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Getting More From New 5-ASA Therapies: Will Better Science Lead to Better Patient Adherence?

A Report From a Symposium Presented at the 2008 Advances in Inflammatory Bowel Diseases Meeting
December 5, 2008
Hollywood, Florida

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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: 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 current armamentarium of oral 5-ASA options for the treatment of ulcerative colitis.
2. Discuss the current challenges of 5-ASA administration in terms of both individual patient pharmacokinetics and compliance with current regimens.
3. Cite the current evidence regarding the efficacy of the once-daily formulation of sacheted mesalamine micropellets.
4. Explain how this new formulation might fit into the US landscape of treatment options.

Accreditation Statement: This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Postgraduate Institute for Medicine (PIM) and *Gastroenterology & Hepatology*.

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Getting More From New 5-ASA Therapies: Will Better Science Lead to Better Patient Adherence?

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Optimal Release Profile of Oral 5-ASA Agents

Gary R. Lichtenstein, MD, began the symposium with a discussion on the optimal release profile of oral 5-aminosalicylic acid (5-ASA) agents. There are many different formulations of 5-ASA approved in the United States for use in patients with inflammatory bowel disease (Table 1). Why so many? The answer lies in the metabolic pathway of oral 5-ASA. After ingestion, 5-ASA is delivered directly into the intestinal tract. If the drug is not specially formulated, it will be absorbed by the small intestine into the blood. From there it is metabolized into N-acetyl-5-ASA by the liver. Both 5-ASA and N-acetyl-5-ASA are excreted by the kidney into the urine. Because the mechanism of action of 5-ASA is generally perceived to be topical, the optimal delivery site for the treatment of ulcerative colitis (UC) is the large intestine.[1] A number of different tactics for delivering 5-ASA to the colon without absorption by the small intestine have been devised, resulting in multiple approved preparations.

The first approved oral 5-ASA agent, sulfasalazine,[2] was introduced in the 1940s. It is made up of two molecules, a molecule of 5-ASA and one of sulfapyridine; the 5-ASA was recognized as the active agent in the classic 1977 study by Azad Kahn and colleagues.[3] There is olsalazine,[4] an orally administered 5-ASA dimer, which has been approved for maintenance of remission in UC. Balsalazide, which is approved for mild-to-moderate active UC, is an oral formulation that links 5-ASA to an inert carrier by an azo bond.[5]

5-ASA (mesalamine) can also be delivered as a monomer and is available in several formulations. One is delayed-release mesalamine (Asacol), which is approved for mild-to-moderate active UC and for maintenance

Table 1. Oral 5-ASA Formulations

Agent	Formulation	Availability
Sulfasalazine (Azulfidine®)	5-ASA linked to sulfapyridine by azo-bond	Tablet: 500 mg (200 mg 5-ASA)
Olsalazine (Dipentum®)	5-ASA dimer linked by azo-bond	Capsule: 250 mg (225 mg 5-ASA)
Balsalazide (Colazal®)	5-ASA linked to inert carrier by azo-bond	Capsule: 750 mg (262 mg 5-ASA)
Delayed-release mesalamine (Asacol®)	Eudragit® S-coated tablets (delayed-release)	Tablet: 400 mg
MMX mesalamine (Lialda™)	Advanced, multimatrix system (delayed-release)	Tablet: 1,200 mg
Controlled-release mesalamine (Pentasa®)	Ethylcellulose-coated microgranules (moisture-activated)	Capsules: 250, 500 mg
Extended-release mesalamine (APRISO™)	Delayed- and extended-release granules in a polymer matrix core	Capsule: 375 mg

Adapted from Baumgart DC, Sandborn WJ. *Lancet*. 2007;369: 1641–1657.

of remission in UC. The caplets are coated with an acrylic-based resin that dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and colon.[6] Mesalamine is also available in a multimatrix system (MMX, Lialda) formulation that has a delayed release to the colon.[7] This agent is approved for the treatment of mild-to-moderate active UC. The third mesalamine formulation is a controlled-release form (Pentasa) made from ethylcellulose-coated microgranules; it is approved for the treatment of mild-to-moderate active UC.[8] The most recently approved 5-ASA agent is a delayed- and extended-release Intellicor formulation that integrates mesalamine granules in a polymer matrix core designed for release at a pH of 6 or greater (Apriso).[9] This agent is approved for the maintenance of remission in UC.

The different formulations of 5-ASA are released in different areas of the gastrointestinal tract.[10] The bonded agents sulfasalazine, olsalazine, and balsalazide are released in active form into the colon. Asacol is released in the terminal ileum and colon and Lialda is released in the ileum and colon. Pentasa is released partially in the small bowel, where about 50% of the drug is available, with the remainder releasing in the colon directly.

