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New 5-ASA Formulations for the Treatment of Ulcerative Colitis: A Review of Recent Data and Future Directions in Therapy

Introduction by

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Abstract

Mesalamine (5-aminosalicylic acid; 5-ASA) is the current, standard first-line therapy for the treatment of mild-to-moderate ulcerative colitis. 5-ASA acts topically, and therefore much effort has focused on the development of orally available 5-ASA formulations with the goals of maximizing the amount of drug delivered to sites of active inflammation within the intestine. However, differences in intestinal pH, as well as in the orocaecal transit time, result in patient-to-patient variations of the intestinal concentrations of 5-ASA and, therefore, inconsistent treatment results. Additionally, the required high pill burden of most formulations can reduce patient adherence to therapy. Recently, higher-concentration formulations of both azo-bonded and pH-dependent 5-ASA formulations have been tested in phase III trials. These formulations show promise in terms of both the effective delivery of drug to the colonic mucosa and in reducing overall pill burden to increase patient adherence. Further, ongoing study and mounting evidence on the mechanism and efficacy of 5-ASA agents for the chemoprevention of colorectal cancer (CRC) provide another justification for the promotion of adherence to 5-ASA therapy, as both active treatment and manintenance therapy in the ulcerative colitis population.

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with ulcerative colitis.

Statement of Need/Program Overview: Ulcerative colitis (UC) affects 11 per 100,000 individuals in the United States. According to the American College of Gastroenterology guidelines, treatment for UC should induce and maintain remission of symptoms and mucosal inflammation to improve patients' quality of life. Aminosalicylates (5-ASAs) are recommended for the induction and maintenance of remission in patients with mild-to-moderate disease. Topical, rectally administered therapy may be appropriate for distal disease, whereas oral 5-ASA treatment is recommended for extensive disease. A combination of oral and rectal therapies may be more effective than either agent alone. Multiple oral 5-ASA formulations have been developed, which differ in their method of delivery of active drug to the colon. Administration of 5-ASA therapy represents a challenge to community physicians due to the varying manifestations of UC throughout the colon and the need to select the drug delivery system best suited to each patient. Because of the large pill burden and need for thrice daily dosing required with most 5-ASA formulations, patient adherence to maintenance regimens are another issue of concern. A discussion among UC thought leaders regarding data on novel formulations of 5-ASA products could address concerns regarding systemic absorption rates, delivery of 5-ASA throughout the colon, and novel formulations that reduce pill burden and simplify dosing schedules, thus providing an excellent educational opportunity for physicians attempting to choose the right agent for their individual patients.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe the disease factors that can potentially affect optimization of 5-ASA therapy for UC
2. Describe the patient factors that can potentially affect optimization of 5-ASA therapy for UC
3. Review emerging data on existing and novel 5-ASA formulations
4. Explain the application of these data in the clinical setting to address individual patient needs

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Introduction: Limitations of Current 5-ASA Formulations

Gary R. Lichtenstein, MD

Mesalamine (5-aminosalicylic acid; 5-ASA) is the current, standard first-line therapy for the treatment of mild-to-moderate ulcerative colitis (UC).[1,2] Its primary mechanism of action is uncertain, but is thought to involve induction and activation of the nuclear peroxisome proliferator-activated receptor gamma (PPARγ). Interestingly, lack of PPARγ expression in intestinal cells has been proposed to be a pathogenic mechanism in the development of UC.[3-5] However, other possible biologic targets and effects of 5-ASA include inhibition of prostaglandin and leukotriene synthesis.[6] 5-ASA acts topically, and therefore both oral and rectal formulations of the drug have been developed. Although rectal delivery results in a high concentration of the drug within the intestinal lumen, patient compliance with the prescribed regimen has been found to be poor. Therefore, these formulations are mainly used as adjuvants.[1,2] Conversely, much effort has focused on the development of orally available 5-ASA formulations with the goals of maximizing the amount of drug delivered to sites of active inflammation within the intestine.

Current 5-ASA Formulations

Free 5-ASA is almost completely absorbed into the systemic circulation, after which it is extensively metabolized and excreted. Thus, several strategies have been used to prevent oral 5-ASA from being absorbed systemically, allowing more drug to reach the inflamed sites in the colonic mucosa. In this article, we detail 4 general strategies. The use of: azo-bonded pro-drugs, pH-dependent delayed-release formulations, controlled-release agents, and combined delayed-release and controlled-release formulations.

