
The role of methotrexate in psoriatic arthritis: what is the evidence?

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ABSTRACT

Methotrexate is a popular and widely used medication for the treatment of psoriatic arthritis. Herein we review the body of evidence for its use and examine its benefits as well as its limitations, both as a monotherapy and in combination with other DMARDs and biological drugs.

Psoriatic arthritis (PsA), a chronic systemic inflammatory arthritis, is a disorder clinically and genetically distinct from rheumatoid arthritis (RA), with greater similarity and inclusion within the phenotypes rheumatologists typically refer to as spondyloarthritis (SpA) (1, 2). PsA is a multifaceted disease; the most prominent clinical manifestations include peripheral and axial joint involvement, enthesitis, dactylitis, and skin and nail disease. Within the last few years, several carefully done reviews on PsA treatment recommendations have been published in order to update and establish the optimal management of this disease in light of the development of newer agents that might modify the natural course of the disease (3-5). Nevertheless, and because of its historical kinship to the treatment of rheumatoid arthritis, the disease-modifying anti-rheumatic drug methotrexate (MTX) is often employed as a first line of treatment (6). However, little data are available from randomised controlled trials (RCTs), in spite of widespread experience, to suggest that this should be established as a standard or first line treatment for psoriatic arthritis. Our focus here is to review the evidence, from RCTs, as well as expert opinions published in reviews and commentaries for the use of MTX in the treatment of PsA.

Historically, MTX has been used either as monotherapy or in combination with tumour necrosis factor inhibitor (TNFi) therapy to treat PsA patients.

The Methotrexate in Psoriatic Arthritis (MIPA) randomised placebo-controlled trial raised questions about the effectiveness of MTX monotherapy for PsA. These investigators were unable to show any statistically significant differences between those treated with MTX versus placebo and concluded that MTX did not improve synovitis and could not be recommended as a first line treatment even though their study also demonstrated that treatment with MTX did show reductions in patient and physician global assessment scores as well as Psoriasis Area and Severity Index (PASI) scores (7). The weaknesses and limitations of this trial have been discussed in the literature including the small sample size and the fact that the doses employed were, on average, lower than typically employed in modern times to treat RA (8). Furthermore, other investigators have reported evidence that suggests treating PsA with MTX alone shows moderate improvement in joint and skin disease and that doses >15mg per week may show greater clinical efficacy than lower doses (9); however, other important PsA manifestations such as spondylitis, enthesitis and dactylitis have not been systematically studied and require further investigation. Consistent with this latter concept, several investigations reveal that methotrexate monotherapy for ankylosing spondylitis does not appear to provide any benefits for the spine (10), although concomitant skin disease does respond. As MTX is evidently unsuccessful for treating axial disease, it raises the unresolved issue of whether or not the widespread manifestations seen in PsA have a different pathogenesis and hence a varied response to specific therapies. Clearly, there is still much uncertainty about the general usefulness of MTX monotherapy treatment for PsA.

The clinical benefit of MTX combination treatment with biologics, such

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as TNF inhibitors, for PsA has been studied in many trials (11), although it remains unclear whether concomitant treatment with MTX contributes in any way to an improved clinical outcome. Whether or not the addition of MTX would deter antibody formation against the TNF inhibitors and thereby improve their efficacy through reduction in their clearance is a question of much interest that still needs to be addressed. Similarly, from the current available data, it is not possible to tell if MTX employed concomitantly with TNFi has an additive or synergistic effect.

It has been shown that the clinical efficacy of TNF inhibitors for RA is increased with the simultaneous addition of methotrexate therapy, including reduction in structural joint damage (12). In psoriatic arthritis, it is not definitively established whether or not there is a beneficial effect for co-medication with MTX along with conventional synthetic disease-modifying anti-rheumatic drugs to enhance TNF effectiveness. Utilising a cohort design, Lie and colleagues demonstrated the combination to have a better 5-year retention rate for the first TNF inhibitor treatment of AS and SpA (13), although an accompanying editorial cited numerous residual confounding errors that could have easily accounted for the calculated effect of the combination treatments (14).

Whether MTX is suggested as monotherapy for PsA, combination with TNFi is not yet recommended by EULAR or GRAPPA mainly because of insufficient evidence. In 6 randomised controlled trials, concomitant MTX and TNFi therapy did not appear to improve the efficacy of TNFi treatment (15). Similarly, results from the Norwegian study NOR-DMARD also revealed that concomitant MTX treatment did not improve the efficacy of TNFi therapy in psoriatic arthritis patients (16). It is important to note that trials investigating TNFi treatment for PsA were mainly designed to investigate the safety and efficacy of a single TNFi (*e.g.* adalimumab, etanercept, infliximab) (17-19). Therefore, treatment with TNFi was compared to placebo and not directly to treatment with methotrexate; although patients were

stratified by baseline MTX use. The RESPOND study, a randomised open-label study, compared MTX treatment to infliximab plus MTX treatment in patients with PsA (20). These investigators noted that patients treated with the combination showed improved ACR20, PASI 75 and DAS28 responses compared to patients treated with MTX alone. While each trial has its merits, further investigation into combination therapy is warranted. Regardless of the evidence, or lack thereof, combination therapy is commonly observed in clinical practice.

