GASTROENTEROLOGY & HEPATOLOGY™
The Independent Peer-Reviewed Journal

January 2009 www.clinicaladvances.com Volume 5, Issue 1, Supplement 2

New Formulations to Improve 5-ASA Response and Convenience

A Review of Selected Presentations from the
73rd American College of Gastroenterology
Annual Scientific Meeting
October 3–8, 2008
Orlando, Florida

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A CME Activity
Approved for
1.0 *AMA PRA*
Category 1 Credit(s)™

Release date: January 2009
Expiration date: January 31, 2010
Estimated time to complete activity: 1.0 hours

PIM Postgraduate Institute for Medicine

Supported through an educational grant from
Procter & Gamble Pharmaceuticals.

Sponsored by Postgraduate Institute for Medicine.

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) is an inflammatory disease of the colon, which, along with Crohn's disease, comprises inflammatory bowel disease (IBD). 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. Timed-release and controlled-release mesalamine formulations release 5-ASA in the proximal jejunum, whereas a pH-dependent mesalamine formulation has a methacrylic acid polymer B coating that only dissolves at a sustained pH of 7 from the distal ileum to the colon. Balsalazide is a prodrug that is cleaved in the colon by bacteria to release 5-ASA. 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.

Educational Objectives: After completing this activity, the participant should be better able to:
1. Cite the latest data regarding 5-ASA pharmacokinetics and how they relate to dosing options of various formulations.
2. Describe novel formulations and concentrations of 5-ASA currently under investigation.
3. Identify patient populations that may benefit from new formulations and dosing strategies.

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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Introduction

Ulcerative colitis (UC) is estimated to have an annual incidence of 2–7 per 100,000 persons, and affects up to 500,000 individuals in the United States.[1] The etiology of the disease remains unclear, although recent research suggests dysregulation of the immune system may produce an excessive autoimmune response against the normal intestinal flora.[2] Management of UC involves treatment and alleviation of the inflammatory symptoms typically associated with the disease, which may include bloody diarrhea, frequent stools, fever, anemia, and weight loss. Several therapeutic options are available for patients with mild-to-moderate UC, including the frontline therapy of 5-aminosalicylic acid (5-ASA), as well as corticosteroids, immunomodulatory agents, and biologic therapies.[3,4]

Although the exact mechanism of action is unknown, 5-ASA is thought to act as an anti-inflammatory agent through induction and activation of the nuclear peroxisome proliferator-activated receptor γ (PPARγ).[5] The expression of PPARγ is known to be abrogated in UC.[6] Other mechanisms of action have also been attributed to the anti-inflammatory actions of 5-ASA, including inhibition of synthesis of prostaglandins and leukotrienes.[7]

5-ASA acts topically within the lumen of the intestine to reduce UC-associated inflammation. However, free 5-ASA is readily absorbed into the systemic circulation. Multiple oral formulations of 5-ASA have been developed with the purpose of preventing systemic absorption of 5-ASA.

The oldest oral 5-ASA formulation, sulfasalazine, is comprised of a 5-ASA molecule linked to a sulfapyridine carrier with an azo bond. The azo bond is selectively cleaved by intestinal bacterial azoreductase enzymes, freeing the 5-ASA moiety within the colon.[8] Although effective, the sulfapyridine carrier molecule can produce a myriad of dose-related adverse events.[9] More recently approved azo-bonded formulations include osalazine and balsalazide A more frequently utilized 5-ASA strategy is delivery via a pH-dependent delayed release, which contains the 5-ASA within a pH-sensitive enteric coating that only disintegrates when it is exposed to the pH levels within the terminal ileum.[10] In addition, there are controlled-release formulations containing ethylcellulose-coated 5-ASA microspheres encapsulated within a moisture-sensitive semi-permeable membrane, which is gradually broken down through the intestine in a time-dependent manner.[11] Multimatrix (MMX) mesalamine tablets contain 5-ASA suspended in lipophilic and hydrophilic matrices within a pH-dependent enteric coating, delaying release until the terminal ileum.[12] Extended release capsules contain 5-ASA granules in a polymer matrix with a pH-dependent enteric coating that dissolves in the intestine.[13]

The risk of developing colorectal cancer is elevated in individuals with UC, and this risk increases incrementally, depending on the extent of colonic involvement, family history of disease, severity of inflammation, and long-term use of 5-ASA medication. A recent estimate suggested that this risk could be as high as 18% in patients with a 30-year history of UC disease.[14] Other reports suggest the annual incidence of colorectal cancer in UC ranges from 1 in 500 to 1 in 1,600 persons.[15] The role of 5-ASA as a chemopreventative agent has come under increasing investigation in recent years. The rationale for its use in chemoprevention is based primarily on its ability to prevent both clinical and endoscopic relapse, and recent data has shown that endoscopic and histologic remissions can reduce the risk of colorectal cancer in patients with UC. One meta-analysis demonstrated that 5-ASA had a protective association in reducing the risk of either colorectal cancer and/or dysplasia, with an odds ratio of 0.51.[16] However, it is still unclear if this protective benefit is attributed to the prevention of UC-related inflamma-

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tion by 5-ASA use, or another chemopreventative benefit of 5-ASA.[17]

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New Formulations to Improve 5-ASA Response and Convenience

A Review of Selected Presentations from the 73rd American College of Gastroenterology Annual Scientific Meeting
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The efficacy and safety of a new 800 mg tablet formulation of delayed-release mesalamine has been evaluated for UC in a series of three studies, the Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA (ASCEND) I, II, and II trials.[1-3] Each of these was a 6-week, multi-center, randomized, double-blind, active-controlled phase III clinical trial that compared the 800 mg tablet, dosed at 4.8 g/day, to the 400 mg delayed-release tablet, dosed at 2.4 g/day. At the 2008 American College of Gastroenterology (ACG) annual meeting, the results of several subanalyses combining results of all three ASCEND trials, were presented. Two of these combined analyses compared the efficacy of the 800 mg tablet mesalamine, whereas the other compared the safety of this formulation, with that of the 400 mg tablet. The efficacy studies evaluated a combined total of 1,220 patients with moderately active UC and the safety analysis included a combined total of 1,459 patients with mildly to moderately active UC.

