Psoriatic Disease: Update on Traditional Disease-modifying Antirheumatic Drugs

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ABSTRACT. We present an update on the effects of methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), and cyclosporine (CSA) in psoriatic arthritis (PsA) by reviewing data published from January 2010 to June 2014. The most relevant study on MTX, the Methotrexate In Psoriatic Arthritis (MIPA) trial, did not show a significant difference between this drug and placebo in improving peripheral synovitis. The trial, however, had several limitations. A cohort study on a small number of patients found that MTX does not inhibit radiographic progression. In a large observational study, 86% of LEF-treated patients met PsA Response Criteria (PsARC) at Week 24. No studies of sufficient relevance on SSZ were published in the examined time frame. In an open-label trial, CSA alone was compared to adalimumab (ADA) alone and to the combination ADA/CSA. The ADA arms showed a significantly higher response rate, but as many as 65% of CSA-treated patients were PsARC responders at Month 12. No relevant data on the effects of these 4 drugs on psoriatic enthesitis, dactylitis, or spondylitis have recently been published, and no new safety signals have been reported. Observational data from 2 registers suggest that concomitant MTX increases the retention rate of tumor necrosis factor-α inhibitors. The studies published in the examined time frame confirm that MTX, SSZ, LEF, and CSA have moderate symptom-modifying effect on psoriatic synovitis, and probably little effect on the other manifestations of PsA. (J Rheumatol Suppl. 2015 Nov;93:61–4; doi:10.3899/jrheum.150639)

Key Indexing Terms:
METHOTREXATE LEFLUNOMIDE SULFASALAZINE
CYCLOSPORINE PSORIATIC ARTHRITIS

Over the last decade, the concept has emerged of psoriatic disease (PD), an inflammatory disorder affecting multiple organs. In addition to psoriasis, patients with PD may present a number of clinical manifestations including arthritis, uveitis, metabolic syndrome, cardiovascular disease, liver inflammation, and depression. Here we present an update of the effects of methotrexate (MTX), sulfasalazine (SSZ), leflunomide (LEF), and cyclosporine (CSA) on the articular manifestations of PD. Because 2 systematic reviews on the efficacy and safety of traditional disease-modifying antirheumatic drugs (DMARD) in psoriatic arthritis (PsA) published in 2012 already provide a comprehensive overview of data published before 2010[1,2], the present update will be focused on data published from January 2010 to June 2014 (Table 1).

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Efficacy Data

Methotrexate. Until 2010, the efficacy of MTX in improving the symptoms of psoriatic synovitis had been evaluated by a few low-quality studies. Since 2010, 3 relevant studies on this topic have been published. In the NOR-DMARD register, 430 patients with PsA were compared with 1218 patients with rheumatoid arthritis (RA). After 6 months, both groups showed improvement in most disease activity indices; the change was more evident in patients with RA. The 2-year retention rate was similar in PsA and RA patients (65% and 66%, respectively). The authors concluded that, in a real-life setting, MTX treatment of PsA was associated with improvement in disease activity and that its 2-year retention rate was not different from that of RA[3]. In the Methotrexate in PsA (MIPA) trial, 109 patients taking MTX were compared with 112 patients treated with placebo. At Month 6, only the improvement in patient and assessor global score was significantly higher in MTX-treated patients. The responder rate according to the PsA Response Criteria (PsARC)[4], which was the primary outcome, was not superior in the MTX group. The authors concluded that low-dose oral MTX was not better than placebo in improving synovitis and that there was "insufficient evidence to support the use of MTX as a standard treatment for PsA."[5] The MIPA trial had, however, the following limitations: long enrollment time period (> 5 yrs), dropout rates higher than anticipated (38% and 46% for the MTX and placebo arms, respectively), high number of imputed data, and relatively low dose of the drug (target dose

Table 1. The most relevant studies on DMARD efficacy in patients with psoriatic arthritis (PsA), as published between January 2010 and June 2014.

