

# Pharmacotherapy for Moderate to Severe Inflammatory Bowel Disease: Evolving Strategies

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## Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are life-long inflammatory bowel diseases (IBDs) with a progressive course characterized by exacerbations and remissions.<sup>1,2</sup> The guiding principle of pharmacotherapy is to induce and maintain remission,<sup>1,2</sup> and selection of pharmacotherapy is based primarily on the severity of disease, and the patient's response to previous therapy.<sup>3</sup>

## Defining Moderate to Severe Disease

Composite instruments, such as the Mayo score in UC and the Crohn's Disease Activity Index (CDAI), were designed to assess disease activity;<sup>4</sup> however, they are often used, sometimes with modifications, to define moderate to severe IBD. For example, the Canadian Association of Gastroenterology (CAG) defines moderate to severe UC as a Mayo score of 6 to 12.<sup>5</sup> The American College of Gastroenterology (ACG) includes a CDAI score of 220 to 450 in the definition of moderate to severe CD (Table 1<sup>1,2,6-8</sup>).<sup>1</sup> In clinical practice, patients who require treatment with oral corticosteroids are considered to have moderate CD.<sup>3</sup> Because they do not assess the patient's risk of disease progression, using composite disease activity scores to define disease severity is imperfect; therefore, experts advocate for a more comprehensive definition that measures the impact on the patient (ie, symptoms, quality of life, and disability), inflammatory burden (ie, mucosal lesions and extent of disease), and disease course (ie, flares, extra-intestinal manifestations, and intestinal resection).<sup>4</sup> The Mayo score and CDAI have been used to define disease severity in clinical trials, including premarketing clinical trials of biologics for IBD.<sup>4</sup> In the future, the US Food and Drug Administration (FDA) is expected to require patient-reported outcomes and objective measurements of disease as end points in clinical trials evaluating drugs for IBD.<sup>9</sup>

Redefining moderate to severe disease has the potential to more accurately identify patients who may ben-

## Abstract

Moderate to severe disease causes substantial morbidity in inflammatory bowel disease (IBD). The approach to pharmacotherapy for patients with moderate to severe ulcerative colitis and Crohn's disease is undergoing a fundamental transformation to change the course of disease in these patients. Disease severity is being redefined to consider the impact on the patient, its inflammatory burden, and the disease course. Prevention of disease progression and complications are replacing symptomatic remission as the goal of therapy. To achieve these goals, the treatment approach is evolving from a stepwise to a treat-to-target approach, with patients stratified to treatment according to their risk of disease progression or complications. The primary drug classes for induction and maintenance of remission in moderate to severe IBD are corticosteroids, thiopurines, tumor necrosis factor antagonists, and vedolizumab. Use of these drug classes is changing as IBD management evolves. This article reviews the efficacy, adverse effects, drug interactions, and special issues for each class. The role for each class is formulated based on results of key clinical trials and meta-analyses, as well as clinical practice guideline recommendations.

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For author information and disclosures, see end of text.

■ **Table 1.** Definitions of Disease Severity in UC and CD<sup>1,2,6-8</sup>

Ulcerative Colitis		Crohn's Disease
<b>American College of Gastroenterology</b>		
<b>Mild</b>	<4 stools/day (with or without blood) No systemic signs of toxicity Normal ESR	CDAI of 150–220 Ambulatory Able to tolerate oral alimentation without signs of dehydration, systemic toxicity (high fevers, rigors, and prostration), abdominal tenderness, painful mass, intestinal obstruction, or >10% weight loss
<b>Moderate</b>	≥4 stools/day Minimal signs of toxicity	CDAI of 220–450 Failed to respond to treatment for mild–moderate disease <i>or</i> Has more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia
<b>Severe</b>	≥6 bloody stools/day Signs of toxicity (fever, tachycardia, anemia) Increased ESR	<u>Severe/fulminant:</u> CDAI >450
<b>Fulminant</b>	≥10 stools/day Continuous bleeding Toxicity Abdominal tenderness and distension Blood transfusion requirement Colonic dilation on abdominal plain films	Persistent symptoms despite outpatient treatment with corticosteroids/biologics <i>or</i> Has high fevers, persistent vomiting, intestinal obstruction, significant peritoneal signs, cachexia, or abscess
<b>American Gastroenterological Association Clinical Pathways</b>		
<b>Low risk</b>	<u>Low risk for colectomy:</u> Limited anatomic extent Mild endoscopic disease	<u>Low risk for rapid progression:</u> Age at initial diagnosis >30 years Limited anatomic involvement No perianal and/or severe rectal disease Superficial ulcers No prior surgical resection No stricturing and/or penetrating pattern
<b>Moderate to high risk</b>	<u>High risk for colectomy:</u> Extensive colitis Deep ulcers Age <40 years High CRP and ESR Corticosteroid dependent History of hospitalization <i>C. difficile</i> infection CMV infection	<u>Moderate/high risk for rapid progression:</u> Age at initial diagnosis ≤30 years Extensive anatomic involvement Perianal and/or severe rectal disease Deep ulcers Prior surgical resection Stricturing and/or penetrating pattern

CD indicates Crohn's disease; CDAI, Crohn's Disease Activity Index; CMV, cytomegalovirus; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate, UC, ulcerative colitis.

efit from more aggressive treatment. As shown in Table 1,<sup>1,2,6-8</sup> clinical care pathways recently developed by the American Gastroenterological Association (AGA) stratify patients for treatment based on risk factors for a poor prognosis.<sup>6,7</sup> In UC, patients are stratified according

to their risk for colectomy.<sup>6</sup> Risk factors for colectomy include extensive disease, deep ulcers, age less than 40 years, high erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), corticosteroid dependence, history of hospitalization, *C. difficile* infection, and cyto-

megalovirus infection. Patients with limited and mild endoscopic disease have a low risk of colectomy.<sup>10</sup> In CD, patients are stratified according to risk for rapid progression to bowel damage and disability.<sup>7</sup>

### Goals of Therapy

The primary goal of therapy in IBD is to achieve and maintain corticosteroid-free symptomatic remission.<sup>1,2</sup> In patients with moderate to severe CD, achieving remission has been linked to fewer hospitalizations and surgeries, greater employment, and improved quality of life.<sup>11</sup> With greater appreciation for the progressive nature of IBD and the availability of more effective therapy, clinicians are setting more ambitious goals for pharmacotherapy of IBD that have the potential to change the course of the disease.<sup>11</sup> Potential goals include mucosal healing, prevention of complications, surgery, and disability, maintenance of normal gastrointestinal (GI) function, and restoration of normal quality of life.<sup>1,2,12</sup> Instead of defining remission as symptomatic improvement alone, some experts propose the goal should be deep remission, which is defined as sustained clinical remission with complete mucosal healing and normalization of serological inflammatory markers (eg, CRP, ESR).<sup>13,14</sup> The International Organization for the Study of Inflammatory Bowel Diseases recently proposed goals for treat-to-target strategies in IBD.<sup>8</sup> For UC, the goal is resolution of rectal bleeding and normalization of bowel habits, and a Mayo endoscopic subscore of 0 (optimal) or 1 (minimal). For CD, the goal is resolution of abdominal pain and normalization of bowel habits with absence of ulcers during endoscopic evaluation.<sup>8</sup>