Clinical trial data have shown that different formulations of 5-ASA yield different colonic mucosal concentrations of the drug. For example, De Vos and colleagues determined the intramucosal 5-ASA concentrations in ileocolonic biopsy specimens from 61 patients with irritable bowel syndrome.[11] Patients had been treated for one week with near equimolar doses of different preparations of 5-ASA. The authors found that Asacol produced the highest concentrations of 5-ASA (mean wet weight 298.5 ng/mg), followed by Pentasa (25.7 ng/mg) and olsalazine (11.0 ng/mg).

A second study, by Naganuma and colleagues,[12] compared the mucosal concentration of 5-ASA in biopsies taken from the rectum and sigmoid colon of 13 UC patients who were treated with oral sulfasalazine and from 5 patients treated with Pentasa. They found that the concentrations of 5-ASA in the sulfasalazine group were far higher than those in the Pentasa group (49.4 µg/g vs. 6.6 µg/g in the rectum, $P<.01$; 63.9 µg/g vs 18.0 µg/g in the sigmoid colon, $P<.05$).

The question then arises: are differences in mucosal concentration clinically relevant? In the study by Naganuma and colleagues, higher concentrations of 5-ASA were associated with less active disease.[12] The average mucosal concentration of 5-ASA was 56.3 µg/g for the 11 patients without blood in the stool but was only 9.8 µg/g for the 13 patients with blood in the stool ($P<.01$). In looking at the Disease Activity Index (DAI) score in this cohort, the authors found that it was inversely correlated with the concentration of 5-ASA seen in the rectum.

Similar results were reported by Frieri and colleagues.[13] In their study, 6 endoscopic biopsies were taken from each of 21 patients with UC who were receiving oral 5-ASA doses of 2.4–3.2 g/day. The investigators found that the mucosal concentrations of 5-ASA were significantly higher in patients with endoscopic scores of 0–1 than they were in those with scores of 2–3 (16.1 ng/mg vs. 5.5 ng/mg; $P=.03$). The 5-ASA concentrations were also significantly higher in patients with lower histological inflammation scores (17.4 ng/mg vs 8.9 ng/mg; $P<.01$). Thus, it may be that maintenance of high mucosal 5-ASA concentrations in all colonic segments could contribute to improved clinical outcomes in UC patients.

In contrast to colonic mucosal concentrations, it appears that systemic exposure to 5-ASA is comparable among the various preparations. Sandborn and Hanauer published a review of the primary literature in 2003.[14] They noted that the urinary and fecal excretion of total 5-ASA were comparable for all oral 5-ASA formulations and pro-drugs, including sulfasalazine, olsalazine, balsalazide, Asacol, and Pentasa. They suggested, therefore, that the selection of a 5-ASA preparation for the treatment of UC should be based on other factors such as efficacy, dose-response, toxicity, compliance issues related to dose forms and dosing schedules, and costs.

Is 5-ASA Treatment Effective for Crohn's Disease?

Sulfasalazine was studied for Crohn's disease (CD) in the 1970s and 1980s in the National CD Cooperative Study and the European CD Cooperative Study. In both studies, sulfasalazine was found to be more effective than placebo treatment for the induction of remission; however, the effect was mainly seen in patients with colonic disease.[15,16] Three placebo-controlled trials of Pentasa for the treatment of CD have been conducted with conflicting results. A meta-analysis of these data conducted by Hanauer and Strömberg subsequently found only a slight benefit with mesalamine over placebo.[17] In the analysis, a total of 304 patients received 4 g/day of controlled-release mesalamine and 311 patients received placebo. The average reduction in Crohn's Disease Activity Index (CDAI) scores from baseline was 63 points in the treatment groups and 45 points in the placebo groups, a net reduction of 18 points in favor of mesalamine ($P=.04$). Although this difference is statistically significant, the clinical impact of an 18-point reduction in CDAI score is minimal.

5-ASA and Renal Tubular Dysfunction

While it is clear that 5-ASA is an effective treatment for patients with UC, physicians often ask if 5-ASA therapy causes nephrotoxicity. There are some published data that address this question. In one study, Schreiber and colleagues[18] monitored routine indices of kidney func-

tion as well as sensitive markers of glomerular or tubular dysfunction in 223 patients with IBD. They found that patients receiving high amounts of 5-ASA showed an increased prevalence of tubular proteinuria and higher levels of urinary gamma-glutamyltransferase (GGT) and alkaline phosphatase (AP). The AP and GGT levels indicated that proximal tubular epithelial cells were the source of the proteinuria. All other kidney function tests were normal. Thus, the authors concluded that high doses of 5-ASA may be associated with proximal tubular proteinuria, but that the possible impact of chronic inflammation was impossible to determine.

