Is there still a place for methotrexate in severe psoriatic arthritis?

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***Abstract*:** The management of psoriatic arthritis (PsA) has long been equated with that of rheumatoid arthritis (RA), particularly because methotrexate (MTX) was found efficient in RA in the 1990s. However, results of collective evidence-based medicine, included and argued in this narrative review, do not currently support the use of MTX as first-line therapy in severe PsA. A recent Cochrane systematic review examining the efficacy of MTX in PsA concluded that low-dose MTX was only slightly more effective than placebo. Questions about a structural effect of MTX in PsA remains non-elucidated. Even if tolerance data on MTX are more consensual and adverse events generally non-severe, subjective side effects such as fatigue might lead to MTX withdrawal based on the patient's decision. PsA patients with axial disease, radiographic lesions, and extensive and disabling skin or joint involvement should receive early treatment with targeted therapy and no longer with MTX. Finally, the usefulness of MTX combined with targeted therapies is limited. MTX does not affect efficacy but only seems to increase the therapeutic maintenance of monoclonal TNF inhibitors. This narrative review may help clarify the place of MTX in PsA management. It allows for reflection on the evolution of current concepts and practices.

Keywords: bDMARDs, biologic therapy, methotrexate, psoriatic arthritis, TNFα, tsDMARDS

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Introduction

Among chronic inflammatory arthritides, psoriatic arthritis (PsA) is distinct because of its large phenotypic heterogeneity and the lack of any specific diagnosis markers. However, PsA management, especially for its peripheral involvement, has long been equated with that of rheumatoid arthritis (RA), particularly because methotrexate (MTX) was found efficient in RA in the 1990s. The historical indication of MTX in cutaneous psoriasis has reinforced this parallelism of thought. Nevertheless, studies demonstrated that treating enthesopathy, dactylitis, axial involvement, and nail impairment with MTX provides no benefit compared with new targeted therapies. Most recent international guidelines based on randomized studies focusing on peripheral articular involvement have followed this trend. Since 2015, the American College of Rheumatology (ACR), Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), European League Against Rheumatism (EULAR), as well as national guidelines have progressively (but not uniformly) restricted the use of MTX, as a peripheral treatment option or as a conditional first-line treatment with an early switch to targeted therapies if necessary. Therefore, we can legitimately question whether there is still a place for MTX in severe PsA. Further randomized placebo-controlled trials assessing MTX efficacy are not likely to be conducted in the future because of ethical considerations and recruitment difficulties.

This narrative review of the literature may help rheumatologists clarify the place of MTX in PsA management. Are there specific conditions for which it should be indicated? Other conditions for which it should be avoided? Should one continue to combine it with targeted therapies? How does the risk/benefit analysis, taking into account the impact on the patient's quality of life and tolerance, compare with that of new targeted

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therapies? The analysis of the literature allows for reflection on the evolution of current concepts and practices.

International guidelines

Since 2018, three different international guidelines have been published: ACR,[1] EULAR,[2] and GRAPPA.[3,4] MTX alone or combined with a targeted therapy is effective in cutaneous psoriasis and may be beneficial in associated conditions such as enthesitis, dactylitis, and nail disease. However, international guidelines have not established clear recommendations about combination treatment [biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs or tsDMARDs)] with MTX. According to the performance of bDMARDs and tsDMARDs, all recommendations suggest close monitoring and tight control throughout the first line of treatment to prevent potential structural damage. Targeted therapies now prevail, and the delay to clinical remission is now one of the main challenges for naive patients, to prevent structural damage. Indeed, these latest recommendations suggest switching to or adding bDMARDs or Janus kinase inhibitors (JAKi, tsDMARDs) for patients not responding to non-steroidal anti-inflammatory drugs or MTX. Nevertheless, a door is clearly open for bDMARDs and small molecules as first-line treatments for PsA patients with 'severe' disease or 'poor prognosis'. Furthermore, all these guidelines agree about the absence of an indication for conventional synthetic DMARDs (csDMARD) including MTX for associated axial disease. These factors restrict the scope of the use of MTX, even though it is widely prescribed as first-line treatment.

Is there still a place for MTX as first-line treatment?