### Evolving Treatment Strategies

Accumulating evidence suggests that early combined immunosuppression (ECI) is more effective than step-care in preventing complications in patients with moderate to severe CD.<sup>15-17</sup> Therefore, similar to the evolution of treatment for rheumatologic diseases, the treatment of IBD is undergoing a transition from step-care to a treat-to-target approach.<sup>8</sup> Most recently, the REACT (Randomised Evaluation of an Algorithm for Crohn's Treatment) trial compared standard step-care and algorithm-based care with ECI.<sup>17</sup> This real-world study was conducted in community GI practices and included patients with any disease severity or duration. Remission rates at 1 year, the primary outcome of the study, were similar with step-care and ECI (61.9% vs 66.0%, respectively;  $P = .52$ ). However, at 2 years, ECI was associated with a lower rate of surgery (HR, 0.69;

95% CI, 0.50-0.97) and serious complications (HR, 0.73; 95% CI, 0.61-0.87). The composite of hospitalization, surgery, and serious complications was significantly reduced with ECI (27.7% vs 35.1%;  $P = .0003$ ) with a number needed to treat (NNT) of 14. The incidence of serious drug-related adverse effects (AEs) was 1% in both groups.<sup>17</sup>

The focus of this article is pharmacotherapy for the management of moderate to severe UC and CD. Four primary classes of drugs are used to induce and maintain remission for this level of disease severity: corticosteroids, thiopurines, tumor necrosis factor (TNF) antagonists, and vedolizumab. Clinical practice guidelines from the ACG, AGA, and CAG provide evidence-based recommendations that help define the role of each agent, and when they should be used together.<sup>1,2,5,18</sup> In special circumstances, methotrexate, cyclosporine, and tacrolimus may be used as alternatives, but these immunosuppressants are beyond the scope of this article.

### Corticosteroids

Oral corticosteroids (eg, prednisone) are commonly used to induce remission in IBD.<sup>1,2</sup> "Gut-specific" oral formulations deliver budesonide to the bowel, reducing systemic corticosteroid exposure. Budesonide (Uceris) delivers the drug to the colon and is FDA-approved for inducing remission in mild to moderate active UC.<sup>19</sup> Budesonide (Entocort EC) delivers the drug to the ileum and ascending colon and is FDA-approved for mild to moderate active CD.<sup>20</sup> These formulations are not interchangeable.<sup>19,20</sup> Their role in moderate to severe disease is not well-defined, and their high cost puts them out of reach for most patients.

### Efficacy

Oral corticosteroids are superior to placebo for inducing remission in UC (relative risk [RR] of no remission: 0.65; 95% CI, 0.45-0.93), with an NNT of 3 to achieve 1 remission.<sup>21</sup> The efficacy of prednisone for inducing remission in CD was established in the National Cooperative Crohn's Disease study and the European Cooperative Crohn's Disease study.<sup>22,23</sup> At doses of 0.5 to 0.75 mg/kg/day and 1 mg/kg/day, the NNT to achieve 1 remission was 3 and 2, respectively.<sup>24</sup> Standard corticosteroids, like prednisone, are more effective than budesonide for inducing remission in CD (RR, 0.82; 95% CI, 0.68-0.98), but have a higher incidence of corticosteroid-related AEs (RR, 1.64; 95% CI, 1.34-2.00).<sup>21</sup> Although corticosteroids induce symptomatic remission in IBD, response rates for mucosal healing appear low.<sup>25-27</sup>

## AEs

With long-term use, corticosteroid toxicity includes osteoporosis, cataracts, adrenal suppression, impaired wound healing, immunosuppression, weight gain, and hyperglycemia.<sup>28,29</sup> In a registry study, corticosteroids were associated with an increased risk of serious infection (HR, 1.57; 95% CI, 1.17-2.10;  $P = .002$ ) and mortality (HR, 2.14; 95% CI, 1.55-2.95;  $P < .001$ ) in CD.<sup>30</sup> Strong cytochrome P450 3A4 inhibitors (eg, clarithromycin and voriconazole) can substantially increase budesonide exposure, increasing the risk of iatrogenic Cushing syndrome.<sup>31</sup> The World Congress of Gastroenterology encourages greater use of biologic agents to limit corticosteroid exposure.<sup>32</sup>

## Role in Therapy

The CAG recommends oral corticosteroids as first-line therapy for inducing remission in moderate to severe UC.<sup>5</sup> The AGA also considers a short course of corticosteroids with early initiation of a thiopurine as an option for inducing remission in patients at high risk for colectomy.<sup>6</sup>

For induction of remission in CD, the ACG recommends prednisone 40 to 60 mg/day until symptoms resolve and the patient begins to gain weight.<sup>1</sup> For inducing remission in patients at moderate to high risk of disease progression, the AGA recommends a TNF inhibitor rather than a corticosteroid.<sup>7</sup>

Because corticosteroids are ineffective and have a substantial burden of toxicity with chronic use, they have no role in maintaining remission in UC or CD.<sup>1,5,7,24,33</sup> In fact, the CAG considers maintenance of corticosteroid-free remission an important goal of therapy in UC.<sup>5</sup>

## Special Issue: Corticosteroid-refractory and -dependent Disease

Up to 40% of patients with IBD become corticosteroid-dependent.<sup>24</sup> In CD, patients who require corticosteroids to remain well are considered corticosteroid-dependent and are not considered to be in remission.<sup>1</sup> Patients with UC who do not respond to 14 days of oral prednisone 40 to 60 mg/day are considered corticosteroid-refractory, while those who are unable to taper corticosteroids after 3 months without disease flaring are considered corticosteroid-dependent.<sup>5</sup> In UC, corticosteroid dependence increases the risk of relapse and colectomy.<sup>5</sup> The CAG and AGA recommend a TNF inhibitor, which has demonstrated corticosteroid-sparing activity. Vedolizumab, which reduces the risk of colectomy, is also recommended for patients with UC who are corticosteroid-dependent or -refractory.<sup>5,6,34</sup>

## Thiopurines

Thiopurines are first-line immunosuppressants in IBD, but a 2- to 6-month delay in onset of action limits their role.<sup>6,7,35</sup> Although azathioprine and mercaptopurine are considered equivalent options for managing IBD, most studies have been conducted with azathioprine.<sup>36,37</sup>