A more recent study was performed by Gisbert and colleagues.[19] In this retrospective analysis, creatinine clearance levels over 4 years were calculated for 62 IBD patients receiving 5-ASA treatment and for 88 IBD patients who were not receiving 5-ASA treatment. Creatinine clearance was estimated from measurements of serum creatinine levels recorded before the start of 5-ASA therapy and every year thereafter for up to 4 years. Both serum creatinine levels and creatinine clearance were similar in patients who did and who did not receive 5-ASA treatment, and a multivariate analysis revealed that 5-ASA treatment was not correlated with serum creatinine levels or creatinine clearance. The authors suggested that renal impairment in IBD patients receiving 5-ASA formulations is exceptional and routine serum creatinine monitoring may not be necessary. Dr. Lichtenstein noted, however, that medical and legal concerns might prompt physicians to order blood urea nitrogen (BUN) and creatinine level testing as well as a urinalysis perhaps once a year as part of routine monitoring.

The Optimal Release Profile for 5-ASA

Based on all of the data presented, Dr. Lichtenstein concluded that the optimal release profile for 5-ASA should deliver the drug topically to local colonic tissue, yielding high fecal recovery and low plasma and urinary concentrations. In practice, there are a number of approved 5-ASA formulations that produce variable mucosal 5-ASA concentrations of the drug. In addition, the site of delivery within the intestinal tract differs among the existing 5-ASA formulations. Although the potential impact on efficacy in CD remains uncertain, higher mucosal 5-ASA levels have been correlated to clinical and endoscopic improvement in UC patients. With its low risk of adverse events (AEs), 5-ASA remains a safe and effective drug for the treatment of patients with UC.

Table 2. 5-ASA Approved Dosing

Agent	Availability	Approved Dosing Regimens
Sulfasalazine[1] (Azulfidine®)	Tablet: 500 mg (200 mg 5-ASA)	Acute UC: 1 g QID Maint: 2 g/day in divided doses
Olsalazine[2] (Dipentum®)	Capsule: 250 mg (225 mg 5-ASA)	Maint: 500 mg BID
Balsalazide[3] (Colazal®)	Capsule: 750 mg (262 mg 5-ASA)	Acute UC: 750 mg TID
Delayed-release mesalamine[4] (Asacol®)	Tablet: 400 mg	Acute UC: 800 mg TID Maint: 1.6 g/day in divided doses
MMX mesalamine[5] (Lialda™)	Tablet: 1,200 mg	Acute UC: 2.4–4.8 g QD
Controlled release mesalamine[6] (Pentasa®)	Capsules: 250, 500 mg	Acute UC: 1 g QID
Extended-release mesalamine[7] (APRISO™)	Capsule: 375 mg	Maint: 1.5 g QD

1. Azulfidine® (sulfasalazine) [package insert]. New York, NY: Pharmacia & Upjohn Company; 2006.
2. Dipentum® (olsalazine) [package insert]. Kalamazoo, MI: Pharmacia & Upjohn Company; 2001.
3. Colazal® (balsalazide) [package insert]. Morrisville, NC: Salix Pharmaceuticals, Inc.; 2003.
4. Asacol® (mesalamine) [package insert]. Cincinnati, OH: Procter & Gamble Pharmaceuticals, Inc.; 2007.
5. Lialda™ (mesalamine) [package insert]. Wayne, PA: Shire US Inc.; 2007.
6. Pentasa® (mesalamine) [package insert]. Wayne, PA: Shire US Inc.; 2007.
7. APRISO™ (mesalamine) [package insert]. Morrisville, NC: Salix Pharmaceuticals, Inc.; 2008.

New Oral 5-ASA Formulations: What's On the Horizon?

William J. Sandborn, MD, began his discussion by taking a look at oral 5-ASA formulations and their approved dosing regimens (Table 2). As discussed earlier in the symposium, sulfasalazine was first introduced in the 1940s. Although effective, the sulfapyridine portion of the drug causes toxicity.[20] Asacol, in 400 mg tablets, was approved in the 1980s to be given in doses ranging from 1.6 g/day up to 4.8 g/day. This is generally accomplished by taking 2 to 3 tablets twice or three times per day.[6] Pentasa, in 250 mg capsules, was approved in the 1990s at a dose of 2–4 g/day.[8] Again, this requires the patient to take numerous capsules several times per day. A 500 mg capsule was later introduced, which simplified dosing somewhat. Both forms of mesalamine are very well tolerated in comparison with sulfasalazine. Balsalazide, approved in 2000, has good delivery to the colon and is also very well tolerated.[5] This formulation is given at a dose of 2.25–6.75 g/day, still requiring up to 9 tablets daily. In 2007, Lialda 1,200 mg tablets were approved for the treatment of active UC at a dosage of 2.4–4.8 g given only once daily,[7] making this formulation more patient-friendly than its predecessors.

