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IMMUNO-MODULATORS IN INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is an idiopathic disease caused by a dysregulated immune response to host intestinal microflora. The two major types of inflammatory bowel disease are ulcerative colitis (UC), which is limited to the colonic mucosa, and Crohn disease (CD), which can affect any segment of the gastrointestinal tract from the mouth to the anus, involves "skip lesions," and is transmural. There is a genetic predisposition for IBD, and patients with this condition are more prone to the development of malignancy.

The two goals of therapy are the achievement of remission (induction) and the prevention of disease flares (maintenance). There are several studies, primarily involving anti-TNF agents (and occasionally immune modifiers); that have shown that the elimination of inflammation (as demonstrated by endoscopic and histologic criteria) results in a decrease in the rate of surgery, the use of corticosteroids, and the rate of hospitalization.

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The immune-modifying agents are used if corticosteroids fail or are required for prolonged periods for milder disease; they can be used up front for moderate and severe disease. Historically, anti-TNF agents have been administered when Crohn disease has been unresponsive to steroids and immunosuppressants. Here are the few newly used immune modifying drugs used for the management of IBD.

Thiopurine agents

The American Gastroenterological Association (AGA), in accordance with the US Food and Drug Administration (FDA), recommends that patients undergo assessment of the thiopurine methyltransferase (TPMT) genotype or phenotype before starting therapy with AZA or 6-MP. Individuals who have low enzyme activity or are homozygous deficient in the TPMT muation are at risk of very severe leukopenia, with potential septic complications, and may not be good candidates for therapy with these drugs.

Janus kinase (JAK) inhibitor

The oral JAK inhibitor tofacitinib (Xeljanz) has been approved for the treatment of moderate to severe ulcerative colitis. Unpublished studies in the package insert show an induction of remission in 15% to 20% of patients within 8 weeks; at 1 year, maintenance of remission was

demonstrated in approximately 35% of patients. The side-effect profile of tofacitinib is very similar to that of mercaptopurine and azathioprine, with the additional concern for elevations of cholesterol. Like the above immune modulators, tofacitinib is associated with an increase in malignancies. Strong inhibitors of CYP3A4 (eg, clarithromycin) can increase serum concentrations of tofacitinib, while inducers of CYP3A4 (eg, rifampin) can decrease serum concentrations of tofacitinib. Tofacitinib should not be used with other biologic agents or with immunosuppressant drugs such as azathioprine or mercaptopurine. Live vaccines should be avoided.

Anti-TNF-alpha monoclonal antibodies

Infliximab

Infliximab (Remicade) is an anti-TNF-alpha monoclonal antibody that is administered by infusion for the treatment of Crohn disease. Infliximab is FDA approved for both ulcerative colitis and Crohn disease; it appears to have a higher efficacy rate in Crohn disease. Infliximab is generally administered as 3 separate infusions of 5 mg/kg for the induction of remission of moderate to severe IBD at weeks 0, 2, and 6, followed by infusions every 8 weeks for maintenance of remission. Vande Casteele et al found that targeting the trough concentrations of infliximab to levels of 3-7 μg/mL results in a more efficient use of this agent in patients with IBD.

Adalimumab, certolizumab,golimumab

Other anti-TNF agents include adalimumab (Humira), which is given by subcutaneous (SC) injection every 2 weeks after a loading dose of 6 injections over 4 weeks ; certolizumab pegol (Cimzia), which is given by SC injection every 4 weeks (only approved for Crohn diesase); and golimumab (Simponi), which is given by subcutaneous (SC) injection every 4 weeks after two loading doses (only approved for ulcerative colitis).