## Efficacy

Results from the UC SUCCESS trial suggest that combination therapy with infliximab and azathioprine is more effective for inducing remission than either agent alone.<sup>38</sup> The study compared azathioprine, infliximab, and the combination in TNF inhibitor-naïve patients with moderate to severe UC. At week 16, corticosteroid-free remission was observed in 39.7% of patients given combination therapy, 23.7% given azathioprine alone ( $P = .032$ ), and 22.1% given infliximab alone ( $P = .017$ ). Results from meta analyses found thiopurine monotherapy ineffective for inducing remission in UC, but effective for maintaining remission, with a 21% lower risk of relapse than placebo.<sup>35,37</sup>

The role of thiopurines in moderate to severe CD is defined in part by the SONIC trial comparing azathioprine, infliximab, and the combination for induction of remission in 508 treatment-naïve adults.<sup>16</sup> At week 26, corticosteroid-free remission was observed in 56.8% of patients with combination therapy, 44.4% with infliximab alone ( $P = .02$ ), and 30.0% with azathioprine alone ( $P < .001$  vs combination therapy;  $P = .006$  vs infliximab). Cochrane reviews found thiopurine monotherapy ineffective for inducing remission in CD, but more effective than placebo for maintaining remission (RR, 1.19; 95% CI, 1.05-1.34) in studies ranging from 4 to 30 weeks.<sup>36,39</sup> Results from a network meta-analysis found infliximab (OR, 1.6), adalimumab (OR, 2.9), and infliximab plus azathioprine (OR, 3.0) more effective than azathioprine monotherapy for maintaining CD remission.<sup>40</sup>

## AEs

Although current thiopurine treatment may increase the RR of lymphoma by up to 5-fold, the absolute risk is low.<sup>41-43</sup> Based on a 3-fold higher RR, the number needed to harm (NNH) for 1 additional lymphoma case per year of treatment ranges from 325 for patients aged 70 to 79 years to 4598 for those aged 20 to 29 years.<sup>42</sup> Other AEs include bone marrow suppression, pancreatitis, hepatotoxicity, nausea, and allergic reactions.<sup>5</sup> During all phases of thiopurine therapy, periodic monitoring for bone marrow suppression is necessary.<sup>24,44</sup>

■ **Table 2.** TNF Inhibitors for Moderate to Severe IBD<sup>49-52</sup>

	<b>Adalimumab (Humira)</b>	<b>Certolizumab pegol (Cimzia)</b>	<b>Golimumab (Simponi)</b>	<b>Infliximab (Remicade)</b>
<b>Pharmacology</b>	Human antibody	Pegylated Fab' fragment of humanized antibody	Human antibody	Human-murine antibody
<b>FDA-approved indications<sup>a</sup></b>	CD: induction, including infliximab failure; maintenance UC: induction; maintenance	CD: maintenance	UC: induction, including patients who are corticosteroid-dependent; maintenance	CD: induction; maintenance Fistulizing CD: induction, maintenance of fistula closure UC: induction; maintenance; corticosteroid elimination
<b>Route</b>	SC	SC	SC	IV
<b>Regimen for UC</b>	Induction: 160 mg at week 0, then 80 mg at week 2 Maintenance: 40 mg every 2 weeks starting at week 4	—	Induction: 200 mg at week 0, then 100 mg at week 2 Maintenance: 100 mg every 4 weeks	Induction: 5 mg/kg at weeks 0, 2, and 6 Maintenance: 5 mg/kg every 8 weeks
<b>Regimen for CD</b>	Induction: 160 mg SC at week 0, followed by 80 mg at week 2 Maintenance: 40 mg every 2 weeks starting at week 4	Induction: 400 mg SC at weeks 0, 2, and 4 Maintenance: 400 mg SC every 4 weeks	—	Induction: 5 mg/kg IV at weeks 0, 2, and 6 Maintenance: 5 mg/kg IV every 8 weeks
<b>Unique adverse effects</b>	Injection site reactions	Injection site reactions	Injection site reactions	Infusion reactions Serum sickness Increased mortality in class III/IV heart failure

CD indicates Crohn's disease; FDA, US Food and Drug Administration; IBD, irritable bowel disease; IV, intravenous; SC, subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis.  
<sup>a</sup>All TNF inhibitors are FDA-approved for use in patients with an inadequate response to conventional therapy.

Thiopurines are inactivated by thiopurine methyltransferase (TPMT), an enzyme with variable activity that is an inherited trait.<sup>45</sup> Conventional thiopurine doses can cause life-threatening bone marrow suppression in patients with low or intermediate TPMT activity.<sup>45</sup> The Clinical Pharmacogenetics Implementation Consortium and CAG recommend determination of TPMT genotype before thiopurines are used.<sup>5,45,46</sup>

### Drug Interactions

Fatal pancytopenia can occur if the thiopurine dose is not reduced during coadministration of allopurinol or febuxostat.<sup>47</sup> Nonetheless, coadministration is not contraindicated if the thiopurine dose is reduced and bone marrow suppression monitoring is implemented.<sup>47</sup> Azathioprine and mercaptopurine can decrease the international normalized ratio with warfarin.<sup>48</sup>

### Role in Therapy

Guidelines from the CAG and the ACG, as well as a clinical care pathway from the AGA, help define the role of thiopurines in UC.<sup>2,5,6</sup> Thiopurine monotherapy is not

recommended for induction of remission; however, it is an option for maintenance therapy for selected patients achieving remission on oral corticosteroids.<sup>5,6</sup>

Clinical practice guidelines from the ACG and the AGA, and the AGA clinical care pathway, also help define the role of thiopurines in CD.<sup>1,7,18</sup> The AGA recommends a TNF inhibitor or a TNF inhibitor plus a thiopurine over a thiopurine alone for inducing remission in moderate to severe CD.<sup>18</sup> Although TNF inhibitors are preferred for maintenance of remission, thiopurines remain an option for maintaining a corticosteroid-induced remission. The AGA did not have sufficient data to differentiate between TNF inhibitor-thiopurine combination therapy and a TNF inhibitor alone for maintenance of remission.<sup>18</sup>

### TNF Inhibitors

TNF inhibitors are FDA-approved for the management of moderate to severe IBD in patients with an inadequate response to conventional therapy. As shown in [Table 2](#),<sup>49-52</sup> these drugs differ by indication, route of administration, and dosing regimen. With the exception of infliximab, TNF inhibitors can be self-administered by subcutaneous injection.<sup>49-52</sup>

**Efficacy**

The paucity of head-to-head trials makes it difficult to compare the efficacy of TNF inhibitors in IBD. Infliximab is widely considered as the agent with the most extensive clinical trial data for both UC and CD.<sup>32</sup> In CD, an adequate head-to-head trial of TNF inhibitors would require enrollment of over 3000 patients, so it is unlikely such a trial will ever be performed.<sup>53</sup>

