Although the dogma of dividing the major auto-inflammatory maladies of the gastrointestinal tract into 2 distinct entities—ulcerative colitis (UC) and Crohn’s disease (CD)—has persisted for decades, a more nuanced view presents inflammatory bowel disease (IBD) as a spectrum of chronic and recurring diseases of the intestines. This review will address the concept of a targeted, personalized approach to IBD treatment, with a focus on 5-aminosalicylates (5-ASAs).

Epidemiologic data on IBD are fractionated into the pigeon holes 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 is 6 to 8 per 100,000 and 130 to 200 per 100,000, respectively. Although there are patients who fall more clearly into one category than another, the concept of indeterminate colitis (IC) is poorly defined and therapeutic guidelines are lacking. Thus IC might represent part of an immunologic continuum, rather than a well-defined clinical subset of UC and CD.
Challenging Traditional IBD Classifications

The Montreal classification has been used to characterize the phenotype of classically defined CD into inflammatory, penetrating (or fistulizing), and fibrostenotic. However, Crohn’s colitis has not been well defined in the literature and may be difficult to classify, for example, the patient who presents with diarrhea and pancolitis with minimal bleeding, the patient with left-sided colitis and a cecal patch, or the patient on therapy for colitis now with an endoscopic distribution of disease demarcated by “skip areas.”

The many forms of UC (eg, ulcerative proctitis, left-sided colitis, universal colitis) may be a series of diseases rather than a single class. Just as rectal cancer is treated in a different fashion than more proximal colonic adenocarcinomas, UC may be a pathologic state with many etiologies. Serologic markers may help to provide a window for observing an abnormal antibody-antigen response and thus could potentially help identify patients at risk for rapid progression of disease who may benefit from early intervention. Molecular diagnostics, such as antibody serologic and biomarkers, hold the promise of enhancing the understanding of IBD subtypes and stratifying patients on the basis of immunophenotypes.

A broad differential diagnosis is increasingly recognized as important in distinguishing active inflammation from other conditions (eg, medication-induced pseudo-refractory IBD [including infections, eg, Clostridium difficile, cytomegalovirus], irritable bowel syndrome, celiac disease, lactose and/or fructose intolerance, dietary indiscretion, bile acid diarrhea, obstructive stricturing or fistulizing CD requiring surgery) and in stratifying optimal therapeutic response to biologic agents and immunosuppressives. In select patients with moderately to severely active IBD, early intervention with effective therapy is associated with significant improvement in mucosal healing and reduction in the progression of disease. However, these latter approaches using biologic therapy in a “top-down” fashion (as D’Haens argues in his revolutionary Lancet paper) and possibly in combination with immunomodulators (as illustrated in the SONIC [Study of Biologic and Immunomodulator Naive Patients in Crohn’s Disease] trial) are reserved for those patients in whom systemic corticosteroids are either being considered or being used. Corticosteroids have a myriad of adverse effects, including acne, hyperglycemia, avascular necrosis of the femoral neck, cataracts, among others. There is proven benefit for using 5-ASAs in patients with mild to moderate UC, although their role in CD is more controversial.

Molecular Classification of IBD

IBD nomenclature does not accurately reflect the complexity of the 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. While new genes continue to highlight host microbial interactions, 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 approximately 30% of patients with UC and 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. In these patients, if the markers are more consistent with a molecular pattern of CD, physicians may consider anti-tumor necrosis factor (TNF) therapy as an option rather than total colectomy.

Serologic profiling already has proven helpful in patient stratification. Although controversial, high levels of perinuclear antineutrophil cytoplasmic antibodies (pANCA) have consistently correlated with postoperative pouchitis. Additionally, anti-CBir1, an antibody to flagellin of the polyflagellated organisms, is associated with an increased incidence of chronic pouchitis in patients who have high pANCA levels, and with acute pouchitis in those with low pANCA levels. Expression of anti-Saccharomyces cerevisiae antibody (both immunoglobulin [Ig] subtypes A and G) correlates with a younger age of onset and more aggressive fibrostenotic disease. Also, antibodies against the CD-related bacterial sequence I2, Escherichia coli outer membrane porin C, and CBir1 flagellin identify a unique subset of immunologically vulnerable patients with complicated/aggressive CD.

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.

