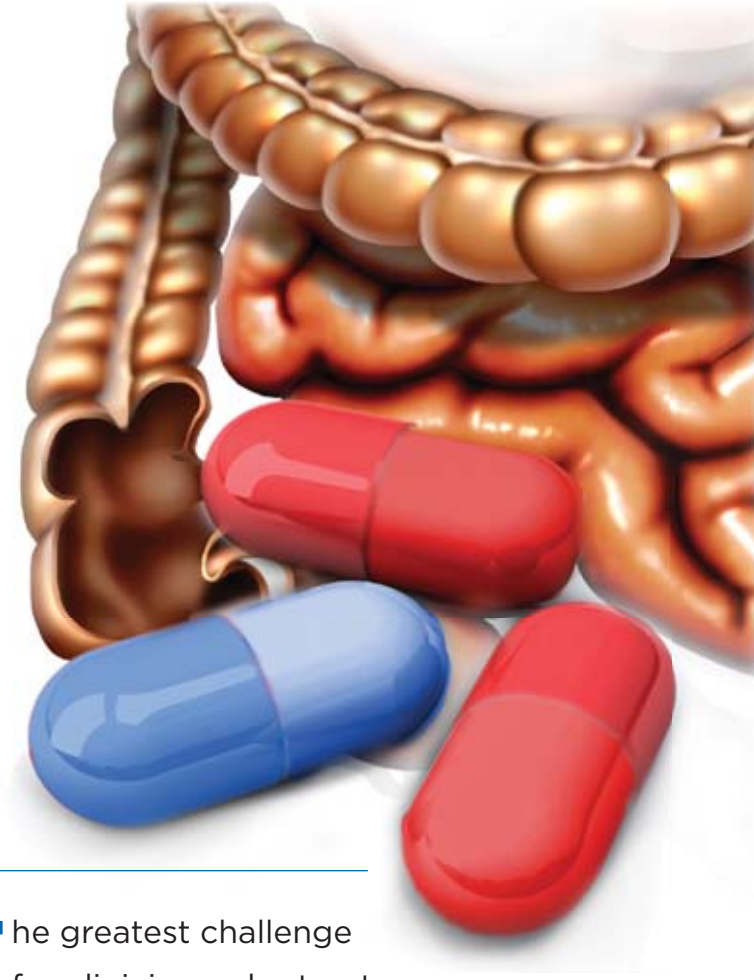
Ulcerative Colitis:
Diagnosis and Treatment



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The greatest challenge for clinicians who treat patients with inflammatory bowel disease (IBD) is to move from symptom-oriented (step-up) strategies toward prevention-oriented (early intervention) strategies aimed at tight inflammation control and alteration of the natural history of IBD. This review focuses on a personalized approach to the treatment of patients with ulcerative colitis (UC).

Challenging the Traditional IBD Diagnosis

Traditionally, IBD has been divided into 2 distinct entities: UC and Crohn's disease (CD). A nuanced view presents IBD as an immuno-inflammatory spectrum of chronic and recurring diseases of the intestines defined by individual molecular signatures. This newly gained perspective holds the promise of moving treatment in a more proactive, personalized direction, toward targeting molecules and risk assessment, rather than treating symptoms of the disease.

One of the major questions facing clinicians is whether IBD is a single entity or a spectrum of multiple disorders. This distinction becomes particularly difficult to make when attempting to classify CD. Three distinct manifestations of CD have been described—inflammatory, fistulizing, and fibrostenotic.[1-3] However, Crohn's colitis has not been well defined in the literature.[4] Some patients present with CD-like features—such as UC with rectal sparing or UC with nonepithelial granulomas. Other manifestations of the heterogeneity of colitis are a superficial mucosal CD involving left-sided refractory colitis with rectal involvement (which may actually represent a type of mixed collagenous colitis or vascular collagen disorder still undefined), rectal disease with cecal patch, and a form of UC with post-treatment alterations.[4]

The many forms of UC (eg, ulcerative proctitis, left-sided colitis, universal colitis) led Brooke[5] to suggest that, rather than a single disease entity, UC represents a pathologic state with many etiologies. Indeterminate colitis (IC) might represent part of an immunologic continuum, rather than a well-defined clinical subset of UC and CD.[6,7]

IBD is a dysregulated immune response to luminal microbial antigens. Serologic markers may provide a window for observing an abnormal antibody–antigen response and may help identify patients at risk for rapid progression of disease who may benefit from early intervention.[8] Molecular diagnostics, such as antibody serology, biomarkers, and genotyping hold the promise of enhancing the understanding of IC and stratifying patients with IBD on the basis of immunophenotypes and immunogenotypes.[9]