Drug	Study Design	No. Patients	Main Results
MTX[3]	Observational (NOR-DMARD register; PsA vs RA)	430 PsA 1218 RA	At Month 6, more clinical improvement in RA than in PsA. Similar 2-year retention rate (65% PsA and 66% RA)
MTX vs placebo[5]	RCT (MIPA trial)	109 MTX 112 Placebo	At Month 6, only physician global and patient global scores better in MTX-treated patients
MTX vs MTX + IFX[7]	Open-label RCT (RESPOND trial)	58 MTX 57 MTX + IFX	At Week 16, higher ACR20 response in combo (86.3% combo, 66.7% MTX)
MTX[8]	Observational (TNFi vs MTX)	65 TNFi 70 MTX	At 1–2 and 3–4 years, TNFi more effective on radiographic progression
LEF[11]	Observational	514	At Week 24, 86.4% PsARC responder in the 440 still taking therapy
CSA vs ADA vs CSA + ADA[12]	Open-label trial	57 CSA 58 ADA 55 CSA + ADA	At Month 12, higher PsARC in combo (65% CSA, 85% ADA, 95% combo)
MTX vs MTX + TNFi[15]	Observational (DANBIO register)	354 TNFi 410 MTX + TNFi	MTX use associated with greater TNFi retention rate
MTX vs MTX + TNFi[16]	Observational (NOR-DMARD register)	170 TNFi 270 MTX + TNFi	Similar response rate but TNFi retention rate superior in concomitant MTX

ACR20: American College of Rheumatology 20% improvement; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; IFX: infliximab; LEF: leflunomide; CSA: cyclosporine; ADA: adalimumab; TNFi: tumor necrosis factor inhibitor; RA: rheumatoid arthritis; RCT: randomized controlled trial; PsARC: PsA response criteria.

15 mg/weekly). In the RESPOND study, 57 patients with PsA taking infliximab (IFX) and MTX in combination were compared with 58 patients with PsA receiving MTX alone. As expected, at Week 16 the combination therapy was significantly more effective than MTX alone. However, the proportion of patients achieving the primary efficacy endpoint (American College of Rheumatology 20 response at Week 16[6]) in the MTX-only population was quite high (66.7%)[7]. Taken together, the available data seem to indicate that MTX has a moderate symptom-modifying effect on psoriatic synovitis. More specific and large randomized controlled trials (RCT) should be conducted to weigh the efficacy of MTX.

The effect of MTX on radiographic progression was recently addressed in a cohort analysis of patients followed prospectively in a PsA clinic[8]. In that study, 65 patients treated with tumor necrosis factor-α inhibitors (anti-TNF-α) were compared with 70 patients receiving MTX. The proportion of patients with progression of radiographic damage at 1–2 years and 3–4 years was significantly higher in the MTX group. Multivariate analysis showed that MTX treatment was associated with an increase in radiographic progression compared to TNF-α inhibitors. An exploratory study conducted on a small number of patients (28 taking TNF-α inhibitors and 13 MTX) using high-resolution micro-computerized tomographic imaging showed that both therapies did not stop progression of bone apposition in the metacarpophalangeal joints[9]. The available data suggest that MTX is not a disease-modifying agent in PsA; however, well-performed RCT on this topic are needed.

There are scarce data on whether MTX might be beneficial for enthesitis, dactylitis, and spondylitis in PD. The general opinion of experts is that MTX has no or little effect on these clinical manifestations.

Leflunomide. In the well-known RCT published in 2004, LEF was proven to be better than placebo but with a small effect size in psoriatic synovitis[10]. After 2010, other data on this drug have come from a large observational study[11]. Of the 514 patients with PsA enrolled in this study, 74 (12.3%) discontinued treatment and 380 of the remaining 440 (86.4%) achieved a PsARC response at Week 24. Significant improvement was also observed in dactylitis. There are no data on the effect of LEF on enthesitis, spondylitis, or radiographic progression. Available data suggest that, in PsA, LEF has a moderate symptom-modifying effect on peripheral synovitis and might improve dactylitis. Its effects on the other articular manifestations of PD are unknown.

Sulfasalazine. At least 7 RCT and some open-label or case-control studies on SSZ in PsA were published before 2010. The resulting evidence indicates that this drug is effective in improving the symptoms of peripheral synovitis, although with a modest effect size. Dactylitis, enthesitis, spondylitis, and radiographic progression do not seem to be affected by this drug. However, with the exception of peripheral synovitis, the level of evidence supporting these statements is very low. Since 2010 no further relevant studies on the effect of SSZ on the articular components of PD have been published.

