INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Inflammatory Bowel Disease***
-January 2023-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of Inflammatory Bowel Disease (IBD) agents. The NPTC reviewed the evidence and most recent American[1-3], British[4-6], and European[7-8] guidelines for treating Ulcerative Colitis (UC) and Crohn Disease (CD). For each condition, the guidelines provide recommendations for 4 clinical situations: both induction of remission and maintenance of remission in both mild-moderate and moderate-severe symptoms. Following clinical review and analysis, the NPTC voted to **ADD mesalamine (any once-daily oral formulation)** and **ADD either azathioprine or 6-mercaptopurine** to the National Core Formulary (NCF), which already includes adalimumab, methotrexate, prednisone and sulfasalazine. The NPTC also voted to **REMOVE the rheumatology consultation requirement** for adalimumab.

Discussion:

5-ASA (mesalamine) drugs work as topical anti-inflammatories. These are first-line to induce and maintain remission in mild-moderate UC. Formulations target specific areas of the colon: suppository for proctitis, enema for colon distal to the splenic flexure, and oral formulations for the entire colon. Newer oral formulations offer the convenience of once daily dosing. The prodrug sulfasalazine is broken down by colonic bacteria into 5-ASA and sulfapyridine, which is systemically absorbed and may cause side effects. Guidelines include it as a second-line option for induction of remission in CD.[3]

Budesonide is a topical, minimally absorbed steroid recommended as second-line for mild-moderate UC and first-line for mild-moderate CD. Formulations target specific areas of the colon: foam for proctosigmoiditis, older oral formulations for ileocecal CD, and multi-matrix (MMX) for the entire colon. Evidence is of low quality except for MMX induction of remission in mild-moderate UC.[9] Though often used for asthma maintenance, budesonide is ineffective for maintenance of remission in IBD.

Conventional steroids can induce remission at any level of severity, but due to systemic side effects are not first-line for mild-moderate UC.

Thiopurines (azathioprine, 6-mercaptopurine) may be used as monotherapy for maintenance or as an add-on therapy for induction. Combined with steroids, they may improve effectiveness or allow steroid-sparing. Combined with TNF inhibitors they may improve effectiveness and limit immunogenicity. Due to potential for hepatotoxicity, cytopenia, cholestasis, and pancreatitis, follow protocols for dose titration and lab monitoring. Prior to initiating treatment, obtain TPMT phenotypic testing and consider genotypic testing for NUDT15. Variants of these genes can dramatically reduce metabolism of thiopurines.

Methotrexate (MTX) is not useful for UC. In CD, combined with TNF inhibitors, MTX may improve effectiveness and limit immunogenicity, but this has only been shown with IM formulations.[10-11] Requires lab monitoring.

Biologics and small molecules are recommended second-line after steroid/thiopurines for mod-severe UC and CD, but may be initiated earlier in severe cases. After induction with a biologic, guidelines disagree regarding switching to thiopurines or MTX for maintenance vs. continuing the same biologic. Most biologics require IV administration, which most IHS care facilities cannot provide.

TNF inhibitors (infliximab, adalimumab, golimumab, certolizumab) have boxed warnings for serious infections and malignancy. Pre-screen for TB, HIV, Hep B/C. Over time, patients may develop anti-drug antibodies that reduce drug effectiveness or autoantibodies that cause autoimmune diseases like vasculitis. These diseases usually resolve with drug cessation. Co-administration with thiopurines or MTX can limit this immunogenicity.[12] Golimumab (approved for UC) and certolizumab (approved for CD) are administered subcutaneously, but there is no evidence of superiority vs. adalimumab. Adalimumab is administered subcutaneously, approved for both UC and CD, and likely to have biosimilars approved later this year.

Integrin antibodies (natalizumab, vedolizumab) work by preventing entry of leukocytes into affected areas, so there is less concern for systemic immunosuppression. Natalizumab, approved for CD, was originally approved to treat multiple sclerosis, and requires periodic testing for JC virus antibodies to prevent progressive multifocal leukoencephalopathy. Vedolizumab, which targets more specific integrins, doesn't require JC virus testing.[13] It is approved for both UC and CD.

The only head-to-head DB RCT of biologics for UC randomized 769 adults with moderate-severe UC to either vedolizumab or adalimumab. More patients reached clinical remission at week 52 (the primary outcome) in the vedolizumab group than in the adalimumab group (31.3% vs. 22.5%, *p*=0.006). On the other hand, fewer patients reached corticosteroid-free clinical remission at week 52 (a second secondary outcome) in the vedolizumab group than in the adalimumab group (difference, −9.3 percentage points; 95% CI, −18.9 to 0.4). These contradictory results cast uncertainty on whether vedolizumab is more efficacious than adalimumab.[14]

IL-12/23 antibodies (ustekinumab, risankizumab): Risankizumab was recently approved for CD. Ustekinumab, approved for both UC and CD, had statistically identical outcomes vs. adalimumab in the only head-to-head trial for CD.[15]

Janus kinase inhibitors (tofacitinib): Tofacitinib, approved for UC, offers the convenience of oral dosing. Boxed warnings include serious infections, malignancies, major adverse cardiac events, venous and arterial thromboses, and mortality.

Findings:

The addition of oral, once-daily mesalamine and a thiopurine (either azathioprine -OR- 6-mercatopurine) offer IHS clinicians both first- and second-line options named to the NCF for each clinical scenario of IBD:

Formulary Options	**Ulcerative Colitis**				**Crohn**			
	Mild-Mod		Mod-Severe		Mild-Mod		Mod-Severe	
	Induction	Maintain	Induction	Maintain	Induction	Maintain	Induction	Maintain
1st line	Mesalamine	Mesalamine	Prednisone	Thiopurine	Prednisone	Observe	Prednisone +/- MTX or thiopurine	Thiopurine Or MTX
2nd line	Prednisone	Thiopurine	Adalimu-mab	Adalimu-mab	Sulfasala-zine	Thiopurine	Adalimumab +/- MTX or thiopurine	Adalimumab +/- MTX or thiopurine

Despite these additions, the NPTC recognizes that moderate-severe IBD can be exceptionally challenging to treat and that many of these patients will require therapeutics beyond the NCF. The NPTC looks forward to upcoming results from head-to-head trials of current and new therapeutics.

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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