New 5-ASA formulations continue to be developed. Mesalamine granules (Apriso), which are a delayed- and extended-release formulation that can be given once a day, were recently approved.[9] Asacol, in a new 800 mg tablet formulation, is currently undergoing evaluation for once-a-day dosing.

Mesalamine Granules

As discussed earlier, different formulations of 5-ASA have different sites of delivery in the gastrointestinal tract (Figure 1). Delayed-release mesalamine and MMX mesalamine release at about pH 7, which for the average person is reached first in the terminal ileum. For this ideal patient, a release in the terminal ileum works well, allowing most of the drug to be delivered to the colon. There are data, however, that indicate that patients with IBD may have abnormally low colonic pH values, thereby reducing the bioavailability of 5-ASA from pH-dependent formulations.[21] Therefore, there may be an advantage to a formulation that releases at a somewhat lower pH, provided that once the 5-ASA is released there is a mechanism for extending the release throughout the colon.

Apriso is a newly approved formulation that has both delayed- and extended-release properties. The capsule contains granules composed of mesalamine in a polymer matrix with an enteric coating that dissolves at pH 6 and above.[9] Results from several trials have been reported for mesalamine granules. Kruis and colleagues[22] conducted a dose-ranging study of mesalamine granules in which 321 patients were placed into three groups: 0.5 g 3 times a day (1.5 g group), 1.0 g 3 times a day (3.0 g group), and 1.5 g 3 times a day (4.5 g group). After 8 weeks of treatment, clinical remission was seen in 50% of the 1.5 g group, 66% of the 3.0 g group, and 55% of the 4.5 g group. Hierarchical testing showed no significance between the groups, indicating a lack of dose response. The safety profile was found to be similar among the three groups.

A second trial was then conducted to test a dose escalation of mesalamine granules for patients who fail to respond to the lowest dose.[23] A total of 233 patients with mild-to-moderate UC were randomized 1:1 to receive mesalamine 1.5 g/day in 3 doses as either granules or as delayed-release tablets for 8 weeks. Patients who displayed an insufficient response at week 3 were increased to a dose of 1.0 g 3 times a day for a total of 3.0 g daily. In this study, the granule preparation was shown to be noninferior to the tablets. At week 3, the remission rates were 47% in the granules group and 42% in the tablets group. At week 8, after the allowed dosage increase, the remission rates were 67% for the granules and 68% for the tablets.

Dr. Sandborn made two points about these trials. First, he reiterated that the lower dose of mesalamine granules is effective for the induction of remission in UC, so it is reasonable to start patients on the lowest dose. Secondly, he noted that if a physician would like to use a higher dose for nonresponders, the fact that there were no significant differences in safety among the groups in the first trial is reassuring.

A key result for mesalamine granules was recently reported by Kruis and colleagues.[24] Their study, which randomized 380 patients with mild-to-moderate UC to 3 g daily mesalamine granules, administered in either 3-times-daily or once daily regimens, showed that both doses were equally as effective for the induction of remission, with the added benefit of reducing pill burden upon the patients. Week 8 remission rates in this study were 79% in the once daily group and 76% in the 3 times daily group. Both regimens were equally well tolerated.

Once-daily Apriso has also been tested in phase III trials for the maintenance of remission in UC with good results, leading to FDA approval for this indication in late 2008. In a dose-comparison study, Kruis and colleagues compared 0.5 grams, 1.5 grams, and 3 grams of mesalamine granules given once daily for 1 year.[25] A total of 647 patients who had achieved clinical and endoscopic remission within the 12 weeks prior to the study start were randomized 1:1:1 to the 3 dosage groups. A relapse in this study was defined as a Clinical Activity Index (CAI) score of greater than 4 and at

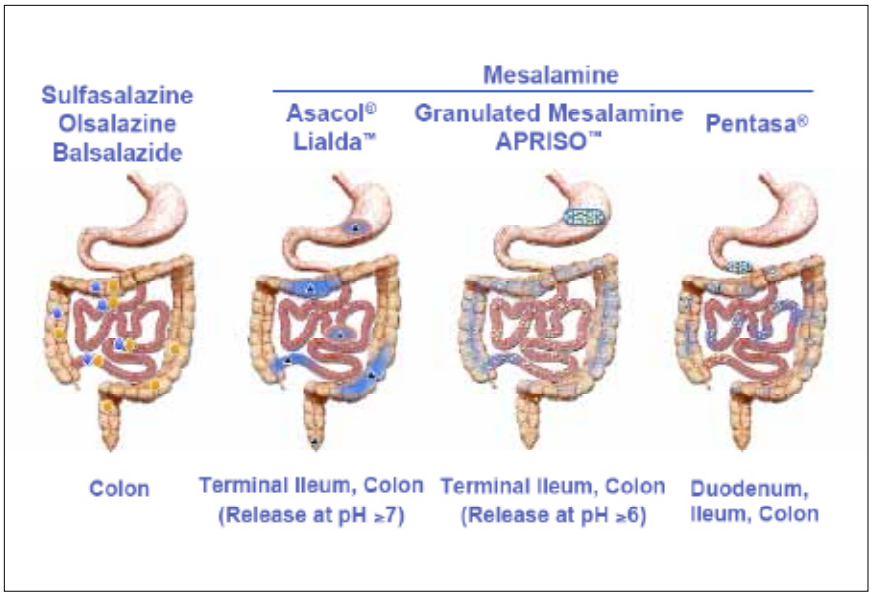

Figure 1. Oral 5-ASA formulations: sites of delivery.