Sulfasalazine

The first formulation of 5-ASA used in the treatment of UC was sulfasalazine. Sulfasalazine consists of a sulfapyridine carrier and a 5-ASA molecule linked via an azo bond. The drug has low bioavailability until it reaches the colon, where the azo bond is cleaved by bacterial azoreductase enzymes, allowing the release of the active 5-ASA moiety.[7] However, the untoward effects of the sulfapyridine moiety can result in poor treatment tolerability among patients. Many dose-related adverse effects have been observed, including nausea, vomiting, dyspepsia, anorexia, and headache.[8,9] Because patients have had such poor experiences, other formulations of 5-ASA have been explored.

Alternative Azo-bonded Agents

The strategy of using an azo bond to form a 5-ASA pro-drug has been used in various formulations. Like sulfasalazine, the release of 5-ASA from these formulations is restricted to the colon. However, these alternative azo-bonded agents employ non-sulfur containing carrier moieties, which are inert and produce little toxicity. For example, balsalazide comprises a 5-ASA molecule azo-bonded to an inert benzoic acid derivative (4-amino-benzoyl-beta-alanine).[10] Another agent, olsalazine, is a dimer of two 5-ASA molecules connected via an azo-bond.[11]

Enteric Coating

Another strategy used in the delivery of 5-ASA is enclosure within an enteric coating, making it resistant to gastric breakdown. This coat disintegrates when the pro-drug reaches the higher pH in the lower intestinal tract thus providing a delayed release of the active drug. Formulations that are pH-dependent in their release of 5-ASA are used commonly in the United States. This formulation is reserved to the treatment of UC in the terminal ileum and colon.[12]

Controlled Release

Controlled-release administration is accomplished by formulations that encapsulate 5-ASA within ethylcellulose-coated microgranules. These 5-ASA microspheres are then encapsulated within a moisture-sensitive semi-permeable membrane.[6] Only one controlled-release formulation has been developed and approved for the treatment of UC in the United States. The drug begins its gradual release of 5-ASA in the duodenum.

Multiple-Release Formulations

A fourth strategy for effective oral administration of 5-ASA is a combination of pH-dependent delayed-release with other technologies to provide sustained colonic exposure. Multimatrix mesalamine tablets encapsulate 5-ASA in a system of lipophilic and hydrophilic matrices that provides gradual exposure throughout the colon. These are then enclosed in a pH 7-dependent enteric coating which allows delayed release until the tablet reaches the terminal ileum and the cecum.

Extended-release mesalamine granules are formulated to release from an enteric coating at a pH of 6. 5-ASA–containing granules within the coating then swell, allowing

for gradual and prolonged exposure of active drug in the colonic lumen.

Pharmacokinetics of 5-ASA Delivery Formulations

The availability of 5-ASA in the colonic mucosa varies according to the release of each particular formulation. For example, the delayed release formulation results in approximately 15–30% delivery to the small intestine, while the remainder is delivered to the colon.[13] The controlled-release formulation delivers approximately 50% of the 5-ASA to the small intestine and colon, each.[14] The azo-bonded formulation delivers approximately 99% of the 5-ASA to the colon, with the remaining 1–2% remaining in the small intestine.[15]

Among patients, each of the different 5-ASA formulations are known to achieve variable drug levels within the various tissues of the intestinal mucosa. This is one reason why in vivo studies have shown that the same oral 5-ASA dose does not necessarily result in the same therapeutic effect in different patients. Sources of this variability are unclear, but may be due to differences in local pH conditions.

Additionally, intestinal transit rates differ among patients. The enteric coating of the delayed-release formulations of 5-ASA may result in reduced availability, depending on the successful dissolution of the coating. In fact, many patients report the appearance of undissolved tablets in the stool, suggesting individual difficulty with tablet metabolization. The drug disposition of azo-bonded formulations can also be affected by variations among patients in the presence and activity of the enzymes necessary to metabolize these formulation.

Drawbacks of Current 5-ASA Agents

One serious drawback associated with the use of all orally administered 5-ASA formulations is the lack of efficient delivery to the left side of the colon. Indeed, clinical studies have shown that these 5-ASA formulations instead reach their highest concentration in the right-side of the colon.[16,17] Unfortunately, left-sided UC accounts for 60–80% of new cases.[18,19] The inefficient delivery of 5-ASA to left-sided UC tissue may be a result of the increased transit time through the inflamed distal colon. This is a manifestation—often associated with active disease—that can limit the duration of exposure of these tissues to the drug.[20,21]

There is, however, significant evidence to suggest that rectal 5-ASA administration may result in improved drug delivery to the left side at the colon. A meta-analysis of treatment for left-sided UC confirmed that application of topical rectal formulations resulted in superior clinical improvement when compared with the use of oral formulations.[22] Current clinical guidelines suggest that the optimal treatment for left-sided disease may be a combination of topically- and orally-available 5-ASA.[17]

