Ulcerative Colitis Therapy: Importance of Delivery Mechanisms

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Since the initial observation that mesalamine or 5-aminosalicylate (5-ASA) has an anti-inflammatory effect on ulcerative colitis, investigators have been trying to improve on the delivery mechanisms of this compound. As it is believed that the anti-inflammatory effect of 5-ASAs is mediated topically, current formulations are designed to release 5-ASA in the small intestine and colon, or predominantly in the colon. A dose-response curve is seen with some preparations of mesalamine but not all. In general, 5-ASAs are effective in patients with ulcerative colitis and much less effective in Crohn’s disease. Evidence demonstrates that 5-ASAs are effective for induction of remission and maintenance of remission. Preparations that deliver 5-ASA in a pH-dependent manner are most affected by variability in luminal pH, whereas those that depend on bacterial cleavage for release of the active 5-ASA are most affected by transit time. Most studies have not compared different preparations of mesalamine and examined differences in colonic delivery. Depending on the endpoint examined in the studies, efficacy of the various 5-ASA products appears similar at the most optimal doses. For a given patient, however, it may be necessary to experiment with more than one preparation if an initial trial results in a suboptimal response.


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Sulfasalazine (Azulfidine EN-tabs®; Pharmacia & Upjohn Company, Kalamazoo, MI), the prototypical aminosalicylate, was developed in 1942 and combines an antibacterial agent (sulfapyridine) with an anti-inflammatory agent, mesalamine (5-ASA).¹ Originally used for rheumatoid arthritis, sulfasalazine was subsequently found to also be highly effective in ulcerative colitis.² Sulfasalazine is metabolized by colonic bacterial azo-reductases into 2 components: the sulfapyridine moiety, which is absorbed, metabolized by the liver, and...
then excreted into the urine, and the 5-ASA component, which is acetylated by the colonic epithelium. Approximately 25% of the acetylated 5-ASA is absorbed and excreted in the urine, whereas over 50% is eliminated in the feces. In clinical trials, as many as 30% to 40% of patients were unable to tolerate sulfasalazine at doses of 4 g/day due to both dose-dependent pathways blocking production of chemotactic agents, inhibition of cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, decreasing B cell hyperactivity and antibody secretion, as well as playing a role in the scavenging of oxygen free radicals. More recently it has been suggested that the nuclear factor kappa-B (NF-κB) may play an important role in the inflammatory process of ulcerative colitis. NF-κB refers to a group of transcription factors that control the expression of a variety of inducible genes involved in inflammation. In the inactivated cell, NF-κB remains bound to inhibitory proteins in the cytoplasm but can be activated by a variety of cytokines, infectious agents, and oxidants. NF-κB induces the gene expression for a number of pro-inflammatory mediators and has been found to be activated in inflamed intestinal mucosa. Sulfasalazine inhibits colonic activation of NF-κB in vitro, and mesalamine has been found to inhibit activation of NF-κB in the colonic mucosa of ulcerative colitis patients in vivo. These studies suggest that the anti-inflammatory properties of aminosalicylates rely at least in part on the inhibition of NF-κB expression in inflamed intestinal mucosa.

**Formulation**

Several types of delivery systems have been designed to prevent proximal absorption of 5-ASA and allow delivery of high doses to the distal ileum and colon, the site of inflammation in ulcerative colitis (Figure 1). The first involves coating the 5-ASA with a resin that undergoes pH- or time-dependent dissolution, and the second involves the formulation of a prodrug by linking 5-ASA to an additional compound via an azo bond. The pH-dependent formulations rely on the increased pH of the more distal small bowel and colon for release of the 5-ASA component from the parent compound. These formulations include Eudragit-S-coated mesalamine (Asacol®; Procter & Gamble Pharmaceuticals, Cincinnati, OH), which is soluble only at a pH ≥ 7. Ethylcellulose-coated mesalamine (Pentasa®; Ferring A/S, Wayne, PA) allows for slow release of the active drug in a time-dependent fashion, beginning in the duodenum and extending into the colon. Prodrug formulations rely on the activity of intestinal bacterial azo-reduction for cleavage and release of 5-ASA into the lumen. The prodrug formulations include olsalazine (Dipentum®; Pharmacia & Upjohn Company, Kalamazoo, MI), which consists of a 5-ASA dimer.

