Background:
Rheumatoid arthritis (RA) is a multisystem inflammatory disorder of unknown etiology characterized by chronic destructive synovitis. The prevalence of rheumatoid arthritis in the U.S. Caucasian population is 0.6 – 1% (Helmick, 2008). Prevalence rates in American Indians and Alaska Natives (AI/AN), 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) affect up to 40% of patients, are common in early RA disease and are related to worse outcomes, including functional impairment and mortality (Young, 2007). Effective treatment of rheumatoid arthritis and extra-articular manifestations are a priority in the Indian Health Service (IHS) for maintenance of functional status and of overall health of patients with this condition. As a result of this clinical review, the IHS National Pharmacy & Therapeutics Committee (NPTC) added either adalimumab or etanercept in consultation with a rheumatologist to the National Core Formulary.

Discussion:
Effective strategies for the treatment of RA include non-biologic disease-modifying antirheumatic drugs (DMARDs), biologic agents, and newer “small molecule” agents such as tofacitinib.

Biologic agents are targeted therapies that interfere with specific inflammatory mediators or processes. The TNF (tumor necrosis factor) inhibitors, one class of biologic therapies, block the pro-inflammatory actions of TNF either through receptor binding or via monoclonal antibodies to TNF. The available TNF inhibitors include etanercept, adalimumab, infliximab, certolizumab and golimumab. Etanercept was the first biologic agent approved by the FDA for the treatment of RA in 1998. (Lexicomp online)

Numerous studies show the superiority of biologic agents over placebo for the treatment of RA (Aaltonen, 2012). Although head-to-head studies are limited, a 2009 Cochrane analysis reviewed studies of indirect comparisons and found biologic agents to be equivalent in efficacy and adverse effects to one another. However, TNF inhibitors were associated with lower withdrawal rates than other biologics (Singh, 2012).

The American College of Rheumatology recommends a “treat to target” approach to RA, with the target being remission of disease (Singh, 2015). Strategies for achieving this include:
1) monotherapy with a DMARD, usually methotrexate, for low disease activity
2) combination therapy with two or three DMARDs, preferably including methotrexate, for moderate to severe disease activity
3) combination therapy of a DMARD, preferably methotrexate, with a biologic agent or newer small molecule for moderate to severe disease activity

Other rheumatologic disease societies (EULAR, Canadian, NICE) make similar recommendations for the treatment of RA (Bykerk, 2012; Smolen, 2015).

The high cost of biologic agents remains a significant impediment to their use in certain populations and a major contributor to the high cost of medical care for RA (Erickson, 2015). Several studies from 2012 to 2015 show that combination DMARD therapy is as effective as the combination of a DMARD plus a TNF inhibitor (Van Vollenhaven, 2012; O’Dell, 2013; Scott, 2015; Graudel, 2015). However, adherence to combination DMARD therapy is poor, with rates less than 20% at one year. This is attributed to problems with tolerance and with the large number of pills required on a daily basis (Bonafede, 2015).
Other studies show improved outcomes when comparing biologic agents with traditional DMARDs. A meta-analysis estimating the impact of biologic therapy on patients with RA found that treatment with a biologic led to clinically-relevant greater improvement in physical function than treatment with non-biologic DMARDs (Callhoff, 2013). A study evaluating biologic agents with combination therapy for patients with inadequate response to conventional DMARDs found that all biologic agents had significantly higher odds of achieving ACR 20/50/70 (conventional improvement measures in RA studies) (Orme, 2012). For these reasons, addition of a biologic agent to DMARD therapy in moderate-to-severe RA remains the commonly accepted practice of rheumatologists, with TNF inhibitors the most common initial biologic agents used (Glauser, 2014).

In addition to problems with adherence to a combination DMARD approach, there are other factors limiting the use of combination DMARD therapy in the AI/AN population. The severity of disease in this population frequently requires step-up therapy from combination DMARDs to strategies that include a biologic agent. Additionally, the co-existence of high rates of metabolic syndrome in many Native populations (Schumacher, 2008) limits the optimal use of methotrexate, the cornerstone of RA treatment, secondary to its potential for liver toxicity (Schmauk, 2014).

**Findings:**

Rheumatoid arthritis affects AI/AN disproportionately and is a major source of morbidity with studies estimating that indirect costs of RA are at least equal to, if not more than, the direct costs for treatment (Cardarelli, 2012; Bansback, 2009). The agents currently available on the National Core Formulary are often effective for the treatment of RA. However, the greater severity of disease in this population, as well as the limitations of use of maximal non-biologic DMARD therapy highlight the need for additional agents for RA. There is widespread acceptance and use of biologic agents in patients with RA, and all rheumatology societies include them in their standard-of-care guidelines. Although all biologic agents have similar efficacies and adverse effects, adherence to therapy has been shown to be improved with TNF inhibitors.

Based on the clear clinical efficacy of TNF inhibitors in the treatment of RA, and the need for more effective RA therapies in the AI/AN population, the NPTC added either etanercept or adalimumab to the National Core Formulary, to be used in consultation with a rheumatologist. The Indian Health Service, in cooperation with the University of New Mexico, offers an ECHO Rheumatology Clinic, providing additional supports for RA treatment. Further details can be obtained at IHSecho@salud.unm.edu.

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.

**References:**