagonist that competitively inhibits dihydrofolate reductase, impairs DNA and RNA synthesis in actively dividing cells, and exerts additional anti-inflammatory effects[1]. It was first developed in the 1940s as an anticancer agent and has been repurposed since the 1950s for treating immune-mediated conditions, including psoriasis (PsO) and psoriatic arthritis (PsA)[2]. Despite being the most widely used conventional synthetic disease-modifying antirheumatic drug (csDMARD) in PsA, primarily because of its efficacy, low cost, and ease of administration, MTX continues to raise concerns regarding its tolerance and safety[3].

In clinical practice, adverse events such as intolerance and hepatotoxicity are among the most frequent causes for modifying or discontinuing MTX, making toxicity a major limitation to its long-term use[4]. It is still unknown why some patients with PsA experience subjective intolerance to MTX, whereas others develop biochemical hepatotoxicity, as the clinical factors that determine these distinct adverse responses remain poorly understood. Intolerance, most often presenting with gastrointestinal symptoms such as anorexia, nausea, stomatitis or diarrhea, as well as headache, dizziness, fatigue, and mood disturbance, has been reported in 11%[5] to 45.3%[1] of PsA patients. Despite its frequency, factors associated with MTX intolerance in PsA remain poorly characterized.

Although hepatotoxicity has been extensively studied in rheumatoid arthritis (RA) populations[6], data on PsA remain limited. Patients with PsA appear to be particularly susceptible to hepatotoxicity[7], which can range from asymptomatic, mild and transient transaminase elevations reported in published series from 27.5%[8] to 29.7%[1], to severe outcomes, including fibrosis and even fatal hepatic necrosis[3]. The prevalence of liver fibrosis in PsA varies widely,

ranging from 3.3% to 25% depending on the definition applied and the population studied [3,9–11]. While some studies have linked cumulative MTX dose and treatment duration to mild fibrosis, others dispute this association or even report improvement in many biopsies during treatment[4]. These discrepancies likely reflect differences in the study design, patient selection, and outcome definitions. Mechanistically, MTX-polyglutamate (MTX-PG), the main active metabolite of MTX, induces hepatotoxicity via oxidative stress, inflammation, and apoptosis, partly by depleting hepatic folate and impairing RNA/DNA synthesis[12]. Low folate levels have been identified as predictors of liver enzyme elevation[8], and folic acid supplementation has been proven effective in mitigating these adverse effects. However, the specific clinical factors that predispose patients with PsA to hepatotoxicity remain poorly characterized.

Identifying the distinct clinical profiles associated with MTX intolerance and MTX-induced hepatotoxicity in PsA is essential for optimizing patient monitoring, guiding therapeutic decisions, and minimizing adverse outcomes in clinical practice. This study aimed to describe the prevalence and clinical correlates of MTX intolerance and hepatotoxicity in a well-characterized PsA cohort.

PATIENTS AND METHODS

We conducted a retrospective observational single-centre study based on longitudinal clinical records at a tertiary academic hospital. We included consecutive patients aged ≥18 years with a clinical diagnosis of PsA established by a rheumatologist, all of whom fulfilled the CASPAR classification criteria[13] and were followed in a PsA clinic, who were exposed to MTX between 2013 and 2025. Electronic medical records were reviewed to extract demographic data (age, sex, BMI, and comorbidities), disease characteristics (duration of PsO and PsA, clinical pattern), laboratory parameters (CRP), disease activity scores (DAPSA), number of csDMARDs received, number of targeted/biologic DMARDs (ts/bDMARDs) received, ts/bDMARD treatment persistence in months (defined as treatment duration until discontinuation or switch in routine clinical practice), and documented MTX-related adverse events..All patients received standard folic acid supplementation according to routine clinical practice, and adherence was assessed during follow-up visits based on physician assessment and patient self-report. Two primary outcomes were evaluated: MTX intolerance and MTX-induced hepatotoxicity, which were analyzed using independent models. Patients were classified according to whether MTX intolerance or hepatotoxicity occurred at any time during follow-up. Accordingly, the analyses were intended to explore associations within the cohort rather than to establish temporally