**Mode of Action**

Although 5-ASA agents have been the mainstay of therapy for ulcerative colitis for many years, the exact mechanism of their anti-inflammatory effect has not been fully elucidated. Aminosalicylates have been found to have numerous anti-inflammatory effects, including alteration of the 5-lipoxygenase and leukotriene

<table>
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<tr>
<th>Product</th>
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<tr>
<td>Sulfasalazine</td>
<td>Sulfapyridine + 5-ASA</td>
<td>Colonic bacteria</td>
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<tr>
<td>Pentasa</td>
<td>Mesalamine coated with ethylcellulose</td>
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<td></td>
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<tr>
<td>Asacol</td>
<td>Mesalamine coated with Eudragit-S</td>
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<tr>
<td>Colazal</td>
<td>Balsalazide (5-ASA + 4-aminobenzoyl-B-alanine)</td>
<td>Colonic bacteria</td>
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<td>Dipentum</td>
<td>Olsalazine (5-ASA + 5-ASA)</td>
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and balsalazide (Colazal®; Salix Pharmaceuticals, Inc., Morrisville, NC), which consists of 5-ASA bound to the inert carrier 4-amino-benzoyl-β-alanine. In terms of the amount of 5-ASA contained within each formulation, 6 g of sulfasalazine is approximately equivalent to 2.4 g of Eudragit-S-coated mesalamine, 2 g of ethylcellulose-coated mesalamine, and 6.75 g of balsalazide.

**Pharmacokinetics**

A significant portion of the 5-ASA delivered to the distal small bowel, and to a lesser extent the colon is absorbed by the intestinal epithelium and converted to the inactive metabolite N-Ac-5-ASA that is then either secreted back into the intestinal lumen and excreted in the feces or absorbed systemically and excreted in the urine. 5-ASA can also be absorbed systemically and metabolized in the liver with excretion in the urine as free 5-ASA or N-Ac-5-ASA. Nonabsorbed and unmetabolized 5-ASA is excreted free in the feces. In theory, an ideal 5-ASA formulation would have a high fecal N-Ac-5-ASA:5-ASA ratio with low levels of plasma N-Ac-5-ASA, and 5-ASA concentrations indicating maximal colonic delivery and utilization and metabolism by the colonic epithelium (Figure 2).

A pharmacokinetic study in both healthy volunteers and patients with ulcerative colitis has not found great differences between the various delivery systems. A meta-analysis of pharmacokinetic studies determined plasma concentration and urinary excretion levels of 5-ASA and N-Ac-5-ASA are comparable, as are the fecal excretion levels. Other studies have suggested that pH-dependent delivery systems can lead to increased plasma levels of 5-ASA and its metabolites, whereas other studies have not found this. In patients given a laxative, however, all the formulations had higher fecal excretion rates of unmetabolized 5-ASA and lower urinary and systemic concentration of 5-ASA and N-Ac-5-ASA. This was most pronounced for the prodrug formulations, suggesting that rapid transit through the colon may reduce the amount of time for intestinal bacterial azoreductases to cleave the azo bond. Although highly variable, colonic pH values tend to be decreased in patients with active ulcerative colitis. It has been suggested that this could lead pH-dependent delivery systems to fail in patients with active ulcerative colitis by not fully releasing 5-ASA and allowing its metabolism by the colon. Not only have ulcerative colitis patients been found to have altered colonic transit leading to a more proximal distribution of certain 5-ASA formulations (Eudragit-L-coated mesalamine [Salofalk®; Axcan Pharma Inc., Mont-Saint-Hilaire, Quebec, Canada]), but disease extent may also affect the pharmacokinetic properties of different delivery systems. It is possible that rapid colonic transit or low colonic pH in patients with active ulcerative colitis could reduce the efficacy of these delivery systems, but this has not yet been convincingly supported by clinical trials.