While the effectiveness of MTX treatment on the basis of RCT data remains uncertain, clinicians are still prescribing it, and consideration for its tolerability must also be investigated. Studies that examine MTX tolerability in both RA and PsA have been performed. Recently, Calasan *et al.* (21) used the Methotrexate Intolerance Severity Score (MISS) to investigate the extent of MTX intolerance in a cohort of patients diagnosed with either RA or PsA. Slightly less than half (42.3%) of 291 patients exhibited gastrointestinal intolerance to MTX with co-medication use equal between the two groups (tolerant *vs.* intolerant). Although these adverse effects were shown to be relatively common, suggesting that patients should be closely monitored so as to avoid discontinuation of treatment, PsA patients made up a small minority of the cohort (14.4%). Similarly, the prevalence and severity of MTX intolerance was found to be equal between RA and PsA patients; however, the actual number of PsA patients was significantly lower. Whether or not this data can be extrapolated to larger cohorts or current clinical practice requires further study.

Gastrointestinal intolerance appears to be the primary reason that patients discontinue MTX use (22). However, it is important to note that many of these trials are generally less than 24 weeks in duration and this does not reflect real-life withdrawal rates (22) since median and mean duration of MTX treatment is 10 months and 18 months, respectively. Aside from gastrointestinal intolerance, studies have shown that among PsA

patients, many (up to 1 in 8) treated with MTX withdraw over pulmonary concerns (22). Studies in RA patients have demonstrated the unique clinical scenarios and risks of MTX induced lung disease (23). However, it is not always clear to pinpoint MTX as the cause because patients with RA tend to develop pulmonary complications which are related to the underlying disease itself. Conway *et al.* performed a meta-analysis of double-blind randomised controlled trials of patients with psoriasis, psoriatic arthritis, or inflammatory bowel disease treated with MTX to investigate the risk of increased lung disease in this group (23). A systematic literature search led them to analyse 7 studies that met their criteria. They found no increased risk of adverse pulmonary events in psoriasis, psoriatic arthritis or IBD patients treated with MTX compared to controls. These results were different from a recent meta-analysis of randomised controlled clinical trials in RA where a small but significant risk of lung disease is associated with MTX administration (24). Although pulmonary complications may exist in PsA patients treated with MTX, current evidence does not suggest that MTX actually increases this risk.

Risk of morbidity and mortality from atherosclerosis and other cardiovascular disorders is already known for rheumatoid arthritis (25, 26). Whereas NSAID and corticosteroid treatment in these patients has been shown to lead to adverse cardiovascular events (CVE), studies of methotrexate and TNFi treatment in RA have demonstrated an association with a decreased risk of CVEs (27, 28). It is generally suspected that there is also an increased risk of cardiovascular morbidity and mortality in PsA patients, however the evidence is not as strong as in RA. In order to further investigate this question, Roubille *et al.* (28) recently performed a systematic literature review and meta-analysis of both observational studies and randomised controlled trials that examined CVE in persons with PsA treated with MTX, TNFi, corticosteroids and NSAIDs. In spite of the limited data available (six studies) they were able to conclude that systemic therapy was associated with a decreased risk of car-

diovascular complications in patients with psoriasis or psoriatic arthritis. Certainly more work is needed in this area.

Comorbidities in PsA require particular attention, with more than half of PsA patients exhibiting more than one comorbidity (29). Aside from cardiovascular disease, PsA patients also present with obesity, diabetes, osteoporosis as well as liver and kidney disease at higher frequency compared to the general population (29). Psoriatic arthritis patients are at particularly high risk for development of nonalcoholic fatty liver disease (NAFLD). Treatment with MTX has been shown to lead to increased hepatotoxicity in PsA patients more so than RA patients (29, 30). Interestingly, patients treated with a combination of TNF inhibitor and MTX were found to have less liver fibrosis than those treated with MTX alone (31). Concomitant, pre-existing, or associated liver disease that is commonly found with both skin psoriasis as well as PsA remains a poorly understood phenomenon in terms of cause and effect; nevertheless, the association of obesity and liver test abnormalities seen frequently in practice associated with psoriasis alone as well as in PsA raise questions about risk associated with the modest benefit accompanying methotrexate treatment of PsA.

This review serves to illustrate the fact that although management of PsA often imitates the management of RA, it cannot be assumed that the RA employment of methotrexate as an anchor treatment for most patients, even when used in combination with other biologic or non-biologic DMARDs is the same for PsA. Most certainly, well-controlled studies cannot support the primacy of methotrexate for PsA as they do for RA in spite of common community practice that appears to place methotrexate more into the usual care setting of PsA. The specific presence of obesity and fatty liver in PsA subjects, with or without the addition of alcohol intake, create clinical conundrums in the practical aspects of managing these patients. Nevertheless if evidence is forthcoming, either in the trial literature or in clinical effectiveness research investigations

using real world populations, which support employment of methotrexate to reduce cardiovascular comorbidities in PsA, it is possible that methotrexate might attain a more secure primary role in management of these patients. Currently, the available trial and experiential evidence as well as expert opinion are not sufficiently strong to place MTX in a similar pivotal role as established for RA management.

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