Differential diagnosis is increasingly recognized as important in distinguishing active inflammation from medication–pseudo-refractory IBD—which may include infections (eg, *Clostridium difficile*, cytomegalovirus), overlap with irritable bowel syndrome, celiac disease, lactose and/or fructose intolerance, dietary indiscretion, bile acid diarrhea, and obstructive stricturing or fistulizing CD requiring surgery—and in stratifying optimal therapeutic response to biologics and immunosuppressives.[10] In selected patients with moderate to severe active IBD, early intervention with effective therapy is associated with significant improvement in mucosal healing and reduction in the progression of disease.[11-13]

Molecular Classification of IBD

IBD nomenclature does not accurately reflect the complexity of clinical phenotype. Although the role of serum antibody markers remains controversial, using a combination of markers enhances accuracy and specificity in classifying IBD-related aberrant immunophenotypes. The emerging role of molecular diagnostics is vital in characterizing the immunologic heterogeneity of IBD, and will be a bridge linking clinical immunophenotypes with genotypes.[14,15] More than 140 genes associated with IBD have been identified using genome-wide association studies (GWAS), but account for only 25% of the heritability.[16] At present, common gene variants identified by GWAS will be too insensitive and nonspecific to predict disease in unaffected patients. New genes continue to highlight host microbial interactions,[17-20] and serologic markers indicate dysregulated antibody–antigen immune responses.

Differentiation between types of IBD becomes important in stratifying therapeutic strategies. Poor therapeutic response is an indication for surgery in nearly one-third of patients with UC and approximately 50% to 70% of patients with CD. Patients with refractory left-sided colitis or IC may benefit from serologic testing, in addition to documentation of clubbing and oral aphthae.[15]

Serologic signatures have proven helpful in patient stratification. The incorporation of validated biomarkers, such as fecal calprotectin, which has been shown to correlate with endoscopic disease severity in both CD and UC,[21] into clinical decision making also may help identify patients with active disease.

Serologic diagnostic and biomarker testing provides a molecular snapshot of patients with IBD. New markers and prospective trials are required to correlate immunologic, molecular, and clinical patterns of IBD, and will advance the risk assessment of patients, the selection of prevention-oriented therapies, and the science of IBD.

Epidemiology and IBD Subtypes

Epidemiologic data on IBD are fractionated into the pigeonholes of separate diagnoses, with an incidence of 7 to 9 per 100,000 and a prevalence of 200 to 250 per 100,000 for UC; the incidence and prevalence of CD are 6 to 8 per 100,000 and 130 to 200 per 100,000, respectively.[22-24] Although there are patients who fall more clearly into one category than another, the concept of IC is poorly defined and therapeutic guidelines are lacking.

The majority of patients with IBD have moderate disease. Three-fourths of patients have active UC,[25] and

two-thirds of patients with CD have moderate to severe disease that requires alternatives to treatment with mesalamine therapies.[26]

Treatment Options for UC

Treatment goals for patients with IBD are universal: induce remission as quickly as possible, maintain remission as long as possible, facilitate mucosal healing, improve quality of life, minimize toxicity, and minimize cost.

For patients with UC, oral and rectal 5-aminosalicylic acid (5-ASA) agents (including free 5-ASA and 5-ASA prodrugs), corticosteroids (IV [eg, hydrocortisone] or oral [eg, prednisone, methylprednisolone]), immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP]), and cyclosporine are used to induce remission. Uceris is a new, daily-dose, extended-release formulation of budesonide for inducing remission of UC (see "Novel Steroid Options for UC," page 46). For maintenance of remission of UC, 5-ASAs and 6-MP or AZA may be used. Additionally, the anti-tumor necrosis factor (TNF) agents infliximab, and more recently adalimumab, are approved for the reduction of signs and symptoms, induction of clinical remission and mucosal healing, and elimination of corticosteroid use in patients with moderately to severely active UC who have had an inadequate response to conventional therapies.[27]

Probiotics and novel antibiotics (eg, rifaximin) have the potential to revolutionize the treatment of patients with IBD.[28,29] For example, anti-inflammatory interleukin (IL)-10 levels have been associated with *Bifidobacterium infantis*.[30] A greater understanding of gut microecology and the gut microbiome is emerging and further clinical trials are warranted.[31] Treatment with *Trichuris suis* is used to treat both UC and CD, and studies of this therapy in patients with UC are ongoing.[32,33]

Colitis-associated arthritis[34] responds best to sulfasalazine and this may be related to the antibiotic properties of sulfapyridine rather than the anti-inflammatory properties of 5-ASA.[35,36]

5-ASA: First-Line Therapy

Mechanisms of Action

The specific goals of 5-ASA therapy are to quickly induce complete remission, facilitate mucosal healing, and minimize steroid use and toxicity. The effectiveness of the compound is related to its mucosal concentration,[37] and systemic dosages remain low after oral sulfasalazine and rectal 5-ASA administration.[38] The putative anti-inflammatory actions of 5-ASA include modulation of inflammatory cytokine production, decreased transcriptional activity of nuclear factor-kappa B (NF-κB) by modulating RelA/p65