Articular efficacy of MTX

Discrepancies in international guidelines for the use of MTX as first-line therapy in the management of peripheral arthritis in PsA may reflect the paucity of data and conflicting results of published studies. In the pivotal study of MTX in psoriasis, MTX was found efficacious as compared with placebo in improving joint symptoms at 8 weeks in 21 patients.[5] However, in this first double-blind randomized controlled trial, high doses of intravenous MTX were used, with a high incidence of adverse events, including one death in a 39-year-old man (complication of bone-marrow aplasia).[5] These data were weakly supported by results of another double-blind placebo-controlled randomized trial reporting an improvement in the physician assessment of disease activity.[6] In this trial, although MTX was superior to placebo in achieving a reduction in surface area of skin involvement, MTX did not demonstrate significant differences *versus* placebo in patient assessment of disease activity, morning stiffness, or tender or swollen joint counts.[6] Of note, this trial included only 37 patients, but the route and doses of MTX used (oral and $\leqslant$15 mg/week) were more conventional[6] and closer to the current use of MTX. A 6-month double-blind randomized controlled trial with a much larger sample of patients with active PsA (n = 221) compared MTX 15 mg/week with placebo.[7] MTX was given initially at 7.5 mg/week and then increased to 10 and 15 mg/week at 4 and 8 weeks, respectively. When appropriate, investigators could increase MTX up to 20 mg/week at 4 months and 25 mg/week at 5 months. At 5 months, 78% of patients received 15 mg/week and only 11% received higher dosages. Despite this possible up-titration dose of MTX, the intention-to-treat analyses did not demonstrate any evidence of effects in global indices [Psoriatic Arthritis Response Criteria (PsARC) ACR20 responders and Disease Activity Score in 28 joints (DAS28) responders] compared with placebo.[7] In addition, linear regression analyses adjusted for age, disease duration, sex, and individual baseline score did not show significant effects on individual outcome measures such as tender or swollen joint count, C-reactive protein level, Health Assessment Questionnaire score, and pain. Finally, only patient and assessor's global assessments were significantly reduced by MTX, thus reflecting a borderline symptom-modifying property of MTX. Nevertheless, only 11% of patients received >15 mg/week, which is probably not fully optimized.[8] The efficacy of MTX monotherapy was also investigated in a post hoc analysis[9] of the TIght COntrol of inflammation in early Psoriatic Arthritis (TICOPA) study.[8] In this open-label study, 188 patients received MTX in the first 12 weeks of the trial.[9] More than half received oral MTX $\geqslant$15 mg/week, with 86 patients reaching 25 mg/week at 12 weeks. Multiple clinical endpoints were assessed at 12 weeks. The proportion of patients reaching minimal disease activity was 22.4%. The proportion with dactylitis decreased significantly; 37 of the 59 patients with baseline dactylitis showed complete resolution. For those with enthesitis at

baseline, the median change in enthesitis score was null. Although MTX was hypothesized to be more efficacious in polyarticular than oligo articular disease, in this post hoc analysis, differences between these forms were related more to the outcome measures than to a differential response to MTX, as suggested by the authors.[9]

Therefore, there is little evidence to support the efficacy of MTX for PsA with peripheral arthritis. A recent Cochrane systematic review examining the efficacy of MTX for PsA concluded that based on eight published trials, ⩽ 15 mg oral MTX might be only slightly more effective than placebo when taken for 6 months.[10] Results for disease response outcomes [e.g. PsARC and disease activity: DAS28 using erythrocyte sedimentation rate (DAS28-ESR)] were of low quality.[10] The effects of MTX on health-related quality of life, radiographic progression, enthesitis, dactylitis, and fatigue; its benefits beyond 6 months; and the effects of high-dose MTX have not been measured or reported in a randomized placebo-controlled trial.

Taking into account all these data, if MTX is used, it would be appropriate to suggest higher doses, probably subcutaneous, to optimize its use.

