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Emerging Treatment Options in Mild to Moderate Ulcerative Colitis

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory condition associated with rectal bleeding and urgency, tenesmus, and diarrhea. Several medical therapies can be used in the treatment of UC. Aminosalicylates are widely used based on their efficacy in the induction and maintenance of remission. Although corticosteroids are effective in patients with more severe disease, systemic use is associated with significant safety concerns. The newer corticosteroid budesonide has lower systemic bioavailability and, consequently, a more favorable safety profile. A budesonide extended-release formulation allows once-daily dosing and delivers the agent locally throughout the colon. Biologic agents used for the treatment of moderate to severe UC include the tumor necrosis factor inhibitors infliximab, adalimumab, and golimumab, and the integrin inhibitor vedolizumab. Rectally administered therapy can also be useful in the treatment of UC. In October 2014, the US Food and Drug Administration approved a budesonide foam formulation for inducing remission in patients with active mild to moderate distal UC extending up to 40 cm from the anal verge. Budesonide foam rapidly distributes to the sigmoid colon and the rectum and avoids some of the drawbacks of suppositories and enemas.

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Mild to Moderate Ulcerative Colitis: Disease State

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Idiopathic inflammatory bowel disease (IBD) represents a spectrum of conditions, with ulcerative colitis (UC) on one end and Crohn's disease (CD) on the other. UC is typically a diffuse continuous superficial inflammation that always begins within the rectum and affects the proximal colon to a varying extent. The disease is limited to the rectum in approximately a third of patients, to the left side of the colon in another third, and to the splenic flexure or beyond in the remaining third. UC does not typically involve the small intestine, although a small percentage of patients may have a limited superficial inflammation of the terminal ileum—a condition termed *backwash ileitis*. Although the inflammation associated with UC is usually superficial, it can extend throughout the mucosa in patients with severe ulcerations, a condition known as *fulminant colitis* or *toxic megacolon*. Approximately 10% of patients have an overlap between UC and CD, in which inflammation is limited to the colon.[1]

Epidemiology and Pathogenesis

IBD is more common in developed countries (Figure 1).[2] In North America, the incidence of UC is 8 to 20 cases per 100,000 people, and the prevalence is 120 to 250 cases per 100,000 people.[2,3] The condition is increasing in developing countries that are assimilating to western lifestyles, particularly in the areas of diet and hygiene.

Although UC can develop at any age (Figure 2), 2 peaks of incidence are seen: one in teenagers and young adults and the other in the fifth or sixth decade of life.[4] Interestingly, the second peak is often associated with individuals who have stopped smoking.

The exact cause of UC is not known. There appears to be a genetic component. The presence of a family member with UC increases the risk of developing the condition. Risk increases substantially if both parents have IBD.[5] Among twins, the penetrance of UC is less significant than that observed with CD.[5] Research into the genetic correlates of the disease have revealed more than 120 genes that are associated with UC.[5] However, none appear to be pathognomonic, and the majority of patients have no known genetic disposition.

Factors that appear to reduce the risk of UC include childhood appendectomy and cigarette smoking.[6] Former smokers have an increased risk of UC compared with people who never smoked, with a relative risk of 4.4 among former heavy smokers.[7] The onset of UC can still occur many years after a person stops smoking cigarettes. Exposure to antibiotics has been shown to increase the risk of CD but is not significant for UC.[8] Patients who take nonsteroidal anti-inflammatory drugs (NSAIDs) may have a colitis that overlaps with UC, but use of NSAIDs does not appear to increase the risk of developing UC.

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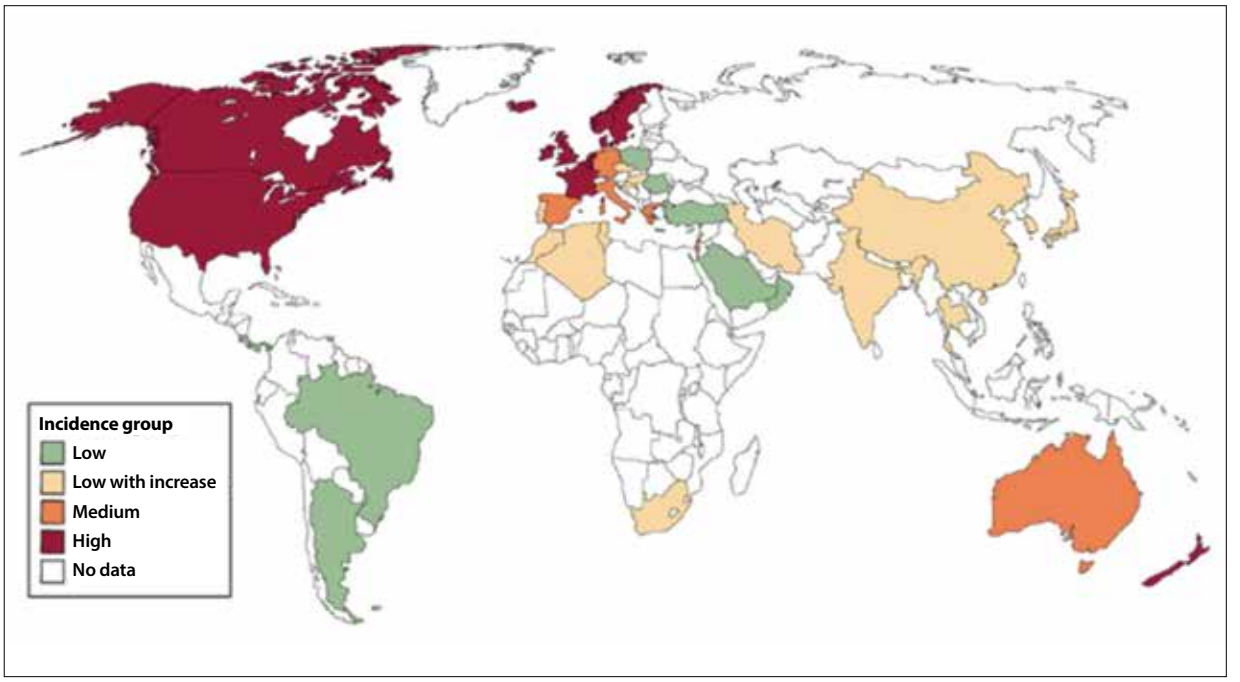

Figure 1. Worldwide incidence of inflammatory bowel disease.