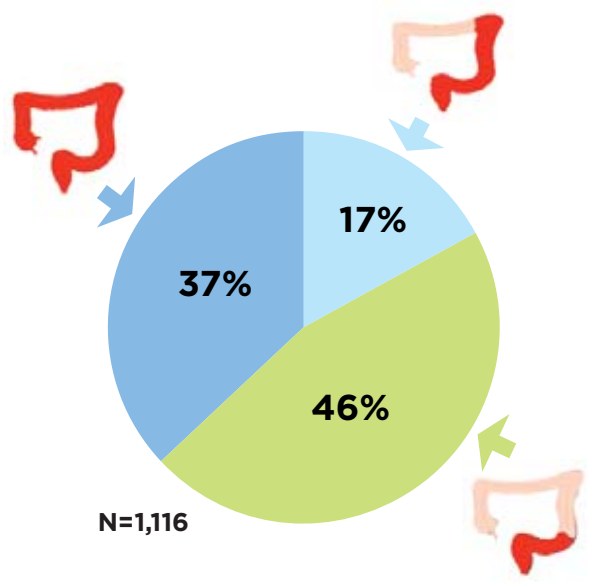

Figure. Disease distribution of ulcerative colitis at presentation to the physician's office.

Based on reference 43.

phosphorylation, and inhibition of the biosynthesis of prostaglandins and leukotrienes.[39]

One proposed mechanism of action of 5-ASA is the inhibition of the cyclooxygenase (COX) and 5-lipoxygenase pathways of arachidonic acid metabolism, resulting in a decrease of proinflammatory prostaglandins and leukotrienes.[40] The role of the COX pathway and prostaglandin biosynthesis in IBD remains to be elucidated. Attention has shifted from the arachidonic acid cascade to NF-κB. The discovery of the role of nucleotide-binding oligomerization domain 2 in the activation of NF-κB emphasizes the importance of NF-κB in the inflammatory signaling cascade and its interaction with luminal bacterial antigens and genetic susceptibility. In vitro studies demonstrate that sulfasalazine inhibits NF-κB, which provides evidence in support of the direct biologic efficacy of 5-ASA.

Recently, it has been postulated that 5-ASA leads to peroxisome proliferator–activated receptor-gamma (PPAR-γ) transcription and protein expression.[41] The PPARs are members of the nuclear receptor superfamily. They are activated by fatty acids and are involved in the complex interplay of metabolic and nutritional signals leading to transcriptional responses. They are expressed in high levels in the colonic epithelium and their ligands are involved in regulation of inflammation.

Table. Mechanisms of Release of 5-ASA–Containing Drugs

Type of 5-ASA	Mechanism of Action	Advantage	Indication
Diffusion-Dependent			
Mesalamine, controlled-release (Pentasa, Shire)	Time-released, moisture-dependent ethylcellulose-encapsulated mesalamine travels in solution and allows free 5-ASA mesalamine to diffuse out of the ethylcellulose beads and begin releasing in the upper intestines and continue throughout the small and large intestines.	Independent of pH or bacteria; mucosal delivery of mesalamine is less affected by rapid intestinal transit time (ie, diarrhea).[45]	Free 5-ASA (mesalamine) is indicated in patients with proximal disease activity, severe diarrhea, strictures (1-mm ethylcellulose microspheres offer advantages), pouchitis (the constant, moisture-dependent release may provide advantages), and postoperative anastomosis.
pH-Dependent			
Mesalamine, delayed-release, pH 7.0 (Asacol, Asacol HD, Delzicol; Warner Chilcott)	The pH-dependent mesalamine preparations are coated with an acrylate resin and are released at variable pH levels, between 6.0 and 7.0 in the distal ileum and colon. (The pH in the ileum and ascending colon is 7.0.)	Free 5-ASA (mesalamine) dosage can be maximized to 4.8-6 g daily, equivalent to a triple dose of sulfasalazine (12 g) with significantly less toxicity. Lialda is a 1.2-g tablet that is a high-dose, delayed-release, pH-dependent mesalamine formulation.[46-48] Once-daily dosage is between 2.4 and 4.8 g (2-4 tablets). Apriso once-daily 1.5-g granulated delayed- and extended-release mesalamine (four 0.375-g capsules) travels in solution.[49-51]	A pH-dependent delivery system is indicated in ileocolonic disease.
MMX mesalamine, pH 7.0 (Lialda, Shire)			
Mesalamine, delayed-release, pH>6.0 (Eudragit-L, Evonik)			
Mesalamine delayed- and extended-release, pH 6.0 (polymer core of slow-release mesalamine; Apriso, Salix)			

5-ASA, 5-aminosalicylic acid; **MMX,** Multi Matrix System

A randomized placebo-controlled trial of rosiglitazone (a PPAR-γ ligand) demonstrated efficacy in treating mild to moderate UC.[42] However, despite these numerous experimental studies, the mechanism of action of 5-ASA remains elusive.