Structural effect of MTX

Questions about a structural effect of MTX in PsA remain non-elucidated. Results of a longitudinal observational cohort suggested that MTX might have a structural protective effect in PsA.[11] Indeed, despite the high importance of radiographic peripheral joint damage measurement due to the potential destructive characteristics of PsA, only one published study used it as a primary outcome measure.[12] In this study, among 19 patients with PsA under MTX treatment for 2 years, 63% showed increased radiographic damage score based on the method of Steinbrocker as compared with 47% of matched controls.[12] Patients with erosive PsA treated with tumor necrosis factor-α (TNF-α) inhibitors (TNFi) had a better radiographic outcome than those receiving MTX.[13] In addition, bDMARDs demonstrated their early efficacy *versus* placebo in slowing structural or low-level progression in extension studies.

Cutaneous efficacy of MTX

In several countries, MTX is the first-line systemic treatment recommended for moderate-to-severe psoriasis in adults.[14] However, its use is theoretically limited to severe, reluctant and disabling psoriasis that does not respond adequately to other treatments such as phototherapy, PUVAtherapy, and retinoids. The prescription of MTX in international practice is heterogenous.[15] Indeed, in a recent practice survey in France, only 57% of the dermatologists prescribed MTX as a first-line systemic treatment for adult psoriasis.[16] There are only scarce data on the efficacy of MTX with an up-to-date methodology. A recent randomized placebo-controlled study compared the efficacy of subcutaneous MTX at 17.5 mg/week that could be increased to 22.5 mg/week in case of inadequate response after 8 weeks to placebo.[17] Despite this intensified dosing schedule, only 41% of patients in the MTX group achieved a 75% reduction in the Psoriasis Area Severity Index (PASI) compared with 10% of the placebo group ($p=0.002$).[17] These findings were confirmed in a recent prospective, multicenter, real-life study showing that 38.3% of patients with psoriasis achieved the PASI75 in the intention-to-treat analysis.[18] These results are to be considered with caution. First, 10–16 weeks are required to assess the efficacy of MTX (consistent with the kinetics of the molecule). Second, MTX has an inconsistent effect on nail involvement.[19,20] Because of the slow growth of nails, the evidence for the effect of MTX on psoriatic nail involvement is limited owing to the short follow-up in appropriate studies. In the METOP study, an intensified subcutaneous MTX dosing scheme was compared with placebo. Only 13.6% of all patients with a baseline active nail involvement showed complete clearance of this involvement.[17]

Tolerance of MTX and discontinuation

Tolerance data on MTX are more consensual than those for efficacy. The most common side effects include gastrointestinal effects, abnormal liver function results, and respiratory symptoms. The most severe adverse effects associated with MTX are medullar aplasia and MTX pneumonitis; however, these adverse effects are rare.[21,22] Gastrointestinal disorders associated with MTX are the main cause of MTX discontinuation. MTX withdrawal was estimated at 8–33%, occurring during the first 6 months of treatment.[23,24] In the Cochrane MTX for PsA review, four studies reported serious adverse events and also reported associated withdrawals, but MTX discontinuation was comparable to that with placebo [risk ratio, 1.32 (95% confidence interval (CI), 0.51–3.42)].[10] However, long-term data are lacking (> 6 months) and for higher dosages (>15 mg/

week). Wilsdon *et al.*[10] could not confirm a potential dose-ranging effect, but it has already been reported by others.[18] Other general side effects such as fatigue might lead to MTX withdrawal based on patient decision.[25]

Is there still a place for MTX combined with targeted therapies?