A second, real drawback of current 5-ASA formulations is the need for multiple daily administrations. The rationale for multiple daily dosing is to ensure that therapeutically active concentrations of 5-ASA are maintained within the colon. There is evidence to suggest that this is an effective strategy.[1,2] However, patient adherence to this rigid dosing schedule has been poor. Some reports estimate that 50% of UC patients do not adhere to dosing instructions, although this percentage varies among studies.[23] One study followed 94 UC patients during more than 6 months of maintenance therapy with a delayed-release 5-ASA formulation and found a 40% overall rate of adherence.[24]

In another study, 99 patients with quiescent UC were monitored over a 2-year period. Of these, 39 (40%) experienced recurrence, and 81 (82%) were found to be non-adherent.[25] The impact of non-adherence on clinical outcome and disease control is significant, affecting morbidity, quality of life, and even the risk of colorectal cancer.[25,26] In fact, a recent case-control study of nearly 19,000 UC patients found that those who were adherent to 5-ASA therapy had a decreased risk of developing colorectal cancer compared with those who were non-adherent (adjusted odds ratio [OR]=0.60).[27]

For patients who do not benefit, or cease to benefit, from 5-ASA administration, corticosteroids are the first-choice as alternate therapy. The benefit of steroid therapy in UC is clear: It often results in rapid and effective induction of response and remission. Unfortunately, many patients develop steroid-dependency, characterized by chronically active disease requiring several courses of steroid to achieve remission.[28] These patients then tend to relapse, either during steroid tapering or relatively soon after steroid discontinuation.

In a pivotal population study of 185 adults with UC, the patients' natural history was followed after the patients received steroid therapy (N=63).[29] At a 30-day follow-up, three distinct patient groups were identified: 1) those who achieved a complete response; 2) those who showed a partial response; 3) and those who received no benefit from the therapy (54%, 30%, and 16%, respectively). However, at a 1-year follow-up, many patients who initially responded to steroid therapy were no longer receiving benefit (49%, group 1; 22%, group 2; and 29%, group 3).

Approximately the same proportions of patients were identified in a similar, but smaller study of pediatric UC patients. At 30 days of therapy, Mayo Clinic researchers found that 50% of patients fell into group 1, 29% into group 2, and 21% into group 3.[30] After 1 year, 43% of these patients had either developed steroid-dependent disease or had required surgery, further showing that although many individuals initially respond to steroids, this response is often not maintained.

While it can be tremendously effective, corticosteroid therapy is also associated with significant adverse effects, many of which are irreversible. One significant toxicity is bone disease. Osteonecrosis is a serious complication of inflammatory bowel disease (IBD) associated with steroid use in several reports.[31-33] A small study found that 4.3% of patients with IBD who received steroid therapy over a mean of 42 weeks developed osteonecrosis.[34] Osteoporosis is also a commonly reported adverse effect of steroid therapy. The prevalence of IBD-associated osteoporosis ranges from 2–30%,[35] and the relative contributions of IBD and steroid therapy to the development of osteoporosis are unknown. However, it is clear that the risk of osteoporosis increases with steroid use.[36] Prolonged steroid use is also associated with the development of cataracts, although the mechanism of this is unknown.[37,38] A multitude of other toxic effects are also associated with steroid therapy, some of which are potentially serious, including mood changes, lightheadedness, and irregular heartbeat.

Conclusion

Mesalamine remains the standard first-line treatment for UC. Clinicians must continue to strive for optimal administration methods and improved treatment adherence among patients. In part because of poor adherence and in part because of the progressive nature of UC, this remains a frustrating disorder for physicians and a painful and sometimes debilitating disease for patients. Thankfully, most patients benefit significantly from a stepwise administration of available treatments beginning with mesalamine and evolving through a multimodal regimen to rescue with corticosteroids.

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New 5-ASA Formulations for the Treatment of Ulcerative Colitis

As one of the longest-standing, safest, and most effective therapies for UC, 5-ASA, remains a first-line treatment to induce and maintain response and remission in distal or extensive mild-to-moderate disease.[1] Several mechanisms of action for 5-ASA activity in UC have been proposed, including inhibition of prostaglandin synthesis through activation of the PPARγ, a regulator of gene transcription highly expressed in the colonic epithelium.[2-5]

It is well established that the efficacy of 5-ASA is dependent on the ability to achieve high concentrations of the drug within the colonic lumen and maximize topical exposure of the mucosa to the drug. Because of a high rate of absorption of free 5-ASA across the intestinal epithelium into the systemic circulation, oral preparations of 5-ASA are most frequently administered in formulations with modified pharmacokinetic properties.