Clinicians should question whether the site of 5-ASA release is a determinant in optimizing and individualizing therapy. Two therapeutic strategies expose jousting views: One is that all 5-ASA preparations are equivalent and that dose escalation leads to optimization; the other is that differences in the mode of 5-ASA delivery translate into differences in clinical efficacy. Often overlooked is the distribution of UC—more than 50% of patients have left-sided disease (Figure)[43]—as well as the variability in colonic pH. Colonic pH may be lower in patients with UC than in those without IBD; thus, employing 5-ASA formulations that release at a lower pH (eg, granulated mesalamine [Apriso, Salix Pharmaceuticals]) may improve drug delivery to the colon while avoiding release in the small intestine.[44]

Both mesalamine (free, unconjugated 5-ASA) and mesalamine prodrugs (azo-bonded 5-ASA) have similar modes of action. Sulfasalazine, the archetypal azo-bonded 5-ASA designer drug, is engineered to release free 5-ASA in the colon, protecting it from proximal absorption.[35,36] Intolerance and hypersensitivity to the sulfapyridine moiety limit the dose

Table. Mechanisms of Release of 5-ASA–Containing Drugs (continued)

Type of 5-ASA	Mechanism of Action	Advantage	Indication
Colonic flora–dependent, azo-bonded			
Sulfasalazine (Azulfidine, Pfizer)	There are currently 3 variations of colonic-releasing, azo-bonded 5-ASA drugs: 1. Sulfasalazine consists of 5-ASA bonded to sulfapyridine; 2. Balsalazide links an inert polymer of 4-aminobenzoyl-β-alanine to 5-ASA; 3. Olsalazine consists of 2 molecules of 5-ASA linked to each other.	In these azo-bonded 5-ASA forms, the molecule reaches the colon primarily intact and the azo bond is cleaved by colonic bacterial azo-reductase, thereby releasing free, unconjugated 5-ASA (mesalamine). A high-dose, 1.1-g balsalazide tablet allows for lower pill burden and twice-daily dosing.[52,53]	This formulation is indicated for patients with universal and distal colitis.
Sulfasalazine, delayed-release (Azulfidine EN-Tabs, Pfizer)			
Balsalazide disodium (Colazal, Giazo; Salix)			
Olsalazine sodium (Dipentum, Pfizer)			
Topical/rectal formulations			
Mesalamine suppository (Canasa, Aptalis)	Rectal preparations include 5-ASA suspensions (4-g mesalamine enema and 500-mg mesalamine suppository) that are instilled directly into the rectum.	Advantages of topical preparations include direct exposure to diseased mucosa.	These agents are indicated for patients with left-sided colitis and proctitis.
Mesalamine enema (Rowasa, Meda Pharmaceuticals)			

5-ASA, 5-aminosalicylic acid; **MMX,** Multi Matrix System

of sulfasalazine and have led to the development of new 5-ASA–containing analogs. The newer topical and oral 5-ASA agents are delivered to different anatomic sites, ideally corresponding to the distribution of active disease (Table).[45-53] Although these agents are less toxic than sulfapyridine, mesalamine allergies (eg, high fevers, allergic pneumonitis) and intolerance (eg, worsening IBD symptoms) may occur and discontinuation of 5-ASA therapy my be required. Interstitial nephritis has been reported with the 5-ASA moiety alone[54] and mandates periodic renal function monitoring.

Treatment of UC

Until the introduction of balsalazide, all of the newer 5-ASA agents had been shown to induce and maintain remission of UC nearly as well as sulfasalazine and usually as well as one another. The advantage of some of the newer 5-ASA preparations is that patients can tolerate higher doses. Recently, novel dual-delivery systems (delayed- and extended-release) allow for effective dose de-escalation, with lower doses of active 5-ASA delivered to the site of active colitis.[49-51]

In the first head-to-head trial comparing an equimolar dose of balsalazide (6.75 g) with pH-dependent mesalamine (2.4 g), balsalazide showed superior efficacy in patients with new-onset left-sided UC (62% vs 37%) and shorter time to response (10 vs 25 days); response rates also were higher in patients with right-sided UC, although the difference was less significant compared with patients with left-sided disease.[55] A stratification study confirmed that among patients with new-onset left-sided UC, more than 60% of those treated with balsalazide were in remission at 1 month compared with 40% of those treated with pH-dependent mesalamine.[56] Additionally, patients with right-sided UC who were treated with balsalazide had less rectal bleeding, better sigmoidoscopic-evident healing, and improved stool frequency. A twice-daily balsalazide dosing regimen (three 1.1-g tablets, twice daily, for a total of 6.6 g/d) has been

shown to be well tolerated and effective in relieving signs and symptoms of mild to moderate UC.[52,53] This regimen reduces pill burden and should improve adherence and convenience for patients.