**Efficacy: Placebo-Controlled Trials**

The efficacy of 5-ASA formulations in active ulcerative colitis has been demonstrated in several placebo-controlled trials (Figure 3). Controlled-release ethylcellulose-coated mesalamine evaluated in a dose-ranging study of 1 g, 2 g, and 4 g per day was found to be effective therapy for mild to moderate ulcerative colitis. Significant clinical improvement was seen at both the 2-g dose (79%) and 4-g dose (84%). In
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Figure 3. Clinical improvement in active disease for 5-aminosalicylates versus placebo. Data from Hallauer S et al.," Salvesky CA et al.," Meyers S et al.," and Schmeder KW et al.,".

In addition, both the 2-g and 4-g doses induced significant clinical (25% each) and endoscopic (44% and 48%, respectively) remission when compared to placebo (12% and 31% respectively). While there was no significant difference between the 2-g and 4-g doses for clinical improvement or remission, there was a trend across the 3 escalating doses for improvement in sigmoidoscopic score, rectal bleeding, abdominal pain, and trips to the bathroom suggesting improved efficacy with increasing dose.

Eudragit-S-coated mesalamine capsules at doses of 1.6 g and 4.8 g were compared to placebo in mild to moderate disease with favorable results. After 6 weeks of treatment the 4.8-g dose improvement was noted in 50% of patients compared to 13% in the placebo group. Response in the Eudragit-S-coated mesalamine studies was defined as improvement in the baseline physicians global assessment (PGA) score, improvement in at least 1 clinical assessment (which includes rectal bleeding, stool frequency, patient's functional assessment and sigmoidoscopy score), and no worsening in any clinical assessment. An additional 24% of patients reached complete remission compared to 5% in the placebo group, although this did not reach statistical significance. The 1.6-g dose was not found to be superior to placebo, although the sample size was small (only 11 patients). An additional study that evaluated the efficacy of 2 lower doses (1.6 g and 2.4 g) of Eudragit-S-coated mesalamine demonstrated slightly less efficacy. Both doses were significantly better than placebo for clinical improvement, with the 2.4 g dose being superior to the 1.6 g dose (35% vs 29% respectively).

Only 14% of patients reached remission in both treatment groups.

The efficacy of 2.4 g and 4.8 g of Eudragit-S-coated mesalamine has been directly compared in patients with mild to moderate disease. There was no significant difference in success rates (54% for 2.4 g and 59% for 4.8 g) as defined by either partial response or complete remission when patients with mild disease were included in the analysis. Patients with moderate disease who received the higher dose were found to have significantly higher treatment success rates (72% vs 56%) as well as faster median time to resolution of increased stool frequency and rectal bleeding (19 days vs 29 days).

A dose-ranging study of olsalazine (0.75 g, 1.5 g, and 3 g) found it to be superior to placebo in patients with mild to moderate ulcerative colitis. Compared to placebo, significantly more patients receiving doses of 1.5 g and 3 g were found to have improved colitis activity (16%, 27%, and 50%, respectively) suggesting a dose-response relationship.

An unpublished placebo-controlled trial compared 6.75 g and 4.5 g of balsalazide in active ulcerative colitis. After 4 weeks of treatment there was no significant difference between the 3 treatment groups in clinical remission or symptom improvement. Possible explanations for this finding include the short duration of the trial, low percentage of newly diagnosed patients, and high percentage of patients having previously relapsed on a 5-ASA agent.