Adapted from Baumgart DC, Sandborn WJ. *Lancet.* 2007;369:1641–1657. and from Sandborn WJ. *J Clin Gastroenterol.* 2008;42:338–344.

least a 3-point increase from baseline. At 1 year, 69%, 61%, and 75% of patients in the 0.5 grams, 1.5 grams, and 3.0 grams groups, respectively, were still in clinical remission. The difference between the 1.5 grams group and the 3.0 grams group was statistically significant. The investigators reported that mesalamine was equally well-tolerated in all 3 groups.

Two placebo-controlled, double-blind phase III studies were then conducted to evaluate Apriso for the maintenance of remission.[9] Study 1 enrolled 305 patients and study 2 enrolled 257 patients, for a total of 562 patients. Patients were in remission at the start of the studies (a modified Sutherland Disease Activity Index [DAI] score of 0 or 1) and were then randomized 2:1 to receive either mesalamine granules 1.5 grams daily or placebo for 6 months. Endoscopy was performed at baseline and at the end of the studies, or if clinical symptoms developed. Relapse was defined as a rectal bleeding subscale score of 1 or more and a mucosal appearance subscale score of 2 or more using the Sutherland DAI. At month 6, 68% and 51% of the treatment and placebo groups, respectively, were still in remission in study 1 (P<.001), and 71% and 59% of the treatment and placebo groups were still in remission in study 2 (P=.046). Apriso was well-tolerated.[26] The most common adverse events in the treatment and placebo groups, respectively, were UC flare (11% vs. 24%); headache (11% vs. 8%); and diarrhea (8% vs. 7%). Renal, hepatic, or pancreatic adverse events were seen in 6% of patients in the treatment groups and 5% of patients in the placebo groups.

Delayed-release Mesalamine 800 Milligram Tablets

The 400 mg tablet of delayed-release mesalamine (Asacol) has been approved for many years for the induction of remission and for maintenance of remission in UC. Typical dosages for Asacol would be 2 tablets, 3 times per day for a total of 2.4 grams. Sometimes, the physician desires a higher dosage of 4.8 grams per day, which requires 12 tablets per day using the standard formulation. The new formulation is an 800 mg tablet, allowing for a 4.8 gram per day dosage to be reached with 6 tablets.

Several studies were conducted looking at any differences in efficacy between 2.4 grams per day of Asacol and 4.8 grams per day of the 800 mg tablets. In the ASCEND I trial, 301 patients with mild-to-moderate UC were randomized to delayed-release mesalamine 2.4 grams per day using Asacol or 4.8 grams per day using 800 mg tablets.[27] The primary efficacy end point was overall improvement, defined as complete remission or a response to therapy from baseline to week 6. Both treatment groups showed equal rates of improvement at week 6, with 51% of the 2.4 grams per day group and 56% of the 4.8 grams per day group achieving the primary endpoint. When analyzed by baseline disease severity, however, patients with moderate disease benefited from the higher dosage (57% of the 2.4 grams per day group and 72% of the 4.8 grams per day group; P=.038). Both regimens were well tolerated.

The result in patients with moderate disease changed the focus of the ASCEND II trial, in which the

primary endpoint was disease improvement in patients with moderate disease.[28] A total of 386 patients with mild-to-moderate UC were randomized 1:1 to treatment with delayed-release mesalamine either 2.4 grams per day (Asacol 400 mg tablet) or 4.8 grams per day (800 mg tablet) for 6 weeks. The definition of overall improvement was the same as in the ASCEND I trial. The primary efficacy population was 268 patients with moderate disease. Again, at week 6, the higher dosage of mesalamine was more effective for patients with moderate disease, with 72% of the higher dosage group achieving overall improvement compared with 59% of the lower dosage group (P=.036). Again, both regimens were found to be well tolerated.

The question was asked again in the ASCEND III trial, with a larger population of 772 patients with moderate disease.[29] The same effect was seen, although the variation between the lower and higher dosages was smaller and not statistically significant. At week 6, overall improvement was seen in 70% of the higher dosage group and 66% of the lower dosage group.

