Are DMARDs effective for rheumatologic diseases besides rheumatoid arthritis?

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Evidence-based answer

It's unclear whether disease-modifying antirheumatic agents (DMARDs) as first-line therapy in nonrheumatoid rheumatologic diseases are effective because the question has not been studied. As second-line therapy, the use of some DMARDs appears to be beneficial for patients with psoriatic arthritis (strength of recommendation [SOR]: **A**, based on systematic reviews of good-quality randomized controlled trials) and ankylosing spondylitis (SOR: **B**, based on systematic reviews of moderate quality trials). Data on the safety and efficacy of DMARDs as second-line therapy for other arthritic conditions is limited (SOR: **C**, based on small prospective cohort trials).

Clinical commentary

There are many options, but remember the risks

Traditionally, nonsteroidal anti-inflammatory agents (NSAIDs) have been the mainstay of treatment for rheumatologic disorders other than rheumatoid arthritis. Methotrexate has been used in psoriatic arthritis because it also controls the skin disorder; sulfasalazine has been used in arthritis associated with inflammatory bowel disease, as it helps the bowel disorder itself. However, little evidence shows a definitive benefit for the arthritis.

The advent of tumor necrosis factor (TNF) blockers has changed the direction of research in this area; these agents are being used more and more in inflammatory arthritides. While staying up to date on the TNF antagonists, it's important to remember the complications associated with them—particularly the increased risk of infections and increased propensity for neoplastic disorders. Consider those on TNF blockers as relatively immunosuppressed (number needed to harm [NNH]=59 for infection and 154 for malignancy).[1]

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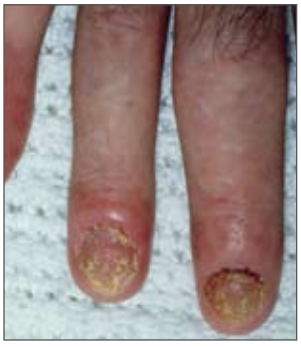
Psoriatic arthritis affecting the joints and nails



FAST TRACK

As second-line therapy, some DMARDs benefit patients with psoriatic arthritis and ankylosing spondylitis

Evidence summary

The use of DMARDs has become standard of care for rheumatoid arthritis, for both therapy and prevention of progression of this debilitating disease. However, the use of DMARDs in nonrheumatoid rheumatologic disease is still under investigation, and at this point, the use of DMARDs as first-line therapy is not recommended; however, second-line therapy with DMARDs is common.

For psoriatic arthritis, DMARDs are beneficial as a second-line therapy

A Cochrane systematic review identified 13 randomized controlled trials enrolling

FAST TRACK

A review of 54 studies found NSAIDs are still the preferred first-line therapy for psoriatic arthritis

a combined 1022 patients with psoriatic arthritis randomly assigned to receive a DMARD—methotrexate, sulfasalazine (Azulfidine), azathioprine (Imuran/Azasan), or etretinate (Tegison; no longer available in the US)—compared with placebo.[2] All agents were better than placebo; however, only 2 agents (parenteral high-dose methotrexate and sulfasalazine) had clinically important benefits for more than half the patients. The studies were too small to establish toxicity or to evaluate the other agents.

NSAIDs are still the preferred first-line therapy, concluded a recent publication on the treatment of psoriatic arthritis, which looked at 54 different studies; however, second-line therapy could include methotrexate, sulfasalazine, etanercept (Enbrel), infliximab (Remicade), cyclosporine, or combination therapy.[3] Sulfasalazine appeared to be clinically beneficial for peripheral psoriatic arthritis.

Etanercept vs placebo. An initial study (60 patients) of etanercept vs placebo among patients who were permitted to stay on methotrexate or prednisone showed a response rate of 87% vs 23% (*P*<.0001; number needed to treat [NNT]=1.56).[4]

Infliximab vs placebo. A study of infliximab vs placebo involving 104 patients had similar results, with good response in 65% vs 10% (NNT=1.81) at 16 weeks; infliximab also inhibited radiographic progression by 22%.[5]

Cyclosporine. Although it is effective, reserve cyclosporine for patients who do not improve on other regimens, because of its nephrotoxicity.[3]

DMARDs show some benefit in treating ankylosing spondylitis

Two recent Cochrane systematic reviews on ankylosing spondylitis examined the use of sulfasalazine and methotrexate as second-line agents.[6,7] Eleven trials were included in the sulfasalazine analysis, with a total of 895 patients. Sulfasalazine demonstrated some benefit in reducing erythrocyte sedimentation rates (ESRs) and morning stiffness, but there was no evidence that the drug reduced pain or improved physical function, spinal mobility, or rate of enthesitis. Sulfasalazine was well tolerated and may be useful in early mild disease for patients with peripheral arthritis and high ESRs. On the other hand, evidence was insufficient to determine whether methotrexate benefited patients with ankylosing spondylitis.

In other trials, infliximab and etanercept showed good potential for benefit in treating ankylosing spondylitis.

One study of infliximab vs placebo showed 61.2% vs 19.2% patients with good clinical benefit at 24 weeks and only mild or moderate adverse events (*P*<.001; NNT=2.38).[8]

Similarly, a smaller study (84 patients) showed that 60% of patients on etanercept vs 20% on placebo had good clinical benefit at only 12 weeks (*P*<.001, NNT=2.5).[9]

For other rheumatic diseases, studies are mixed

Due to cyclosporine's toxicity, less toxic DMARDs are being evaluated to replace it for treatment of other rheumatic diseases. A recent randomized controlled trial of 100 patients with antineutrophil cytoplasmic antibody–associated systemic vasculitis showed methotrexate may be able to replace cyclosporine for both induction of remission (methotrexate=89.8% vs cyclosporine=93.5%; *P*=.041) and maintenance of remission (69.5% vs 46.5% at 18 months; *P*=.023).[10]

Initial trials on other rheumatic diseases have been small and have had varied results. There are mixed studies on the effectiveness of adding methotrexate to corticosteroids for giant cell arteritis.[11,12]

There has been no evidence of efficacy for the new TNF antagonists in either a small study on Sjögren's syndrome (n=14)[13] or a larger study on Wegener's granulomatosis (n=180).[14]

The studies for use of DMARDs in lupus or scleroderma are of limited quality.

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Recommendations from others

The Italian Society for Rheumatology consensus guidelines recommends TNF antagonists be considered in active psoriatic arthritis resistant to (a) NSAIDs, (b) at least 2 local steroid injections, and (c) at least 2 conventional DMARDs for patients with peripheral arthritis or enthesitis. They also recommend TNF antagonists be considered for psoriatic spondylitis resistant to NSAIDs.[15]

The Assessment in Ankylosing Spondylitis (ASAS) International Working Group and the European League Against Rheumatism (EULAR) recommendations for the treatment of ankylosing spondylitis, based on a systematic review of the literature and expert opinion, indicate that:

- There is good evidence for using NSAIDs and COX-2 inhibitors for symptomatic treatment.
- Conventional DMARDs are not well supported.
- TNF antagonists show a large benefit in both pain and function.

The ASAS/EULAR recommendation indicate that there is no evidence that any of these treatments actually modify the disease progression.[16] ■

Acknowledgments

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FAST TRACK

For Sjögren's syndrome, lupus, giant cell arteritis, and scleroderma, study results are mixed or limited

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