Levine et al[57] conducted a randomized, double-blind study comparing 2 doses of balsalazide (6.75 and 2.25 g) and mesalamine (2.4 g) in patients with active, mild to moderate UC. At week 8, rates of remission were similar for all 3 treatment groups, as were safety profiles. The primary difference between balsalazide (6.75 g) and mesalamine appeared to be the time to symptom resolution (10 vs 25 days, respectively). Kornbluth et al[58] compared the colonic mucosal concentration of 5-ASA in patients treated with a mean of 6.75 g per day of balsalazide with those treated with a mean of 3.74 g per day of pH 7.0–dependent mesalamine and demonstrated that patients who received balsalazide had significantly higher mean mucosal concentrations of 5-ASA than patients who received mesalamine.

Because of the predominance of left-sided disease, the combination of oral and topical aminosalicylates is critical in inducing and maintaining remission.[59,60] Safdi et al[59] elegantly demonstrated that although topical mesalamine was more effective than oral in patients with left-sided UC, the combination of 2.4 g of oral mesalamine and mesalamine enemas produced earlier and more complete cessation of rectal bleeding. For maintenance of remission, D'Albasio et al[60] found that a combination of 1.6 g of oral mesalamine with twice-weekly mesalamine enemas produced higher rates of remission compared with oral therapy alone (61% vs 31%, respectively). Topical mesalamine (enema and suppository formulations), used as infrequently as twice per week, is effective in maintaining remission in patients with distal colitis. A systematic review compared the efficacy of combined oral and topical 5-ASA with oral therapy alone and found a significant increase in remission rates in mild to moderate UC with combined therapy, and intermittent topical therapy was superior to oral therapy in maintaining remission in quiescent UC.[61]

Biddle et al[62] established that 75% of patients (9 of 12) randomized to receive mesalamine enemas remained in remission at 1 year compared with 85% of patients (11 of 13) on placebo who had relapsed by week 16. Similarly, mesalamine suppositories were associated with long-term remission in patients with ulcerative proctitis; at 12 and 24 months, 86% and 89% of patients on placebo had relapsed compared with 32% and 46% of patients treated with mesalamine suppositories, respectively.[63] A meta-analysis established that in patients with left-sided UC and ulcerative proctitis, topical mesalamine showed greater efficacy and fewer side effects than oral therapies and topical steroids.[64] Additionally, Campieri et al[65] demonstrated that mesalamine suppositories were effective in inducing remission in patients with ulcerative proctitis (distal colitis up to 20 cm). In that study, 74% of patients who received mesalamine suppositories (1.5 g) achieved clinical remission at week 4 compared with 39% of patients who received placebo.

The pH-sensitive 5-ASAs were evaluated in a placebo-controlled trial in patients with active mild to moderate UC.[66] In contrast to a 71% maintenance of remission rate, complete remission was induced in 24% of patients on mesalamine 4.8 g, 9% of patients on mesalamine 1.6 g, and 5% of patients on placebo.[67] Partial response was achieved in 50% of patients in the high-dose mesalamine group compared with 18% in the low-dose group and 13% in the placebo group.[66] The ASCEND (Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA) II trial found 4.8 g of delayed-release mesalamine (Asacol) to be superior to 2.4 g in patients with moderate UC, with response rates of 72% and 59%, respectively; remission rates were similar in both groups at 24%.[68] ASCEND I and II were the first head-to-head—although non–placebo-controlled—comparisons of 2.4 versus 4.8 g of Asacol in patients with mild to moderate UC. In ASCEND III, the response rate at 6 weeks was 70% for patients taking 4.8 g of Asacol (6 tablets, 800 mg each) compared with 66% for those taking 2.4 g of Asacol (6 tablets, 400 mg each).[69]

Delzicol, released in early 2013, is a new delayed-release capsule formulation of mesalamine that has been shown to be equivalent to Asacol delayed-release tablets.[70] It is available as a 400-mg delayed-release capsule. The prescribing information indicates that patients should take 800 mg, 3 times per day, for a total of 2.4 g per day for the treatment of mildly to moderately active UC. For maintenance of remission, patients should take 1.6 g daily, in divided doses. The medication should be taken at least 1 hour before or 2 hours after a meal.

The dosing for Delzicol could be problematic in clinical practice. For example, patients may find it difficult to take the drug 3 times a day when it is supposed to be ingested 1 hour before or 2 hours after a meal. Because medication compliance is an extremely important issue in treating patients with UC, this may present a significant challenge to long-term compliance.