aligned predictors of these outcomes. MTX intolerance was defined as discontinuation or dose reduction owing to subjective adverse effects (e.g., gastrointestinal symptoms, fatigue, or headache) documented in clinical records. Hepatotoxicity was defined as MTX discontinuation or dose reduction due to persistent elevation of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels (≥2 times the upper limit of normal). Persistent elevation was defined as abnormal values confirmed in at least two consecutive determinations despite routine clinical management. Baseline liver function tests were available prior to MTX initiation, and patients with alternative causes of transaminase elevation (including alcohol intake, viral hepatitis, or other hepatotoxic drugs) were systematically assessed and excluded according to standard clinical practice. When both subjective intolerance and liver enzyme abnormalities were present, the patients were classified according to the clinician-documented primary reason for MTX dose reduction or discontinuation, as recorded in the medical records, without post hoc adjudication by the investigators. Additionally, we assessed whether patients met the EULAR definitions for difficult-to-manage and treatment-refractory PsA[14]. These definitions were operationalized by reviewing the full available clinical history of each patient and were recorded if fulfilled at any time during follow-up. Due to the retrospective design, data availability depended on routine clinical documentation, and analyses were performed using available data. All variables were available for the full cohort, except EULAR definitions for difficult-to-manage and treatment-refractory PsA outcomes, which were available in a subset of patients (163 out of 341). Continuous variables were expressed as mean ± SD when normally distributed and as median (range) otherwise, whereas categorical variables were expressed as counts and percentages. Between-group comparisons were performed using the Student's t-test or Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. Multivariate logistic regression was used to explore the associations between clinical variables and MTX intolerance or hepatotoxicity. Independent variables were selected by clinical relevance and $p < 0.20$ in bivariate analysis, limiting predictors to avoid overfitting. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS Statistics v26.0. The study was approved by the local ethics committee (reference 110/25) and was conducted in accordance with the Declaration of Helsinki.

RESULTS

Patients' characteristics

In total, 341 patients diagnosed with PsA were included in this study (Table I). The cohort had a balanced sex distribution (49.0% men and 51.0% women) with a mean BMI of 28.4 ± 5.6 kg/m². PsO onset occurred at 33.2 ± 17.4 years, with PsA diagnosed at 49.1 ± 12.6 years, resulting in a median skin–joint delay of 13 years (range 0–62). Peripheral arthritis was predominant (96.2%), followed by dactylitis (37.8%), nail involvement (33.7%), and enthesitis (18.8%). Median CRP was 3.3 mg/L (range 0.2–84.6), median DAPSA 6.1 (range 0–44.0), and PSAID-12 and PSAID-9 scores were 3.1 (range 0.1–9.0) and 3.4 (range 0.1–9.4), respectively. Patients had received a mean of 1.4 ± 0.6 csDMARDs and 0.8 ± 1.3 ts/bDMARDs, targeting 1.6 ± 0.8 pathways. MTX was the most prescribed csDMARD, with intolerance in 26.7% and hepatotoxicity in 10.3% of the patients. Dyslipidemia (35.2%), hypertension (30.8%), hyperuricemia (29.8%), and diabetes (14.1%) were common. According to the EULAR criteria, 15.3% of patients had difficult-to-manage PsA and 9.2% were treatment-refractory.

Associations with MTX intolerance and hepatotoxicity (bivariate analysis)

In the subgroup analysis based on MTX intolerance, the female sex was significantly more common among intolerant patients (60.4% vs. 47.6%; p = 0.036). These patients also had a shorter delay between PsO and arthritis onset (7 vs. 16 years; p = 0.010), a higher prevalence of clinical enthesitis (29.7% vs. 14.8%; p = 0.002), and received more csDMARDs (1.8 vs. 1.3; p = 0.001) and ts/bDMARDs (1.3 vs. 0.7; p = 0.001). Regarding MTX-induced hepatotoxicity, female sex was less prevalent (31.4% vs. 53.3%; p = 0.014), whereas dactylitis (54.3% vs. 35.9%; p = 0.034), hypertension (45.7% vs. 29.1%; p = 0.044), and elevated uric acid levels (45.7% vs. 27.9%; p = 0.030) were more frequent. Treatment-refractory PsA was also more common in patients with hepatotoxicity (23.8% vs. 7.0%; p = 0.013). No significant differences were observed in the persistence of ts/bDMARD therapies across the groups, except for shorter persistence of TNFi (12 vs. 36 months; p = 0.001) and IL-17i (12 vs. 24 months; p = 0.041) in the intolerance group. The results are summarized in Table II.