Treatment of IBD Subtypes

The majority of patients with IBD have moderate disease. Approximately, three-fourths of patients have active UC and two-thirds of patients with CD have moderate to severe disease that requires alternatives to treatment with mesalamine therapies. The treatment goals for patients with IBD are universal—to 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-ASA agents, corticosteroids (administered orally or intravenously), immunomodulators (eg, azathioprine [AZA], 6-mercaptopurine [6-MP]), and infliximab are used to induce remission. Cyclosporine has been used to induce remission as well, with faster time to symptom relief, but there is an increased burden on patients and providers for monitoring. Laharie et al recently presented the findings of a study comparing cyclosporine and infliximab that showed equivalent efficacy for short-term remission and...
avoidance of colectomy. For maintenance of remission of UC, 5-ASAs and 6-MP/AZA or infliximab may be used. Additionally, infliximab is 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.

For patients with CD, steroids are still recommended as possible first-line agents. There are no good controlled trials evaluating antibiotics (eg, metronidazole, ciprofloxacin [alone, or in combination], rifaximin). Immunomodulators (eg, 6-MP, AZA, metothrexate [MTX]), anti-TNF drugs (eg, infliximab, adalimumab, certolizumab), and natalizumab are used to induce remission. For maintenance of remission, immunomodulators and biologics can be used. There are limited data for 5-ASAs in both the induction and maintenance of remission in CD.

Probiotics and novel antibiotics (eg, rifaximin) have the potential to revolutionize the treatment of patients with IBD. For example, anti-inflammatory interleukin (IL)-10 levels have been associated with Bifidobacterium infantis. However, a greater understanding of gut microecology and further clinical trials are needed.

**5-ASAs: Mechanism of Action**

5-ASA acts locally in the colon and is absorbed by colonic epithelial cells. The effectiveness of the compound is related to its mucosal concentration, and systemic dosages remain low after oral sulphasalazine and rectal 5-ASA administration. 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 ReI/p65 phosphorylation, and inhibition of the biosynthesis of prostaglandins and leukotrienes.

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 in pro-inflammatory prostaglandins and leukotrienes. 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.

Clinicians should question whether the site of 5-ASA release is a determinant in optimizing and individualizing therapy. Two therapeutic strategies expose opposing views: one is that all 5-ASA preparations are equivalent; the other is that subtle differences in the mode of 5-ASA delivery translate into differences in clinical efficacy.

Recently, it has been postulated that 5-ASA leads to peroxisome proliferator-activated receptor-gamma (PPAR-γ) transcription and protein expression. 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. A randomized placebo controlled clinical trial of rosiglitazone (a PPAR-γ ligand) demonstrated efficacy in treating mild to moderate UC. However, despite these numerous experimental studies, the true basic mechanism of action of 5-ASA remains unknown.

Because 5-ASAs work topically within the lumen of the gastrointestinal tract, achieving maximal concentration of the agent at the site of active disease is tantamount. The specific goals of 5-ASA therapy are to quickly induce complete remission, to facilitate mucosal healing, and to minimize steroid use and toxicity. Often overlooked is the distribution of UC; more than 50% of patients have left-sided disease (Figure 1).

In 1942, 5-ASA was combined with an antibiotic sulfapyridine in a molecule named sulphasalazine. Thirty-five years later, Azad Khan et al demonstrated that 5-ASA was the therapeutically active moiety of this drug with proven anti-inflammatory effects in IBD. 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. However, intolerance and hypersensitivity to the sulfapyridine moiety limit the dose of sulfasalazine, and have led to the
TREATMENT OF UC

5-ASA delivered to the site of active colitis (Table). 46-48

5-ASA agents had been shown to induce and maintain remission of active disease (Figure 2; Figure 3). Although these agents are less toxic than sulfasalazine, allergies to 5-ASA are less common than to sulfapyridine. Interstitial nephritis has been reported with the 5-ASA moiety alone 45; although rare, the potential for this adverse event (AE) mandates periodic renal function monitoring. One potential untoward reaction to 5-ASA is intolerance to the drug, presenting as bloody diarrhea mimicking the underlying IBD itself. In cases of severe refractory UC, it is advisable to consider discontinuing the 5-ASA along with initiation of salvage therapy in hopes of preventing colectomy.

Figure 2. Oral aminosalicylate delivery in the small and large intestine.

5-ASA, 5-aminosalicylic acid

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 (Figure 2, Figure 3). Although these agents are less toxic than sulfasalazine, allergies to mesalamine have been reported. Interstitial nephritis has been reported with the 5-ASA moiety alone 45; although rare, the potential for this adverse event (AE) mandates periodic renal function monitoring. One potential untoward reaction to 5-ASA is intolerance to the drug, presenting as bloody diarrhea mimicking the underlying IBD itself. In cases of severe refractory UC, it is advisable to consider discontinuing the 5-ASA along with initiation of salvage therapy in hopes of preventing colectomy.