Attempts to compare different 5-ASA formulations based on efficacy rates in placebo-controlled trials should be made with caution. Factors such as severity of colitis, duration and extent of disease, and assessment parameters vary between trials and make each study unique and cross-study comparison of efficacy inappropriate.
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Efficacy: 5-ASA Comparative Trials

Studies directly comparing these agents are more limited in number, but provide insight into whether there are significant efficacy differences between the formulations. Several trials have supported the notion that sulfasalazine is highly effective for treating active ulcerative colitis, but less well tolerated than the newer 5-ASA agents. Sulfasalazine 3 g was found to be equivalent to Eudragit-S-coated mesalamine 1.5 g in achieving clinical and endoscopic remission. Despite excluding patients with known sensitivity to salicylates and sulfanomides, the sulfasalazine group still suffered a higher incidence of adverse events than the mesalamine group (24% vs 14%). More recently sulfasalazine 3 g was compared to balsalazide 6.75 g without excluding patients with known hypersensitivity and found a significantly higher rate of withdrawal due to adverse events in the sulfasalazine group than the balsalazide group (31% vs 7%). In those patients who were able to tolerate treatment, similar improvement was seen in both groups.

The efficacy of Eudragit-S-coated mesalamine and balsalazide in active ulcerative colitis has been compared in a number of controlled trials. Green and colleagues compared 12 weeks of treatment with balsalazide 6.75 g to Eudragit-S-coated mesalamine 2.4 g in 99 patients with moderate to severe disease. Assessment was based on clinical symptoms, stool frequency (rectal steroid foam), and sigmoidoscopic evaluation. Symptomatic remission was defined as absence of or mild symptoms and complete remission defined as symptomatic remission with no use of relief medication. With scores of 0 or 1. At 12 weeks, 64% of patients in the balsalazide group had achieved symptomatic remission compared to 43% of patients in the Eudragit-S-coated mesalamine group, with 62% and 37% achieving complete remission respectively. As early as 2 weeks into treatment, significantly more patients achieved complete remission with balsalazide than with Eudragit-S-coated mesalamine (10% vs 2%, respectively). The authors concluded that balsalazide provided relief more rapidly and in a greater number of patients than Eudragit-S-coated mesalamine.

Two similar studies found a less dramatic difference between these 2 agents, possibly related to a higher proportion of relapsed patients than in the Green study indicating a patient population with more refractory disease. Pruitt and colleagues studied the 6.75-g dose of balsalazide and 2.4-g dose of Eudragit-S-coated mesalamine in patients with mild to moderate disease. This study also found an earlier response to treatment with balsalazide as evidenced by significant improvement in sigmoidoscopic score as early as 2 weeks into treatment. Clinical improvement appeared to be dose related for balsalazide with a significantly greater proportion of patients treated with the standard dose showing improvement in stool frequency, rectal bleeding, sigmoidoscopic score, and PGA score. An improvement in rectal bleeding, sigmoidoscopic score, PGA score, overall symptom assessment, and patient functional assessment favored standard-dose balsalazide over Eudragit-S-coated mesalamine, but was not statistically significant. Using a sigmoidoscopic score of normal to mild, a PGA score of quiescent, and clinical symptoms of no rectal bleeding and normal stool frequency as definition for complete remission, there was no significant difference among the 3 therapies (23%, 19%, and 19% respectively).

Patients who failed to reach clinical remission in the Eudragit-S-coated mesalamine groups from the Pruitt and Levine studies were crossed over in an open-label fashion to receive balsalazide 6.75 g. As determined by...
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the PGA score, 61% of these patients reached clinical remission by 8 weeks of therapy. Possible explanations for this finding may be that individual patients respond more favorably to specific delivery systems or that these patients received a 5-ASA agent for a longer period of time. It is difficult to draw specific conclusions of these findings, as the reverse experiment of treating balsalazide failures with Eudragit-S-coated mesalamine has not been performed.