A high-strength pH–dependent formulation of 5-ASA—MMX mesalamine (Lialda, Shire), taken once or twice daily, has been well tolerated and has induced remission in patients with mild to moderate UC. The formulation is a 1.2-g tablet and has been evaluated for twice-daily (one 1.2-g tablet, twice daily; 2.4 g/d) and once-daily (four 1.2-g tablets, once daily; 4.8 g/d) administration.[46-48,71] Lichtenstein et al[46] showed that after 8 weeks of treatment, rates of clinical and endoscopic remission were significantly higher for patients taking

MMX mesalamine compared with patients taking placebo (34.1% and 29.2% for 2.4 g/d and 4.8 g/d, respectively, vs 12.9% for placebo; $P<0.01$). Increasing the dose to 4.8 g per day for an additional 8 weeks resulted in clinical and endoscopic remission and symptom resolution for nearly 60% of patients in a median time of 15 days.[47] In a separate study by Kamm et al, once- or twice-daily MMX mesalamine resulted in maintenance of clinical and endoscopic remission.[48]

A granulated pH 6.0 delayed- and extended-release formulation of 5-ASA (Apriso) with a polymer matrix core has been approved by the FDA for the maintenance of remission at 1.5 g per day. Lichtenstein et al[72] demonstrated maintenance of remission in nearly 79% of patients who switched from different 5-ASA formulations compared with almost 60% who maintained remission on placebo. In a European dose-ranging study that evaluated this pH 6.0–releasing granulated formulation of 5-ASA in patients with mildly to moderately active UC, remission rates were 66% for patients taking 3 g per day (1 g, 3 times daily), 50% for those taking 1.5 g per day (0.5 g, 3 times daily), and 55% in those taking 4.5 g per day (1.5 g, 3 times daily).[49] Although there was no placebo arm in the study, clinical remission rates in all 3 treatment groups were high. With the exception of endoscopic improvement, which was better in the 3-g per day group than in the 1.5-g per day group, no significant differences among the 3 groups were observed. These findings suggest that the novel delivery mechanism of granulated mesalamine may lead to release of active drug at the site of active disease allowing for effective dose de-escalation.

In another study, 2 doses of mesalamine granules—a 3-g dose given once daily and a 1-g dose given 3 times per day—were similarly safe and effective in producing clinical and endoscopic remission in patients with mildly to moderately active UC.[50] This provides evidence that decreasing the dosing frequency may improve adherence to medication while maintaining efficacy. Once-daily, 1.5-g granulated mesalamine delayed-release (Eudragit-L, Evonik; dissolving at pH >6.0) and extended-release (polymer matrix core, containing slowly eluting mesalamine) have been shown to maintain remission in nearly 80% of patients who switched from different 5-ASA formulations compared with almost 60% who maintained remission on placebo.[51] Dose de-escalation with granulated mesalamine 1.5 g per day may improve long-term adherence to medication and remission. Mesalamine granules also have demonstrated higher rates of induction of remission of UC compared with budesonide (54.9% vs 39.5%).[73] And in a comparison of MMX mesalamine and Asacol (Warner Chilcott), patients with UC who took MMX mesalamine maintained remission longer than those on Asacol.[74]

A recent meta-analysis confirmed the benefit of 5-ASA for inducing and maintaining remission in UC.[75] The optimal dose appeared to be 2.4 g per day, with no apparent benefit from increasing the dose. Similarly, the optimum dose to prevent relapse was 2.0 to 2.4 g per day. These recommended doses are expressed in mesalamine or equivalent.

Initial mesalamine dosing strategies followed the divided dosing paradigm used with sulfasalazine, which was developed to minimize sulfapyridine-related adverse events (AEs). Several studies have assessed the safety and efficacy of once-daily mesalamine administration. The PODIUM (Pentasa Once Daily In Ulcerative colitis for Maintenance of remission) trial assessed the use of pH-sensitive mesalamine (Pentasa, Shire) 2 g per day taken as a single daily dose versus 2 divided doses over 1 year in left-sided UC.[76] For once-daily dosing and divided dosing, remission rates were 69% versus 61%, respectively, and mucosal healing rates were 84% versus 78.6%, respectively, and there was no difference in AEs. The QDIEM (QD Dosing Investigation for Efficacy in UC Maintenance) study, a large, randomized controlled trial conducted by Sandborn et al,[77] assessed Asacol 1.6 and 2.4 g per day in once- or twice-daily divided doses for maintenance of remission in 1,023 patients with mild to moderate UC in clinical remission. More than 90% of patients in both dosage groups at 6 months, and 85.4% at 12 months, remained in remission without differences in AEs or treatment withdrawal rates. An active-control randomized trial of 824 patients with UC in clinical remission by D'Haens et al[78] demonstrated noninferiority of MMX mesalamine 2.4 g once daily compared with pH-sensitive mesalamine 0.8 g twice daily. The aforementioned studies were not placebo-controlled but did demonstrate similar efficacy and safety profiles for the assessed end points. Furthermore, a meta-analysis of 10 randomized controlled trials in UC demonstrated no difference in the rates of maintenance of remission in patients with quiescent UC treated with once-daily mesalamine and also showed a mild but significant benefit in induction of remission in patients with mildly active UC, with improved adherence and a similar AE profile.[79]

A recent cost–benefit analysis suggested that inflammation-targeted treatment using 5-ASA therapy for patients with stool samples positive for inflammation may cost less than continuous treatment for all UC patients.[80] Further studies correlating tight inflammation control and inflammatory biomarker monitoring are warranted.