TREATMENT OF UC

Until the introduction of balsalazine, 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. Recently, novel dual-delivery systems (delayed- and extended-release formulations) allow for effective dose de-escalation, with lower doses of active 5-ASA delivered to the site of active colitis (Table). 46-48

In the first head-to-head trial comparing an equimolar dose of balsalazine (6.75 g) with pH-dependent mesalamine (2.4 g), balsalazine showed superior efficacy in patients with new-onset left-sided UC (62% vs 37%) and shorter time to response (10 vs 25 days) compared with pH-dependent mesalamine. Also, response rates were higher with balsalazine compared with pH-dependent mesalamine in patients with right-sided UC, although the difference was less significant compared with patients with left-sided disease. 49,50 A stratification study confirms that among patients with new-onset left-sided UC, more than 60% of those treated with balsalazine were in remission at 1 month compared with 40% of those treated with pH-dependent mesalamine. Additionally, patients with right-sided UC who were treated with balsalazine had less rectal bleeding, better sigmoidoscopic-evident healing, and improved stool frequency.

Levine et al 51 conducted a randomized, double-blind study comparing 2 doses of balsalazine (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 balsalazine (6.75 g) and mesalamine appeared to be the time to symptom resolution (10 vs 25 days, respectively). Kornbluth et al 52 compared the colonic mucosal concentration of 5-ASA in patients treated with a mean of 6.75 g per day of balsalazine with those treated with a mean of 3.74 g per day of pH 7-dependent mesalamine and demonstrated that patients who received balsalazine 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. 53,54 Safdi et al 53 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 54 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 (enemas and suppositories) used as infrequently as twice per week was effective in maintaining remission in patients with distal colitis.

Biddle et al 55 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 56; 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. 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. 57 Additionally, Campieri et al 58 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 mild to moderate UC. 59 Complete remission was achieved in 24% of patients on mesalamine 4.8 g, 9% of patients on mesalamine 1.6 g, and 5% of patients on placebo. Partial response was noted in 50% of patients in the high dose mesalamine group compared with 18% in the low-dose group and 13% in the placebo group. The ASCEND II trial found 4.8 g of delayed-release mesalamine 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%. 60
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).61 This study met its primary end point of non-inferiority of the 2 doses. Subset analyses showed efficacy with the higher dose in those patients requiring steroids or multiple UC medications.

Another pH-dependent formulation of 5-ASA—multimatrix (MMX) mesalamine—taken once or twice daily has been shown to be well tolerated and to induce remission in patients with mild and moderate UC. The formulation is a 1.2-g tablet and has been evaluated for twice-daily (1, 1.2-g tablet, bid; 2.4 g/d) and once-daily (4, 1.2-g tablets, once daily; 4.8 g/d) administration. Lichtenstein et al 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; \( P < 0.01 \)).62,63 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.64 In a separate study by Kamm et al, once- or twice-daily MMX mesalamine resulted in maintenance of clinical and endoscopic remission.65

A granulated pH 6–releasing formulation of 5-ASA with a polymer matrix core has been approved by the FDA for the maintenance of remission at 1.5 g per day. Lichtenstein et al66 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.

A European dose-ranging study that evaluated this pH 6–releasing formulation of 5-ASA in patients with mildly to moderately active UC yielded remission rates of 66% for patients taking 3 g per day, 50% for those taking 1.5 g per day, and 55% for those taking 4.5 g per day.66 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 this mesalamine may lead to release of the drug at the site of active disease.

In another study, 2 dosing strategies of mesalamine granules—a 3-g dose given once daily and a 1-g dose given 3 times per day—were shown to be similarly safe and effective for inducing clinical and endoscopic remission in patients with mildly to moderately active UC.47

A recent meta-analysis confirmed the benefit of 5-ASA for inducing and maintaining remission in UC.67 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 g to 2.4 g per day. These recommended doses are expressed in mesalamine or equivalent.

**Figure 3. Drug doses needed to provide equal amount of 5-ASA.**

4-ABA, 4-aminobenzoyl-G-l-alanine; 5-ASA, 5-aminosalicylic acid; SASP, sulfasalazine

**TREATMENT OF CD**

Compared with UC, the role of 5-ASA therapy in maintenance of remission of CD is not well defined. The results of ACCENT I (A Crohn’s disease Clinical trial Evaluating infliximab in a New Long term Treatment regimen), which established the efficacy of infliximab for maintenance therapy in CD, challenge the lack of effectiveness of maintenance strategies previously established by the multicenter National Cooperative Crohn’s Disease Study and European Cooperative Crohn’s Disease Study.68-70 These trials did not demonstrate a statistically significant benefit of sulfasalazine in the maintenance of remission of CD. Notably, only 20% to 30% of patients with CD have colonic disease alone, and most sulfasalazine is released in the colon. Subsequent smaller trials confirmed the lack of efficacy of sulfasalazine. All of these studies were flawed, in that they analyzed different disease sites (ileal, ileocolonic, colonic), different groups of patients (medical vs surgical), and different doses of medication.