Cyclosporine. Before 2010, data on the efficacy of CSA had been provided by 2 small RCT and some open-label studies. These data suggest that this drug can improve peripheral synovitis but has little or no effect on spondylitis and radiographic progression. No data on enthesitis and dactylitis were available at that time. Since then, only 1 study with CSA

used as a monotherapy in PsA has been published[12]. In that open-label, non-randomized, controlled trial, CSA alone (57 patients) was compared with adalimumab (ADA) alone (58 patients) and with ADA and CSA in combination (55 patients). At Month 12, the primary efficacy endpoint (PsARC response) was met by 65% of CSA-treated, 85% of ADA-treated, and 95% of combination-treated patients. Although the proportion of responders in the CSA group was significantly lower than in the other groups, the number of patients who responded to CSA alone was quite high. Dactylitis and enthesitis were present in only about 7–15 patients in each therapy arm. While most of the ADA-treated patients showed an improvement in these manifestations, only 28% (dactylitis) and 15% (enthesitis) of the CSA monotherapy patients responded to the treatment. On the basis of all existing evidence, it can be affirmed that CSA can improve peripheral synovitis but has no effect on the other articular manifestations of PD. However, as for the other synthetic DMARD, the level of evidence supporting these conclusions is low.

Combination therapies. The only RCT aimed at evaluating the combination of 2 synthetic DMARD in PsA was published in 2008[13]. That trial showed that adding CSA to MTX-unresponsive patients was better than adding placebo, although the only significant difference was the reduction of inflamed joints as detected by ultrasound. The combination MTX and LEF in PsA has never been tested in an RCT. A small experiment in 11 unresponsive patients in whom LEF was added to MTX showed only modest improvement in the mean value of the disease activity score[14].

As already reported in the MTX and CSA sections, 2 small open-label controlled trials on the combination of these 2 drugs with IFX and ADA, respectively, have been published[7,12]. In both studies, combination therapy was superior to monotherapy in improving peripheral synovitis, dactylitis, and enthesitis. However, because in the RESPOND trial the monotherapy arm was treated with MTX only, it cannot be excluded that the superiority of the combination therapy was entirely due to IFX. In contrast, in the CSA plus ADA trial, both drugs were singularly inferior to their combination, although the difference was less pronounced for ADA.

Interesting data on the longterm usefulness of concomitant MTX in patients with PsA treated with TNF-α inhibitors come from observational studies. Data from the NOR-DMARD and the DANBIO registers showed that concomitant MTX use did not lead to a better clinical response but was associated with a higher retention rate of TNF-α inhibitor therapy[15,16]. Finally, it should be mentioned that in the phase III trials of TNF-α inhibitors in PsA, concomitant MTX did not lead to better disease control. Although the existing evidence is insufficient to establish whether DMARD combination is indicated in PsA, concomitant MTX might at least increase the retention rate of TNF-α inhibitors.

Safety. Since 2010, no new safety signals in addition to those already known for the 4 synthetic DMARD have been reported. A systematic review of observational studies in patients with psoriasis has revealed that MTX is likely to increase the risk of liver fibrosis. The authors of that review suggested considering all patients taking this drug to be at risk of this adverse event, pending further research[17]. Another systematic review showed that liver function tests, procollagen-3 N-terminal peptide, and liver ultrasound have poor clinical utility in detecting MTX-induced liver fibrosis in patients with psoriasis, and that there are insufficient data to evaluate newer methods including Fibroscan[18]. In a 1-year prospective study on 225 patients with PsA, CSA alone or in combination with other immunosuppressive agents did not induce a reactivation of the viruses commonly tested in clinical practice[19].

Studies published from 2010 to 2014 confirm that MTX, SSZ, LEF, and CSA have moderate symptom-modifying effect on psoriatic synovitis. They do not seem to influence radiographic progression and they are likely to be ineffective on the other articular manifestations of PD. However, the evidence supporting these statements remains poor.

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