



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Non-biologic DMARDs
-May 2016-



Background:

The IHS National Pharmacy & Therapeutics Committee (NPTC) discussed non-biologic Disease-modifying Antirheumatic Drugs (DMARDs) in the treatment of Rheumatoid Arthritis (RA) at the May 2016 meeting. The medications addressed were methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, azathioprine, and combination therapy. Prior to the review, the National Core Formulary (NCF) included methotrexate, sulfasalazine, and hydroxychloroquine. Having considered the clinical data, IHS procurement and utilization trends, and pharmacoeconomic analyses, the **NPTC added leflunomide** to the NCF.

Discussion:

RA is an autoimmune condition that affects 0.6-1% of the American population (Helmick, 2008). Prevalence rates in American Indians and Alaska Natives (AI/AN) however, although not available for all populations, are considerably higher, with the highest rates in the Pima (3.2% in men, 7% in women [DelPuente, 1989]) and Chippewa (4.8% in men, 8.2% in women [Harvey, 1981]) populations. Data exist showing that RA is also more severe in AI/AN populations, with younger age of onset and more frequent use of combination therapies and corticosteroids for adequate control of disease (Peschken, 2010). Extra-articular manifestations of RA (e.g., nodules, Sjogren's syndrome, anemia of chronic disease, cardiopulmonary disease) effect up to 40% of patients, are common early in RA disease and are related to worse outcomes, including functional impairment and mortality (Young, 2007). Available treatment options include lifestyle changes, non-biologic DMARDs, biologic DMARDs, miscellaneous DMARDs and kinase inhibitors, combination regimens and surgery. Both the 2015 American College of Rheumatology (ACR) and the 2013 European League Against Rheumatism recommendations encourage early pharmacological treatment to a target of remission (Jasvinder, 2015; Smolen, 2013).

Methotrexate (MTX) is a folic acid antagonist. It inhibits the synthesis of DNA, RNA and proteins by irreversibly binding to dihydrofolate reductase. It interacts with numerous drugs and has a large number of potential adverse reactions. A supplement of folic acid 1mg daily is recommended in conjunction with MTX therapy to decrease the risk of toxicities (Kremer, 2014). A Cochrane review in 2014 evaluated MTX use vs. placebo. A clinically important and statistically significant improvement was found with MTX use in the ACR 50 score, a measure based on ACR criteria of at least a 50% improvement in the number of tender or swollen joints and other outcomes such as pain and disability (Absolute Treatment Benefit [ATB] 15%, 95% CI: 8% to 23%). There was also a statistically significant improvement in physical function on a scale of 0-3 at 12-52 weeks (Mean Difference [MD] -0.27, 95% CI: -0.39 to -0.16). Methotrexate group patients, however, were twice as likely to discontinue the study (16% vs. 8%). No patients in either group met remission criteria (Lopez-Olivio, 2014).

Sulfasalazine (SSZ) has been considered as a RA treatment since the 1940s. Its active metabolite, 5-aminosalicylic acid, is thought to modulate local chemical mediators of the inflammatory response, especially leukotrienes (Weisman, 2014). A 2010 Cochrane review considered 6 trials comparing SSZ with placebo. A statistically significant benefit was found with SSZ for tender and swollen joints and pain. Placebo patients were 4 times more likely to withdraw due to lack of efficacy, while SSZ patients had significantly higher withdrawals due to adverse reactions (OR=3.0) (Suarez-Almazor, SSZ, 2010).

Hydroxychloroquine (HCQ) is an antimalarial agent with an unclear mechanism of action in treating RA. A 2010 Cochrane review looked at 4 studies comparing antimalarial agents with placebo. A statistically significant benefit was found for HCQ (Standardized Mean Differences [SMD] for outcomes -0.33 to -0.52). Overall withdrawals due to lack of efficacy were significantly higher in the placebo group while there was no difference in withdrawals due to toxicity (Suarez-Almazor, Antimalarials, 2010).

Leflunomide (LFN) is a newer treatment for RA, approved in 1998. It is an isoxazol derivative with an active metabolite, A77 1726, which inhibits the enzyme dihydro-orotate dehydrogenase. This activates the rate-limiting step for de novo synthesis of pyrimidines, reducing the proliferation of activated autoimmune T-lymphocytes and resulting in decreased autoimmune response and synovial inflammation (Fox, 2015). A Cochrane review in 2010 evaluated 33 trials comparing LFN monotherapy or in combination with another DMARD with placebo. With regard to ACR 20 improvement criteria, there was a 28% absolute difference in improvement in LFN compared to placebo. Withdrawals due to adverse events were 10% greater, but the study concluded that LFN appeared to improve all clinical outcomes and delay radiologic progression at 6 and 12 months compared to placebo (Osiri, 2010).

Azathioprine was originally a post-transplant anti-rejection drug that was later used to treat RA. It has metabolites that are incorporated into replicating DNA and halt replication, and it also blocks the purine synthesis pathway. A Cochrane 2009 review looked at 3 small trials comparing azathioprine with placebo, and while there was a statistically significant benefit found for joint scores (standardized weighted MD - 0.98, 95% CI: -1.45 to -0.50), there were significantly higher withdrawals due to adverse reactions (OR=4.56, 95% CI: 1.16 to 17.85). The reviewers concluded that other drugs should be used before azathioprine in treating RA (Suarez-Almazor, 2009).

DMARDs are commonly used in combination. The 2007 MASCOT study was a double-blind, placebo-controlled, multi-phase study comparing patients who had inadequate response to SSZ alone randomized to regimens of SSZ plus MTX, SSZ plus placebo, or placebo plus MTX. At 18 months, the combination group had more favorable disease activity results, though it was not statistically significant (Capell, 2007). The 2014 tReach trial was a single-blinded trial randomizing patients to one of 3 arms: (1) MTX + SSZ + HCQ + intramuscular glucocorticoids (GC), (2) MTX + SSZ + HCQ + oral GC taper, (3) MTX + oral GC taper. At 12 months, functional improvement was seen in all 3 groups though there were no significant differences, and no differences in disease activity score reduction found between regimens. The triple therapy group, however, attained the reduction sooner (De Jong, 2014). Additionally, a Cochrane 2010 review compared MTX alone to combinations with other non-biologic DMARDs. No significant advantage was found for DMARD naïve patients in the MTX combination group versus monotherapy (Katchamart, 2010).

Findings:

Clinical studies and meta-analyses demonstrate that methotrexate, sulfasalazine, hydroxychloroquine and leflunomide are all effective options in the treatment of RA. Agency-specific procurement and utilization data support routine use of LFN across the IHS.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the [NPTC website](#).

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