Independent associations with MTX intolerance and hepatotoxicity (multivariate analysis)

In the logistic regression model for MTX-induced hepatotoxicity (Table III), after adjusting for potential confounders, arterial hypertension (OR 4.40; 95% CI 1.49–13.03; p = 0.007) and treatment-refractory PsA (OR 6.23; 95% CI 1.40–27.69; p = 0.016) were independently

associated with MTX-induced hepatotoxicity, while MTX intolerance was inversely associated (OR 0.09; 95% CI 0.01–0.72; p = 0.023). Female sex showed a non-significant trend towards a protective effect. In contrast, no independent associations were identified for MTX intolerance, as variables showing trends in the bivariate analysis did not remain significant after adjustment in the logistic regression model.

DISCUSSION

In this study, we identified distinct clinical profiles associated with MTX intolerance and MTX-induced hepatotoxicity in patients with PsA. The observed prevalence of these conditions in our cohort provides a clinically relevant benchmark for routine practice. Female sex was associated with MTX intolerance in bivariate analysis, whereas hepatotoxicity was more frequent in men. These differences may reflect variations in MTX exposure, as women, being more prone to subjective adverse effects such as gastrointestinal intolerance or fatigue, might discontinue or reduce MTX earlier, which may not only limit the cumulative hepatotoxic risk but also explain the inverse association between intolerance and hepatotoxicity observed in our multivariate analysis. This inverse association may reflect an “early-stop” phenotype, in which intolerance-driven MTX discontinuation limits cumulative hepatic exposure and subsequent biochemical toxicity. This may support the clinical relevance of early detection of tolerability issues in relation to more severe biochemical adverse events in susceptible individuals. In this context, by pragmatically distinguishing between subjective MTX intolerance and biochemical hepatotoxicity in a real-world setting, our study provides a clearer clinical framework for interpreting MTX discontinuation in PsA. This finding should be interpreted in the context of a real-world definition of MTX intolerance based on clinician-documented symptoms, for which no standardized definition is currently available, and some degree of misclassification cannot be excluded.

The observation that patients with MTX intolerance exhibited a higher prevalence of clinical enthesitis, whereas those with hepatotoxicity had more frequent dactylitis, should be interpreted cautiously. These patterns may reflect distinct PsA phenotypes, driven by specific domains, that can influence treatment trajectories and potentially modify the risk of MTX-related toxicity, although they are unlikely to represent causal relationships. Enthesitis often responds poorly to MTX[15], which may lead to more frequent therapeutic adjustments and greater exposure to MTX-related adverse effects, potentially contributing to intolerance. In

contrast, dactylitis is recognized as a marker of more severe PsA[16], potentially requiring prolonged MTX treatment and being associated with hepatotoxicity over time.

The mechanisms of MTX-induced hepatotoxicity differ across diseases, although current evidence remains inconsistent. Some studies have reported higher hepatotoxicity rates in PsO than in PsA and RA[17], whereas others have suggested greater hepatic involvement in PsA[1,4,8]. Conversely, some analyses found no significant differences between RA and PsO[18]. These discrepancies highlight the heterogeneity of existing data and the lack of specific studies on MTX hepatotoxicity in PsA[8,11], leaving the risk profiles of these patients poorly defined. Furthermore, hepatotoxicity has traditionally been linked to cumulative MTX exposure in RA[8], whereas it is more often associated with hepatic steatosis and metabolic comorbidities in PsO[19]. PsA appears to present an intermediate profile, in which both inflammation and metabolic factors contribute to liver toxicity.