Adapted from Cosnes J et al. *Gastroenterology*. 2011;140(6):1785-1794.[2]

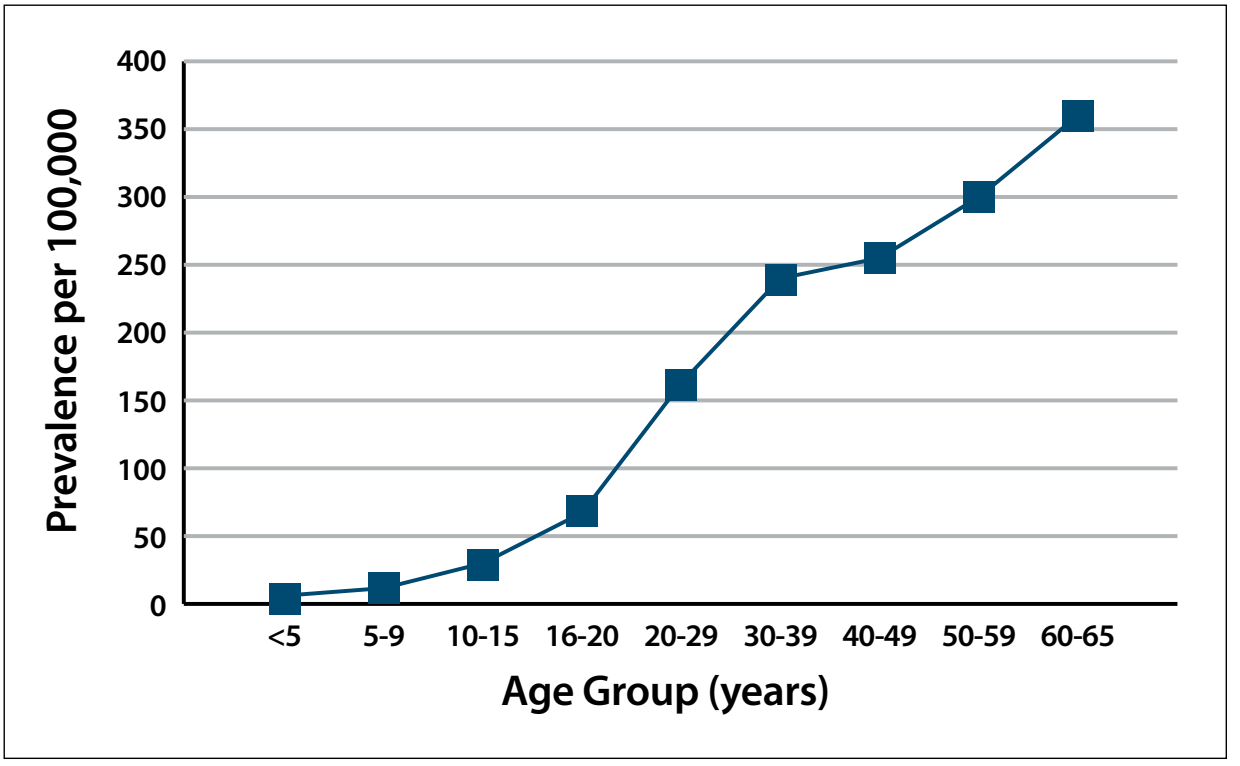

Figure 2. Age-specific prevalence of ulcerative colitis in the United States.

Adapted from Kappelman MD et al. *Dig Dis Sci*. 2013;58(2):519-525.[4]

Signs and Symptoms

The symptoms of UC depend on 2 factors: the extent of disease involvement in the colon and the severity of inflammation within the affected bowel. Typically, the inflammation is diffuse and continuous, and therefore the disease severity remains relatively constant throughout the affected area. Because UC nearly always affects the rectum, associated symptoms, such as rectal bleeding, rectal urgency, and tenesmus, tend to predominate.[9]

The presence of diarrhea depends on the extent of colonic involvement. Patients with more extensive colitis are more likely to experience diarrhea, rectal bleeding, rectal urgency, and nocturnal bowel movements.[9] Patients with UC may experience abdominal cramping, but abdominal pain is uncommon. Extensive or severe disease can lead to weight loss that can be accompanied by nausea, vomiting, and fever in patients with severe inflammation. Patients with distal colitis (ulcerative proctitis) are less likely to have diarrhea and instead tend to be constipated. The passage of bowel through the inflamed area can cause rectal bleeding and urgency. Extraintestinal manifestations, such as joint pain, erythema nodosum, or, uncommonly, pyoderma gangrenosum, are more frequent in patients with long-standing disease.[9]

Diagnosis

Endoscopic examination of the colon using either flexible sigmoidoscopy or colonoscopy is the primary test used in the diagnosis of UC. Regardless of the presence of diarrhea, endoscopic examination is usually warranted in patients presenting with rectal bleeding, particularly those who are young. Manifestations of UC tend to be diffuse, with continuous inflammation of varying degrees of severity. The inflammation may be mild—manifested by edema, loss of mucosal vasculature, and a fine granularity—and can progress to superficial and pinpoint ulcerations, or even gross ulcerations in patients with more severe disease.

Clinical Course

UC nearly always starts in the rectum and may involve a more proximal portion of the colon, depending on the patient. Once the upper demarcation is determined, it typically remains static.[9] In a small proportion of patients, however, disease can progress proximally to involve more of the bowel, or it can retreat more distally. Although the disease course of UC is typically described as waxing and waning, it is most often a persistent inflammation. The risk of relapse is often dependent on how clinical remission is maintained. However, even patients receiving maintenance therapy can develop UC flare-ups. These flare-ups may be related to intercurrent infections or the use of certain medications (in particular, NSAIDs). In some patients, the cause is unknown.

Table 1. The Mayo Ulcerative Colitis Scoring System

Finding	Points
Stool pattern	
Patient reports a usual number of daily stools	0
1-2 more stools than usual	1
3-4 more stools than usual	2
5 or more stools than usual	3
Most severe rectal bleeding of the day	
None	0
Blood streaks seen in the stool less than half the time	1
Blood in most stools	2
Pure blood passed	3
Endoscopic findings	
Normal or inactive colitis	0
Mild colitis: mild friability, erythema, decrease in vascularity	1
Moderate colitis: friability, marked erythema, vascular pattern absent, erosions seen	2
Severe colitis: ulcerations and spontaneous bleeding	3
Global assessment by physician	
Normal	0
Mild colitis	1
Moderate colitis	2
Severe colitis	3

Data from Schroeder KW et al. *N Engl J Med.* 1987;317(26):1625-1629.[10]

Assessing Ulcerative Colitis Disease Severity

Multiple factors are used to assess disease severity in UC, including the frequency of bowel movements, the extent of rectal bleeding, the endoscopic appearance, and the effects of the condition on a patient's quality of life and day-to-day activities. Mild disease, which is typically considered to be fewer than 5 bowel movements per day, does not negatively affect daily life, as patients are able to adapt to the bowel frequency. Moderate to severe disease is characterized by more frequent bowel movements—up to 10 per day—with bleeding. This degree of severity may interfere with patients' attendance at work or school.

Clinical trials in UC have classically used the Mayo Score, which is based on the frequency of bowel movements, the number of bowel movements with blood, and an overall assessment of how the symptoms impact daily activities (Table 1).[10] There is not one simple method of evaluating a patient's disease severity. One patient may develop proctitis that is severe and disabling, whereas another patient may have extensive colitis that is mild and has a limited effect on daily activities. There can also be disparities between a patient's symptoms and the endoscopic appearance. There

are patients with mild endoscopic disease who have severe symptoms, and there are patients with more severe colonic inflammation who have no quality-of-life impairments.

Prognosis in Ulcerative Colitis

UC is a chronic, lifelong disease. Most UC patients lead normal lives and have a typical lifespan. Fertility is similar to that in the general population, and most women are able to conceive and have children.

