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

Background:
Rheumatoid arthritis (RA) treatment can be grouped into two different classes; traditional non-biologic disease modifying antirheumatic drugs (DMARDs) and biologic DMARDs which comprise both the tumor necrosis factor (TNF) inhibitors and miscellaneous non-TNF biologic DMARDs including the Janus Kinase (JAK) inhibitors. The purpose of this Formulary Brief is to summarize the clinical findings from the miscellaneous non-TNF biologic DMARDs review, which consisted of abatacept, anakinra, rituximab, tocilizumab and tofacitinib. As a result of this pharmacotherapeutic analysis and IHS usage and procurement trends review, **no modifications were made** to the IHS National Core Formulary (NCF).

Discussion:
The American College of Rheumatology (ACR) published RA guidelines in 2015 with a treat to target goal and recommends that patients who have established moderate-to-severe RA and have failed non-biologic DMARDs be treated with any of the following; combination non-biologic DMARDs, TNF inhibitors, or non-TNF biologics (specifically excludes anakinra) or Janus Kinase (JAK) inhibitors[1].

Abatacept (Orencia®) is a soluble fusion protein, inhibiting T-cell activation by binding to CD80 and CD86 on antigen presenting cells, reducing autoantibody formation and pro-inflammatory cytokines[2]. Abatacept is indicated for moderate-to-severe RA in adults either as monotherapy or in combination with methotrexate (MTX) or other non-biologic DMARDs[2]. It can be administered as an IV infusion or subcutaneously. Common adverse drug reactions (ADRs) include nasopharyngitis, URI, cough, back pain, dyspepsia, UTI, rash and infusion-related reactions including headaches, dizziness and hypertension[2]. Abatacept can increase the risk of serious and potentially fatal infections, lymphoma, lung cancer, and COPD exacerbations[2].

Anakinra (Kineret®) is a recombinant human interleukin-1 receptor antagonist that prevents degradation of cartilage and bone resorption[3]. It is indicated in adults with moderate-to-severe RA who fail one or more DMARDs and is given as a daily SC injection with MTX or other non-TNF biologic DMARDs[3]. Common ADRs are headaches, infections, injection site reactions, arthralgias and nasopharyngitis[3]. Serious infections include pneumonia, osteomyelitis, cellulitis, bursitis, herpes zoster and neutropenia. Patients with asthma are at an increased risk of infections[3].

Rituximab (Rituxan®) is a chimeric and human monoclonal CD20 antibody causing B-lymphocyte depletion reducing progression of RA and structural damage[4]. It is approved for moderate-to-severe RA in adults and is used in combination with MTX in those who fail TNF inhibitors[4]. Rituximab is given as an IV infusion and has a Black Box warning for fatal infusion reactions, which happen most frequently with the first infusion[4]. Other Black Box Warnings include mucocutaneous reactions, progressive multifactorial leukoencephalopathy and Hepatitis B reactivation[4]. The most common ADRs with rituximab are peripheral edema, hypertension, fever, fatigue, chills, headaches and neuropathy[4].

Tocilizumab (Actemra®) is a humanized recombinant IgG1k monoclonal antibody inhibiting IL-6 receptors thus leading to a reduction of cytokines and acute phase reactant production[5]. Tocilizumab is indicated in adults with moderate-to-severe RA who fail one or more DMARDs and is given IV every 4 weeks or SC weekly[5]. Tocilizumab carries a Black Box Warning for fatal infections including tuberculosis, invasive, fungal, bacterial, viral and protozoal infections[5]. Common serious infections are pneumonia, cellulitis, UTI, diverticulitis, herpes zoster, upper respiratory infections and nasopharyngitis[5]. Other serious ADRs include neutropenia, thrombocytopenia, increased ALT and hyperlipidemia[5].

Tofacitinib (Xeljanz®) prevents cytokine growth factor mediated gene expression and intracellular activity of immune cells and B cells by inhibiting JAK enzymes[6]. It is an oral, twice-daily formulation approved for adults with moderate-to-severe RA as either monotherapy or in combination with non-biologic DMARDs[6].

It carries a Black Box Warning for increased risk of fatal infections (tuberculosis, invasive, fungal, bacterial, viral and protozoal) and malignancy[6]. Other serious ADRs include lymphocytopenia, neutropenia, lipid abnormalities, increase in PR interval and decrease in heart rate. Use caution in patients with cardiovascular disease, diverticulitis and interstitial lung disease[6].

Numerous Cochrane Library reviews performed between 2009-2015 evaluated the miscellaneous non-TNF biologic DMARDs and concluded that they were safe and efficacious[7-12]. Anakinra was shown to be relatively safe and modestly effective but less efficacious than etanercept and adalimumab[7-8]. Etanercept had fewer withdrawals due to ADRs than adalimumab, anakinra and infliximab[9]. Abatacept was modestly efficacious and safe but should not be used in combination with other biologic DMARDs[10]. Tocilizumab was beneficial in decreasing RA disease activity and improving function, however, it significantly increased cholesterol levels[11]. Rituximab with MTX was significantly more efficacious than MTX alone for improving the symptoms of RA and preventing disease progression[13]. Overall, biologic DMARDs had statistically significantly higher rates of serious infections, tuberculosis reactivation, total ADRs and withdrawals due to ADRs[12].

A 2014 meta-analysis showed tocilizumab to be superior to TNF inhibitors and comparable to MTX in reduction of pain, and anakinra to be less effective to other biologic DMARDs[14]. Additionally, tocilizumab was superior to rituximab and abatacept in a 2014 retrospective review by Pascat, et al.[15]. A 2015 review of 54 trials comparing the effects of biologic DMARDs showed that all were effective compared to placebo. When combined with a non-biologic DMARD, certolizumab had the greatest efficacy followed by tocilizumab then anakinra[16]. When used alone, TNF inhibitors (certolizumab, etanercept) were reported to be the most efficacious, followed by tocilizumab/abatacept[16].

Findings:
The miscellaneous biologic DMARDs are safe and effective and are indicated in treating adults with moderate-to-severe RA who fail initial non-biologic DMARD therapy. All of these therapies can be used as monotherapy or in combination with MTX (or other non-biologic DMARDs) except rituximab which should be used only in combination with MTX. There are several Black Box Warnings and disease-specific concerns that should be addressed prior to selecting a miscellaneous biologic DMARD. Non-biologic DMARDs remain the standard initial treatment for RA according to recent ACR guidelines. The IHS National Pharmacy & Therapeutics Committee concluded that miscellaneous non-TNF biologic DMARDs have a role in treating RA however declined to name a specific agent to the NCF.

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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