The baseline characteristics between the 2.4 g/day and 4.8 g/day treatment arms were approximately the same. The mean patient age was 42 and 44 years, and approximately half of the patients in each group were male (52.1% versus 51.7%). The vast majority of patients were Caucasian (89.0% in each arm). Approximately three-quarters of patients in each arm were diagnosed with left-sided colitis (75.9% versus 76.5%), with pancolitis (18.4% versus 18.1%) and proctitis (5.7% versus 5.4%) comprising the remaining diagnoses. Over half of the patients had received two or more prior medications for their disease, and the majority in each group had previously received oral 5-ASA therapy (75.2% versus 77.2%). The mean baseline ulcerative

Table 1. ASCEND I, II & III Responders at 3 Weeks Who Sustained Response Through Week 6

Data reproduced from Lichtenstein et al.[4]

	2.4 g/day (N=618)	4.8 g/day (N=602)
	Responders at 3 Weeks With Sustained Response Through Week 6	
Stool Frequency Improvement	89%	88%
Rectal Bleeding Improvement	91%	91%
Clinical Remission (rectal bleeding and stool frequency = 0)	75%	80%

colitis disease activity index (UCDAI) was the same in both groups (7.6).

P306 Early and Sustained Efficacy of Delayed-Release Oral Mesalamine in Moderately Active Ulcerative Colitis Patients: Combined Results from the ASCEND I, II, and III Trials

GR Lichtenstein, D Ramsey, EV Loftus

In the first combined analysis, Lichtenstein and colleagues investigated to see if patients who experienced an early response at 3 weeks to 5-ASA therapy were able to sustain that response at 6 weeks.[4] To determine this, the authors evaluated two hallmark symptoms of UC, stool frequency and rectal bleeding, which were graded on a 4 point scale (score of between 0–3). Improvement in either of these symptoms was defined as a decrease from baseline of 1 point or more. Additionally, they compared the rates of clinical remission between the two treatment groups, which was defined as a complete resolution (score=0) of both rectal bleeding and stool frequency.

At 3 weeks, more patients receiving 4.8 g/day mesalamine exhibited improvement versus those receiving 2.4 g/day, in terms of decreased stool frequency (73% versus 64%, respectively) and decreased rectal bleeding (76% versus 74%); only the difference in stool frequency improvement reached statistical significance (P=.003). Significantly more patients in the 4.8 g/day group also achieved clinical remission at 3 weeks (20% versus 26%, P=.02). At 6 weeks, the 4.8 g/day arm again achieved superiority in each outcome measured. Compared with the 2.4 g/day group, a greater proportion of patients in the 4.8 g/day group experienced decreased stool frequency (73% versus 78%) and rectal bleeding (79% versus 83%). The decrease in rectal bleeding achieved statistical significance (P=.04). A larger proportion of patients in the 4.8 g/day group exhibited clinical remission at 6 weeks (43% versus 37% in the 2.4 g/day group); however, it did not reach statistical significance.

Importantly, regardless of treatment group, the majority of patients who responded at 3 weeks sustained this response at the 6-week endpoint (Table 1). In the 2.4 g/day arm, 89% and 91% of patients who exhibited improvement at 3 weeks in stool frequency or rectal bleeding, respectively, sustained their response at 6 weeks. Similar results were observed in the 4.8 g/day arm as well (88% and 91%, respectively). Most patients who achieved a clinical remission at 3 weeks also sustained this remission at 6 weeks, as well (75% and 80% in the 2.4 g/day and 4.8 g/day, respectively).

The investigators concluded that delayed-release oral mesalamine produced early and sustained efficacy for patients with moderately active UC. These results provide important evidence supporting the role of 5-ASA therapy in moderate UC, as early and sustained symptom relief is a key goal in the treatment of patients experiencing a flare.[5] It is important to note that the group treated with 4.8 g daily had a significant decrease in stool frequency and a greater number of patients in remission than the 2.4 g group, at 3 weeks.

P284 Increased Efficacy of Delayed-Release Mesalamine 4.8 g/day (800 mg tablet) Compared to 2.4 g/day (400 mg tablet) for Treatment of Moderately Active Ulcerative Colitis in Patients with a History of More Difficult to Treat Disease: Combined Analysis from Three Randomized, Double-Blind, Active-Controlled Trials

SB Hanauer, D Ramsey, WJ Sandborn

In another combined analysis, Hanauer and colleagues determined the efficacy of each 5-ASA dosage specifi-