Some patients with UC become incapacitated by persistent or refractory symptoms. Rare complications include fulminant disease and toxic megacolon. Patients with UC are at greater risk of developing colorectal cancer than the general population.[11] This risk is related to the extent and persistence of inflammation and the duration of the disease. Today, with the use of regular surveillance for precancerous changes and effective treatment, the risk of cancer has been markedly reduced.

Disclosure

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Current Treatment Approaches for Mild to Moderate Ulcerative Colitis

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The primary goals of therapy for patients with UC are to induce remission, maintain remission (ie, minimize risk of relapse), and enhance quality of life (Table 2). Mucosal healing is also now recognized as an important treatment goal. At the same time, we aim to prevent and treat complications of the disease and avoid short-term and long-term toxicities of therapy. A variety of medical therapies are used in the treatment of UC, including aminosalicylates, corticosteroids, immunomodulators, and biologic agents.

Table 2. Goals of Therapy for Patients With Ulcerative Colitis

Inducing remission
Maintaining remission
Mucosal healing
Restoring and maintaining nutrition
Maintaining patient's quality of life
Surgical intervention (selection of optimal time for surgery if needed)

Anti-Inflammatory Agents

Oral 5-aminosalicylic acid (5-ASA) is widely used in the treatment of UC based on its efficacy in inducing and maintaining remission.[1,2] Various formulations of 5-ASAs have been developed, all with the end goal of adequately delivering mesalamine directly to the bowel, where it exerts a topical local effect on the mucosa. One group of aminosalicylates is the pH-dependent compounds. These agents include various formulations of mesalamine: delayed-release, granulated, and

one that uses Multi Matrix System (MMX) technology. They release mesalamine starting in the ileum and continuing in the colon. Another formulation is an ethyl cellulose–encapsulated timed-release mesalamine, which releases the active agent in the beginning of the duodenum. Other aminosalicylates, such as sulfasalazine, olsalazine, and balsalazide, are linked via an azo bond to a carrier compound; the active drug is released when bacterial enzymes in the intestines cleave the azo bond.

In multiple clinical trials, oral 5-ASA preparations have demonstrated significantly greater efficacy over placebo for the induction of remission in patients with active UC.[1] These findings have led to the regulatory approval of these agents for the treatment of patients with active UC. Stringent analyses have found no differences in the efficacy or safety of the various 5-ASA formulations.[1]

High-dose mesalamine (4.8 g/day) has not demonstrated superior remission rates over moderate dosing (2.4 g/day) in patients with UC.[1] A post hoc analysis suggested that higher doses may be beneficial in patients who have received other prior therapies (which indicates more refractory disease).[3] However, this association has not yet been prospectively evaluated as a primary endpoint. The conventional dosing of 5-ASAs has been 2 or 3 times daily. Recent evidence, however, indicates that once-daily dosing is as effective and safe as the more frequent dosing strategy.[4] UC patients who fail to achieve remission with 8 weeks of mesalamine therapy can achieve remission following a further 8 weeks' treatment with high-dose MMX mesalamine therapy.[5]

Mesalamine is fairly well tolerated, with relatively few adverse events.[1] Typically, intolerance to mesalamine occurs in fewer than 5% of patients. One significant concern is an association between mesalamine and renal impairment, including the potential for interstitial nephritis.[6] Recent analyses indicated that approximately half of interstitial cases develop in the first year of therapy.[7,8]

Therefore, it has been proposed that patients starting treatment with a 5-ASA undergo blood urea nitrogen testing, creatinine measurement, and urinalysis before starting therapy, several months after starting therapy, and perhaps annually thereafter. This recommendation has not been universally accepted, and there is controversy regarding whether renal dysfunction is related to mesalamine or represents an extraintestinal manifestation of UC.

Other adverse events associated with mesalamine include nausea, vomiting, and worsening of colitis. In patients with worsening symptoms, a treatment break of several days can help distinguish whether the symptoms are a consequence of medical therapy or disease progression.

Corticosteroids

It has been more than 50 years since corticosteroids were first recognized for their efficacy in the treatment of UC, and they continue to be used today. In a 2001 population-based cohort study that included 185 patients with UC, systemic corticosteroids were associated with a complete remission rate of 54%, a partial remission rate of 30%, and no response in 16%.[9] After 1 year, 49% of patients had a prolonged response, 22% had corticosteroid dependence, and 29% required surgery.[9]

There are significant potential toxicity concerns with corticosteroids. Skeletal toxicities include risks for osteoporosis, striae, and loss in bone mineral density (BMD).[10] Recent data indicate that prednisone (7.5 mg or equivalent) administered for 3 months is sufficient to alter BMD.[11,12] Therefore, BMD assessment with DEXA scanning is advocated for patients receiving corticosteroids. In addition, corticosteroids have been associated with anxiety, depression, and hyperglycemia.

These adverse events led to the development of a less toxic corticosteroid. Budesonide has a lower systemic bioavailability—and therefore less toxicity—than conventional corticosteroids. This budesonide formulation, which incorporates MMX technology, allows once-daily oral dosing that delivers the agent throughout the colon. The randomized, double-blind, placebo-controlled CORE (Colonic Release Budesonide) I and II studies compared budesonide MMX at 2 doses (9 mg and 6 mg) vs placebo in patients with mild to moderate UC.[13,14] These studies used a primary endpoint of combined clinical and endoscopic remission, stringently defined as a score of 1 or less on the UC Disease Activity Index with a score of 0 for rectal bleeding and stool frequency, no mucosal friability on colonoscopy, and reduction of at least 1 point on the endoscopic index. In a pooled analysis of the 2 trials, budesonide MMX at 9 mg was significantly more effective than placebo at week 8 as assessed by a rate combining clinical and endoscopic remission (17.7% vs 6.2%; P=.0002; Figure 3).[15] Symptom resolution and colonoscopic improvement rates were also significantly superior with budesonide MMX (9 mg) vs placebo.[16] The safety profile of budesonide MMX was similar to that of placebo. Budesonide MMX has been associated with minimal adverse events, such as fluid retention and acne. In general, corticosteroids are not effective for maintaining remission, and budesonide MMX is not indicated for maintenance therapy.[16,17]

Corticosteroids may be considered in patients who have active symptoms despite optimized mesalamine therapy. In the population of patients with moderate or severe UC, it may also be reasonable to initiate treatment with corticosteroids when needed, given the potential long-term benefits. The use of corticosteroids might be considered a "tipping point" in the treatment of UC, indicating a more virulent disease course. If corticosteroids are required twice within a year or if a patient has a severe flare of IBD mandating parenteral corticosteroids, there is a need for a corticosteroid-sparing agent. Although immunomodulators were historically used for these patients, most clinicians would now advocate the use of biologic treatment.