The CAG found no evidence to support the use of one TNF inhibitor over another in UC.<sup>5</sup> Results from a network meta-analysis did not find any significant differences in efficacy for induction or maintenance of remission in UC among adalimumab, golimumab, and infliximab.<sup>54</sup> Data from other indirect and network meta-analyses suggest greater efficacy of infliximab than adalimumab for induction of UC, and comparable efficacy overall for infliximab and golimumab.<sup>55,56</sup>

In CD, evidence to support the preferential use of certolizumab pegol for induction of remission and maintenance of remission ahead of other available agents is lacking. In a phase 3 clinical trial, certolizumab pegol was not more effective than placebo for inducing remission in moderate to severe CD.<sup>57</sup> A network meta-analysis estimated the pairwise treatment effects of immunosuppressants and biologics for induction and maintenance of CD.<sup>40</sup> In pairwise comparisons of TNF inhibitors, infliximab plus azathioprine (OR, 3.1; 95% credible interval [CrI], 1.4-7.7) and adalimumab (OR, 2.1; 95% CrI, 1.0-4.6) had a 98% probability of being more effective than certolizumab pegol for induction of CD. For maintenance therapy, infliximab plus azathioprine (OR, 2.6; 95% CrI, 1.3-6.0) and adalimumab (OR, 2.5; 95% CrI, 1.4-4.6) had a 99% probability of being more effective than certolizumab pegol. There was no difference between adalimumab and infliximab plus azathioprine for maintenance of remission.

Fistulizing CD occurs in 20% to 40% of patients, and may require both surgical and medical therapy.<sup>58</sup> Infliximab is effective and FDA-approved for treating patients with CD and fistulae.<sup>49,58,59</sup> Adalimumab has also demonstrated efficacy in a placebo-controlled trial of patients with CD and fistulae.<sup>60</sup> Adding 12 weeks of ciprofloxacin to adalimumab therapy was more effective for achieving fistula closure than adalimumab therapy alone.

**AEs**

Treatment with a TNF inhibitor increases the risk of infection, especially tuberculosis, necessitating screening for active and latent disease before and during treatment.<sup>61</sup> Because of other infectious risks, including sepsis, and

invasive fungal and opportunistic infections, vaccination status should be optimized before treatment.<sup>49,61</sup> Risk of hepatitis B virus reactivation may be increased in patients who have had chronic infection, thus baseline screening is recommended in patients at risk. Monitoring for viral reactivation during treatment in patients with prior hepatitis B exposure, and consultation with an experienced provider for treatment recommendations in cases of reactivation are recommended. The NNH is estimated to be 500 for 1 patient to develop an opportunistic infection with a TNF inhibitor.<sup>62</sup> Exercise caution when considering TNF inhibitors in patients with these disorders.<sup>49-52</sup>

Because TNF inhibitors are often coadministered with thiopurines (a class of drugs already linked to an increased risk of lymphoma), establishing whether they increase the risk of malignancy is challenging.<sup>61</sup> Of particular concern are reports of hepatosplenic T-cell lymphoma, a rare and aggressive form of lymphoma that occurs primarily in adolescent and young men with IBD.<sup>61</sup> Alternatives to TNF inhibitors should be considered for patients with a history of malignancy or lymphoproliferative disorder.<sup>32</sup>

TNF inhibitors (eg, adalimumab, certolizumab pegol, and golimumab) that are administered by subcutaneous injection can cause injection-site reactions, while infliximab can cause infusion reactions that may be prevented by premedication with a corticosteroid and antihistamine.<sup>2, 49-52</sup> TNF inhibitors have been reported to increase the risk of death and hospitalization for worsening heart failure in patients with class III/IV heart failure.<sup>49</sup>

**Drug Interactions**

In terms of vaccination, patients receiving TNF inhibitors are considered to be highly immunosuppressed.<sup>63</sup> Administration of TNF inhibitors should be delayed for 3 months after the administration of live vaccines.<sup>32</sup> Because coadministration with biologic drugs may increase the risk of infection, live vaccines should not be coadministered with TNF inhibitors.<sup>49-52</sup>

**Role in Therapy**

Guidelines from the ACG, CAG, and an AGA clinical care pathway help define the role of TNF inhibitors in UC.<sup>5,6,8</sup> A TNF inhibitor with or without a thiopurine is an option for induction and maintenance of remission in outpatients who are at high risk for colectomy.<sup>8</sup> A TNF inhibitor is also an option to induce remission in patients with an inadequate response to a thiopurine or corticosteroid and in those who are corticosteroid-dependent.<sup>5</sup> If the response to induction therapy with a TNF inhibitor

is suboptimal, the dose should be increased to achieve complete remission.<sup>5</sup>

For induction of remission, in regards to the CAG's recommendation of a TNF inhibitor in combination with a thiopurine or methotrexate, the rationale is that combination therapy appears more effective, and helps prevent a secondary loss of response due to the development of anti-drug antibodies (ADAs) to the TNF inhibitor.<sup>6,8</sup> After 8 to 12 weeks, patients should be assessed for symptomatic response.<sup>5</sup> Patients who respond to induction with a TNF antagonist should continue to receive the drug for maintenance therapy.<sup>6,8</sup>

Clinical practice guidelines from the ACG, AGA, and an AGA clinical care pathway help define the role of TNF inhibitors in CD.<sup>1,7,18</sup> For patients with moderate to high risk of CD progression, the AGA recommends a TNF inhibitor, preferably in combination with a thiopurine, to induce remission and a TNF inhibitor to maintain remission.<sup>18</sup> For patients who have achieved corticosteroid-induced remission, a TNF inhibitor with or without a thiopurine is a preferred option for maintenance therapy.<sup>7,18</sup>

### Special Issue: Treatment Failure

Failure to respond to initial treatment with a TNF inhibitor, which has an estimated incidence of 10% to 30%, is considered a "primary failure."<sup>32</sup> The loss of TNF inhibitor efficacy over time is considered a "secondary failure."<sup>32</sup> The incidence of secondary failure during the first year of maintenance therapy is estimated at 30% to 40%.<sup>64-66</sup> After treatment failure, the response to a second TNF inhibitor may depend on why the first agent was discontinued.<sup>67</sup> A systematic review found that remission rates with a second TNF inhibitor were highest in CD when the first agent was discontinued because of intolerance (61%), followed by secondary failure (45%), and primary failure (30%).<sup>67</sup>

The development of ADAs may be linked to lower trough levels of TNF inhibitors.<sup>68-70</sup> For patients who experience secondary failure with a TNF inhibitor during maintenance therapy of either UC or CD, therapeutic drug monitoring should be used to optimize therapy if it is available.<sup>4,6</sup> If the TNF inhibitor concentration is subtherapeutic and ADAs are low or absent, the dose should be increased or the dosing interval shortened. If the concentration is subtherapeutic and ADAs are high, another TNF inhibitor should be tried.<sup>4,5</sup> Adalimumab is FDA-approved for the induction of remission in patients with CD who are no longer responding or are intolerant

of infliximab.<sup>50</sup> In a controlled trial of patients who failed infliximab therapy, significantly more patients achieved remission at 4 weeks with adalimumab than placebo (21% vs 7%, respectively;  $P < .001$ ).<sup>71</sup>

