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Novel Formulations and Dosing Strategies for 5-ASA

A Summary of Selected Recent Worldwide Literature

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists treating patients with mild-to-moderate 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. 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. Describe the current armamentarium of oral 5-ASA options for the treatment of UC.
2. Review the current challenges of 5-ASA administration in terms of both individual patient pharmacokinetics and compliance with current regimens.
3. Summarize the current evidence regarding the efficacy of novel granulated mesalamine formulations.

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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Novel Formulations and Dosing Strategies for 5-ASA

A Summary of Selected Recent Worldwide Literature

Chronic and uncontrolled intestinal inflammation are hallmark symptoms of inflammatory bowel disease (IBD). IBD directly affects nearly 1 million Americans, approximately half of whom are diagnosed with ulcerative colitis (UC) and half with Crohn's disease.[1,2] Although the pathogenesis of IBD is not well understood, it is thought that IBD-related inflammation occurs when a genetically or environmentally compromised individual experiences an abnormal immune response to normal intestinal flora.[3,4] This abnormal immune response results in the chronic inflammation and symptoms associated with IBD.

UC and Crohn's disease are clinically distinct entities, differentiated according to their respective symptoms, in addition to anatomical and histological characteristics that are specific to each disease. The most frequently presenting symptom in UC patients is rectal bleeding.[5] Other clinical presentations may be shared between the two diseases, and are not exclusively used to diagnose UC or Crohn's disease. These symptoms include diarrhea, presence of mucous in the stool, fecal urgency, weight loss, and the extraintestinal symptoms associated with chronic inflammation such as fever and a general sense of malaise.

Anatomically, UC is differentiated from Crohn's disease by determining the extent of colonic involvement as well as its characterization as an inflammatory disorder of the mucosa, whereas Crohn's is understood to include transmural involvement of the entire organ. UC inflammation is restricted to the colon, and does not extend into the small intestine or other parts of the gastrointestinal tract. UC is further categorized according to the location of the disease within the colon.[6] Approximately 30% of UC cases are classified as pancolitis, inflammation of the entire colon. Left-sided colitis, including the rectum, sigmoid, and descending colon, comprises 40% of UC diagnoses. The remaining 30% of UC cases are classified as proctitis, in which inflammation is confined to the rectum or rectosigmoid region. Another hallmark of UC intestinal inflammation is that it occurs continuously along the intestinal lining.[7] Conversely, the intestinal inflammation associated with Crohn's disease displays a characteristic "skip" pattern along the colonic wall. During endoscopy, samples of intestinal tissue may also be removed for later histologic analysis in order to help confirm a UC diagnosis. The inflammatory ulcerations typically caused by UC are superficial, penetrating only the surface of the mucosal wall.

UC severity is evaluated according to symptom presentation. The majority of UC cases are identified as mild-to-moderate in intensity; however, many patients experience acute and severe inflammatory flares, which may require hospitalization.[8] Guidelines from the American College of Gastroenterology are utilized to diagnose the degree of UC disease severity.[9] Mild disease is defined by the occurrence of up to four bloody stools per day, with no other presentation of symptoms. Moderate UC is characterized by four to six bloody stools daily and minimal symptomatic toxicity. When patients experience over six bloody stools per day, in addition to associated symptoms of systemic inflammation that include fever, tachycardia, and anemia, a diagnosis of severe UC is made. The most severe form of UC is described as fulminant, and is characterized by more than ten bloody stools per day, continuous bleeding, abdominal tenderness, and a dilated colon. Patients with severe and fulminant UC typically have other complications, including fever, weight loss, and increased levels of inflammatory markers, including C-reactive protein (CRP). Often, the severe blood loss experienced by patients with severe and fulminant UC requires blood transfusion.