Challenges in Drug Delivery

One of the most commonly prescribed modified 5-ASA formulations is mesalamine. Mesalamine is well-tolerated and allows for formulations that trigger release of 5-ASA in a pH-dependent manner, achieving the delivery of therapeutic concentrations in the distal small bowel and colon.[2] However, despite the development of this and other controlled-release and azo-bonded formulations, many patients do not experience a clinically significant benefit from current 5-ASA therapies.

Differences in intestinal pH, as well as in the orocaecal transit time, result in patient-to-patient variations of the intestinal concentrations of 5-ASA and, therefore, inconsistent treatment results. Additionally, the required high pill burden of most formulations can reduce patient adherence to therapy.[6] These limitations have resulted in ongoing research into the development of newer 5-ASA-based compounds and delivery systems, with the goals of improving outcomes through more effective colonic delivery and less burdensome regimens.

Balsalazide

Balsalazide is an azo-bonded 5-ASA formulation that has been shown to deliver the compound directly to the colon with an efficiency of greater than 99%, minimizing its absorption into the systemic circulation.[7] Balsalazide effectively reduces the clinical symptoms associated with active UC. It can also induce remission in patients with UC while presenting fewer challenges with tolerability compared to sulfasalazine, another major azo-bonded 5-ASA formulation.[8-11]

Recently, a highly-concentrated form of balsalazide was evaluated for the treatment of mild-to-moderate UC in a Phase III, double-blind, randomized, and placebo-controlled clinical trial. The efficacy, safety, and impact on quality of life (QoL) of balsalazide in this trial were detailed in three separate reports, described below.

In this study,[12] 249 patients (mean age, 44 years) were randomly assigned to receive either balsalazide in three 1.1 g tablets twice daily, or placebo, over an 8-week period. All patients were diagnosed with mild-to-moderate active UC, with a baseline modified Mayo disease activity index (MMDAI) score of 6–10. The MMDAI, uses 4 criteria, has a maximal score of 12, with a greater score indicating more active disease.

The first presentation evaluated the activity of balsalazide during the study.[12] The primary endpoint was clinical improvement, defined as a decrease in the MMDAI score of 3 or more points, with a decrease in the rectal bleeding subscore of 1 or more points. At baseline, the mean MMDAI score of all patients was 7.9 (standard deviation [SD]=1.4), and was similar between treatment groups. The mean MMDAI subscores were also similar between groups, including daily frequency of bowel movement (2.0; SD=0.9), rectal bleeding (1.9; SD=0.5), physician's global assessment (1.9; SD=0.4), and endoscopy or sigmoidoscopy score (2.1; SD=0.4).

At the end-of-study evaluation, a significantly higher percentage of patients in the balsalazide group achieved the primary endpoint of clinical improvement compared with the placebo group (55% vs 40%, P=.0237; Figure 1). Importantly, the mean decrease from baseline of the total MMDAI score was also greater in the balsalazide arm compared with the placebo arm (3.4 vs 2.3 point decrease, P=.0018). The greater improvement in total MMDAI score in the balsalazide group was evident in each MMDAI subscore as well. These results translated into a statistically significant increase in the number of patients experiencing clinical remission in the balsalazide group compared with the placebo group (39% vs 23%, P=.0096).

The safety and tolerability of balsalazide was evaluated in all patients who had received at least one drug treatment and at least one post-baseline safety assessment.[13] Over the 8-week study period, more patients in the placebo arm experienced an adverse effect (AE) compared with those in the balsalazide arm (68% vs 55%; Figure 2). Additionally, the number of serious AEs was also increased in the placebo group (5% vs 2%). The most commonly reported AEs were worsening of UC and headache, both of which occurred

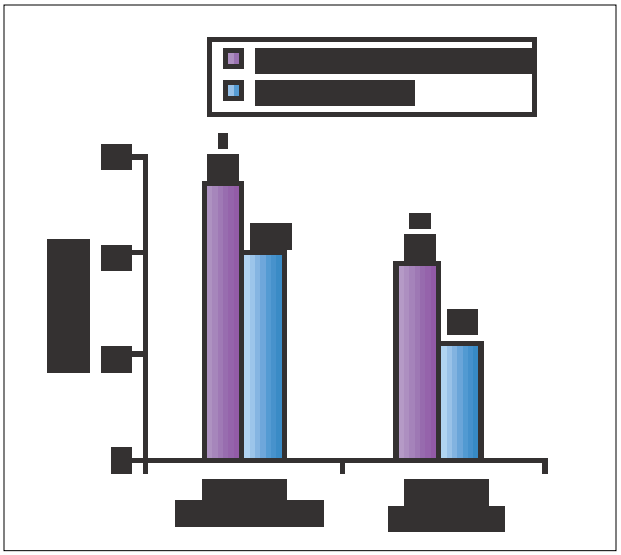

Figure 1. Percentage of patients treated with balsalazide 6.6 g/d or placebo who achieved clinical improvement and clinical remission after 8 weeks of treatment.