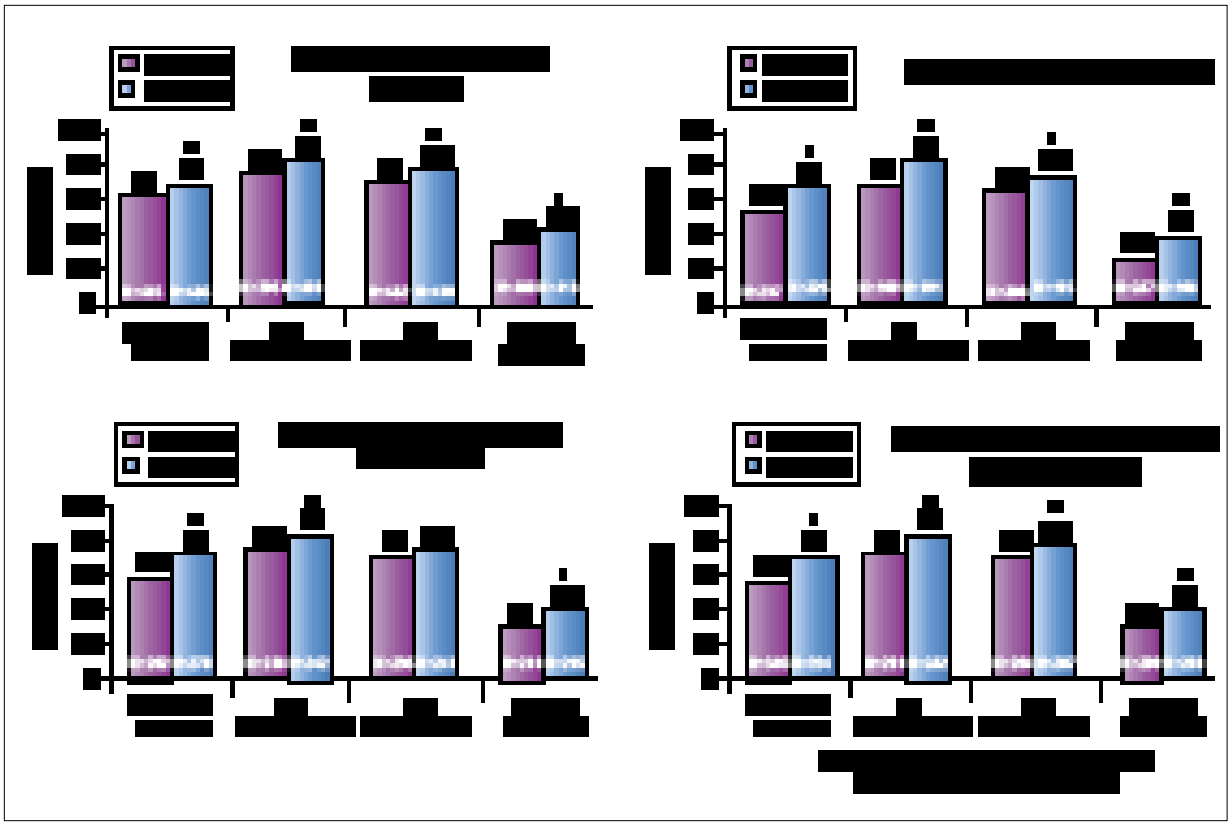

Figure 1. Overall improvement at week 6 in previous therapy subgroups.

Table 2. ASCEND I, II, III – Summary of Reported Adverse Event Experience

	2.4 g/day (400 mg Tablet) N=732	4.8 g/day (800 mg Tablet) N=727
Patients with AEs (%)	211 (28.8%)	209 (28.7%)
Patients withdrawn due to AEs(%)	31 (4.2%)	28 (3.9%)
AEs assessed (%):	409	394
Mild	257 (62.8%)	218 (55.3%)
Moderate	121 (29.6%)	146 (37.1%)
Severe	31 (7.6%)	30 (7.6%)
AEs assessed (%):	409	394
Doubtfully related to drug	297 (72.6%)	266 (67.5%)
Possibly related to drug	93 (22.7%	105 (26.6%)
Probably related to drug	19 (4.6%)	23 (5.8%)

cally in patients with a history of more difficult to treat UC.[6] The investigators reported that compared with the 2.4 g/day group, the 4.8 g/day treatment group exhibited a statistically superior rate of overall improvement at week 6 (69% versus 62%, P=.006). Overall improvement, or treatment success, was defined as an improvement in the PGA score, based on assessment of rectal bleeding, stool frequency, and sigmoidoscopy, with no worsening in any individual clinical assessment (patient functional assessment was also factored in ASCEND I and II). The authors then evaluated the rates of response and clinical remission at 6 weeks according to previous-therapy subgroup.

A therapeutic advantage was attributed to the 4.8 g/day dosage among patients who had a prior history of UC medications (Figure 1). Among patients who had previously used two or more UC medications, including oral 5-ASA agents, rectal therapies, steroids, or immunomodulators, a significantly higher rate of treatment success (70% versus 56%, P<.05) and clinical remission (40% versus 30%, P<.05) was observed in the 4.8 g/day treatment arm compared with the 2.4 g/day treatment arm, respectively. This improvement in the 4.8 g/day dosage arm also remained significant when patients were separately analyzed according to their prior treat-

ments. In those who had previous use of oral 5-ASAs, a significantly greater proportion of patients in the 4.8 g/day treatment arm achieved treatment success (69% versus 61%, $P<.05$). Similar superiority in treatment success was also observed for patients with a previous use of steroids (67% versus 52%, $P<.05$) or a previous use of rectal therapies (71% versus 58%, $P<.05$). Among each of these patient subgroups, significantly higher rates of clinical remission were also achieved in the 4.8 g/day treatment arm in patients with a prior history of 5-ASA use (42% versus 36%, $P<.05$), steroid use (38% versus 25%, $P<.05$), and rectal therapies (40% versus 31%, $P<.05$).