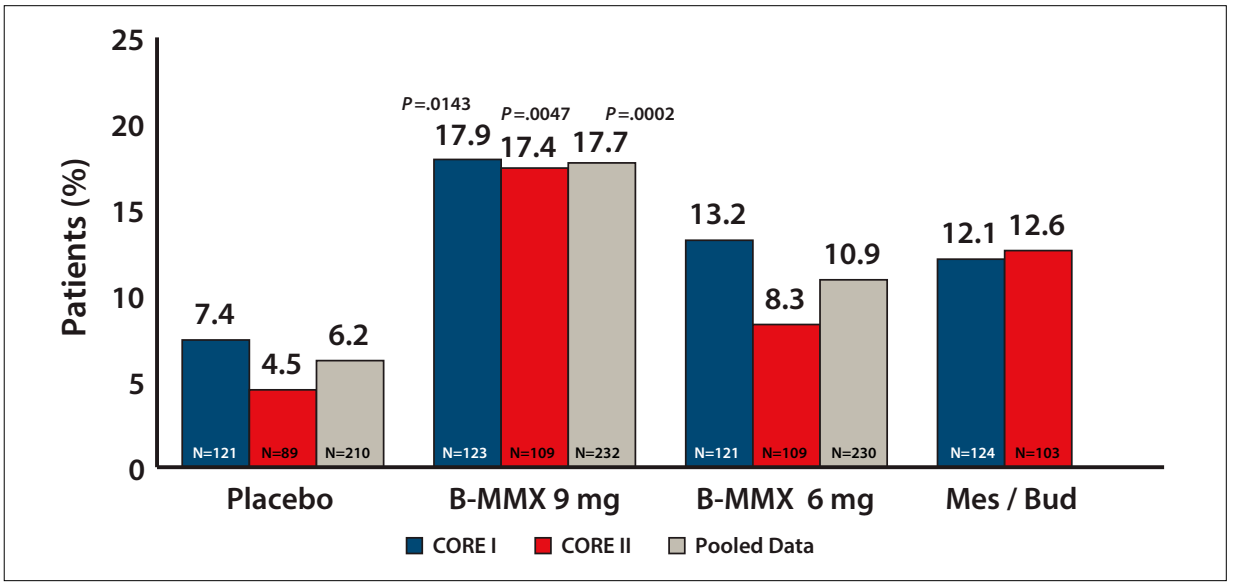

Figure 3. Combined clinical and endoscopic remission in the CORE I and II trials, which compared budesonide MMX at 2 doses (9 mg and 6 mg) vs placebo in patients with mild to moderate UC.

Bud, budesonide; B-MMX, budesonide MMX; CORE, Colonic Release Budesonide; Mes, mesalamine. Data from Sandborn WJ et al. *Gastroenterology*. 2012;143(5):1218-1226.e1-2,[13] Travis SP et al. *Gut*. 2014;63(3):433-441,[14] and Sandborn WJ et al. *Aliment Pharmacol Ther*. 2015;41(5):409-418.[15]

Azathioprine

The immunosuppressive agent azathioprine has been used for the treatment of UC since the 1960s, although neither azathioprine nor 6-mercaptopurine are approved by the US Food and Drug Administration (FDA) for this indication. For many years, azathioprine was one of the only agents available and avoided the adverse events associated with conventional corticosteroids (given its corticosteroid-sparing nature). It is now recognized that azathioprine is more effective for maintaining remission than for inducing it.[18,19] In addition, azathioprine does not begin to exert a clinical effect until approximately 2 to 3 months after initiation of therapy, as shown in a study of CD.[20] Given its lack of significant benefit for induction therapy, many clinicians now favor the use of biologic therapy.

Overview of Biologic Agents

Multiple factors are weighed when considering the use of biologic therapy for patients with UC. Patient-related factors include current and prior therapies; disease activity, location, and extent; demographics; and comorbidities. Treatment-related factors include the therapy's efficacy, safety, cost, and convenience. Biologic therapy is indicated for UC patients with:

- Corticosteroid-refractory disease.
- Corticosteroid-dependent disease.
- Disease that is refractory to or intolerant of immunomodulators.
- Disease that is refractory to or intolerant of anti–tumor necrosis factor (TNF) agents (for consideration of anti-integrin therapy).

Patients with clinical predictors of a poor outcome at diagnosis might also benefit from biologics. Biologic therapy for patients with UC includes the anti-TNF agents infliximab, adalimumab, and golimumab and the integrin inhibitor vedolizumab (Figure 4).

Efficacy of Tumor Necrosis Factor Inhibitors

Infliximab is a TNF inhibitor that is administered intravenously, typically throughout a 2-hour infusion. The ACT (Active Ulcerative Colitis Trials) 1 and 2 studies evaluated the efficacy of infliximab in the induction and maintenance of remission in patients with moderately to severely active UC despite treatment with concurrent medications.[21] Infliximab was significantly more effective than placebo at weeks 8, 30, and 54. In ACT 1, clinical response rates were higher with infliximab administered at 5 mg or 10 mg than with placebo (45%, 44%, and 20%, respectively; $P<.001$ for both comparisons). In a post hoc analysis, infliximab-treated patients were also more likely to avoid colectomy.[22]

Adalimumab is a subcutaneously administered TNF inhibitor that was evaluated in the ULTRA 2 (Ulcerative Colitis Long-Term Remission and Maintenance With Adalimumab 2) trial, a randomized, double-blind, placebo-controlled trial conducted in 494 patients with moderate to severe UC receiving concurrent oral corticosteroids or immunosuppressants.[23] Adalimumab was significantly

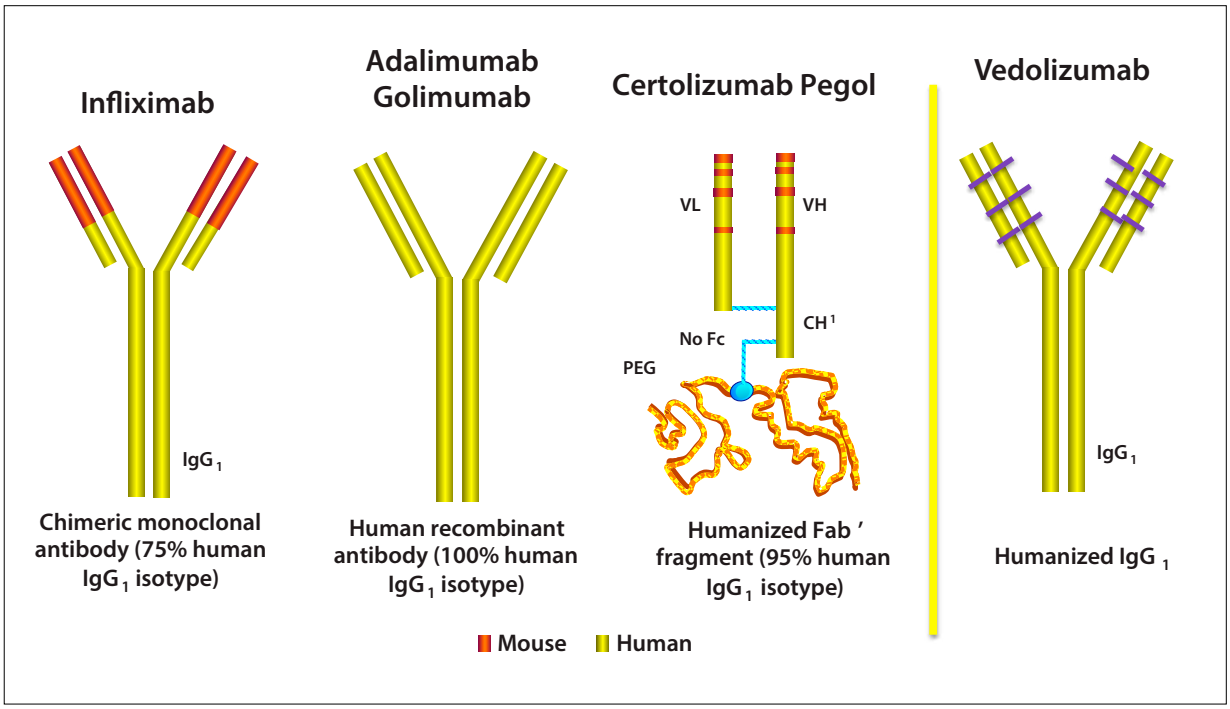

Figure 4. Biologic agents approved for Crohn's disease or ulcerative colitis.