With the introduction of mesalamine, higher doses of active 5-ASA have shown increased efficacy for both the induction and maintenance of remission in patients with CD.71 A meta-analysis of 10 randomized controlled trials evaluating mesalamine maintenance therapy in 1,371 patients with CD showed no statistically significant difference in relapse rates between treatment and placebo; however, mesalamine treatment was associated with significantly lower relapse rates in patients with limited ileal disease of long duration.72

A recent meta-analysis yielded 6 randomized placebo-controlled trials and suggests that 5-ASA may be more effective than placebo with a number needed to treat of 11.73 Although the evidence was of low quality, and there
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<th>Type</th>
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<td><strong>Diffusion-dependent</strong></td>
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<td>Mesalamine controlled-release (Pentasa, Shire)</td>
<td>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.</td>
<td>Independent of pH or bacteria; mucosal delivery of mesalamine is less affected by rapid intestinal transit time (ie, diarrhea).</td>
<td>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.</td>
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<td><strong>pH-dependent</strong></td>
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<td>Mesalamine delayed-release (pH 7.0) (Asacol, Warner Chilcott)</td>
<td>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.)</td>
<td>Free 5-ASA (mesalamine) dosage can be maximized to 4.8 to 6 g daily, equivalent to a triple dose of sulfasalazine (12 g) with significantly less toxicity.</td>
<td>A pH-dependent delivery system is indicated in ileocolonic disease.</td>
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<td>MMX mesalamine (pH 7.0) (Lialda, Shire)</td>
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<td>Mesalamine delayed-release (pH&gt;6.0) (Eudragit-L, Degussa Rohm)</td>
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<td>Mesalamine delayed-and extended-release (polymer core of slow-release mesalamine; pH 6.0) (Apriso, Salix)</td>
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<td><strong>Colonic flora-dependent, azo-bonded</strong></td>
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<td>Sulfasalazine (Azulfidine, Pfizer)</td>
<td>There are currently 3 variations of colonic-releasing, azo-bonded 5-ASA: olsalazine consists of 2 molecules of 5-ASA linked to each other; balsalazide links an inert polymer of 4-aminobenzoyl-a-alanine to 5-ASA; sulfasalazine consists of 5-ASA bonded to sulfapyridine.</td>
<td>In these azo-bonded 5-ASA forms, the molecule reaches the colon primarily intact, and the azo bond is cleaved by colonic bacterial azoreductase, thereby releasing free, unconjugated 5-ASA (mesalamine). A high-dose, 1.1-g balsalazide tablet allows for lower pill burden and twice-daily dosing.</td>
<td>Indicated for patients with universal and distal colitis.</td>
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<td>Sulfasalazine delayed-release (Azulfidine EN-Tabs, Pfizer)</td>
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<td>Balsalazide disodium (Colazal, Salix)</td>
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<td>Olsalazine sodium (Dipentum, Pfizer)</td>
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<td><strong>Topical/rectal formulations</strong></td>
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<td>Mesalamine suppositories (Canasa, Axcan Pharma)</td>
<td>Rectal preparations include 5-ASA suspensions (4-g mesalamine enema and 500-mg mesalamine suppositories) instilled directly into the rectum.</td>
<td>Advantages of topical preparations include direct exposure to diseased mucosa.</td>
<td>Indicated for patients with left-sided colitis and proctitis.</td>
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<td>Mesalamine enema (Rowasa, Alaven)</td>
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5-ASA, 5-aminosalicylic acid; MMX, multimatrix
was not a sufficient number of trials to recommend or advise against 5-ASA use in preventing relapse, further trials might be helpful.

Optimization of Oral 5-ASAs

Although there are no studies evaluating combinations of oral 5-ASA drugs, combination therapy can be considered in patients who fail to respond to mesalamine monotherapy or 5-ASA pro-drug monotherapy. 5-ASA non-responders may benefit from a combination of pH-dependent polymer-coated mesalamine, moisture-dependent mesalamine, and azo-bonded 5-ASA preparations (sul-fasalazine, olsalazine, balsalazide). The selection of pH-releasing agent may, in the future, be reliant upon determination of the small bowel of stool pH to insure release of drug or prevent wasted small bowel release. 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 rather than a static process. In a patient not responding to an initial 5-ASA therapeutic choice, dosages may be optimized (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.

References

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AUTHOR DISCLOSURES—


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