The authors found that 5-ASA, particularly the higher 4.8 g/day dosage evaluated here, has a role in patients with moderately active UC that is considered more difficult to treat, including those previously treated with oral 5-ASAs, rectal therapies, steroids, or multiple UC medications.

P281 Safety of Delayed-Release Oral Mesalamine 4.8 g/day (800 mg tablet) Compared to 2.4 g/day (400 mg tablet) for Treatment of Active Ulcerative Colitis: Combined Analysis from Three Randomized, Double-Blind, Active-Controlled Trials

WJ Sandborn, M Hosterman

Sandborn and Hosterman provided the final combined analysis of the three ASCEND studies with a report comparing the safety profiles of the two 5-ASA formulations.[7] The authors noted that among the three trials, no significant differences were apparent between the two 5-ASA treatment groups regarding overall adverse event experience (Table 2).

Overall, 28.8% and 28.7% of patients in the 2.4 g/day and 4.8 g/day arms, respectively, experienced an adverse event. The majority of these (62.8% and 55.3%, respectively) were assessed as mild in intensity, although moderate (29.6% and 37.1%, respectively) and severe (7.6% and 7.6%, respectively) adverse events were also reported. Relatively few patients in either the 2.4 g/day or the 4.8 g/day 5-ASA treatment group withdrew from the study due to adverse events (4.2% and 3.9%, respectively) demonstrating no statistically significant differences between the two doses. Most of the adverse events that occurred during the studies were assessed as only doubtfully related to 5-ASA (72.6% and 67.5% in the 2.4 g/day and 4.8 g/day treatment arms, respectively).

Headache was the most frequently reported adverse event in both the 2.4 g/day and 4.8 g/day treatment arms (4.9% and 4.7%, respectively). Other commonly reported adverse events were related to the digestive system, including worsening of UC signs and symptoms, nausea, vomiting, diarrhea, and abdominal pain. More patients in the 2.4 g/day compared with the 4.8 g/day treatment arm had a serious adverse event (1.8% versus 0.8%). Actually, a higher number of serious adverse events were reported in the 2.4 g/day group versus the 4.8 g/day group (22 versus 8 events, respectively). Not surprisingly, the majority of these were related to the digestive system (including worsening UC, nausea, vomiting, epigastric pain, and cholecystitis), although single reports of pancreatitis, nephritis, and pericarditis also occurred.

Nephrotoxicity has been associated in some patients with 5-ASA administration.[8] Importantly, an examination of the percent change from baseline to study exit found no evidence of a dose-related increase in levels of serum creatinine among these current study populations.

Overall, the dosage of 4.8 g/day 5-ASA did not demonstrate a significantly different safety profile compared to that of the 2.4 g/day dosage. Further, the authors noted that the adverse events observed in patients receiving 4.8 g/day with the 800 mg 5-ASA tablet were consistent with those reported in the post-marketing experience of the 400 mg tablet.

P282 MMX™ Mesalamine Therapy for the Induction of Remission Beyond 8 Weeks: How Long Before Symptom Resolution?

WJ Sandborn, M Kamm, GR Lichtenstein, M Sumner, R Joseph

Mesalamine with an MMX release system is a recently approved oral formulation, which uses MMX technology to distribute 5-ASA throughout the colon.[9] In addition to a pH-dependent delayed-release enteric coating, an included excipient is thought to slow the release of 5-ASA even further. Two phase III studies, SPD476-301 and SPD476-302, found that MMX mesalamine was effective in the induction of remission in patients with active mild-to-moderate UC.[10,11] Both studies showed a significant improvement in the rates of clinical and endoscopic remission with MMX mesalamine compared with placebo. Additionally, an analysis that pooled both of these study populations showed no difference in the remission rate in patients receiving 2.4 g daily versus 4.8 g daily, finding that the 8-week remission rate was 37.2% and 35.1% in patients receiving 2.4 g/day and 4.8 g/day MMX mesalamine, compared with 17.5% in patients receiving placebo ($P<.001$).[12]

Table 3. Pharmacokinetic 5-ASA Parameters of Two Mesalamine Formulations

Formulation	Lag time (hrs)	Time to max concentration (hrs)	Max concentration (ng/mL)	Area under curve 0–96 hrs (ng.hr/mL)
MMX mesalamine	3.5+/-1.4	7.0+/-3.0	711+/-540	4,069+/-3,028
Delayed-release mesalamine (Giuliani, Italy)	4.3+/-2.5	8.8+/-3.2	790+/-626	4,444+/-2,610

Data from Wray and colleagues.[15]

In a recently published article, 304 patients selected from these phase III studies who had failed to achieve clinical and endoscopic remission after the initial 8-week study period were administered an additional 8 weeks of MMX mesalamine (4.8 g/day) in an open-label trial.[13] In that extension study, an additional 59.5% of patients achieved remission at week 8, suggesting that extended treatment with high dose MMX mesalamine may be an effective alternative to step-up therapy in these patients. Here, Sandborn and colleagues examined how long it took for these patients to achieve symptom resolution.[14]

Time to symptom resolution was calculated from the point at which treatment in the open-label extension was initiated (after 8 weeks treatment in the double-blind studies) until the first day of rectal bleeding cessation and normalization of stool frequency. The investigators reported that the median time to symptom resolution was 15 additional days of treatment, following the initial 8 weeks.

