Management of Psoriatic Arthritis

Traditional Disease-Modifying Rheumatic Agents and Targeted Small Molecules

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KEYWORDS

• Traditional disease-modifying antirheumatic drugs • Small molecules
• Treatment psoriatic arthritis • Psoriatic arthritis

KEY POINTS

- Traditional disease-modifying antirheumatic drugs (DMARDs) remain first-line treatment for psoriatic arthritis in many centers.
- New targeted small molecules are alternative choices for patients that do not tolerate or do not respond to conventional DMARDs or tumor necrosis factor inhibitors.
- Additional research and drug development is needed to address unmet needs in the treatment of PsA.

INTRODUCTION

Traditional disease-modifying antirheumatic drugs (DMARDs) are the first line for the treatment of psoriatic arthritis (PsA) around the world.[1,2] Despite findings in several reviews and metaananalyses that demonstrated sparse high-quality evidence in support of the efficacy of these drugs in PsA,[3–6] they are still recommended as first choice for peripheral arthritis in published guidelines and recommendations.[7,8] Several factors may explain the paradox between evidence and clinical use, a practice not unique to PsA[9] and include:

1. The lack of large, well-designed clinical trials
2. The perception of many rheumatologists that DMARDs are effective at least in some patients
3. General knowledge and comfort with the side effect profiles of these agents

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4. The relatively low cost in most countries; particularly compared with biologics
5. The perception that delay in starting a biologic to determine if DMARDs are effective will not negatively impact function and quality of life.

Tumor necrosis factor inhibitors (TNFi) are very effective in the treatment of not only peripheral arthritis, but also other manifestations such as skin, enthesitis, dactylitis, and axial involvement as well, and greatly altered the expectations of patients and physicians on the long-term outcomes of this disabling disease.[5,6,10–12] With the increased understanding of immunopathogenesis of PsA, new therapeutic agents targeting different biologic pathways are in development or approved for psoriasis and/or PsA, such as the interleukin (IL)-12 and IL-23 inhibitor ustekinumab, IL-17 inhibitors secukinumab and ixekizumab, and the anti–IL-17R agent brodalumab.[13] In addition to biologics, novel targeted small molecules, orally available, are currently in clinical development for the treatment of psoriasis and PsA, including the phosphodiesterase 4 inhibitor apremilast and Janus kinase (JAK) inhibitors.[13] Targeted small molecules have theoretic advantages over biologics: they are less complex, easier and cheaper to produce, can be administrated orally, have broader target selectivity, and inhibit intracellular signaling.[14] In this review, we focus on the efficacy and safety of traditional DMARDs and new targeted small molecules for the treatment of PsA.

TRADITIONAL DISEASE-MODIFYING RHEUMATIC AGENTS

The DMARDs methotrexate (MTX), sulfasalazine (SSZ), leflunamide, and cyclosporine are prescribed in PsA. High-quality experimental evidence to support the use of these agents in PsA is scarce. Studies that address the efficacy and safety of DMARDs in PsA are summarized in **Table 1**. We focus attention in more recent clinical trials and observational studies not included in most of the systematic reviews, with special attention to reports that provide evidence to support the efficacy and safety of traditional DMARDs in PsA therapy.

Methotrexate

Since 2003, 2 randomized, control trials (RCT) have been published.[15,16] In the first, Scarpa and colleagues[15] randomized 35 patients with early oligoarthritis (<12 weeks' disease duration) to nonsteroidal antiinflammatory drugs (NSAIDs) alone or NSAIDs plus MTX for 3 months; thereafter, all patients continued with the combination. A significant improvement was noted at 3 and 6 months compared with baseline in both groups. However, at 3 months, patients on the MTX/NSAIDs combination had a significantly better joint response than patients with NSAIDs alone, although no differences were noted between the 2 groups at 6 on MTX/NSAIDs. In this study, patients with early oligoarthritis demonstrated an improved response to MTX compared with NSAIDs, and that delay of 3 months in the administration of MTX did not significantly lower treatment response at 6 months, although differences in radiographic progression were not addressed in the study.

In the Methotrexate In Psoriatic Arthritis (MIPA) trial, 221 patients were randomized to MTX (target dose 15 mg/wk) or placebo and outcomes assessed at 6 months with the PsA response criteria (PsARC) as the primary one.[16] At 6 months, no differences in any of the individual outcomes (PsARC, American College of Rheumatology 20/50/70 Response [ACR20/50/70], Disease Activity Score C-reactive protein) were noted, except for patient global and physician global assessments, which were higher in the MTX compared with the placebo group.[16] The results of this trial indicate that MTX is not effective for PsA, but several flaws in this trial emerged. First, despite the study's short duration, only 65% and 69% of patients in the active and placebo