Randomized trials have shown that concomitant use of MTX increases the efficacy of TNF inhibitors in RA, but its benefit in PsA has not been demonstrated. Most TNFi, namely adalimumab,[26] etanercept,[27] infliximab,[28] and golimumab,[29] provided similar benefits in active PsA with and without MTX. A systematic review of TNFi trials in PsA also confirmed these individual findings.[30] All randomized controlled trials found no or minor differences in efficacy for peripheral arthritis, as assessed by ACR response rates, between patients receiving MTX or not. However, at the time of this review,[30] no randomized trials designed to compare TNF inhibitor monotherapy *versus* concomitant MTX had been performed; comparisons reported were based on stratification rather than randomization, and baseline differences need to be taken into account. Since then, few studies have looked specifically at the contribution of MTX in addition to TNFi. In a phase III study, 851 patients with PsA were randomized to one of three treatment arms: oral methotrexate (20 mg) plus subcutaneous placebo given weekly ($n=284$), subcutaneous etanercept (50 mg) plus oral placebo given weekly ($n=284$), or subcutaneous etanercept (50 mg) plus oral methotrexate (20 mg) given weekly (combination therapy; $n=283$). Overall, combining MTX and etanercept did not improve the efficacy of etanercept alone (ACR20: 60.9% *versus* 65.0%, minimal disease activity: 35.9% *versus* 35.7%).[31] Analyses based on data from the Norwegian longitudinal observational study of DMARDs (NOR-DMARD) found similar responses in patients receiving TNFi with or without concomitant MTX, but drug survival was superior in patients receiving combination therapy.[32] Another study specifically examined the effects of adding or withdrawing MTX in patients receiving adalimumab. This was an observational study of patients with PsA ($N=1424$) who initiated adalimumab therapy during routine clinical care in Germany.[33] PsA patients who added MTX or stopped MTX showed similar modest improvements in mean DAS28 score at 6 months after the change, from 3.36 to 3.24 for MTX addition [mean difference, −0.12 (95% CI, −0.46 to 0.22); $p=0.47$] and from 2.54 to 2.43 for MTX removal [mean difference, −0.10 (95% CI, −0.36 to 0.16); $p=0.44$]. Changes in pain and function assessments showed a similar pattern.[33]

Data regarding interleukin 17 inhibitors are similar. Ixekizumab demonstrated sustained efficacy in patients with PsA for up to 1 year of treatment, with or without concomitant MTX.[34] Results from the Spirit-H2H study were similar:[35] ixekizumab delivered consistent efficacy in several clinical domains of the disease regardless of the concomitant MTX use. A pooled analysis of 2049 patients from four phase III studies of secukinumab in patients with PsA showed no clear difference between efficacy outcomes in patients with and without concomitant MTX use.[36]

Ustekinumab significantly ameliorated active PsA compared with placebo regardless of MTX use at baseline.[37] Recently, a dedicated, investigator-initiated, randomized, placebo-controlled trial of active PsA specifically examined whether outcomes of treatment with ustekinumab combined with MTX (newly initiated or ongoing) differed from those with ustekinumab alone (+placebo). The aim of the trial was to evaluate the non-inferiority of efficacy on arthritis (DAS28 at week 24) and compare efficacy in PsA domains for ustekinumab + MTX *versus* ustekinumab + placebo. Data from this trial confirmed that additional MTX had no positive impact on ustekinumab efficacy for arthritis, enthesitis, dactylitis, skin, or function.[38]

Data for JAKi are scarce. In the tofacitinib PsA studies (OPAL Broaden, OPAL Beyond), 98.4% of patients received concomitant treatment with MTX, so comparing mono and combination therapy was impossible.[39] Nevertheless, patients who were stable on tofacitinib 5 mg twice daily with background MTX might be able to discontinue MTX without clinically meaningful changes in disease activity.[40] In the SELECT PsA phase III trials, the efficacy of upadacitinib was generally consistent when administered as monotherapy or when combined with csDMARDs.[41]

A recent meta-analysis of 15 studies of bDMARDs in mono *versus* combination therapy with MTX found no clinical improvement of PsA outcomes with combination therapy.[42]

Considering that the combination of targeted therapies with MTX provides limited or no benefit in terms of efficacy, what about therapeutic survival? In the NOR-DMARD registry, concomitant MTX

was associated with better 1-year TNFi survival in PsA patients ($p=0.02$).[43] Another study from this register found similar efficacy responses to TNFi in patients with and without concomitant MTX, but drug survival was superior in patients receiving comedication. The effect of MTX on drug survival was most prominent in patients receiving infliximab.[32] In contrast, analysis of data in the Canadian Rhumadata clinical database and registry found that concomitant MTX did not demonstrate improved 5-year retention with adalimumab or etanercept (52% for combination therapy *versus* 67% for monotherapy; $p=0.74$).[44] A retrospective analysis of 487 PsA patients with ustekinumab treatment in Hungary showed that concomitant MTX did not have a significant effect on ustekinumab survival.[45] No clear data are available for interleukin 17 inhibitors or JAKi at this time.[46]

Other conditions one should be aware of

As previously mentioned, bDMARDs and tsDMARDs must now be positioned as first-line therapies in PsA patients with 'severe' disease or 'poor prognosis'. Indeed, pivotal studies have extensively demonstrated that patients with erosive PsA treated by targeted therapies had better clinical and radiographic outcomes than those receiving MTX.