P683 A Pharmacokinetic and Scintigraphic Comparison of MMX™ Mesalamine and Delayed-Release Mesalamine

H Wray, R Joseph, M Palmen, D Pierce

In a second study investigating MMX mesalamine, Wray and colleagues compared the pharmacokinetic and pharmacodynamic profiles of a single dose of MMX mesalamine with a single dose of pH-dependent delayed-release mesalamine product marketed in Italy.[15]

The pharmacokinetics of each of these mesalamine formulations was evaluated in an open-label, two-way cross-over study of 8 healthy male subjects. The participants ranged in age between 18–65 years, and were randomized to receive either 1 MMX mesalamine tablet (1.2 g/tablet) or 3 pH-dependent delayed-release mesalamine tablets (400 mg/tablet). Each tablet was radiolabeled with 153Sm (1.5 MBq/tablet or 0.5 MBq/tablet, respectively). After hospital admittance, participants began fasting 8 hours prior to dosing, and continued until 4 hours following dosing. In conjunction with the mesalamine dosage, participants also were administered 20 radio-opaque beads. Evaluations were performed over the subsequent 96 hours, after which the subjects were discharged and asked to continue stool collection until all radio-opaque beads were recovered.

Table 4. Tablet Disintegration, Hours Post-Dose

Disintegration	Initial	Complete
MMX mesalamine	4.75+/-1.31	17.37 +/-8.63
Delayed-release mesalamine (Giuliani, Italy)	6.16+/-1.80	7.27+/-2.13

Data from Wray and colleagues.[15]

Each 5-ASA formulation displayed a similar pharmacokinetic profile (Tables 3 and 4). The time to maximal concentration was 7.0 ± 3.0 hours and 8.8 ± 3.2 hours for MMX mesalamine and pH-dependent delayed-release mesalamine, respectively. Additionally, similar maximum concentrations and clearance (calculated as area-under-the-curve) of 5-ASA were achieved over the 96 hour period by each formulation. 5-ASA released by MMX mesalamine reached a maximal concentration of 711 ± 540 ng/mL, and an area-under-the-curve of 4,069 ± 3,028 ng/hr/mL, whereas 5-ASA released by the pH-dependent delayed-release formulation reached a maximal concentration of 790 ± 626 ng/mL and an area-under-the-curve of 4,444 ± 2,610 ng/hr/mL.

Although initial tablet disintegration occurred earlier for MMX mesalamine compared with pH-dependent delayed-release mesalamine (4.75 ± 1.31 hours versus 6.16 ± 1.80 hours), total disintegration of MMX mesalamine took a much longer time to complete (17.37 ± 8.63 hours versus 7.27 ± 2.13 hours, respectively). These data show that MMX mesalamine and the Italian pH-dependent mesalamine formulation have a similar pharmacokinetic

profile, despite scintigraphic data suggesting that MMX mesalamine may have a prolonged period of disintegration. After administration of both formulations, gastrointestinal transit was completed in approximately 70 hours.

P279 Once-Daily 1.5-g Granulated Mesalamine is Effective and Safe in Maintenance of Remission in Mild-to-Moderate Ulcerative Colitis

G Gordon, R Pruitt, M Ringold, S Sedghi, K Merchant, A Shaw, J Yuan, E Bortey, W Forbes

An important goal of UC therapy is maintenance of remission, and 5-ASA has been demonstrated to have benefit in UC maintenance.[16] Granulated mesalamine is a novel formulation which allows both delayed and extended release of 5-ASA, beginning in the terminal ileum and continuing throughout the colon. Here, Gordon and colleagues conducted a study to determine the safety and efficacy of granulated mesalamine in the maintenance of UC remission in patients with mild-to-moderate disease.[17]

This study randomized nearly 300 patients who were in UC disease remission. Remission was defined as a rectal bleeding score of 0 and a mucosal appearance score of less than 2 in the revised Sutherland Disease Activity Index (DAI).[18] Patients were randomized in a 2:1 fashion to receive either 1.5 g/day granulated mesalamine (4 x 375 mg capsules) or placebo. Treatment was continued over a 6 month period. The primary study endpoint was the proportion of patients who continued to be relapse-free after the 6-month study period. A treatment failure was considered in cases where the patient either experienced an adverse event of worsening of UC symptoms, or in patients who required treatment initiation to treat a UC flare.

The study found that granulated mesalamine was more effective than placebo in maintaining long-term UC remission, as a significantly greater proportion of patients receiving the granulated mesalamine was relapse-free at 6 months compared with placebo (79% versus 58%, $P<.001$). The patients in the granulated mesalamine group were 21% more likely to remain relapse-free at the 6-months study endpoint, with a 77% and 56% probability calculated for the granulated mesalamine and placebo groups, respectively. In addition, patients in the granulated mesalamine group had a superior rate of favorable change from baseline in physician-rated disease activity (78% versus 64%, $P=.005$).

The majority of adverse events experienced by the study population were mild or moderate in intensity. An equal proportion of patients in either arm (64%) reported experiencing an adverse event. Only 11% of patients receiving granulated mesalamine reported an adverse event of a UC flare, compared with 27% of patients in the placebo group.The study authors concluded that these data together support the efficacy and safety of granulated mesalamine in maintaining UC remission.[19]

P343 Developing an Ulcerative Colitis Endoscopic Index of Severity (UCEIS): Results of a Pilot Phase

S Travis, WJ Sandborn, J-F Colombel, SB Hanauer, M Lemann, B Sands, P Marteau, M Abreu, G Lichtenstein, B Feagan, D Altman, J-Y Mary, D Schnell, B Yacyshyn, P Krzeski, CA Bernhardt

There are currently nine separate indices used to endoscopically assess UC disease activity.[18] However, none of these have been adequately validated. Further, each of these indices is subject to interobserver variation.[20] The magnitude of the interobserver variation has not been completely quantified, although it may potentially influence trial outcome and patient management.[21] For example, a recent study which re-evaluated a therapeutic trial of 335 UC patients found that an independent observer disagreed with the reported sigmoidoscopy score in up to 23% of cases.[22] Here, Travis and colleagues conducted a pilot phase of an international initiative, which ultimately aims to develop and validate an improved scale, the UC endoscopic index of severity (UCEIS) scale.[23] The goals of this pilot phase were to evaluate the extent of interobserver variation as well as to compare the concordance of the Baron score and the visual analogue scale (VAS) assessments among observers.