### Special Issue: Biosimilars

Biosimilar TNF inhibitors are expected to become available soon in the United States, with biosimilars for adalimumab and infliximab reaching the market first.<sup>72</sup> A Biologics License Application (BLA) for CT-P13 (Remsima), a biosimilar for infliximab, has been under FDA review since August 2014.<sup>73</sup> In November 2015, Amgen submitted a BLA for ABP 501, a biosimilar for adalimumab, on the basis of studies in rheumatoid arthritis and plaque psoriasis.<sup>74</sup> A key issue in biosimilar regulatory approval is whether there are adequate efficacy and safety data to allow extrapolation of indications from the originator molecule to the biosimilar. Observations that have led to concerns about extrapolating a biosimilar indication to IBD include (1) not all TNF inhibitors are effective for IBD, (2) efficacy of a TNF inhibitor for rheumatoid arthritis does not predict efficacy for IBD, and (3) a complex mechanism of action for TNF inhibitors in IBD introduces more potential differences between agents.<sup>72,75,76</sup>

Regulatory agencies in different countries have approached the issue of extrapolating data to IBD in other ways. Consequently, the infliximab biosimilar, CT-P13, received approval for IBD in Europe, but not in Canada.<sup>76</sup> A point of contention for Canadian regulatory authorities was that CT-P13 did not demonstrate comparable antibody-dependent cellular cytotoxicity with infliximab in 1 model.<sup>76</sup> It is too early to know how the FDA will interpret extrapolation data for biosimilars in IBD. Another important issue is whether biosimilars might stimulate the development of ADAs in patients previously treated with infliximab or adalimumab.<sup>77</sup> Small prospective and retrospective studies have assessed the use of CT-P13 in patients with IBD, including some with a history of prior TNF inhibitor use.<sup>78-80</sup> A randomized clinical trial is currently underway to evaluate switching from infliximab to CT-P13 in patients with a variety of disorders, including IBD.<sup>76</sup>

### Integrin Inhibition: Vedolizumab

Vedolizumab (Entyvio), the newest agent for IBD, is an integrin inhibitor that prevents migration of T cells into the GI tract. It is approved by the FDA for the treatment of moderate to severe active UC or CD, in adults who failed therapy with a TNF inhibitor, an

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immunomodulator, or corticosteroid, or adults who are corticosteroid-dependent or -intolerant.<sup>81,82</sup> Integrins are a family of cell-surface glycoproteins on some B and T lymphocytes. They have alpha ( $\alpha$ ) and beta ( $\beta$ ) subunits that determine the organs to which they migrate, and the signal pathway they use to gain access to those organs. The  $\alpha 4\beta 7$  family of integrins is expressed on lymphocytes that colonize the gut, and associated lymphoid tissue; the signal pathway with which they interact is the mucosal addressin cell adhesion molecule-1. This interaction mediates inflammation in both UC and CD.<sup>81</sup> Vedolizumab is an intravenous humanized monoclonal antibody that binds specifically with the  $\alpha 4\beta 7$  integrin.<sup>81</sup>

### Efficacy

Two phase 3 placebo-controlled trials, referred to as GEMINI 1, evaluated vedolizumab for induction and maintenance in 895 patients with UC who did not tolerate or respond adequately to a corticosteroid, TNF inhibitor, or immunomodulator.<sup>83</sup> Patients who responded to vedolizumab at week 6 of the first phase of the study were randomized to receive vedolizumab given every 4 weeks, vedolizumab given every 8 weeks, or placebo for up to 1 year. In the induction study, the clinical response rate at week 6, the primary outcome, was significantly greater with vedolizumab compared with placebo (47.1% vs 25.5%, respectively;  $P < .001$ ). Significantly more patients given vedolizumab than those given placebo experienced clinical remission (16.9% vs 5.4%;  $P = .001$ ) and mucosal healing (40.9% vs 24.8%;  $P = .001$ ). In the maintenance study, the 1-year clinical remission rate was 41.8% for vedolizumab given every 8 weeks, 44.8% for vedolizumab given every 4 weeks, and 15.9% for placebo ( $P < .001$  for each dose of vedolizumab vs placebo).<sup>83</sup> A Cochrane review evaluating vedolizumab in UC found it significantly superior to placebo for induction of remission (RR, 0.86; 95% CI, 0.80-0.91), clinical response (RR, 0.68; 95% CI, 0.59-0.78), and endoscopic remission (RR, 0.82; 95% CI, 0.75-0.91).<sup>84</sup> Vedolizumab was also superior to placebo for prevention of relapse (RR, 0.67; 95% CI, 0.59-0.77), but the quality of data was moderate, due to fewer events in the maintenance study.<sup>84</sup>

Vedolizumab was evaluated for moderate to severe active CD in 3 placebo-controlled trials.<sup>85,86</sup> GEMINI 2, a set of integrated induction and maintenance studies similar to GEMINI 1, enrolled patients who could not tolerate or had an inadequate response to a corticosteroid, an immunomodulator, or a TNF inhibitor.<sup>85</sup> The primary outcome of the induction study, the CDAI-100 response,

was not significantly different for vedolizumab compared with placebo (31.4% vs 25.7%, respectively;  $P = .23$ ), but the clinical remission rate was significantly higher with vedolizumab than placebo (14.5% vs 6.8%;  $P = .02$ ). For the maintenance study, the 1-year clinical remission rate was 39.0% for vedolizumab given every 8 weeks, 36.4% for vedolizumab given every 4 weeks, and 21.6% for placebo ( $P \leq .004$  for both doses of vedolizumab vs placebo).