*P=.0237; †P=.0096.

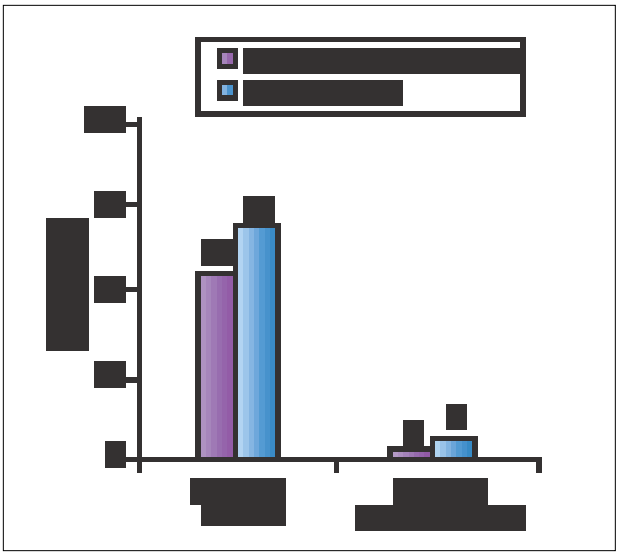

Figure 2. Percentage of patients treated with balsalazide tablets or placebo who experienced an adverse event during 8 weeks of treatment.

more frequently in the placebo group (14% more frequently for both AEs) than in the balsalazide group (7% and 6%, respectively). At the conclusion of the study, all patients were offered enrollment into an open-label extension study, during which time no serious AEs were considered to be drug-related. From these results, balsalazide was determined to be safe and well tolerated in adult UC patients.

The effect of balsalazide on patient QoL, quantified using two assessments, was also evaluated to more fully determine the safety and efficacy of the drug.[14] First, patients completed the inflammatory bowel disease questionnaire (IBDQ) both after the first 2 weeks of therapy and at the end of the study. The IBDQ is a well-established self-reporting survey method to assess UC patient QoL.[15] The comprehensive IBDQ score ranges from 32 to 224, with higher scores indicative of superior QoL.

Of the 249 study participants, QoL data were gathered from 172 patients (115 in the balsalazide arm and 57 in the placebo arm). At baseline, the mean total IBDQ score for all patients was 131.3 (range: 37–223). After 2 weeks of study treatment, patients in the balsalazide group reported significantly superior improvements in the total IBDQ score compared with the placebo group (27.9 vs 20.1, P=.0064; Figure 3). This statistically significant difference continued at the end-of-treatment IBDQ assessment (32.7 vs 29.7 points, P=.0302).

When each disease criteria category was assessed separately, it was found that patients in the balsalazide group reported significantly greater improvements in the categories of bowel symptoms, emotional function, and social function (P≤.0105) after 2 weeks versus those in the placebo group.

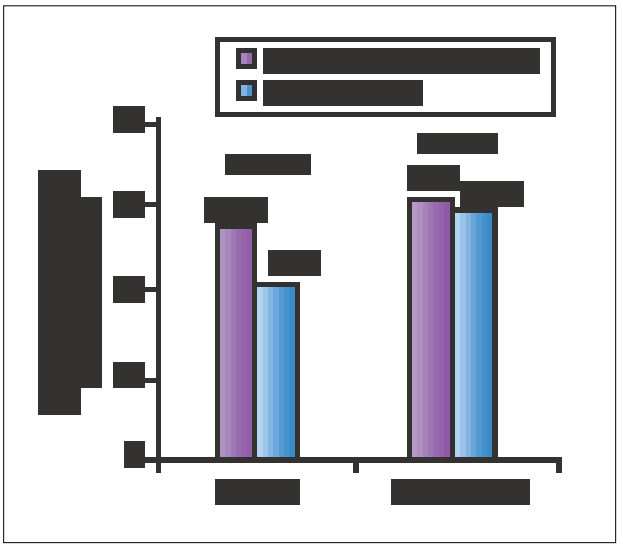

Figure 3. Mean improvement from baseline in total IBDQ score among patients treated with balsalazide 6.6 g/d or placebo after 2 and 8 weeks/EOT.