A total of 10 observers considered to be UC specialists separately assessed 16 sigmoidoscopies from a pool of 24 digitally recorded videos. The 24 sigmoidoscopy videos were chosen of 334 from a previously conducted therapeutic trial. Videos representing samples ranging from normal to severe disease activity were selected, and independently assessed by a blinded central reader. The 10 experts, who were blinded to the patients' symptomatic and histologic activity, evaluated and scored the sigmoidoscopies according to their own custom, without reference to a specific endoscopic index. Terms used in the Baron score of endoscopic activity were also identified as being present or absent, allowing the Baron score to be used as the reference index. The Baron score rates endoscopic disease activity using a 4 point scale (from 0-3, where 3 is the most severe).[24]

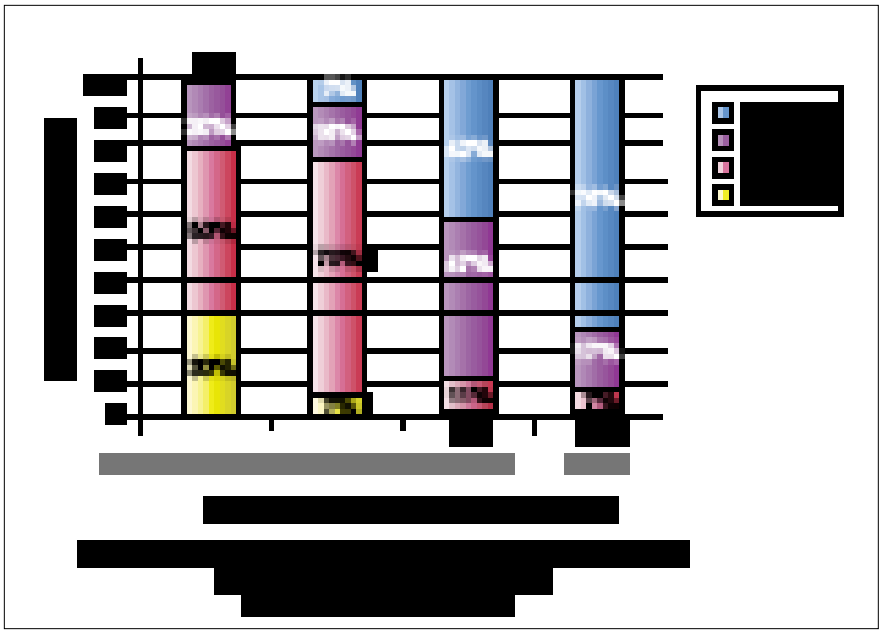

Figure 2. Interobserver variation among endoscopists rating mucosal inflammation via Baron's score.

The study found substantial interobserver variation in endoscopic scoring of UC by the Baron's score among the 24 digital videos (Figure 2). A 76% concordance was observed among the 10 experts and the blinded central reader in the assessment of a severe Baron's score (grade=3). Similarly, there was a 70% agreement between the experts and the central reader when assessing a Baron's score of mild disease (grade=1). The remaining two Baron's grades, 0 and 2, showed a concordance in assessment of 30% and 47%, respectively. A median of 50% (range: 31–63) of the assessments differed between the experts and the central reader by 1 grade or more. In 2% of the assessments, the Baron's score determined by the experts differed from that of the central reader by 2 grades or more.

Of the 24 videos, 10 scored a mean VAS of less than 20 mm, 7 of which were rated as normal by the central reader. A total of 3 videos scored a mean VAS between 20–40 mm, all of which were rated as mild by the central reader. However, of the 8 videos with a mean VAS score of 41–70 mm, only 3 were rated as moderate by the central reader, and none of the 3 videos that had a VAS score of 70 mm or more were rated as severe by the central reader.

According to the investigators, the results of this pilot phase show that substantial interobserver variation exists among UC specialists performing endoscopic disease scoring. Therefore, interobserver variation is an important factor to consider when assessing clinical trial inclusion criteria, as well as when evaluating outcome and response in a clinical trial.

P288 A Patient Support Program (PSP) to Enhance Medication Adherence and Quality-of-Life in Patients Prescribed Mesalamine for Ulcerative Colitis—A Pilot Study

M Tukey, K Falchuk, A Cheifetz, A Moss

Medication adherence is a critical determinant of efficacy in patients receiving 5-ASA for UC. A recent systematic review found that patients who were nonadherent to their 5-ASA therapy had over a 3-fold increased risk of developing a UC flare compared to adherent patients.[19] Several strategies have been investigated for their ability to improve patient adherence, including educational and behavioral interventions.[25] Here, Tukey and colleagues evaluated the feasibility and impact of a patient support program on improving both medication adherence and quality of life in UC patients prescribed 5-ASA.[26]

In this randomized and controlled study, patients (N=44) either participated in a 23-week patient support program delivered by a nurse, or standard follow-up. The patient support arm consisted of three support phone calls from a nurse. Medication adherence was calculated using Steiner's formula, based on refill intervals.[27] Patient quality of life was evaluated using the shortened version of the IBDQ.[28] At baseline, the median Simple Colitis Clinical Activity Index scores, which define remission as less than 2.5, were 1.5 and 2 in the control and patient

support arms, respectively. The median baseline score of the short IBDQ, which is measured between 0–7, was 6 and 5.7, respectively.