The investigators then did a subgroup analysis of the three ASCEND trials to determine which patients drove the trend toward improved efficacy with the higher dose of delayed-release mesalamine.[30] They found that patients with more difficult-to-treat, moderate disease derived the most benefit from the higher dosage. These were the patients who had previously used oral 5-ASA therapy and had relapsed, had previously used rectal therapies and had relapsed, were steroid-refractory, or had previously used at least 2 medications. Dr. Sandborn summed the data by noting that in his practice, he generally uses 2.4 grams daily of Asacol or the equivalent dose with other formulations for patients with mild disease or for patients with newly diagnosed, treatment-naïve moderate disease. Patients who have an established diagnosis, have previously received any of a variety of therapies, and have moderate disease are probably better served by treatment with the higher dose.

Incorporating New 5-ASA Formulations Into Your Practice

Russell D. Cohen, MD, rounded out the symposium with a discussion of incorporating the new 5-ASA formulations into clinical practice. He noted that 5-ASA for long-term maintenance of remission in UC is underused—about 40% of patients who are eligible for this treatment do not receive it.[31] Further, of the patients who do receive prescribed 5-ASA maintenance therapy, up to 60% are nonadherent or take less than 70% of their medication.[32]

There are a number of factors that cause patient nonadherence. These include patient-related factors (single, male, refusal to take medication when feeling well), economic factors, and the relationship between the patient and the healthcare professional.[33] However, nearly three-quarters of patients cite "forgetfulness" as their reason for nonadherence, and much of this forgetfulness is related to complexity of the dosage schedule, the number of pills, and the impact of the dosage schedule upon daily life.[32]

Why is this clinically relevant? Lack of adherence to maintenance 5-ASA has been associated with disease relapse. Kane and colleagues[34] prospectively followed 99 UC patients who had been in remission for more than 6 months and who were taking maintenance 5-ASA. The authors verified medication adherence rates based on pharmacy records, where nonadherence was defined as refilling less than 80% of the prescribed medication. Patients who were not adherent with medication had more than a 5-fold increased risk of recurrence than adherent patients did (P<.001). At the end of follow-up, 89% of adherent patients remained in remission whereas only 39% of nonadherent patients were in remission (Figure 2).

Dr. Cohen emphasized the importance of these results. He suggested showing patients the study results to reinforce that the medication must be taken over the long-term, even if the patient feels well. In addition, Dr. Cohen cautioned physicians against stopping maintenance 5-ASA treatment for patients with UC.

Selecting Candidates for New 5-ASA Formulations

Most physicians would consider newly-diagnosed patients to be good candidates for the newer 5-ASA formulations, but may be hesitant to change formulations for established patients. When it comes to patients who are receiving a mesalamine formulation who are not doing well on it, the literature supports a switch to another mesalamine formulation. Lichtenstein and colleagues analyzed the data from 2 double-blind, placebo-controlled trials in which 517 patients with mild-to-moderate UC were randomized to receive Lialda 2.4 grams daily or 4.8 grams daily or placebo for 8 weeks.[35] Among the 259 patients who transferred from prior low-dose 5-ASA therapy within 5 days of study entrance, the remission rate was 38% in the high-dosage group, 32% in the low-dosage group, and 21% in the placebo group; the difference between the high-dosage group and the placebo group was significant (P=.018). Thus, it is possible to put about a third of patients who are not responding to their current 5-ASA formulation into remission simply by switching to a newer, higher-dose formulation of 5-ASA. Encouraging efficacy results have been reported in a placebo-controlled setting with the 800 mg tablet of delayed-release mesalamine. In the ASCEND I, II, and III studies, response rates of up to