*QoL data were contributed by 115 patients who received balsalazide and 57 patients who received placebo, but data were not available for all patients at all time points.

EOT=end of treatment; IBDQ=inflammatory bowel disease questionnaire.

Balsalazide patients also experienced improved emotional and social function scores (P≤.0192) compared with patients in the placebo group. In a second assessment of QoL, patient interview information revealed that a significantly higher

Table 1. Treatment Success (ITT Set to Failure) at Week 6 of the ASCEND III Trial

Patient Subgroup	4.8g/d	2.4g/d	*P* value†
Previous Use of Oral 5-ASAs	70.4% (238/338)	63.8% (206/323)	.070
Previous Use of Rectal Therapies	69.8% (134/192)	60.6% (114/188)	.062
Previous Use of Steroids	64.3% (101/157)	53.5% (84/157)	.051
Previous Use of 2 meds or more*	69.6% (160/230)	58.1% (136/234)	.011

*Including oral 5-ASAs, rectal therapies, steroids, or immunomodulators

†Cochran-Mantel-Haenszel *P* value

proportion of patients in the balsalazide arm rated themselves as satisfied or very satisfied with the treatment compared with those in the placebo arm (73% vs 56%, *P*=.0230).

The ASCEND III Trial

In a separate study by Sandborn and colleagues, a higher dosage delayed-release mesalamine tablet was evaluated in a non-inferiority Phase III trial.[16] ASCEND III was a multinational, double-blind study that randomly assigned 772 patients to receive either the high concentration delayed-release tablet (4.8 g/day; n=389) or a currently available delayed-release mesalamine tablet (2.4 g/day) as an active control (n=383). Study participants had moderately active UC, diagnosed with a Physician's Global Assessment (PGA) score of 2. Non-inferiority, a primary study endpoint, was defined as an improvement from the baseline PGA score by the end of the 6-week study period, accompanied by no worsening of other clinical assessments.

After the 6-week treatment, a majority of patients in each treatment group achieved the primary endpoint of non-inferiority (70% in 4.8 g/day group versus 66% in 2.4 g/day group). Both mesalamine formulations were shown to be effective in improving several secondary endpoint measurements, including clinical remission, rectal bleeding, bowel movement frequency, and histologic improvement as assessed by sigmoidoscopy.

Patients with a history of more clinically active disease displayed a particular benefit from receiving the higher-concentration mesalamine formulation compared with the standard formulation. This benefit was most apparent in those patients with a history of having received more than 2 UC medications, of whom 69.6% experienced treatment success in the 4.8 g/day arm, compared with 58.1% in the 2.4 g/day arm (*P*=.011).

This trend also continued when patients were categorized according to specific treatment history (Table 1). Patients who had used oral 5-ASA (70.4% vs 63.8%, *P*=.070), or rectal 5-ASA (69.8% vs 60.6%, *P*=.062), and those who had previously taken corticosteroids (64.3% vs 53.5%, *P*=.051) all experienced greater benefit with the 4.8 g/day dosage compared with the 2.4 g/day dosage. Overall, the 4.8 g/day mesalamine dosage displayed a safety profile comparable to the 2.4 g/day dosage, and was well tolerated.

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Commentary: Strategies to Optimize the Use of 5-ASA Therapy

Alan V. Safdi, MD

Effective delivery of a therapeutic agent to its site of action is a critical determinant of patient response to therapy. The colonic mucosal concentration of 5-ASA has been found to be an important predictor of its therapeutic effect. This was clearly shown in a study by Naganuma and colleagues, which found that the concentration of 5-ASA in the rectum was inversely correlated with patient response, measured by an improvement in the disease activity index ($P<.001$).[1] Therefore, the optimal 5-ASA agent for UC is that formulation which achieves the highest delivery of the 5-ASA drug to the colon, allowing for the accumulation of high concentrations of 5-ASA to the sites of inflammation. Additionally, from a pharmacological standpoint, 5-ASA formulations which exhibit similar distribution patterns among multiple patients are useful in order to achieve more consistent and predictable drug concentrations. For instance, pH-dependent delayed-release formulations display much greater pharmacokinetic variations compared with azo-bonded formulations, likely due to pH differences within and among patients. Alternatively, azo-bonded formulations may allow more consistent levels of 5-ASA to be achieved. This was shown in one study by Kornbluth and colleagues, which compared the colonic mucosal concentrations of 5-ASA after administration of either the azo-bonded balsalazide agent (n=13) or a pH-dependent delayed-release formulation (n=17).[2] Biopsies from 3 distinct mucosal areas revealed that 5-ASA concentrations were consistently superior after balsalazide treatment (102%, 84%, and 102% greater at 5, 15, and 25 cm from the anal verge, respectively).