After 3 months, the median rate of medication compliance was 69% (IQR: 51–84%) and 74% (IQR: 65–84%) in the control and patient support arms, respectively. A similar median change in the short IBDQ score was apparent in both arms (-0.2 and -0.1 in the control and patient support groups, respectively). A total of 2 patients in the control arm experienced a disease flare and 0 patients in the intervention arm had a flare. None of the differences in these outcomes was considered to reach statistical significance.

The study authors concluded that a nurse-delivered patient support program was feasible and effective in patients in UC remission receiving 5-ASA therapy. However, further study with a larger patient cohort will be required to determine if this intervention can significantly improve medication adherence in this patient population.

P1041 A Dynamic Model of Colonic Concentrations of Delayed-Release 5-Aminosalicylic Acid (Asacol)

M Thorpe, K Putt, E Ehrenpreis, B Hannon

Currently, many 5-ASA formulations are administered multiple times daily, in an effort to ensure that therapeutically active concentrations of the agent are maintained at the site of action in the colon. Although multiple dosing does result in treatment efficacy, patients often have difficulty adhering to this multiple dose schedule. The pH-dependent delayed-release formulation of mesalamine has an enteric coating, which is designed to limit release of 5-ASA to the terminal ileum and colon. The standard dose of this 5-ASA formulation is generally administered in three daily doses; however, this regimen could be one factor associated with reduced patient adherence. For example, one study found only a 40% overall rate of adherence in patients prescribed a delayed-release 5-ASA formulation over 6 months.[29] Patient non-adherence to medication may play a significant role in clinical outcome and disease control, and can also affect morbidity and quality of life.[30] One strategy to improve adherence is to administer this 5-ASA formulation in a single daily dose. Here, Thorpe and colleagues conducted a computer simulation of the pharmacokinetic distribution of 5-ASA, comparing a once-daily (2,400 mg) and three-times-daily (800 mg administered 3 times) dosage.[31]

A dynamic computer model constructed with STELLA software was used to predict 5-ASA concentrations in the four major segments of the colon. These predictions were based on published data of gastrointestinal motility, 5-ASA absorption, and defecation-mediated clearance of colon contents. The pharmacokinetic distributions were predicted using both a model of a healthy colon, as well as a colon designed to simulate active UC with variations in motility and defecation frequency.

The investigators found two significant differences in the predictions of either total or colonic regional levels of 5-ASA after modeling either a once-daily or three-times-daily dosage. For both dosing schemes, steady-state concentrations were achieved by 96 hours. In the healthy colon, both dosing regimens resulted in a maximum colonic retention of approximately 5.1 g, and an average colonic retention of 4.1 g. Simulating an increase in defecation rate up to 12 times daily causes these to dramatically decline, with the resulting maximum colonic retention approximately 2.3 g and the average colonic retention of approximately 1.2 g. The 5-ASA was found to be unevenly distributed, with 39% localized to the ascending colon, 33% in the transverse colon, 14% in the descending colon, and 14% in the sigmoid colon. Simulation of UC, including increased rates of colon motility or defecation rate, exaggerated this uneven distribution and resulted in an increased proportion of the drug localized to the proximal colon.

The investigators concluded that because clinical efficacy of 5-ASA is correlated with the actual levels of drug reached in the colon, the pH-dependent delayed-release mesalamine formulation could successfully be administered as a single, once-daily dose. In addition, this study supports the observation that an increased dosage of 5-ASA may be necessary during acute exacerbations of UC, in order to achieve and maintain adequate concentrations within the colon.

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Commentary

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As our safest and most effective long-term treatment option for patients with mild-to-moderate UC, 5-ASA agents remain the mainstay medical therapy for this chronic disease. At the 2008 ACG meeting, researchers examined strategies to further the ongoing goal of refining and optimizing the use of 5-ASA agents, by considering issues of dose-response, patient adherence, and the application of 5-ASA as a chemopreventive agent in this high-risk cohort.

Combined analysis of the ASCEND trials of delayed-release mesalamine demonstrated that the novel 4.8 g daily dose benefits a subset of patients with mild-to-moderate disease. This subset of patients includes:

- Those who have previously been treated with more than two UC medications
- Those with a history of previous 5-ASA use
- Those previously administered steroids
- Those previously administered rectal therapy

The combined results of the ASCEND trials demonstrate that patients meeting any of these criteria are more likely to respond to the 4.8 g daily dose. In patients meeting any of these criteria, treatment should be initiated at the higher dose, rather than starting at 2.4 g and escalating.

The experience of these trials also underscores a general clinical impression regarding safety of 5-ASA agents, showing that the 2.4 g and 4.8 g daily doses are equally safe and well tolerated and that patients on the higher dose require no additional monitoring by their physicians.

With regard to the MMX mesalamine formulation, it is somewhat surprising to note that, in contrast to the findings of the ASCEND trial, there seems to be no difference between the 2.4 g and the 4.8 g daily doses in terms of overall response. This may be because no subgroup analysis was performed in the manner of the ASCEND trials. It may also suggest that in therapy administered once daily, the size of the dose does not affect maximum clinical benefit.