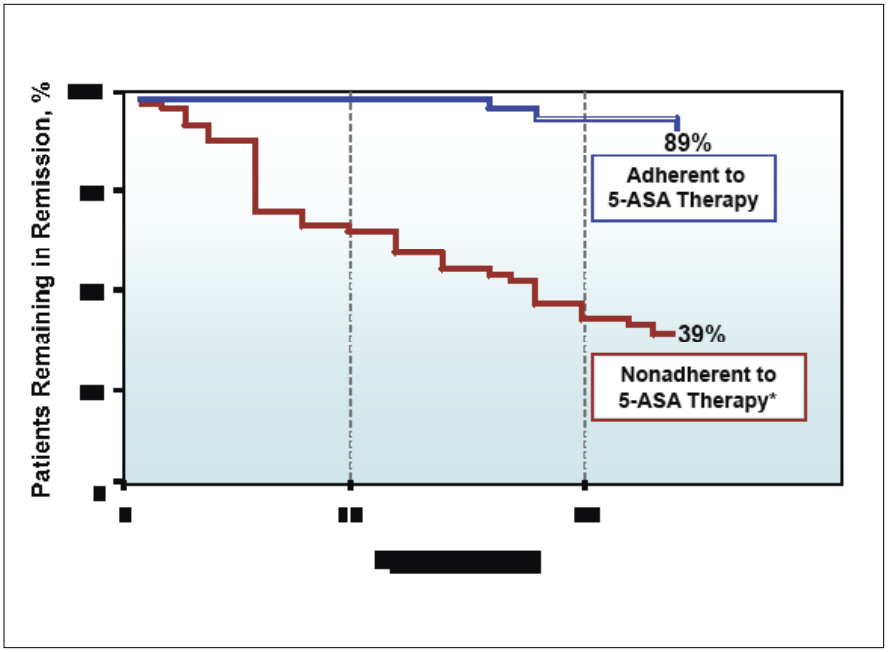

Figure 2. Nonadherence is associated with relapse in UC.

*P<.001.

Kane S et al. *Am J Med.* 2003;114:39–43.

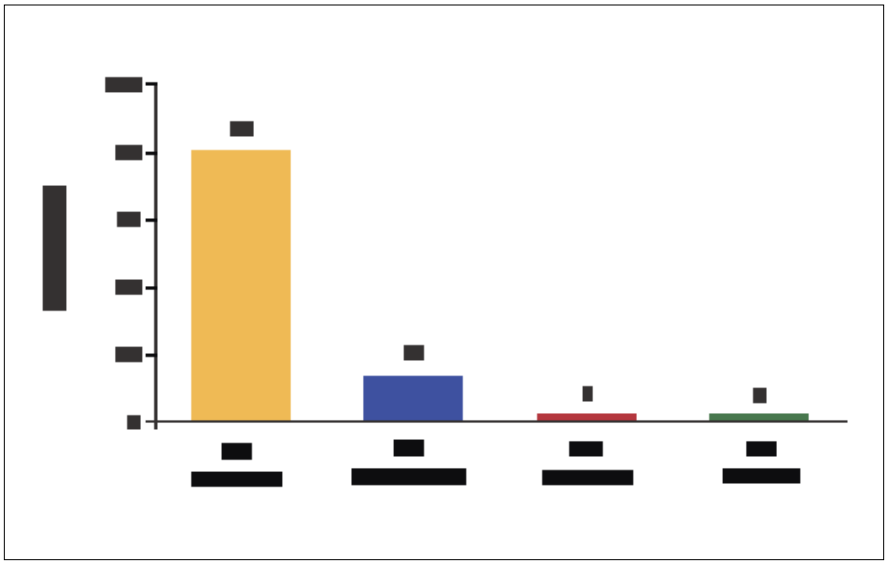

Figure 3. Patient preference of maintenance mesalamine dosage regimen.*

*Patients with UC in remission randomized to mesalamine granules 3 g QD (n=217), 1.5 g QD (n=212), or 0.5 g TID (n=218).

QD=once daily; TID=3 times daily.

Kruis W et al. Poster T1124 presented at Digestive Disease Week, May 17-22, 2008. San Diego, CA.

70% and remission rates of up to 42% were seen with a dosage of 4.8 grams per day.[27-29]

What about patients who are doing quite well on their current 5-ASA formulation? Can they be switched to a more convenient formulation and maintain remission? In a study by Hanauer and colleagues, 189 patients whose UC was in remission were switched from various 5-ASA preparations (sulfasalazine or other oral mesalamine) to either 0.8 mg or 1.6 mg per day of Asacol 400 mg tablets or to placebo.[36] After 6 months, 59% of the 0.8 gram per day mesalamine group and 66% of the 1.6 gram per day mesalamine group were still in remission, both of which were significantly higher rates than the 40% seen in the placebo group (P=.036 and P=.006, respectively, vs placebo). Similarly, Lichtenstein and colleagues randomized 487 UC patients who had achieved remission on oral 5-ASA treatment to receive either 1.5 grams of Apriso once daily or placebo for 6 months.[37] They found that remission rates were significantly higher in the Apriso group than they were in the placebo group (78% vs. 59%; P<.001).

Thus, the data indicate that switching to a newer 5-ASA formulation is effective for patients who are doing well on an older formulation. Why would a physician or patient want to switch? The main reason is convenience for the patient and the implications for long-term adherence. The older formulations of 5-ASA have a very high daily pill load, and, what is more difficult for patients, the number of times per day that pills must be taken is high as well. Dr. Cohen encouraged the audience to consider their own personal experience with daily medications—is remembering taking 2 to 4 pills, 3 to 4 times daily an easy experience? Is it manageable for the patient to continue to do, day after day, for years? Switching the patient to a newer formulation of 5-ASA could cut the daily pill load significantly as well as reduce the dosing schedule to just once or twice per day. Once daily dosing has been shown to increase adherence rates among patients with UC who are receiving maintenance mesalamine treatment.[34] When given a choice between 3 times daily dosing and once daily, patients overwhelmingly prefer once daily dosing (Figure 3).[25]