It is likely that post-colonic wasting is a major reason for the less efficient delivery of the pH-dependent delayed-release formulation. In fact, in a study comprised of healthy volunteers with normal pH distribution, 55% experienced capsule fragments within the stool, which accounted for approximately one-quarter of the administered dose of 5-ASA.[3] These fragments were shown not to be merely inert; instead every fragment contained measurable drug. To further complicate the efficiency of pH-dependent delayed-release formulations, a significant percentage of individuals do not reach a pH of 7 within their intestinal tract. This was shown in a study which found pH levels did not achieve 7 in 25% of 39 healthy volunteers.[4] Several small studies have reported similar results in UC-specific populations.[5-7] In these patients, the pH 7-sensitive enteric coating is never efficiently broken down, leading to post-colonic wasting and inefficient delivery of the 5-ASA.

One study has allowed head-to-head comparison of balsalazide with pH-dependent delayed-release 5-ASA.[8] In this report, 101 UC patients were administered equivalent amounts of each agent (6.75 g balsalazide and 2.4 g mesalamine, daily). At each time point tested, balsalazide treatment resulted in higher rates of symptomatic remission. By 12 weeks of therapy, 88% of patients receiving balsalazide achieved symptomatic remission, compared with 57% receiving mesalamine. Importantly, more patients also achieved complete remission at 12 weeks, measured as having no symptoms with a grade 0 or 1 sigmoidoscopy and no rectal steroid use (62% versus 37%, respectively).

New 5-ASA Formulations

Currently, several novel formulations of 5-ASA are under active clinical investigation. One of these is a high-dose formulation of balsalazide (1.1 g tablet). This high-dose balsalazide is awaiting FDA approval, after promising results from a phase III double-blind, randomized and placebo-controlled trial.[9-11] In this study, patients with mild-to-moderate UC who were administered high-dose balsalazide (3 tablets, twice daily) experienced superior improvement in clinical outcome as well as quality of life. The reduced dosage format of this drug, two times per day, greatly reduces the pill burden and should increase patient adherence.

Mesalamine granules provide another strategy for 5-ASA delivery. These 5-ASA granules are encapsulated within a pH 6-sensitive enteric coating, and contain an additional retarding polymer within the granule core. Because they have a lower pH sensitivity, mesalamine granule capsules may provide superior benefit in patients who do not reach pH 7 within their intestinal tract. However, head-to-head comparisons of this formulation with pH 7-sensitive delayed-release formulations have not yet been performed.

Switching 5-ASA Therapy

5-ASA therapy is established to be highly effective in the setting of mild-to-moderate UC, and is active in up to 80% of patients to both induce and maintain remission.[12-14] However, a significant proportion of patients either do not respond to, or lose response to, 5-ASA therapy. In these cases, simply increasing the dosage of 5-ASA often does not improve response.[15] Additionally, this increases the already heavy pill burden associated with these agents. In light of newer and alternative 5-ASA formulations, another strategy

is for these patients to switch 5-ASA agents. Several studies have now begun to investigate optimal switching strategies in UC patients.

One of the first clues that switching 5-ASA formulations was a viable approach came when it was found that of 17 patients who failed mesalamine (13 did not respond; 4 were intolerant) and went on to receive balsalazide, 24% achieved remission and 6% a significant response.[16] Importantly, the median time to these responses was only seven days, indicating that the lack of response to mesalamine was likely due to inefficient delivery of the 5-ASA to the colon.

These studies indicate that many 5-ASA-refractory patients may benefit from a salvage therapy strategy involving a switch to an alternate 5-ASA formulation. This may be especially beneficial in light of the favorable safety profiles associated with 5-ASA, as opposed to the many toxicities associated with corticosteroid and biologic therapy as treatment alternatives.

Chemoprevention with 5-ASA

It is clearly established that UC patients are at an increased risk for the development of colorectal cancer, with a crude annual incidence rate of as high as 1 in 500 cases.[17] The best strategies to prevent colorectal cancer in UC patients include both prophylactic colectomy and routine and vigilant colonoscopy. However, neither of these are realistic options for most patients. Instead, chemoprevention has gained increasing attention in this setting. Of the potential drugs under investigation, several studies have shown that 5-ASA is a promising agent for chemoprevention. Although the optimal dosing strategy for this purpose is unclear, chronic systemic administration of at least 1.2 g/day seems to be effective from various studies.[18] One retrospective case-control matched analysis showed that 5-ASA at these concentrations reduced the risk of cancer by 81% (P=.006).[19]