Natalizumab

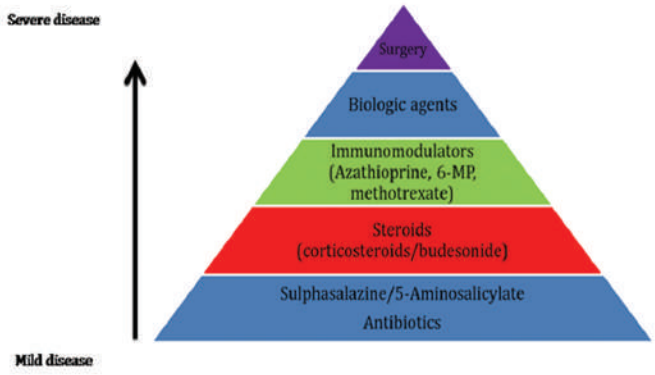
Natalizumab (Tysabri), an agent aimed at preventing the accumulation of lymphocytes in the diseased bowel by blocking the effects of both α4β7 integrin (gut specific) and α4β1 integrin (CNS specific), has been approved by the FDA, but it is only available through a restricted distribution program. Natalizumab is an intravenous medication that has shown efficacy in Crohn disease, but there have been three reports of progressive multifocal leukoencepha lopathy, a potentially fatal opportunistic viral infection. Risk is typically apparent in those with prior immunosuppressant exposure or with a duration of infusion for longer than 2 years. Patients in whom this agent is used should first be tested for John Cunningham (JC) virus, and they should be periodically tested for this during treatment.

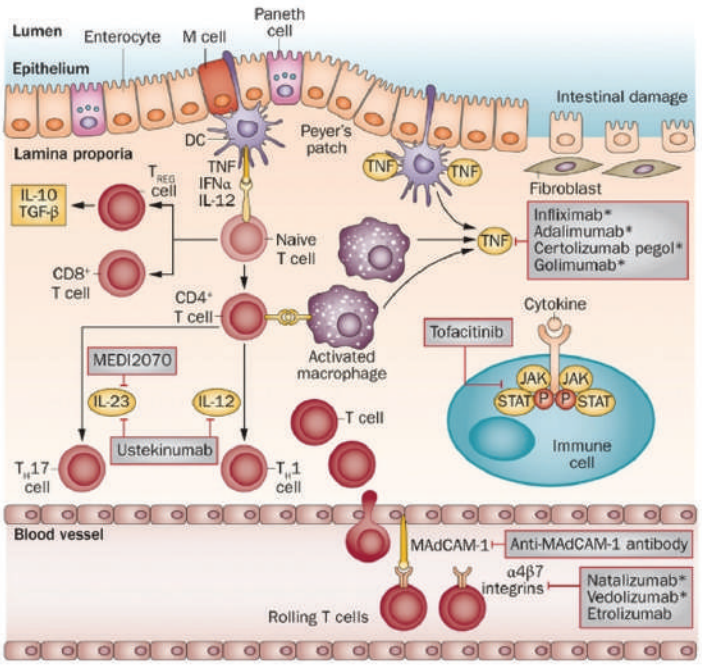
Vedolizumab

Vedolizumab (Entyvio), another integrin antagonist, is approved for Crohn disease and ulcerative colitis. It is specific for α4β7 integrin. Approval was based on several phase 3 clinical trials that simultaneously evaluated vedolizumab for both ulcerative colitis and Crohn disease and involved patients in nearly 40 countries. Among patients with Crohn disease who had a response to induction therapy with vedolizumab, 39.0% of those assigned to vedolizumab every 8 weeks were in clinical remission at week 52, compared with 21.6% assigned to placebo.

Ustekinemab

Ustekinemab (Stelara) is an antibody that blocks IL-12 and IL-23. It is used in patients with moderate to severe Crohn disease after failure with treatment using other agents. In clinical trials ustekinemab induced a clinical response of 34% by week 6 and remission in 21% by week 8 in patients with previously failed anti-TNF treatment. Results were better in patients who had treatment failure with immunosuppressants and corticosteroids, with response of 56% and remission and 40% at the same time periods. Remission was achieved in 53% of patients at 44 weeks.