Notably, we found no association between MTX-induced hepatotoxicity and FIB-4 scores, suggesting that this adverse effect in our cohort may be limited to biochemical alterations, with significant liver fibrosis being unlikely. This is consistent with evidence showing that neither cumulative MTX dose nor treatment duration is associated with increased liver stiffness. In the study by Ruiz-Ponce et al.[7], MTX did not induce significant liver functional alterations at the molecular level, even at high cumulative doses, suggesting that the risk of fibrosis attributed to MTX may have been overestimated in populations with high metabolic risk[9]. In fact, PsA and metabolic syndrome share common pathophysiological pathways that may amplify hepatic vulnerability, and the occurrence of liver fibrosis in this context has been more consistently linked to cardiometabolic factors, such as elevated BMI and diabetes, than to cumulative MTX exposure[3,11]. In our cohort, MTX-induced hepatotoxicity was associated with male sex, hypertension, and hyperuricemia, reinforcing this trend towards a metabolic comorbidity profile and consolidating the multifactorial nature of hepatotoxicity risk in PsA. Previous studies have also linked liver abnormalities in PsA to cardiometabolic factors[7], including associations between MTX-related liver enzyme elevations and higher BMI[1,2], as well as an increased risk of hepatotoxicity in men [8] in line with our findings. Overall, these data support that MTX-related hepatotoxicity in PsA is largely driven by metabolic and cardiovascular comorbidities, with fibrosis being rare and most cases being limited to transient biochemical changes. This pattern observed in our cohort is clinically informative and applicable in daily practice, as it encourages clinicians to consider hepatic risk beyond the cumulative MTX dose alone. However, because detailed data on MTX dose, route of administration, cumulative exposure, and treatment duration were not systematically available, the relative contribution of drug exposure to hepatotoxicity could not be fully assessed in our cohort.

In terms of treatment patterns, our data suggests that patients with MTX intolerance constitute a subgroup requiring more frequent therapeutic modifications, as reflected by the higher number of csDMARDs and ts/bDMARDs received and the lower treatment persistence of both TNF and IL-17 inhibitors. These results are consistent with previous evidence showing that MTX co-therapy improves bDMARD drug survival in PsA, particularly with TNFi[20], suggesting that MTX intolerance could negatively affect the persistence of ts/bDMARD in certain patients. In contrast, patients who developed MTX-induced hepatotoxicity were more frequently classified as having treatment-refractory PsA, indicating a disease phenotype that requires sustained therapeutic intensification, which may be associated with greater cumulative MTX exposure and hepatotoxicity.

This study has some limitations. Its retrospective single-centre design in a tertiary care setting may have introduced biases and may limit the generalizability of the findings. Relevant MTX exposure data, including cumulative dose, route of administration, and time to intolerance or hepatotoxicity, were not recorded, limiting more detailed analyses of MTX-related adverse events. Although most study variables were available for the full cohort, EULAR-defined difficult-to-manage and treatment-refractory PsA outcomes were only available in a subset of patients, which may have affected the precision and interpretability of those specific analyses. Furthermore, although cardiometabolic comorbidities were systematically collected and explored, not all could be retained simultaneously in the final multivariable model in order to maintain parsimony and avoid overfitting. In addition, because patients were classified according to events occurring at any time during follow-up and covariates were not anchored to a single standardized clinical time point, the observed associations should be interpreted as exploratory rather than causal or temporally predictive. Moreover, MTX intolerance was defined according to clinician-documented patient-reported adverse effects, as no standardized definition or validated assessment tools are currently established in routine PsA clinical practice, and adherence was assessed based on physician judgment and patient self-report, without systematically available objective measures. Despite these limitations, the pragmatic, real-world separation of the two commonly conflated MTX discontinuation pathways (subjective intolerance and biochemical hepatotoxicity) represents a key strength of this study and may help improve the clinical interpretation of MTX-related adverse profiles.

CONCLUSIONS

Overall, our findings support the need for individualized risk assessment in patients with PsA treated with MTX, considering the distinct clinical patterns associated with intolerance and hepatotoxicity. Intolerance was more frequently observed in women and was associated with more frequent treatment modifications, whereas hepatotoxicity was more commonly observed in men with cardiometabolic comorbidities. The inverse association between intolerance and hepatotoxicity may reflect an “early-stop” phenotype, in which intolerance-driven MTX discontinuation limits cumulative hepatic exposure. Recognizing these patterns may help inform monitoring strategies and therapeutic decisions, although prospective studies are needed to confirm these associations and develop practical risk stratification tools for personalized management in clinical practice.