Several characteristics are attributed to 5-ASA which may be responsible for their anti-neoplastic effect. 5-ASA increases cellular death (apoptosis) and decreases cellular proliferation, effects observed both in vitro with cancer cell lines and in patients.[20-24] Several mechanisms have been proposed to explain these cellular effects of 5-ASA. For example, a recent report showed that 5-ASA downregulated the expression of the oncogene c-Myc in colon cancer cells.[25] 5-ASA can also induce mitotic arrest in these cells, which may result in apoptosis.[23] Separately, 5-ASA reduces the likelihood of microsatellite instability, decreasing DNA mutations and improving the replication fidelity of cells.[26] Unlike non-steroidal anti-inflammatory drugs (NSAIDs), which are also under active investigation as chemopreventative agents, 5-ASA exerts these effects without the side effect of intestinal bleeding. Recently, the azo-bonded formulation balsalazide proved active in an animal model of intestinal tumor formation. In this study, balsalazide reduced the number of intestinal tumors in a dose-dependent fashion, up to 80%, in B6-Min/+ mice.[27] This process was attributed to inhibition of cell proliferation and possibly the induction of apoptosis.

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New 5-ASA Formulations for the Treatment of Ulcerative Colitis: A Review of Recent Data and Future Directions in Therapy

CME Post-Test: *Circle the correct answer for each question below.*

1. Which of the following strategies is NOT used as a 5-ASA formulation?

   a. pH 7-dependent delayed-release
   b. azo bond with a sulfapyridine carrier
   c. azo bond with a benzoic acid derivative
   d. pH 3-dependent delayed-release

2. In a recent phase III study, _____ of patients receiving a high-dose balsalazide formulation (three 1.1 g tablets, twice daily) experienced clinical improvement.

   a. 14%
   b. 40%
   c. 55%
   d. 68%

3. Which of the following patient subgroups experienced greater benefit with a 4.8 g/day dosage of delayed-release mesalamine compared with a 2.4 g/day dosage?

   a. previous oral 5-ASA use
   b. prior rectal therapy
   c. previous steroid exposure
   d. all of the above

4. Balsalazide delivers 5-ASA to the colon with what efficiency?

   a. 15–30%
   b. 25–30%
   c. 98–99%
   d. 100%

5. The most frequently prescribed pH-dependent delayed-release 5-ASA formulation is dissolved at what pH?

   a. pH 7
   b. pH 6
   c. pH 5
   d. pH 4

6. True or false? Oral 5-ASA formulations achieve their highest concentration in the left side of the colon.

   a. True b. False

7. In a study discussed by Dr. Lichtenstein, of 99 UC patients followed over 2 years, 39 experienced a disease recurrence. Of these 39 patients, what percentage was described as non-adherent?

   a. 56%
   b. 82%
   c. 86%
   d. 92%

8. In a study by Kornbluth and colleagues that was discussed by Dr. Safdi, _____ therapy achieved higher 5-ASA concentrations in the colonic mucosa than pH-dependent delayed-release agents.

   a. balsalazide
   b. sulfasalazine
   c. olsalazine
   d. MMX mesalamine

9. In a study conducted by Pruitt and colleagues, discussed by Dr. Safdi, _____ of individuals who failed to respond to mesalamine achieved clinical remission after switching 5-ASA agents.

   a. 45%
   b. 56%
   c. 61%
   d. 72%

10. Balsalazide reduced the number of intestinal tumors in B6-Min/+ mice, in a dose-dependent fashion, up to _____.

    a. 50%
    b. 60%
    c. 70%
    d. 80%

Evaluation Form: New 5-ASA Formulations for the Treatment of Ulcerative Colitis: A Review of Recent Data and Future Directions in Therapy

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgment for completing this activity.

Please answer the following questions by circling the appropriate rating:
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

1. Describe the disease factors that can potentially affect optimization of 5-ASA therapy for UC	1	2	3	4	5
2. Describe the patient factors that can potentially affect optimization of 5-ASA therapy for UC	1	2	3	4	5
3. Review emerging data on existing and novel 5-ASA formulations	1	2	3	4	5
4. Explain the application of these data in the clinical setting to address individual patient needs	1	2	3	4	5

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice	1	2	3	4	5
Enhanced my current knowledge base	1	2	3	4	5
Addressed my most pressing questions	1	2	3	4	5
Provided new ideas or information I expect to use	1	2	3	4	5
Addressed competencies identified by my specialty	1	2	3	4	5
Avoided commercial bias or influence	1	2	3	4	5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity.

Please list any topics you would like to see addressed in future educational activities.

Additional comments about this activity.

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

☐ Yes, I would be interested in participating in a follow-up survey. ☐ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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