Mesalamine Therapy During Pregnancy

In pregnant patients, 5-ASA and its metabolite, acetyl-5-ASA clearly cross the placenta and thus are

found in both maternal and fetal plasma in women on mesalamine therapy.[81] Currently, per FDA recommendations, all mesalamine therapies, except for olsalazine and Asacol/Asacol HD, are considered pregnancy safety classification B. In 2010, Asacol and Asacol HD were switched to a classification of C for safety in pregnancy by the FDA. Prior studies of mesalamine performed during organogenesis in rats and rabbits at oral doses up to 480 mg/kg per day showed no evidence of fetal malformations. These doses represented approximately 1.6 and 3.2 times the recommended human dose (based on body surface area). The class transition was based on more recent animal studies showing that the inert ingredient of Asacol's enteric coating, dibutyl phthalate (DBP), is associated with adverse reproductive aberrations when given in very high doses.[82] The maximum daily human intake of DBP is about 48 g. Published reports in rats exposed to DBP in utero at doses 17 times the human dose showed reproductive anomalies in male offspring, specifically an injury to androgenic-dependent development. Even higher doses of DBP, approximately 84 times the human dose, resulted in worse outcomes for these male rat offspring, including cryptorchidism, hypospadias, atrophy or agenesis of sex accessory organs, reduced daily sperm production, and permanent retention of nipples. The female offspring appeared to remain unaffected by these same doses. Exposure to DBP at doses equivalent to 106 times the human dose resulted in increased incidences of cleft palate and skeletal abnormalities in both female and male offspring.

It is important to note that the dosage of Asacol/Asacol HD appears to be the critical component in causing these adverse pregnancy outcomes in rats. Before this pregnancy reclassification of Asacol, gastroenterologists had been using this particular mesalamine preparation in varying doses (the maximum dose being 4.8 g daily) for the past decade in pregnant women with IBD without any AEs observed in the mothers or offspring. It appears that Asacol and Asacol HD can be used during pregnancy when administered in the appropriate doses as suggested by studies in human patients and the vast clinical experience of many IBD specialists.

The PIANO registry is a prospective cohort of pregnant women with IBD that has enrolled more than 1,000 patients to date.[83] The analysis of the effect of mesalamine on pregnancy outcomes is pending. Early results have confirmed data from earlier studies that suggest no increase in congenital malformations in children born to mothers exposed to immunosuppressants or anti-TNF drugs compared with mothers who were not exposed to either group of medications. Notably, there was an increase in the number of infections in infants born to mothers exposed to the combination of thiopurines and anti-TNF agents during pregnancy, which merits closer investigation. Developmental milestones were similar among all exposure groups and will be followed in children up to age 4 years.

Optimizing Oral 5-ASAs

Although there are no prospective studies evaluating combinations of oral 5-ASA drugs, combination therapy may be considered in patients who fail to respond to mesalamine monotherapy or 5-ASA prodrug monotherapy. 5-ASA nonresponders may benefit from a combination of pH-dependent polymer-coated mesalamine, moisture-dependent mesalamine, and azo-bonded 5-ASA preparations (eg, sulfasalazine, olsalazine, balsalazide). A flexible dosing schedule in which the patient actively modifies the combination therapy based on clinical response may shorten the duration to response. Lastly, a flexible dosing schedule that combines oral and topical 5-ASA agents is an effective therapeutic strategy that should not be overlooked. With the variety of 5-ASA preparations available, optimization of 5-ASA therapy may be viewed as a dynamic process rather than a static one. In a patient not responding to an initial 5-ASA therapeutic choice, dosage may be optimized (ie, escalated, de-escalated), and oral preparations may be combined with each other, as well as with topical agents, in an attempt to optimize delivery of 5-ASA to the site of active disease.