Fc, fragment crystallizable; Ig, immunoglobulin; PEG, polyethylene glycol; VH, variable heavy chain; VL, variable light chain.

more effective than placebo as assessed by the clinical remission rates at week 8 (16.5% vs 9.3%; *P*=.019) and week 52 (17.3% vs 8.5%; *P*=.004). Patients receiving adalimumab were also more likely to discontinue corticosteroids.

The third TNF inhibitor approved for the treatment of UC is golimumab, a subcutaneously administered agent that was evaluated in the phase 2/3 PURSUIT (Program of Ulcerative Colitis Research Studies Utilizing an Investigational Treatment) trial.[24,25] In this trial, patients were randomized to receive placebo or golimumab at different doses: 100 mg at week 1 followed by 50 mg at week 2 (phase 2 only), 200 mg at week 1 followed by 100 mg at week 2, or 400 mg at week 1 followed by 200 mg at week 2. Week 6 clinical response rates were 51.0% and 54.9% with golimumab administered at 200 mg/100 mg and 400 mg/200 mg, respectively, compared with 30.3% for placebo (*P*≤.0001 for both comparisons).[24] In a maintenance study of the 464 patients who responded to induction therapy in the PURSUIT study, golimumab maintained clinical responses through week 54.[25] At week 54, maintenance golimumab was significantly more effective than placebo as assessed by clinical remission rate and mucosal healing rate.

Safety of Tumor Necrosis Factor Inhibitors

The safety profile of anti-TNF agents is now fairly well recognized. The potential risks include antidrug antibody formation, delayed hypersensitivity reaction, lupus-like reaction, and skin reactions, such as pustular psoriasis.[26] Treatment options for skin toxicities depend on the severity of the reaction. For patients with mild disease, who have a Psoriasis Area and Severity Index score of less than 5%, a topical treatment might be appropriate.[27] Severe skin involvement may require a switch to an agent with a different mechanism of action. Another option is to decrease the dose of the anti-TNF agent. It is recognized in the rheumatologic literature that high drug levels may increase the risk of skin-related adverse events.[28] Anecdotal data indicate that reducing the dose while using therapeutic drug monitoring might be advantageous.

Another adverse event includes increased mortality in patients with advanced heart failure.[29] Although it has been suggested that anti-TNF agents also increase the risk of congestive heart failure, this association has not been well substantiated. Before initiating treatment with a TNF inhibitor, patients should be screened for latent tuberculosis, and, when appropriate, antituberculous chemoprophylaxis should be initiated.

Development of Integrin Inhibitors

Although TNF inhibitors are widely used in the treatment of UC, there are patients who either do not attain a response to an anti-TNF agent, who lose their response, or who develop adverse events associated with anti-TNF therapy. The need for alternative biologic agents for this population

led to the development of the integrin inhibitors, which block the migration of leukocytes into the mucosal tissue.[30]

The first integrin inhibitor to gain regulatory approval for treatment of patients with IBD (specifically CD) was natalizumab, a humanized monoclonal antibody targeting the $\alpha_4\beta_1$ integrin. A significant limitation of natalizumab is that it conferred a small risk of progressive multifocal leukoencephalopathy (PML) in patients with the JC virus.[31] A second integrin inhibitor, vedolizumab, was developed that is directed against the integrin $\alpha_4\beta_7$. This more-selective inhibitor was hypothesized to have a lower risk of PML because it affects lymphocyte migration in the gut but not the brain. The efficacy and safety of vedolizumab for induction and maintenance therapy for UC was evaluated in the randomized, double-blind, placebo-controlled GEMINI 1 trial.[32] At week 6, vedolizumab was significantly more effective than placebo as assessed by clinical remission rates (16.9% vs 5.4%; *P*=.001) and rates of mucosal healing (40.9% vs 24.8%; *P*=.001).[32] At week 52, clinical remission rates were significantly higher with vedolizumab administered every 8 weeks (41.8%) or every 4 weeks (44.8%) compared with placebo (15.9%; *P*<.001 for both). Durable clinical response rates, durable clinical remissions, mucosal healing, and corticosteroid-free remission rates were also higher with vedolizumab than with placebo. Moreover, vedolizumab was beneficial regardless of the patient's treatment history, whether that included prior anti-TNF failure, prior anti-TNF loss of response, or no previous anti-TNF therapy.[32] Vedolizumab, which is administered via intravenous infusion, received FDA approval in 2014 for patients with previously treated moderately to severely active UC.

The main risk associated with vedolizumab is nasopharyngitis.[32] Infusion reactions are infrequent, abnormal liver chemistries are rare, and no cases of PML have been observed in any trials.

Role of Rectal Therapy

When considering the various treatment modalities for UC, it is important to recognize that the rectum requires separate treatment. Patients receiving a biologic agent or mesalamine may require a second agent to address rectal symptoms such as tenesmus, urgency, or worsening continence. Although such rectal symptoms may qualify as mild to moderate by standard definitions, they are often considered severe by patients living with the condition. For example, incontinence can be embarrassing and difficult to manage.

The decision to use rectally administered therapy is guided by the proximal extent of disease and by patient preference. There are clear advantages to rectal delivery over oral therapy in some circumstances. It has long been recognized that left-sided disease and extensive disease have improved responses when topical therapy is added to the existing oral mesalamine regimen.[33,34] Topical mesalamine has been advocated as preferable to oral therapy in patients with proctitis/proctosigmoiditis and left-sided UC because it provides sufficient concentrations of active drug at the inflamed site. Moreover, systemic absorption is considerably low given that the therapeutic efficacy of mesalamine is topical in nature. Other advantages include a generally faster response and a less frequent dosing regimen.[35]

A recent meta-analysis of controlled trials indicated the superiority of topical mesalamine over the oral formulation in patients with mild to moderate distal UC.[36] In clinical practice, rectal application of mesalamine frequently serves as an alternative or an add-on therapy to oral mesalamine therapy.