Kruis and colleagues compared the efficacy of 3 g of olsalazine with 3 g of Eudragit-L-coated mesalamine in patients with mild to moderate ulcerative colitis. After 12 weeks no significant differences were seen in the number of patients achieving endoscopic remission (52% and 48%) or clinical remission (45% and 46%) as defined by a clinical activity index score of less than 1.

Tolerability

5-ASA preparations are better tolerated than sulfasalazine and have been found to be safe in patients known to be intolerant to sulfasalazine. Adverse events related to the 5-ASA preparations are low. Although the Green study reported higher adverse event rates among patients receiving Eudragit-S-coated mesalamine as compared to balsalazide, other studies have not confirmed a difference, and overall the reported rates of adverse events are similar among the different formulations. The most commonly reported adverse events with the 5-ASA formulations include headaches and GI symptoms such as diarrhea, gas, and nausea, but in placebo-controlled trials these events did not occur at significantly higher rates than in those patients receiving placebo. An exception is that olsalazine has been observed to cause higher rates of diarrhea as compared to placebo and Eudragit-L-coated mesalamine. Other rare side effects associated with the 5-ASA preparations include interstitial nephritis, hepatitis, pericarditis, pancreatitis, pneumonitis, dermatitis, myocarditis, and hematologic disturbances. The number of patients necessitating removal from studies due to adverse events has been small (<10%), and most commonly these have been due to failure of therapy or worsening of colitis symptoms. While these withdrawals may simply be due to a failure of the medical regimen, it is important to note that 5-ASA agents have been observed to cause a worsening of colitis, which may be misinterpreted as medically refractory disease.

Conclusion

The availability of diverse delivery systems of 5-ASA compounds has been a major advance in the treatment of ulcerative colitis, as these formulations allow 5-ASA to reach the colon without the high rate of side effects previously seen with sulfasalazine. As a whole these agents have been found to be safe and effective for the treatment of active ulcerative colitis, when given in doses ranging from 2.4 g to 4.8 g. Though each system appears to have a dose-response relationship without an associated increase in adverse events, it is not yet clear whether the upper effective dose limit for these compounds has been reached. Although the clinical relevance of pharmacokinetic differences between the delivery systems are not yet clear, it is possible that these may explain why patients vary in their

Main Points

• Mesalamine has long been recognized as an effective therapy for patients with ulcerative colitis.

• In clinical trials, as many as 30% to 40% of patients were unable to tolerate sulfasalazine at doses of 4 g/day due to both dose-dependent and dose-independent reactions which include headache, dyspepsia, male infertility, and agranulocytosis that have largely been attributed to the sulfapyridine component, which primarily serves as a carrier to prevent proximal absorption.

• The therapeutic benefit of 5-ASA in ulcerative colitis is related to direct contact with the colon, making delivery to the site of active disease critical for its efficacy. Orally ingested 5-ASA is rapidly absorbed in the upper GI tract and does not reach the colon. These findings have led to the development of several formulations devoid of the sulfapyridine component that are designed to still allow delivery of intact 5-ASA to the lower GI tract.

• The availability of diverse delivery systems of 5-ASA compounds has been a major advance in the treatment of ulcerative colitis by allowing 5-ASA to reach the colon without the high rate of side effects as previously seen with sulfasalazine.

• 5-ASA preparations are better tolerated than sulfasalazine and have been found to be safe in patients known to be intolerant to sulfasalazine.

• It has become clear that for a given individual, consistent release of the highest amount of 5-ASA at the site of inflammation will produce the best results. A variety of formulations of 5-ASA that have been found to be safe and effective for the treatment of active ulcerative colitis when given in doses ranging from 2.4 g to 4.8 g are now available to help achieve that goal.
response to specific agents within this class. It is to be expected that individuals will respond differently given the wide variability in duration, location, and symptoms of disease among ulcerative colitis patients. What is clear is that for a given individual, consistent release of the highest amount of 5-ASA at the site of inflammation will produce the best results, and we now have a variety of products to help achieve that goal.

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