Novel Steroid Options for UC

Uceris, a new once-daily, extended-release formulation of budesonide–MMX Multi Matrix System (MMX) is effective for inducing remission in adults with mild to moderate UC and is associated with significantly fewer systemic AEs than conventional corticosteroids. The role of Uceris in maintaining remission in patients with UC needs to be further evaluated with prospective studies. Comparison of mesalamine and budesonide for both induction and maintenance of UC remains to be established.[84-86]

Biologic Therapeutic Options

Anti-TNFs

There is increasing evidence that infliximab is useful for induction of remission in patients with UC who are steroid-refractory or steroid-dependent despite adequate doses of thiopurine, or who are intolerant of these medications. In ACT (Active Ulcerative Colitis Trials) 1 and 2, researchers evaluated the efficacy of infliximab in patients with severe UC.[87] Patients

with moderate to severe disease were randomized to receive IV infliximab (5 or 10 mg/kg) at weeks 0, 2, and 6, and every 8 weeks thereafter, or placebo. In these trials, 64% to 69% of patients who received infliximab 5 mg/kg exhibited a clinical response at week 8 compared with 29% to 37% of patients who received placebo. Infliximab also improved mucosal healing: Mucosal healing occurred in nearly twice as many patients in the infliximab treatment groups in ACT 1 and 2 at week 8 (62% and 60%, respectively) and week 30 (50% and 46%, respectively) as in the placebo groups at week 8 (34% and 31%, respectively) and week 30 (25% and 30%, respectively). Additionally, infliximab demonstrated early and lasting steroid dose reduction: Patients in ACT 1 had a 75% reduction in their median daily dose of steroids from baseline. Also, nearly 3 times as many patients receiving infliximab 5 mg/kg achieved remission without steroids at week 54 compared with patients who received placebo (26% [18 of 70] vs 9% [7 of 79]; *P*=0.006).

Adalimumab also has been effective in patients with UC.[88-90] Adalimumab at doses of 160 and 80 mg has been shown to induce clinical remission in 17% and 9% of patients with UC, respectively, at week 8; additionally, 17% and 9% of patients, respectively, maintained remission at week 52. Mucosal healing was achieved in 25% of patients taking adalimumab compared with 15% of patients on placebo.

Anti-Integrins

Vedolizumab is a gut selective antibody that blocks α4β7 integrin and inhibits its interaction with mucosal addressin cell adhesion molecule-1. Vedolizumab blocks gut lymphocyte recruitment, without interfering with the central nervous system. A randomized, placebo-controlled trial demonstrated that vedolizumab 300 mg (administered at weeks 0 and 2, and then beginning at week 6, every 4 or 8 weeks) was effective in induction and maintenance of remission in patients with moderate to severe UC.[91]

Combining Steroids, Immune Suppression, and Biologics

The American College of Gastroenterology guidelines recommend 5-ASA as first-line therapy for maintenance of remission in patients with UC.[92] Among the goals of therapy are the induction and maintenance of remission of UC, and a reduction in the need for long-term corticosteroid use. Steroids are generally reserved for patients who are refractory to 5-ASAs, or for patients with severe UC with systemic illness. AZA and 6-MP are effective for patients who do not respond to steroids and continue to have moderate disease, and who are not acutely ill enough to require IV therapy. Treatment with IV cyclosporine or colectomy is indicated for patients with severe disease who fail to show significant improvement with 5-ASA, steroids, AZA, or 6-MP, including IV steroids, within 3 to 5 days.[93,94]

The ACT trials support a role for anti-TNF therapies in the reduction of steroid use and maintenance of remission in patients with UC.[87] Approximately 22% of patients who received steroids at baseline had discontinued steroid use by week 30 in both ACT 1 and 2, or by week 54 in ACT 1. When infliximab was administered every 8 weeks, response and remission were maintained at week 30 (53% and 32%, respectively), and at week 54 (45% and 42%, respectively) in patients who had an initial response or remission at week 8 (after 3 infusions of infliximab 5 or 10 mg/kg at weeks 0, 2, and 6).

Along with eliminating the use of steroids and induction of mucosal healing, increasing evidence shows that anti-TNF agents, specifically infliximab, are effective for induction and maintenance of remission in UC. The use of infliximab is expected to facilitate the widespread use of steroid-sparing therapy for patients with UC, thereby reducing the use of ineffective therapies and improving the quality of care.

Personalizing IBD Therapies

In selected patients with moderate to severe UC, an earlier aggressive treatment approach is indicated.[13,95] Some patients with mild to moderate disease may benefit from a decrease in medication dosage, adherence to therapeutic regimens, and in some cases, a reevaluation of the diagnosis. Identification of immunologically vulnerable patients through the use of emerging serologic markers, biomarkers, and genotyping may allow for individualized treatment that improves outcomes.

A greater understanding of the human genome is redefining the science of individuality. Less than 0.1% of our DNA is responsible for IBD susceptibility and therapeutic response.[96-99] We are at the threshold for genotyping patients and bacteria, which will lead to a greater understanding of the pathobiology of IBD and its treatment.[100]

Until genomics can be applied to individualized medicine, predicting IBD progression may be achieved through risk assessment, emerging biomarkers, and optimizing mesalamine therapeutic strategies. In selected patients with moderate to severe UC, early intervention with immunosuppressive or biologic therapies—and limited use of steroids—may slow the progression of IBD, and treatment may move from a symptom-oriented, step-up strategy to a prevention-oriented, early intervention approach.

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