The new 5-ASA formulations have also been shown to have a positive effect upon patient quality of life. Irvine and colleagues examined inflammatory bowel disease questionnaire (IBDQ) scores from 687 patients in the ASCEND I and II trials, which compared the efficacy of 2.4 grams per day (400 mg tablets) and 4.8 grams per day (800 mg tablets) of delayed-release mesalamine for the induction of remission in UC patients.[38] The medication significantly improved IBDQ scores, with a mean increase of 29.6 points at week 3 and 39.7 points at week 6 (P<.0001 for both compared with baseline).

Dr. Cohen concluded by noting that it is important to share all of the available information about nonadherence and relapse with patients in a clear and user-friendly way. He suggested emphasizing the safety of long-term therapy with 5-ASA to patients by telling them that 5-ASA is a topical medication that coats the bowel and is not intended to be absorbed systemically. In addition, sharing the information about quality of life may enhance compliance, because, generally speaking, the most important thing to patients is their quality of life. Lastly, physicians should strongly consider whether changing to a newer formulation of 5-ASA might help with patient compliance and ease the burden of complex dosing and high pill load for the patient as simpler 5-ASA regimens can maintain remission in UC.

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CME Post-Test:
Getting More From New 5-ASA Therapies: Will Better Science Lead to Better Patient Adherence?

Circle the correct answer for each question below.

1. In the study by De Vos and colleagues, which of the following 5-ASA formulations produced the highest intramucosal 5-ASA concentrations in ileocolonic biopsy specimens?

   a. Delayed-release mesalamine
   b. Controlled-release mesalamine
   c. Olsalazine
   d. Balsalazide

2. True or False? According to the studies by Naganuma and colleagues and Frieri and colleagues, higher colonic mucosal concentrations of 5-ASA are associated with more active disease.

   a. True
   b. False

3. According to a dose-ranging study of mesalamine granules by Kruis and colleagues, which of the following dosages was statistically most effective for the induction of remission in mild-to-moderate UC?

   a. 1.5 grams daily
   b. 3.0 grams daily
   c. 4.5 grams daily
   d. All dosages were statistically equally effective

4. Which of the following agents has been approved for the maintenance of remission in UC?

   a. Balsalazide 1.1 gram tablets
   b. Mesalamine granules
   c. Delayed-release mesalamine 800 mg tablets
   d. MMX mesalamine

5. Based on data from the ASCEND I, II, and III trials, 2.4 grams per day of delayed-release mesalamine 800 mg tablets are most effective for which of the following categories of patients?

   a. Patients who have relapsed on other oral 5-ASA therapies
   b. Steroid-refractory patients
   c. Newly-diagnosed, treatment-naïve patients with moderate disease
   d. Patients who have received 2 or more prior therapies

6. According to Kane and colleagues, what percentage of UC patients are nonadherent to their maintenance 5-ASA medication?

   a. 40%
   b. 50%
   c. 60%
   d. 70%

7. According to a second study by Kane and colleagues, __% of adherent patients remained in remission after 1 year of maintenance 5-ASA treatment compared with only __% of nonadherent patients.

   a. 89%, 39%
   b. 39%, 89%
   c. 60%, 40%
   d. 40%, 60%

8. In the study by Lichtenstein and colleagues in which patients in remission were switched from their current 5-ASA formulation to mesalamine granules, what were the 6-month remission rates in the treatment and placebo groups, respectively?

   a. 43%, 66%
   b. 50%, 55%
   c. 59%, 63%
   d. 78%, 59%

9. When patients in the trial by Kruis and colleagues were asked which dosing schedule they preferred for 5-ASA maintenance treatment, 80% preferred:

   a. once per day
   b. twice per day
   c. three times per day
   d. four times per day

10. Which of the following categories of patients should be considered as a candidate for treatment with newer 5-ASA agents?

    a. Treatment-naïve patients with mild-to-moderate disease
    b. Patients with mild-to-moderate disease who have failed 5-ASA previously
    c. Patients in remission who are receiving maintenance 5-ASA treatment
    d. All of the above

Evaluation Form:

Getting More From New 5-ASA Therapies: Will Better Science Lead to Better Patient Adherence?

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 current armamentarium of oral 5-ASA options for the treatment of ulcerative colitis.	1 2 3 4 5
2. Discuss the current challenges of 5-ASA administration in terms of both individual patient pharmacokinetics and compliance with current regimens.	1 2 3 4 5
3. Cite the current evidence regarding the efficacy of the once-daily formulation of sacheted mesalamine micropellets.	1 2 3 4 5
4. Explain how this new formulation might fit into the US landscape of treatment options.	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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