Future studies may determine that a split dose is required for certain patients to achieve optimal clinical response, particularly when administering larger doses. It may be that the efficacy of once-daily dosing is dependent on patients' individual rates of intestinal transit, which can limit colonic exposure to the drug, regardless of the size of the dose or the release formulation. Nonetheless, the study by Sandborn and colleagues demonstrates the possibility of response with the higher dose in as little as two weeks, in patients who have failed an 8-week trial of the 2.4 g daily dose.

Similarly, colonic transit may play a part in understanding the similar pharmacokinetics seen with various 5-ASA formulations. The study by Wray and colleagues suggests that, for some patients, medications that had been previously prescribed for multiple-times-daily dosing, once-a-day administration may be an option, regardless of the formulation. Conversely, although the MMX formulation demonstrated a consistent pattern of 17-hour release, implying longer colonic exposure, that advantage may be mitigated by faster transit through the colon. This may shorten the prolonged exposure in some patients, thereby requiring two or even three daily doses to maximize topical exposure of 5-ASA.

The novel granulated mesalamine formulation represents a continued expansion of our mesalamine delivery options. The current study suggests that modified mesalamine formulations may provide added benefit in the treatment of patients with UC and that the more alternatives available, the better we will be equipped to treat all our patients effectively.

Although there is a generally high degree of concordance (70%) among gastroenterologists in terms of colonoscopic findings, some substantial differences remain, suggesting the need to develop new techniques for endoscopic scoring that will further delineate findings and reduce viewer variability. This will allow for greater portability of results among protocols and investigators. The pilot-phase study of the new UCEIS provides the first step toward validating this scoring system and assuring its usefulness in both the research and community care settings.

The somewhat disappointing results of the nurse-assisted patient support program suggest a need for multiple options for patient support in order to individualize care and motivate better adherence in all patients. Patient

adherence continues to be a complicated issue, with a variety of medication-, patient-, and disease-related contributing factors. Ultimately we may find that each of these factors need to be assessed and addressed as they affect individual patients.

Finally, simulated pharmacokinetic distribution of 5-ASA provides a fascinating model of the effect of different formulations on the release of 5-ASA. The next step in these studies will be to validate these simulations and prove their consistency and accuracy in representing what occurs in actual patients. Once these simulations have been shown to correspond with real patient experience, they will be invaluable in the development of future clinical trials and for identifying targets for the continued modification of 5-ASA release profiles and administration.

New Formulations to Improve 5-ASA Response and Convenience

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

1. Which of the following mesalamine formulation strategies are designed to deliver 5-ASA to the colon?

   a. Azo-bonded prodrug
   b. pH-dependent delayed release
   c. Controlled-release
   d. All of the above

2. Which of the following statements is TRUE regarding a combined analysis of the ASCEND I, II, and III trials, reported by Lichtenstein and colleagues?

   a. Only patients in the 2.4 g/day 5-ASA treatment arm who exhibited a response to therapy by week 3 sustained this response through week 6.
   b. Only patients in the 4.8 g/day 5-ASA treatment arm who exhibited a response to therapy by week 3 sustained this response at week 6.
   c. Regardless of treatment group, a majority of patients who exhibited a response to therapy by week 3 sustained this response at week 6.
   d. Regardless of treatment group, very few patients who exhibited a response to therapy by week 3 sustained this response at week 6.

3. According to the combined analysis of the ASCEND I, II, and III trials, presented by Hanauer and colleagues, what percentage of patients with a history of using 2 or more UC medications achieved clinical remission with 4.8 g/day 5-ASA?

   a. 10%
   b. 20%
   c. 30%
   d. 40%

4. True or False? A safety analysis of the ASCEND I, II, and III trials found evidence of dose-related nephrotoxicity in the 4.8 g/day 5-ASA treatment arm.

   a. True
   b. False

5. In the open-label extension study presented by Sandborn and colleagues, what was the median additional time to symptom resolution observed with MMX mesalamine after the initial 8-week therapeutic trial?

   a. 15 days
   b. 17 days
   c. 20 days
   d. 23 days

6. True or false? Wray and colleagues found that despite differing rates of tablet disintegration, the delayed-release and MMX mesalamine formulations had similar pharmacokinetic properties.

   a. True
   b. False

7. In a study conducted by Gordon and colleagues, a 1.5 g dosage of granulated mesalamine maintained remission in what percentage of patients at 6 months, compared with placebo?

   a. 58%
   b. 63%
   c. 78%
   d. 79%

8. True or False? In a pilot study reported by Travis and colleagues, a 76% concordance rate was documented between the UC experts and the blinded central reader when assessing colonoscopy samples as severe (grade 3).

   a. True
   b. False

9. True or false? A pilot study performed by Tukey and colleagues found that a nurse-directed patient support program significantly increased patient adherence to 5-ASA.

   a. True
   b. False

10. A computer-simulated model designed by Thorpe and colleagues, considering once-daily versus three-times-daily administration of mesalamine, predicted that 39% of distributed 5-ASA was localized to the _____.

    a. ascending colon
    b. transverse colon
    c. descending colon
    d. sigmoid colon

Evaluation Form: New Formulations to Improve 5-ASA Response and Convenience

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. Cite the latest data regarding 5-ASA pharmacokinetics and how they relate to dosing options of various formulations. 1 2 3 4 5
2. Describe novel formulations and concentrations of 5-ASA currently under investigation. 1 2 3 4 5
3. Identify patient populations that may benefit from new formulations and dosing strategies. 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

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

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