Another induction study, GEMINI 3, enrolled 416 patients with moderate to severe CD, approximately 76% of whom failed TNF inhibitor therapy.<sup>87</sup> The primary outcome, clinical remission at week 6 in patients with a history of TNF inhibitor therapy failure, was not significantly different among vedolizumab and placebo (15.2% vs 12.1%, respectively;  $P = .433$ ). However, the percentage of patients experiencing clinical remission at week 10 was significantly greater with vedolizumab than placebo (26.6% vs 12.1%;  $P = .001$ ). The CDAI-100 response at week 6 was significantly greater with vedolizumab compared with placebo (39.2% vs 22.3%;  $P = .001$ ).<sup>86</sup>

### AEs

In phase 3 clinical trials in UC, vedolizumab was well tolerated.<sup>83</sup> In the GEMINI 2 trial for CD, vedolizumab was associated with a numerically higher rate of serious AEs (24.4% vs 15.3%), infections (44.1% vs 40.2%), and serious infections (5.5% vs 3.0%) than placebo.<sup>85</sup> In premarketing clinical trials for UC and CD, the incidence of serious infections was 0.07 per patient-year with vedolizumab and 0.06 per patient-year with placebo.<sup>81</sup> Infusion reactions and hypersensitivity reactions have been reported rarely.<sup>81</sup> A Cochrane review found the adverse event profile of vedolizumab similar to that of placebo, with no significant difference for any events or serious events.<sup>84</sup> Over 1 year of treatment in premarketing clinical trials, 56 of 1434 patients (4%) had detectable anti-vedolizumab antibodies at some time point.<sup>81</sup> Nine patients with persistent antibodies did not achieve clinical remission with vedolizumab.<sup>81</sup>

Natalizumab, the first integrin antagonist to reach the market, was approved for induction and maintenance treatment of CD, in addition to multiple sclerosis.<sup>87</sup> Like vedolizumab, natalizumab is a monoclonal antibody. However, it binds with the  $\alpha 4$  subunit of 2 integrins,  $\alpha 4\beta 7$  and  $\alpha 4\beta 1$ . This second integrin,  $\alpha 4\beta 1$ , binds with vascular cell adhesion molecule-1 (VCAM-1), which mediates lymphocyte migration into the central nervous system (CNS). By inhibiting the interaction between  $\alpha 4\beta 1$  and VCAM-1, natalizumab prevents the migration of T

cells into the CNS.<sup>88</sup> In susceptible patients treated with natalizumab, reactivation of latent JC polyomavirus can cause progressive multifocal leukoencephalopathy (PML), a life-threatening brain infection.<sup>87</sup> Based on a gut-selective mechanism of action, vedolizumab is not expected to cause PML, and no cases have been reported thus far.<sup>82,86</sup> As of June 2013, 3129 patients with IBD had received vedolizumab for a median of 313 days, with 995 patients receiving the drug for at least 24 months. Based on the incidence of PML in patients with multiple sclerosis treated with natalizumab (>1 case in 500 patients), if vedolizumab had a comparable risk of causing PML, 6 or 7 cases would have been observed by then.<sup>84</sup>

### Drug Interactions

A recent study found that vedolizumab did not affect antibody titers after administration of injected hepatitis B vaccine, but it did reduce the humoral response to orally administered cholera vaccine.<sup>89</sup> This observation may be related to gut-specific immune modulation with vedolizumab. Product labeling indicates that administration of live vaccines during treatment with vedolizumab is a risk-versus-benefit decision.<sup>81</sup> Due to the potential for increased infections, coadministration of vedolizumab and TNF inhibitors is not recommended.<sup>81</sup>

### Role in Therapy

A CAG guideline and an AGA clinical care pathway help define the role of vedolizumab in UC.<sup>5,6</sup> Vedolizumab, with or without an immunomodulator, is an option for induction and maintenance in patients who are at high risk for colectomy.<sup>6</sup> Vedolizumab is also recommended for induction of remission in moderate to severe active UC that has not responded to corticosteroids, thiopurines, or a TNF inhibitor.<sup>5,6</sup> Patients who have not achieved corticosteroid-free complete remission with a TNF inhibitor despite dose optimization are also candidates for vedolizumab.<sup>5,6</sup> The symptomatic response to vedolizumab should be evaluated within 8 to 14 weeks, with vedolizumab continued for maintenance therapy in responders.<sup>5</sup> The role of vedolizumab in CD is not yet defined in clinical practice guidelines.

### Conclusion

The therapeutic approach to moderate to severe IBD is evolving from step-care to a treat-to-target approach, with greater focus on early treatment for patients who have the highest risk for disease progression and complications. Although corticosteroids still have a role in

inducing remission, minimizing corticosteroid exposure is an important goal of therapy. Combination therapy with a TNF inhibitor and a thiopurine appears most effective for inducing and maintaining remission in both UC and CD. Biosimilars of TNF inhibitors are expected to become available soon in the United States, but there are concerns about extrapolating data from their use in other diseases to IBD. Vedolizumab provides another option for patients with UC or CD who have not responded to other therapies, but its role in treatment is still being defined.

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## REFERENCES

- Lichtenstein GR, Hanauer SB, Sandborn WJ; Practice Parameters Committee of American College of Gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol*. 2009;104(2):465-483. doi: 10.1038/ajg.2008.168.
- Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol*. 2010;105(3):501-523. doi: 10.1038/ajg.2009.727.
- Dassopoulos T, Sultan S, Falck-Ytter YT, Inadomi JM, Hanauer SB. American Gastroenterological Association Institute technical review on the use of thiopurines, methotrexate, and anti-TNF- $\alpha$  biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology*. 2013;145(6):1464-1478. doi: 10.1053/j.gastro.2013.10.046.
- Peyrin-Biroulet L, Panés J, Sandborn WJ, et al. Defining disease severity in inflammatory bowel diseases: current and future directions. *Clin Gastroenterol Hepatol*. 2015; pii: S1542-3565(15)00787-00789. doi: 10.1016/j.cgh.2015.06.001.
- Bressler B, Marshall JK, Bernstein CN, et al. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. *Gastroenterology*. 2015;148(5):1035-1058. doi: 10.1053/j.gastro.2015.03.001.
- Dassopoulos T, Cohen RD, Scherl EJ, Schwartz RM, Kosinski L, Regueiro MD. Ulcerative colitis care pathway. *Gastroenterology*. 2015;149(1):238-245. doi: 10.1053/j.gastro.2015.05.036.
- Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. *Gastroenterology*. 2014;147(3):702-705. doi: 10.1053/j.gastro.2014.07.022.
- Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110(9):1324-1338. doi: 10.1038/ajg.2015.233.
- Williet N, Sandborn WJ, Peyrin-Biroulet L. Patient-reported outcomes as primary end points in clinical trials of inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2014;12(8):1246-1256. doi: 10.1016/j.cgh.2014.02.016.
- Identification, assessment, and initial medical treatment of ulcerative colitis: clinical care pathway. American