Tables and Figures

Table I. Clinical features of the patients

Total patients	341
Men, n (%)	167 (49.0)
Women, n (%)	174 (51.0)
BMI (kg/m^2)	28.4 ± 5.6
PsO age of onset (years)	33.2 ± 17.4
PsA age of onset (years)	49.1 ± 12.6
Delay between PsO and PsA onset (years)	13 [0 – 62]
PsA pattern	
Peripheral, n (%)	328 (96.2)
Axial, n (%)	67 (19.6)
Mixed, n (%)	55 (16.1)
Nail involvement, n (%)	115 (33.7)
Clinical enthesitis, n (%)	64 (18.8)
Dactylitis, n (%)	129 (37.8)
CRP (mg/L)	3.3 [0.2 – 84.6]
DAPSA	6.1 [0 – 44.0]
PSAID-12	3.1 [0.1 – 9.0]
PSAID-9	3.4 [0.1 – 9.4]
FIB-4	1.3 ± 0.7
Treatment received	
Number of csDMARDs	1.4 ± 0.6
Number of ts/bDMARDs	0.8 ± 1.3
Number of ts/bDMARDs targets	1.6 ± 0.8
Methotrexate *	
MTX intolerance, n (%)	91 (26.7)
MTX-related hepatotoxicity, n (%)	35 (10.3)
Ts/bDMARDs persistence (months)	
TNFi	36 [2 – 228]
IL-12/23i	60 [3 – 144]
IL-23i	16 [1 – 48]
IL-17i	15 [1 – 72]
Apremilast	12 [1 – 84]
JAKi	12 [6 – 60]
Abatacept	3 [3 – 3]
EULAR definition D2M/TR PsA **	
Difficult to manage PsA, n (%)	25 (15.3)
Treatment refractory PsA, n (%)	15 (9.2)
Cardiovascular comorbidities	
Arterial hypertension, n (%)	105 (30.8)
Dyslipidaemia, n (%)	120 (35.2)
Diabetes mellitus, n (%)	48 (14.1)
Uric acid levels ≥7 mg/dl, n (%)	101 (29.8)

Quantitative variables are expressed as mean ± standard deviation (SD) for normally distributed data, and as median with range for non-normally distributed data. BMI body mass index. PsO psoriasis. PsA psoriatic arthritis. MTX methotrexate. csDMARDs conventional synthetic DMARDs. Ts/bDMARDs targeted/biologic DMARDs. AHT arterial hypertension. * MTX intolerance and MTX-related hepatotoxicity were defined as events occurring at any time during follow-up. ** EULAR-defined difficult-to-manage and treatment-refractory PsA outcomes were available for 163 of 341 patients.

Table II. Bivariate descriptive analysis of characteristics of the patients related to methotrexate intolerance and methotrexate-related hepatotoxicity