Several formulations of rectal therapies are available. Mesalamine suppositories have demonstrated efficacy in the treatment of active proctitis and also for the maintenance of remission.[37,38] Their use is often limited, however, by the insufficient spread of active drug beyond the rectum (up to 10-15 cm). The spread of mesalamine liquid enema formulations usually extends to the sigmoid region and the splenic flexure region, and this formulation has been shown to be effective in inducing and maintaining remission in distal colitis.[39-41] However, patient acceptance may be low due to factors such as difficulties in self-administration, retention discomfort, and the necessity for prolonged bed rest. Rectal mesalamine foam was developed to overcome the limitations associated with other formulations. The greater viscosity of foam vs liquid enemas favors retention of the product in the rectum, enhances mucosal adhesion, and provides a consistent mucosal spread.[42]

Disclosure

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Emerging Treatment Approaches in Mild to Moderate Ulcerative Colitis

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There has been an effort to improve the treatment of UC by enhancing the safety profile of corticosteroids while maintaining their efficacy. There has also been a need for a topical agent that overcomes the limitations of other delivery systems, such as liquid enemas (which not all patients can retain) and suppositories (which are designed to treat the rectum only). An ideal topical therapy would be relatively easy to administer, well retained, and effective in treating both the left colon and the rectum. It would treat the signs and symptoms of UC as well as induce remission.

A therapy that was designed to meet these needs is budesonide foam, which recently received FDA approval for the induction of remission in patients with mild to moderate distal UC extending up to 40 cm from the anal verge.[1] This area includes the rectum, which spans the first 10 cm to 15 cm, as well as the sigmoid colon, which spans the next 25 cm to 30 cm. The recommended dosing regimen of budesonide foam is 1 metered 2-mg dose administered rectally twice daily for 2 weeks followed by 1 metered 2-mg dose administered rectally once daily for 4 weeks.

Clinical Trials of Budesonide Foam

Two randomized, placebo-controlled trials were conducted to evaluate the efficacy and safety of budesonide foam in inducing remission in patients with mild to moderate UC.[2] The studies enrolled 546 patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis extending at least 5 cm, but no more than 40 cm, from the anal verge. Patients were randomly assigned to budesonide foam 2 mg or placebo administered rectally twice daily for 2 weeks, followed by once daily for 4 weeks. Patients were permitted to receive concomitant oral 5-ASAs at a dosage of up to 4.8 g/day.

At week 6, the proportion of patients in remission was significantly higher with budesonide foam vs placebo in both study 1 (38.3% vs 25.8%; *P*=.0324) and study 2 (44.0% vs 22.4%; *P*=.0001; Figure 5).[2] The observation of substantial clinical activity after 6 weeks indicates the rapid onset of activity with budesonide foam. Budesonide foam was also superior to placebo as assessed by the proportion of patients with complete resolution of rectal bleeding in study 1 (46.6% vs 28.0%; *P*=.0022) and study 2 (50.0% vs 28.6%; *P*=.0002).[2] Multiple other endpoints, including endoscopic improvement, mucosal healing, and reduction in stool frequency, were all significantly superior with budesonide foam vs placebo. More than half of patients in the 2 trials were receiving concurrent 5-ASAs, with the budesonide foam added on as an adjunctive therapy. Notably, budesonide foam appeared to have similar efficacy regardless of the use of concomitant 5-ASA.[2]

Table 3. Cortisol Concentrations in Studies of Budesonide Foam

Total cortisol >5 µg/dL (138 nmol/L),[a] n/N[b] (%)	Budesonide foam 2 mg/25 mL (%)	Placebo (%)
Baseline	259/268 (96.6)	275/278 (98.9)
Week 1 (bid)	224/263 (85.2)	264/269 (98.1)
Week 2 (bid)	216/257 (84.0)	263/266 (98.9)
Week 4 (qd)	218/235 (92.8)	243/249 (97.6)
Week 6 (qd)	211/224 (94.2)	234/241 (97.1)

[a] Lower limit of normal.

[b] Denominator N is the number of patients with a value for each given week during the study.

bid, twice daily; qd, once daily.

Data from Sandborn WJ et al. *Gastroenterology*. Published online January 30, 2015. doi: 10.1053/j.gastro.2015.01.037.[2]

Most adverse events were mild to moderate, occurring at similar rates with budesonide foam and placebo. A decrease from baseline in serum cortisol concentrations occurred in 17% of patients receiving budesonide foam, although most patients maintained cortisol concentrations within the normal range (Table 3).[2] Moreover, clinically symptomatic adrenal insufficiency was not reported.

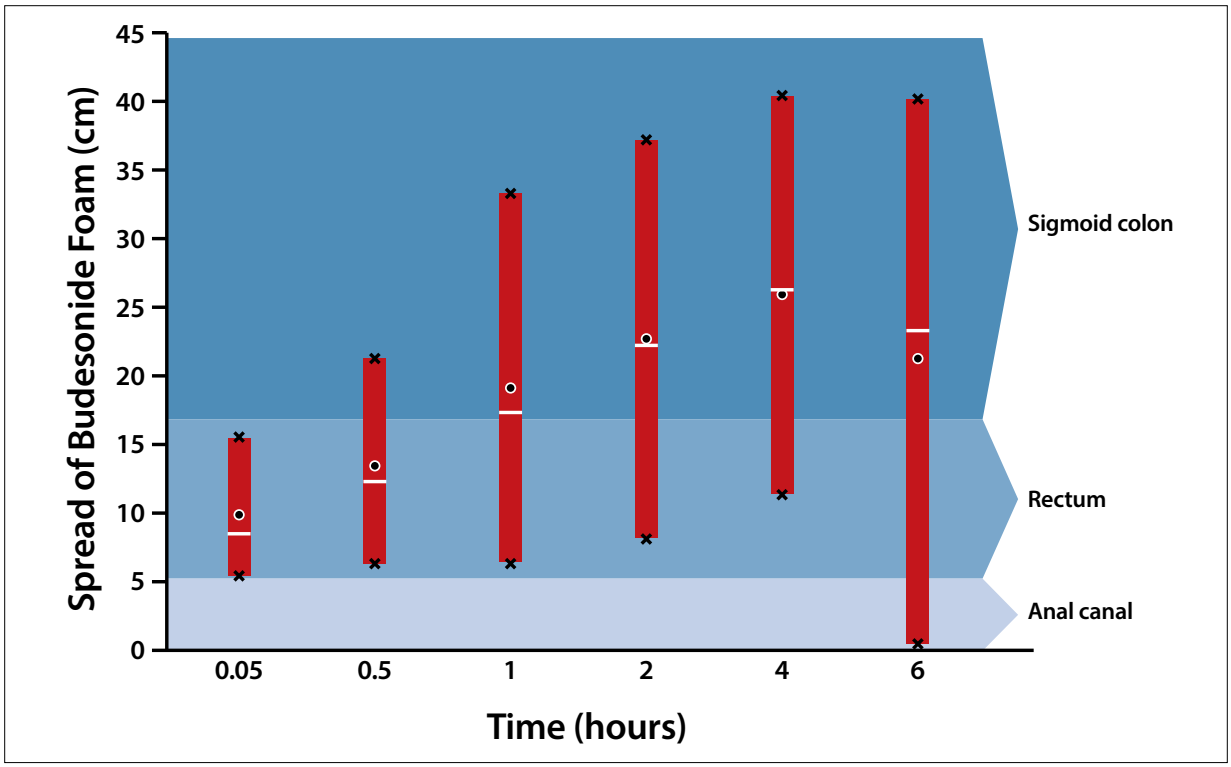

Figure 5. Spread of budesonide foam. From anus: mean (0), median (-), and minimum and maximum (x) values are indicated.