- Gastroenterological Association website. <http://campaigns.gastro.org/algorithms/UlcerativeColitis/index.html>. Published 2015. Accessed November 21, 2015.
11. Lichtenstein GR, Yan S, Bala M, Hanauer S. Remission in patients with Crohn's disease is associated with improvement in employment and quality of life and a decrease in hospitalizations and surgeries. *Am J Gastroenterol*. 2004;99(1):91-96.
  12. Ordás I, Feagan BG, Sandborn WJ. Early use of immunosuppressives or TNF antagonists for the treatment of Crohn's disease: time for a change. *Gut*. 2011;60(12):1754-1763. doi: 10.1136/gutjnl-2011-300934.
  13. Orlando A, Guglielmi FW, Cottone M, Orlando E, Romano C, Sinagra E. Clinical implications of mucosal healing in the management of patients with inflammatory bowel disease. *Dig Liver Dis*. 2013;45(12):986-991. doi: 10.1016/j.dld.2013.07.005.
  14. Ho EY, Cominelli F, Katz J. Ulcerative colitis: what is the optimal treatment goal and how do we achieve it? *Curr Treat Options Gastroenterol*. 2015;13(1):130-142. doi: 10.1007/s11938-014-0044-5.
  15. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet*. 2008;371(9613):660-667. doi: 10.1016/S0140-6736(08)60304-9.
  16. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362(15):1383-1395. doi: 10.1056/NEJMoa0904492.
  17. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. *Lancet*. 2015;386(10006):1825-1834. doi: 10.1016/S0140-6736(15)00068-9.
  18. Terdiman JP, Gruss CB, Heidelbaugh JJ, Sultan S, Falck-Ytter YT; AGA Institute Clinical Practice and Quality Management Committee. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF- $\alpha$  biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology*. 2013;145(6):1459-1463. doi: 10.1053/j.gastro.2013.10.047.
  19. Uceris [package insert]. San Diego, CA: Santarus, Inc; January 2013.
  20. Entocort EC [package insert]. San Diego, CA: Prometheus Laboratories Inc; 2013.
  21. Ford AC, Bernstein CN, Khan KJ, et al. Glucocorticosteroid therapy in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106(4):590-599. doi: 10.1038/ajg.2011.70.
  22. Summers RW, Switz DM, Sessions JT Jr, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology*. 1979;77(4, pt 2):847-869.
  23. Malchow H, Ewe K, Brandes JW, et al. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology*. 1984;86(2):249-266.
  24. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology*. 2006;130(3):940-987.
  25. Papi C, Fasci-Spurio F, Rogai F, Settesoldi A, Margagnoni G, Annese V. Mucosal healing in inflammatory bowel disease: treatment efficacy and predictive factors. *Dig Liver Dis*. 2013;45(12):978-985. doi: 10.1016/j.dld.2013.07.006.
  26. Ardizzone S, Cassinotti A, Duca P, et al. Mucosal healing predicts late outcomes after the first course of corticosteroids for newly diagnosed ulcerative colitis. *Clin Gastroenterol Hepatol*. 2011;9(6):483-489. doi: 10.1016/j.cgh.2010.12.028.
  27. Modigliani R, Mary JY, Simon JF, et al. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives. *Gastroenterology*. 1990;98(4):811-818.
  28. Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. *Otolaryngol Clin North Am*. 2010;43(4):753-768. doi: 10.1016/j.otc.2010.04.003.
  29. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. *Allergy Asthma Clin Immunol*. 2013;9(1):30. doi: 10.1186/1710-1492-9-30.
  30. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT™ registry. *Am J Gastroenterol*. 2012;107(9):1409-1422. doi: 10.1038/ajg.2012.218.
  31. Jones W, Chastain CA, Wright PW. Iatrogenic cushing syndrome secondary to a probable interaction between voriconazole and budesonide. *Pharmacotherapy*. 2014;34(7):e116-e119. doi: 10.1002/phar.1432.
  32. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? *Am J Gastroenterol*. 2011;106(2):199-212. doi: 10.1038/ajg.2010.392.
  33. Kuenzig ME, Rezaie A, Seow CH, et al. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2014;8:CD002913. doi: 10.1002/14651858.CD002913.pub3.
  34. Huang X, Lv B, Jin HF, Zhang S. A meta-analysis of the therapeutic effects of tumor necrosis factor- $\alpha$  blockers on ulcerative colitis. *Eur J Clin Pharmacol*. 2011;67(8):759-766. doi: 10.1007/s00228-011-1079-3.
  35. Gisbert JP, Linares PM, McNicholl AG, Maté J, Gomollón F. Meta-analysis: the efficacy of azathioprine and mercaptopurine in ulcerative colitis. *Aliment Pharmacol Ther*. 2009;30(2):126-137. doi: 10.1111/j.1365-2036.2009.04023.x.
  36. Chande N, Patton PH, Tsoulis DJ, Thomas BS, MacDonald JK. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2015;10:CD000067. doi: 10.1002/14651858.CD000067.pub3.
  37. Timmer A, McDonald JW, Tsoulis DJ, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012;9:CD000478. doi: 10.1002/14651858.CD000478.pub3.
  38. Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. *Gastroenterology*. 2014;146(2):392-400.
  39. Chande N, Tsoulis DJ, MacDonald JK. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2013;4:CD000545. doi: 10.1002/14651858.CD000545.pub4.
  40. Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. *Gastroenterology*. 2015;148(2):344-354. doi: 10.1053/j.gastro.2014.10.011.
  41. Beaugerie L, Brousse N, Bouvier AM, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet*. 2009;374(9701):1617-1625. doi: 10.1016/S0140-6736(09)61302-7.
  42. Kotlyar DS, Lewis JD, Beaugerie L, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. *Clin Gastroenterol Hepatol*. 2015;13(5):847-858. doi: 10.1016/j.cgh.2014.05.015.
  43. Siegel CA, Marden SM, Persing SM, Larson RJ, Sands BE. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol*. 2009;7(8):874-881. doi: 10.1016/j.cgh.2009.01.004.
  44. Imuran [package insert]. San Diego, CA: Prometheus Laboratories Inc; 2014.
  45. Relling MV, Gardner EE, Sandborn WJ, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther*. 2011;89(3):387-391. doi: 10.1038/clpt.2010.320.