An unwilling and unexpected effect of MTX in PsA patients might lead their physicians to neglect the tight control of PsA. Hence, in a study conducted in the Netherlands including 142 patients and scoring disease activity and assessing treatment decisions, 63% of PsA patients were considered to have remaining disease activity, supported by the assessment of several measured domains.[47] Furthermore, residual disease activity was more frequent in patients receiving csDMARD (66%), such as MTX, than a first TNFi (44%). However, treatment was changed at the same frequency (in only 28% of patients receiving csDMARD and 29% of patients receiving a first TNFi).[47] Reasons for not adjusting treatment despite additional therapeutic options might be explained by the lack of structural disease activity assessment in patients despite only weak evidence favoring the protective structural effect of MTX.[12]

There is not enough evidence to support any benefit of MTX for treating axial spondyloarthritis.[48] Hence, MTX is not used to treat PsA axial involvement. No study has examined the use of MTX in axial PsA. All international guidelines agree with the non-use of MTX for axial disease.

In case of severe cutaneous disease, the EuroGuiDerm guidelines indicate that if treatment success is not expected with conventional drugs, first-line biologic agents are recommended rather than MTX.[49] In addition, less than 50% of patients receiving MTX achieved a 75% improvement in the PASI score at week 24.[50]

A retrospective review of a large UK cohort identified 1257 patients who had received MTX for RA or PsA, but MTX had been discontinued: 762 had RA and 193 had PsA. MTX had been stopped in 260 patients with RA and 71 with PsA. These data suggest that about one-third of patients with RA and PsA eventually stop taking MTX, most citing intolerance. In addition, the study found a statistically significant difference between RA and PsA cohorts, with abnormal blood counts (leucopenia and thrombocytopenia) reported more frequently in RA than PsA (11.5% *versus* 6.8%; $p<0.05$) and more PsA than RA patients with liver enzyme abnormalities (27% *versus* 12%; $p<0.05$).[24] Given the metabolic background in PsA patients and the risk of non-alcoholic steatohepatitis, PsA patients may be more susceptible to MTX hepatotoxicity than RA patients. In a population-based cohort study, Danish individuals with psoriasis, PsA or RA receiving MTX between 1997 and 2015 were compared according to four disease outcomes: mild liver disease, moderate-to-severe liver disease, cirrhosis, and cirrhosis-related hospitalization. As compared with RA patients, for PsA patients, mild liver disease and cirrhosis was 1.3–1.6 times more likely after adjusting for demographics, smoking, alcohol use, comorbidities, and MTX dose.[51] Targeting inflammation with TNFi or MTX may have positive cardiovascular effects in RA, PsA, or cutaneous psoriasis, but limited evidence suggests that systemic therapies are associated with decreased risk of all cardiovascular events.[52]

Conclusion

The results of collective evidence-based medicine do not currently support the use of MTX as first-line therapy in active PsA. This opinion is consistent with the latest international recommendations. The lack of consensus between ACR, GRAPPA, and EULAR recommendations may be due to an acceptable safety profile of MTX and its relative low cost. The use of MTX in PsA needs to be accurately individualized based on known efficacy, tolerability, and a shared decision with each patient. PsA patients with axial disease, radiographic

lesions, and extensive and disabling skin or joint involvement should receive targeted therapy and no longer MTX. Evidence is limited for prioritizing MTX as first-line therapy in PsA with enthesitis, dactylitis, or nail involvement because of the overall low quality of evidence provided by randomized controlled clinical trials. Finally, the usefulness of MTX combined with targeted therapies is limited. MTX does not change the efficacy but only seems to increase the therapeutic maintenance of monoclonal TNFi.

Author contribution(s)

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