Adapted from Brunner M et al. *Aliment Pharmacol Ther*. 2005;22(5):463-470.[3]

Potential Advantages of Foam Preparations

A foam preparation offers several advantages over other formulations for rectal delivery. The foam has greater proximal reach than suppositories, which have a limited span of delivery (Figure 6).[3] A drawback to liquid enemas is their poor rectal retention, which can reduce the amount of drug that coats the site of active disease. Moreover, fecal leaking can occur with both suppositories and liquid enemas over time.

With foam formulations, a high concentration of drug can be administered and easily retained. Scintigraphic studies have shown that the foam expands to fill space, creating an even distribution.[3] This enhanced exposure of the mucosa to the active product may maximize the treatment benefit, which might account for the high remission rates observed with budesonide foam even in patients who have failed mesalamine therapy. Another advantage of rectally administered budesonide foam is that it allows the use of lower drug doses compared with delayed-release or suspended-release oral delivery systems.

Other Foam Preparations

A hydrocortisone foam is indicated as an adjunctive therapy for the topical treatment of UC in patients who cannot retain hydrocortisone or other corticosteroid enemas.[4] A drawback to hydrocortisone foam is that it delivers a conventional corticosteroid (as opposed to budesonide, which was designed to minimize systemic effects). Repeated use of hydrocortisone foam may lead to suppression of the hypothalamus-pituitary-adrenal axis. In contrast, the budesonide foam has a high first-pass hepatic metabolism, which lessens the adverse effects associated with systemic corticosteroids.

Future Directions in Moderate to Severe Ulcerative Colitis

Multiple new approaches continue to be explored in the setting of moderate to severe and refractory UC. Several investigational integrin inhibitors are being evaluated, including etrolizumab, which targets the integrin β7, and AMG 181, a gut-specific anti-$\alpha_4\beta_7$ antibody. Etrolizumab demonstrated clinical efficacy in a randomized, controlled, phase 2 trial in patients with moderate to severe UC not responding to conventional therapy.[5] It is being evaluated in a phase 3 trial in patients with UC who are refractory to, or intolerant of, TNF inhibitors.[6] AMG 181 has demonstrated acceptable clinical pharmacology and is undergoing evaluation in clinical trials.[7]

Efforts are also underway to develop therapies that modulate lymphocyte trafficking by targeting sphingosine-1-phosphate (S1P1), which affects egress of lymphocytes out of lymph nodes. The S1P1 receptor agonist fingolimod is

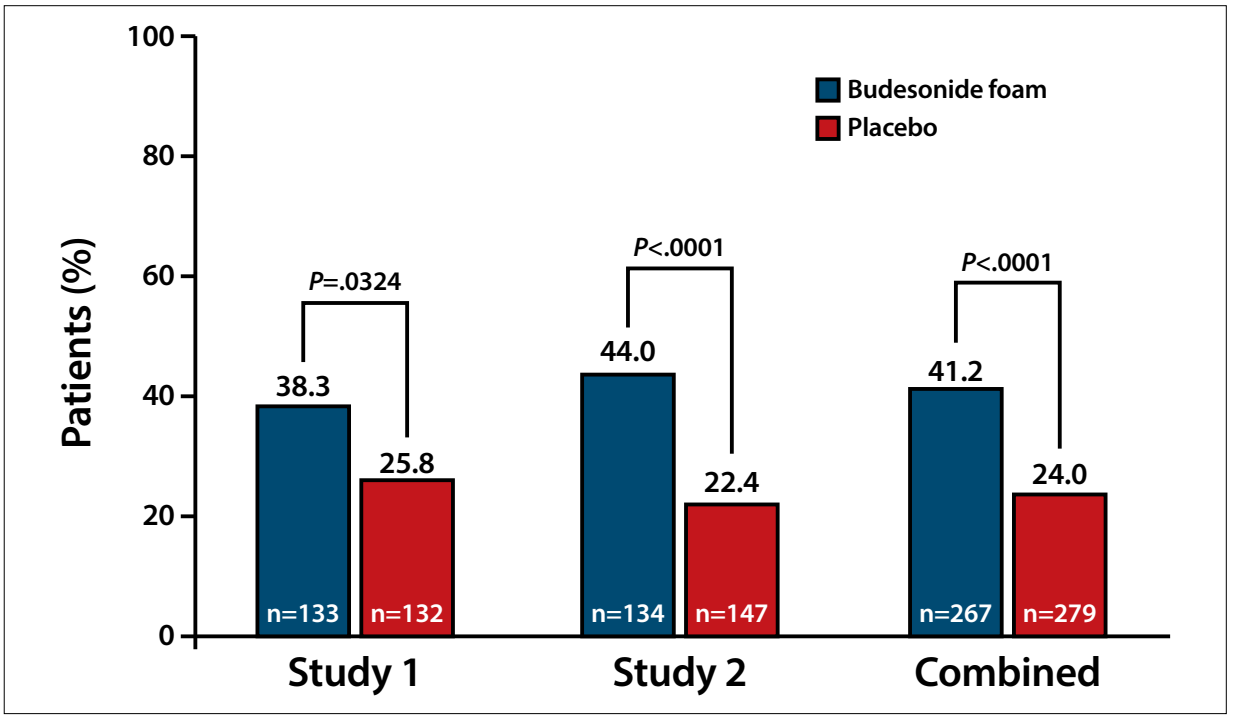

Figure 6. Patients achieving remission at week 6 in 2 randomized, placebo-controlled trials of budesonide foam.

Adapted from Sandborn WJ et al. *Gastroenterology*. Published online January 30, 2015. doi:10.1053/j.gastro.2015.01.037.[2]

FDA-approved for the treatment of multiple sclerosis; however, it lacks specificity and is associated with cardiac toxicity.[8] A more specific S1P1 agonist, RPC1063, has positive phase 2 data in patients with moderate to severe UC.[9]

Several Janus kinase (JAK) inhibitors are being evaluated in the treatment of UC. The pan-JAK inhibitor tofacitinib, which has been shown to affect multiple cytokines, demonstrated efficacy as induction therapy in patients with moderate to severe UC.[10] Tofacitinib is currently being evaluated in phase 3 trials for induction and maintenance of remission in patients with moderately to severely active UC.[11,12] Potential safety concerns with tofacitinib include significant immunosuppression, which is associated with a small increased risk of infection.[10]

More selective JAK inhibitors are also being evaluated. There is speculation that narrowing the spectrum of JAK inhibition could improve the safety profile of these agents. If a new agent can retain the efficacy of tofacitinib while decreasing toxicity, it may yield an overall improvement in the risk/benefit ratio for this class of drugs. The efficacy and safety of these newer agents must be evaluated.

Disclosure

Dr Sandborn is a consultant for Salix, Takeda, Genentech, Amgen, Pfizer, Receptos, Janssen, AbbVie, Shire, and Actavis. He has received research support from Shire, Genentech, Amgen, Pfizer, Receptos, Janssen, and AbbVie.