46. Mayberry JF, Lobo A, Ford AC, Thomas A. NICE clinical guideline (CG152): the management of Crohn's disease in adults, children and young people. *Aliment Pharmacol Ther.* 2013;37(2):195-203. doi: 10.1111/apt.12102.
47. Horn JR, Hansten PD. Another thiopurine-allopurinol tragedy. *Pharmacy Times.* 2015;36.
48. Bungard TJ, Yakiwchuk E, Foisy M, Brocklebank C. Drug interactions involving warfarin: practice tool and practical management tips. *Can Pharm J (Ott).* 2011;144(1):21-25e. doi: 10.3821/1913-701X-144.1.21.
49. Remicade [package insert]. Horsham, PA: Janssen Biotech, Inc; 2015.
50. Humira [package insert]. North Chicago, IL: AbbVie Inc; 2015.
51. Cimzia [package insert]. Smyrna, GA: UCB Inc; 2015.
52. Simponi [package insert]. Horsham, PA: Janssen Biotech, Inc; 2016.
53. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-TNF agents for the treatment of Crohn's disease. *Aliment Pharmacol Ther.* 2014;39(12):1349-1362. doi: 10.1111/apt.12749.
54. Stidham RW, Lee TC, Higgins PD, et al. Systematic review with network meta-analysis: the efficacy of anti-tumour necrosis factor- $\alpha$  agents for the treatment of ulcerative colitis. *Aliment Pharmacol Ther.* 2014;39(7):660-671. doi: 10.1111/apt.12644.
55. Thorlund K, Druyts E, Mills EJ, Fedorak RN, Marshall JK. Adalimumab versus infliximab for the treatment of moderate to severe ulcerative colitis in adult patients naïve to anti-TNF therapy: an indirect treatment comparison meta-analysis. *J Crohns Colitis.* 2014;8(7):571-581. doi: 10.1016/j.crohns.2014.01.010.
56. Thorlund K, Druyts E, Toor K, Mills EJ. Comparative efficacy of golimumab, infliximab, and adalimumab for moderately to severely active ulcerative colitis: a network meta-analysis accounting for differences in trial designs. *Expert Rev Gastroenterol Hepatol.* 2015;9(5):693-700. doi: 10.1586/17474124.2015.1024657.
57. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med.* 2007;357(3):228-238.
58. Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med.* 1999;340(18):1398-1405.
59. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med.* 2004;350(9):876-885.
60. Colombel JF, Schwartz DA, Sandborn WJ, et al. Adalimumab for the treatment of fistulas in patients with Crohn's disease. *Gut.* 2009;58(7):940-948. doi: 10.1136/gut.2008.159251.
61. Nordgaard-Lassen I, Dahlerup JF, Belard E, et al. Guidelines for screening, prophylaxis and critical information prior to initiating anti-TNF- $\alpha$  treatment. *Dan Med J.* 2012;59(7):C4480.
62. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor- $\alpha$  therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. *Am J Gastroenterol.* 2013;108(8):1268-1276. doi: 10.1038/ajg.2013.138.
63. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. *Clin Infect Dis.* 2014;58(3):309-318. doi: 10.1093/cid/cit816.
64. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. *N Engl J Med.* 2007;357(3):239-250.
65. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet.* 2002;359(9317):1541-1549.
66. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology.* 2007;132(1):52-65.
67. Gisbert JP, Marín AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther.* 2015;41(7):613-623. doi: 10.1111/apt.13083.
68. Bond A, Asher R, Jackson R, et al. Comparative analysis of the influence of clinical factors including BMI on adalimumab and infliximab trough levels. *Eur J Gastroenterol Hepatol.* 2016;28(3):271-276. doi: 10.1097/MEG.0000000000000544.
69. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology.* 2009;137(5):1628-1640. doi: 10.1053/j.gastro.2009.07.062.
70. Ungar B, Levy I, Yavne Y, et al. Optimizing anti-TNF- $\alpha$  therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol.* 2015;pii:S1542-3565(15)01492-01495. doi: 10.1016/j.cgh.2015.10.025.
71. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med.* 2007;146(12):829-838.
72. Ben-Horin S, Heap GA, Ahmad T, Kim H, Kwon T, Chowery Y. The immunogenicity of biosimilar infliximab: can we extrapolate the data across indications? *Expert Rev Gastroenterol Hepatol.* 2015;9(suppl 1):27-34. doi: 10.1586/17474124.2015.1091307.
73. Nam I. Celltrion seeks FDA approval for biosimilar Remsima. Wall Street Journal website. <http://www.wsj.com/articles/celltrion-seeks-fda-approval-for-biosimilar-rem-sima-1427869990>. Published April 1, 2015. Accessed November 26, 2015.
74. Amgen's first biosimilar biologics license application for ABP 501 submitted to US Food and Drug Administration [new release]. Thousand Oaks, CA: Amgen; November 25, 2015. <http://wwwext.amgen.com/media/news-releases/2015/11/amgens-first-biosimilar-biologics-license-application-for-abp-501-submitted-to-us-food-and-drug-administration/>. Accessed November 25, 2015.
75. Danese S, Gomollon F; Governing Board and Operational Board of ECCO. ECCO position statement: the use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis.* 2013;7(7):586-589. doi: 10.1016/j.crohns.2013.03.011.
76. Isaacs JD, Cutolo M, Keystone EC, Park W, Braun J. Biosimilars in immune-mediated inflammatory diseases: initial lessons from the first approved biosimilar anti-tumour necrosis factor monoclonal antibody. *J Intern Med.* 2016;279(1):41-59. doi: 10.1111/joim.12432.
77. Devlin SM, Bressler B, Bernstein CN, et al. Overview of subsequent entry biologics for the management of inflammatory bowel disease and Canadian Association of Gastroenterology position statement on subsequent entry biologics. *Can J Gastroenterol.* 2013;27(10):567-571.
78. Papamichael K, Van Stappen T, Jairath V, et al. Review article: pharmacological aspects of anti-TNF biosimilars in inflammatory bowel diseases. *Aliment Pharmacol Ther.* 2015;42(10):1158-1169. doi: 10.1111/apt.13402.
79. Jahnsen J, Detlie TE, Vatn S, Ricanek P. Biosimilar infliximab (CT-P13) in the treatment of inflammatory bowel disease: A Norwegian observational study. *Expert Rev Gastroenterol Hepatol.* 2015;9(suppl 1):45-52. doi: 10.1586/17474124.2015.1091308.
80. Kang YS, Moon HH, Lee SE, Lim YJ, Kang HW. Clinical experience of the use of CT-P13, a biosimilar to infliximab in patients with inflammatory bowel disease: a case series. *Dig Dis Sci.* 2015;60(4):951-956. doi: 10.1007/s10620-014-3392-z.
81. Entyvio [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc; 2014.
82. Lobatón T, Vermeire S, Van Assche G, Rutgeerts P. Review article: anti-adhesion therapies for inflammatory bowel disease. *Aliment Pharmacol Ther.* 2014;39(6):579-594. doi: 10.1111/apt.12639.
83. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2013;369(8):699-710. doi: 10.1056/NEJMoa1215734.
84. Bickston SJ, Behm BW, Tsoulis DJ, et al. Vedolizumab

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for induction and maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2014;8:CD007571. doi: 10.1002/14651858.CD007571.pub2.

85. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med.* 2013;369(8):711-721. doi: 10.1056/NEJMoa1215739.

86. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology.* 2014;147(3):618-627. doi: 10.1053/j.gas-

tro.2014.05.008.

87. Tysabri [package insert]. Cambridge, MA: Biogen Idec Inc; 2015.

88. del Pilar Martin M, Cravens PD, Winger R, et al. Decrease in the numbers of dendritic cells and CD4+ T cells in cerebral perivascular spaces due to natalizumab. *Arch Neurol.* 2008;65(12):1596-1603. doi: 10.1001/archneur.65.12.noc80051.

89. Wyant T, Leach T, Sankoh S, et al. Vedolizumab affects antibody responses to immunisation selectively in the gastrointestinal tract: randomised controlled trial results. *Gut.* 2015;64(1):77-83. doi: 10.1136/gutjnl-2014-307127.