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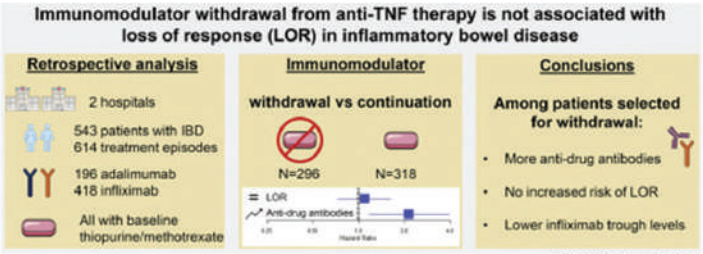


American Gastroenterological Association Guidelines (AGA) (2020)

In January 2020, the American Gastroenterological Association (AGA) released their recommendations on the medical management of adult outpatients with moderate to severe ulcerative colitis (UC) and hospitalized adult patients with acute severe UC (ASUC). [132] The focus of the guidelines is on immunomodulators, biologic agents, and small molecules for induction and maintenance of remission (for moderate to severe UC) and reducing the risk of colectomy (for ASUC).

Adult Outpatients With Moderate-Severe UC

The AGA makes a strong recommendation for using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment.

For patients who are naïve to biologic agents, the AGA recommends that tofacitinib only be used in the setting of a clinical or registry study (no recommendation). (Updated FDA recommendations [07/26/2019] on indications for use of tofacitinib in UC recommends its use only after failure of, or intolerance to, tumor necrosis factor-alpha [TNFα] antagonists.)

Conditional recommendations

For adult outpatients with moderate-severe UC who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab, rather than adalimumab, for induction of remission.

In adult outpatients with moderate-severe UC with previous exposure to infliximab, particularly those with primary nonresponse, the AGA suggests using ustekinumab or tofacitinib, rather than vedolizumab or adalimumab, for induction of remission.

In adult outpatients with active moderate-severe UC, the AGA suggests against using thiopurine monotherapy for INDUCTION of remission. However, in adult outpatients with moderate-severe UC in remission, the AGA suggests using thiopurine monotherapy, rather than no treatment, for MAINTENANCE of remission.

In adult outpatients with moderate-severe UC, the AGA suggests against using methotrexate monotherapy, for induction or maintenance of remission.

In adult outpatients with active moderate-severe UC, the AGA conditionally suggests using biologic monotherapy (TNFα antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for INDUCTION of remission, whereas in those with moderate-severe UC in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNFα antagonists, vedolizumab or ustekinumab), rather than thiopurine monotherapy for MAINTENANCE of remission.

In adult outpatients with moderate-severe UC, the AGA suggests combining TNFα antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate, rather than biologic monotherapy or thiopurine monotherapy.

In adult outpatients with moderate-severe UC, the AGA suggests early use of biologic agents with or without immunomodulator therapy, rather than gradual step-up after failure of 5-aminosalicylates.

In adult outpatients with moderate-severe UC who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib, the AGA suggests against continuing 5-aminosalicylates for induction and maintenance of remission.

Hospitalized Patients With ASUC

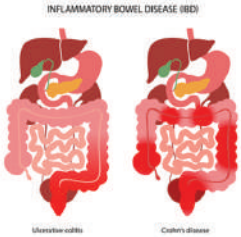
In hospitalized adult patients with ASUC refractory to intravenous (IV) corticosteroids that is being treated with infliximab, the AGA makes no recommendation on routine use of intensive versus standard infliximab dosing.

Conditional recommendations

In hospitalized adults with ASUC, the AGA suggests using an IV methylprednisolone dose equivalent of 40 to 60 mg/d rather than higher dose IV corticosteroids.

In hospitalized adults with ASUC without infections, the AGA suggests against adjunctive antibiotics.

In hospitalized adults with ASUC refractory to IV corticosteroids, the AGA suggests using infliximab or cyclosporine.



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