Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Inflammatory Bowel Disease***
-May 2018-

Background:

The National Pharmacy and Therapeutics Committee has not previously reviewed pharmacotherapy for Crohn's disease and ulcerative colitis, collectively referred to as Inflammatory Bowel Disease (IBD). The IHS National Core Formulary (NCF) currently lists the following medications commonly associated with use in IBD; sulfasalazine, prednisone, methotrexate and adalimumab. The NPTC reviewed the different classes of drugs and indications for IBD in addition to reviewing current guidelines. As a result of this clinical review, **no modifications were made to the NCF**.

Discussion:

It is estimated that 1.6 million people in the United States have IBD with associated healthcare costs of approximately $30 billion. A genetic predisposition coupled with an environmental trigger is felt to contribute to dysregulation of the immune system that leads to chronic inflammation and damage to the gastrointestinal tract. Ulcerative colitis (UC) is limited to inflammation of the mucosal layer involving the rectum and can extend proximally in a contiguous manner in the colon. Crohn's disease (CD) is characterized by transmural inflammation anywhere from mouth to anus in a patchy distribution that can lead to strictures and fistulas. Most patients with UC have a mild-moderate course with varying periods of remission or mild activity and 10-15% will experience an aggressive course. In CD, only 10% will experience a mild course, and 50% of patients will have surgery within 10 years of diagnosis. Severity of disease along with location determines IBD treatment options. The goal of treatment is to induce remission for improved quality of life and maintain remission to allow for mucosal healing which is felt to decrease cancer and surgery risk. Treatment consists of using medications that induce remission of the inflammation and then maintain remission.

There are five drug classes generally used for IBD: 5-aminosalicylic acids (5-ASA), antibiotics, corticosteroids, immunomodulators and biologics. Current guidelines for ulcerative colitis prefer a step-up approach beginning with combined topical and oral 5-ASA to induce remission of mild to moderate disease. Escalation to corticosteroids for non-responders is followed by adding an immunomodulator. Both patients requiring corticosteroids and non-responders are started on a biologic agent. The drug most successful in inducing remission is typically continued for maintenance of remission, although remission should not be maintained by corticosteroids. A step-up approach is also used in patients with Crohn's disease. Generally, induction requires a corticosteroid. A similar escalation with an immunomodulator followed by a biologic agent is employed. Most experts recommend indefinite treatment for maintenance of remission but data supporting this approach is limited.

Findings:

5-ASA: For distal mild-moderate UC disease, a rectal 5-ASA (mesalamine) preparation along with an oral 5-ASA drug (sulfasalazine or mesalamine) is indicated for induction of remission. Rectal 5-ASA can then be used for maintenance of remission. A similar strategy is used in extensive mild-moderate disease but an oral 5-ASA agent is often needed to maintain remission. There is a limited role for the use of 5-ASA in CD. Sulfasalazine is indicated for mild-moderate disease limited to the colon for induction of remission but not maintenance. These low-risk CD patients are typically just observed.

Corticosteroids: If 5-ASA therapy does not induce remission, the addition of a corticosteroid is recommended. For mild-moderate UC, budesonide-MMX is the preferred agent due to minimal corticosteroid-related side effects. The budesonide-MMX (multimatrix) formulation is a proprietary tablet coating designed to release budesonide to the entire colon with once-daily dosing. For low risk CD patients, budesonide CR is used for ileocecal disease. Patients with severe IBD symptoms will require prednisone. Corticosteroids should be tapered after 4 weeks of remission.

Immunomodulators: In UC, the thiopurines (azathioprine or 6-mercaptopurine) dosed by weight should be started for maintenance of remission or when corticosteroid sparing. In severe disease, a thiopurine will often be initiated concurrently with a biologic (e.g., infliximab). Due to their slow onset of action, thiopurines are not generally used for induction of remission. Methotrexate is also an option for patients with CD. It is especially valuable for males who are Epstein-Barr Virus-negative due to the increased risk of lymphoma, and for those who cannot tolerate a thiopurine (~26% of patients). Immunomodulators are often tapered down after several years in patients with a higher risk of adverse drug effects such as lymphoma or recurrent skin cancers.

Biologics: IBD patients with persistent active disease in spite of using the medications above, and those with severe to fulminant disease, can be evaluated for an approved biologic agent. In UC, available biologics include the anti-tumor necrosis factor (anti-TNF) drugs adalimumab, golimumab, infliximab and the anti-integrin monoclonal antibody, vedolizumab. In CD, the use of anti-TNF drugs including adalimumab, certolizumab pegol and infliximab are generally followed by an anti-integrin agent (natalizumab, vedolizumab) or ustekinumab, the interleukin 12/23 inhibitor. There are restrictions in using natalizumab for induction and maintenance of remission due to an association with progressive multifocal leukoencephalopathy. Currently, three biosimilar agents are approved for use in IBD: infliximab-dyyb (Inflectra®), infliximab-abda (Renflexis®), adalimumab-atto (Amjevita®). Of note, etanercept (Enbrel®) has not been shown to be effective in IBD.

Antibiotics: Metronidazole and ciprofloxacin are most often used for CD with abscess and fistulas. They are also used post-operatively to decrease recurrence, and occasionally for disease limited to the colon.

Conclusions:

IBD is a chronic disease of the intestine that causes significant morbidity in patients. Guidelines for treatment continue to evolve as the pathophysiology of the disease is better understood and as newer biologic agents become available for treatment. Given that guideline-recommended, standard of care treatments are currently available on the NCF and noting a low prevalence of IBD diagnoses in the IHS patient population, the NPTC felt no additional medications were warranted on the NCF at this time.

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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