	MTX intolerance (n = 91)	No MTX intolerance (n = 250)	*p* value	MTX-related hepatotoxicity (n = 35)	No MTX-related hepatotoxicity (n =306)	*p* value
Female sex (%)	60.4	47.6	**0.036**	31.4	53.3	**0.014**
BMI [1]	28.2 ± 5.6	28.4 ± 5.7	0.800	29.9 ± 5.2	28.2 ± 5.7	0.244
PsO age of onset (years) [1]	34.9 ± 16.2	32.5 ± 17.9	0.437	38.1 ± 16.3	32.8 ± 17.5	0.335
PsA age of onset (years) [1]	47.7 ± 12.3	49.6 ± 12.7	0.220	49.4 ± 10.2	49.0 ± 12.8	0.874
Delay between PsO and PsA onset (years)[2]	7.0 [0 – 62.0]	16.0 [0 – 59.0]	**0.010**	11.0 [3.0 – 34.0]	13.0 [0 – 62.0]	0.976
PsA pattern						
Peripheral (%)	96.7	96.0	0.764	97.1	96.1	0.755
Axial (%)	16.5	20.8	0.375	17.1	19.9	0.694
Mixed (%)	13.2	17.2	0.373	14.3	16.3	0.754
Nail involvement (%)	28.6	35.6	0.225	42.8	32.7	0.228
Clinical enthesitis (%)	29.7	14.8	**0.002**	25.7	17.9	0.267
Dactylitis (%)	42.8	36.0	0.248	54.3	35.9	**0.034**
CRP (mg/L) [2]	3.5 [0.2 – 74.1]	3.0 [0.2 – 84.6]	0.551	3.7 [0.2 – 22.4]	3.1 [0.2 – 84.6]	0.700
DAPSA [2]	7.2 [0.1 – 28.8]	4.5 [0.0 – 44.0]	0.151	5.2 [0.1 – 20.5]	6.1 [0 – 44.0]	0.784
PSAID-12 [2]	4.9 [0.2 – 8.8]	2.7 [0.1 – 9.0]	0.100	3.1 [2.5 – 8.8]	3.4 [0.1 – 9.0]	0.739
PSAID-9 [2]	5.0 [0.2 – 8.8]	3.2 [0.1 – 9.4]	0.127	3.3 [2.6 – 9.4]	3.7 [0.1 – 9.0]	0.751
FIB-4 [1]	1.2 ± 0.8	1.3 ± 0.6	0.635	1.3 ± 0.7	1.2 ± 0.6	0.542
Treatment received [1]						
Number of csDMARDs	1.8 ± 0.7	1.3 ± 0.5	**0.001**	1.5 ± 0.6	1.4 ± 0.6	0.679
Number of ts/bDMARDs	1.3 ± 1.2	0.7 ± 1.2	**0.001**	1.0 ± 1.2	0.9 ± 1.2	0.485
Number of ts/bDMARDs targets	1.7 ± 0.8	1.6 ± 0.8	0.381	1.5 ± 0.8	1.6 ± 0.8	0.628
Methotrexate *						
MTX intolerance (%)	NA	NA	NA	8.5	28.8	**0.011**
MTX-related hepatotoxicity (%)	3.3	12.8	**0.011**	NA	NA	NA
ts/bDMARDs persistence (months) [2]						
TNFi	12 [2 – 228]	36 [3 – 216]	**0.001**	36 [3 – 216]	30 [2 – 228]	0.550
IL-12/23i	66 [3 – 84]	24 [12 – 144]	0.838	12 [12 – 12]	66 [3 – 144]	0.300
IL-23i	20 [3 – 36]	12 [1 – 48]	0.420	24 [3 – 48]	15 [1 – 36]	0.477
IL-17i	12 [1 – 48]	24 [6 – 72]	**0.041**	36 [6 – 72]	12 [1 – 60]	0.137
Apremilast	12 [1 – 72]	24 [4 – 84]	0.138	48 [36 – 60]	12 [1 – 84]	0.108
JAKi	12 [12 – 36]	12 [6 – 60]	0.817	NA	12 [6 – 60]	NA
Abatacept	NA	3 [3 – 3]	NA	NA	3 [3 – 3]	NA
EULAR definition D2M/TR PsA **						
Difficult to manage PsA (%)	8.3	9.7	0.770	23.8	7.0	**0.013**

Treatment refractory PsA (%)						
Comorbidities						
Arterial hypertension (%)	30.7	30.8	0.996	45.7	29.1	**0.044**
Dyslipidaemia (%)	37.4	34.4	0.612	31.4	35.6	0.623
Diabetes mellitus (%)	13.2	14.4	0.776	14.3	14.0	0.970
Uric acid levels ≥7 mg/dl (%)	27.7	30.5	0.626	45.7	27.9	**0.030**

MTX methotrexate. BMI body mass index. PsO psoriasis. PsA psoriatic arthritis. csDMARDs conventional synthetic DMARDs. Ts/bDMARDs targeted/biologic DMARDs. NA non applicable. * MTX intolerance and MTX-related hepatotoxicity were defined as events occurring at any time during follow-up. ** EULAR-defined difficult-to-manage and treatment-refractory PsA outcomes were available for 163 of 341 patients, and percentages for these variables were calculated using available data.[1] Mean ± SD. [2] Median (range). *p*-values <0.05 are shown in bold.

Table III. Multivariable logistic regression analysis for methotrexate-related hepatotoxicity

Variable	**OR (95% CI)**	***p* value**
Female sex (ref. men)	0.36 (0.11 – 1.23)	0.103
MTX intolerance (ref. no)	0.09 (0.01 – 0.72)	**0.023**
Treatment refractory PsA (ref. no)	6.23 (1.40 – 27.69)	**0.016**
AHT (ref. no)	4.40 (1.49 – 13.03)	**0.007**

Multivariable model adjusted for all included covariates. MTX methotrexate. PsA psoriatic arthritis. AHT arterial hypertension. *p*-values <0.05 are shown in bold.

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