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Emerging Treatment Options in Mild to Moderate Ulcerative Colitis: Discussion

Stephen B. Hanauer, MD, William J. Sandborn, MD, and Gary R. Lichtenstein, MD

Stephen B. Hanauer, MD Dr Lichtenstein discussed the efficacy of the many different oral and topical therapies available for patients with mild to moderate UC. There is no single best approach for all patients. Although rectal therapies may be the most effective approach for patients with distal disease, they may or may not be the most desirable for every patient. Interestingly, most of the oral mesalamine drugs and oral budesonide MMX have demonstrated similar efficacy in both extensive and distal disease. Advantages of some of the new topical therapies include very good tolerance and a low adverse event profile. However, patients are not going to improve unless we select a regimen that they will adhere to.

William J. Sandborn, MD The flexibility of the budesonide foam formulation is very interesting. Budesonide foam has the potential for use as first-line therapy in patients with proctitis and distal colitis and in patients who fail treatment with oral or rectal mesalamine. In patients with distal colitis—in whom the next steps may be systemic corticosteroids, immunosuppressive agents, and biologics—it is exciting to have a therapeutic option that induces remission rates of up to 40%.[1] It is also likely that a rectal corticosteroid could be beneficial in a patient who has attained a partial response with biologics or other therapies. Moreover, the combination of oral and rectal mesalamine tends to be more effective than either drug alone, although this approach has not been directly studied.

There are other scenarios in which the budesonide foam formulation has the potential to be effective. It may be beneficial in the postoperative UC patient population. Oral budesonide is effective in the treatment of antibiotic-refractory pouchitis.[2] For patients who have undergone colectomy with a stapled ileoanal anastomosis and have cuffitis (residual ulcerative proctitis), we often use mesalamine or corticosteroid suppositories. I suspect that budesonide foam would be effective for these patients. There may also be a role for budesonide foam in the treatment of Crohn's proctitis, given that oral budesonide is effective against proximal CD.[3]

Gary R. Lichtenstein, MD I think that is very much the case. Any time we are treating patients with IBD, we try to match the appropriate therapy to the patient. As Dr Hanauer mentioned, one size does not fit all. For each patient, we try to select the optimal therapy that will achieve the greatest efficacy with the fewest side effects, while considering the patient's own preferences.

We also reassess the therapy as treatment is progressing. As Dr Sandborn highlighted in a recent publication,[4] there is a shift toward adopting a treat-to-target approach in IBD, where responses are assessed and therapy is modified if needed. In some cases, patients may have just a small amount of persistent inflammation in the rectum. For these patients, we would consider topical therapy. Although there may not yet be clinical trial evidence to support this strategy, it is used in clinical practice. Therefore, the treatment algorithms used in clinical practice do not always align with available clinical trial data, and we tailor the therapy to the patients directly.

Disclosures

Dr Hanauer has received honoraria from AbbVie, Janssen, UCB, Actavis, Shire, Salix, and Takeda. Dr Sandborn is a consultant for Salix, Takeda, Genentech, Amgen, Pfizer, Receptos, Janssen, AbbVie, Shire, and Actavis. He has received research support from Shire, Genentech, Amgen, Pfizer, Receptos, Janssen, and AbbVie. Dr Lichtenstein is a consultant for Abbott Corporation/AbbVie, Actavis, Alaven, Ferring, Hospira, Janssen Biotech, Luitpold/American Regent, Pfizer Pharmaceuticals, Prometheus Laboratories, Inc, Salix Pharmaceuticals, Santarus, Shire Pharmaceuticals, Takeda, UCB, and Warner Chilcott. He has received research support from Ferring, Janssen Biotech, Prometheus Laboratories, Inc, Salix Pharmaceuticals, Santarus, Shire Pharmaceuticals, UCB, and Warner Chilcott. He has received honoraria for CME programs from Ironwood and Luitpold/American Regent. He has received a grant from Warner Chilcott.

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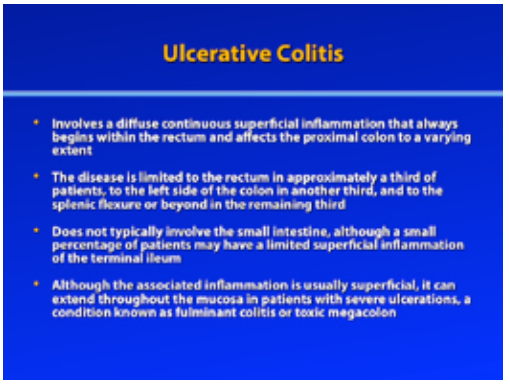

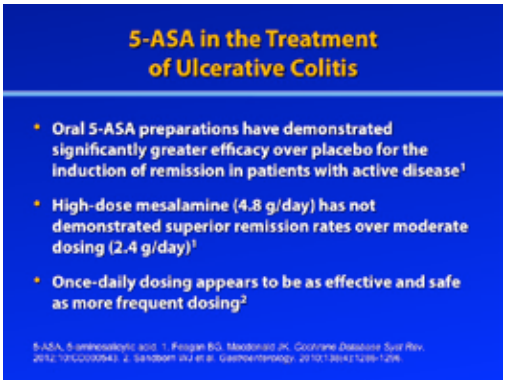

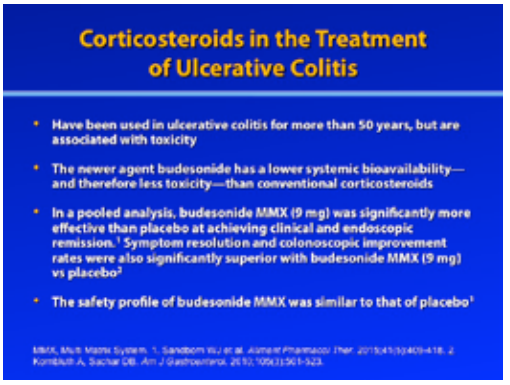

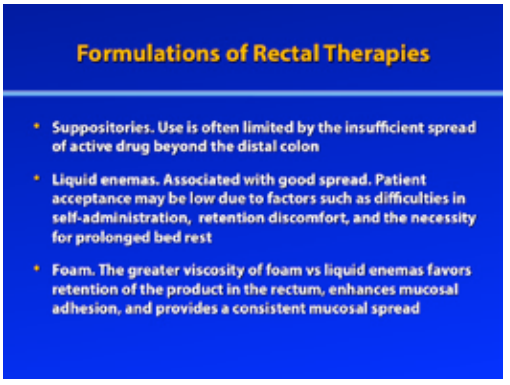

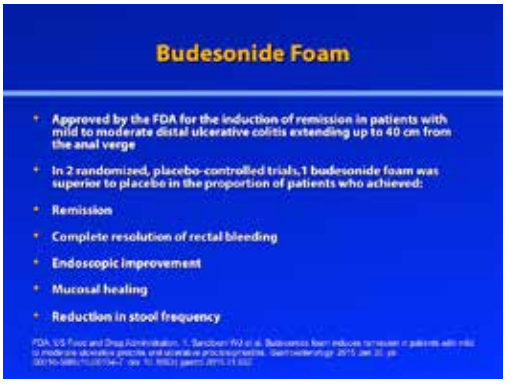

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