There are currently no curative therapies for UC. The goal of treatment is to achieve and maintain long-term remission. For mild and moderate cases of UC, oral or topical 5-aminosalicylic acid (5-ASA, mesalamine) is considered to be the first line of therapy.[10] If the patient exhibits a clinical response to the 5-ASA agent, it is continued in order to achieve and maintain remission.[11] 5-ASA therapies act topically and their success is dependent on the ability to achieve high concentrations of drug within the lumen of the colon. This allows maximal and prolonged exposure of the inflamed intestinal mucosa to

the 5-ASA compound. Because free 5-ASA is absorbed across the gastric and intestinal epithelium, allowing it to enter the systemic circulation and be excreted by the urine, most 5-ASA formulations are designed to limit release of the drug prior to reaching the colon.[12]

Each 5-ASA formulation has been designed with specific pharmacokinetic properties, which are engineered to provide maximal topical exposure of active drug to the area of inflammation.[13] Some 5-ASA formulations are encapsulated with an enteric coating that breaks down at the elevated pH level of 7, as found in the colon. These pH-dependent, delayed-release formulations of 5-ASA are commonly referred to as delayed-release mesalamine. Limitations associated with pH-dependent delayed-release mesalamine formulations include the large number of pills that they may require daily, as well as differences in intestinal pH both within and among patients, which can affect their consistent release.[14,15] Several additional formulation strategies have been developed in order to release the 5-ASA compound more consistently and effectively in the colon. 5-ASA has been formulated linked to a carrier compound with an azo bond (balsalazide, sulfasalazine, olsalazine); cleavage of the azo bond only occurs when it is exposed to bacterial azoreductase enzymes in the intestine, freeing the active 5-ASA moiety. 5-ASA has also been coated with ethylcellulose for moisture-dependent release throughout the intestinal tract as controlled-release mesalamine, available as both tablets and capsules.

The newest formulations of 5-ASA combine pH-dependent coating with other technologies. The MMX mesalamine formulation releases a gel suspension at a pH of 7, which expands to gradually release 5-ASA throughout the colon.

Extended-release mesalamine granules are released in the colon at a pH of 6. Upon release, the granules swell to delay transit through the colon and provide gradual, extended release of 5-ASA throughout the colonic lumen. The delayed and gradual release of these formulations allows for optimal concentration in the colon, sustained exposure, and a smaller daily pill burden.

The following sections describe several publications which focus on the use of 5-ASA in the treatment of UC. These publications include multiple clinical studies that have evaluated different 5-ASA formulations across many regions, including Eastern and Western Europe, and North, Central, and South America.

MMX Mesalamine

Kamm and colleagues evaluated MMX mesalamine, one of the 5-ASA formulation that is both pH-dependent and time-dependent.[16] Prior to this study, two phase III clinical trials had established that MMX mesalamine was effective in the induction of both clinical and endoscopic remission of mild-to-moderate UC. In the first trial, patients were randomized to receive either MMX mesalamine (2.4 g/day twice daily or 4.8 g/day once daily) or placebo.[17] At the conclusion of the 8-week study, significantly more patients receiving MMX mesalamine achieved clinical and endoscopic remission compared with placebo (34.1% and 29.2% versus 12.9%, respectively, $P<.01$). In the second trial, two doses of MMX mesalamine (2.4 g/day or 4.8 g/day) were compared with a conventional dose of delayed-release mesalamine (2.4 g/day divided into three doses) or placebo.[18] Importantly, this study showed that although both doses of MMX mesalamine induced significantly superior rates of clinical and endoscopic remission compared with placebo (40.5% and 41.2% versus 22.1%, respectively, $P=.01$ and $P=.007$), delayed-release mesalamine did not (32.6%). While both of these studies showed MMX mesalamine was effective in the induction of UC remission, neither study directly addressed the safety and efficacy of MMX mesalamine as long-term maintenance therapy.

This was a multi-center, open-label trial of 459 patients with mild-to-moderate UC. Nearly all patients had achieved remission through a previous induction trial with MMX mesalamine, described above, although some patients (n=89) who did not achieve strictly defined remission were allowed into this study at their doctor's discretion.[17,18] Patients were recruited from 101 centers spread across 19 countries from Eastern and Western Europe and the United States. The study was performed between November 2003 and March 2006. Although all 459 patients were evaluable for safety, 8 patients were excluded from an efficacy analysis due to lack of compliance. All patients were randomized to receive 2.4 g/day MMX mesalamine, administered either as a single (once daily) or divided (twice daily) dose. Patients were followed over a 1-year period, and evaluated through clinic visits at months 1, 3, 6, 9, and 12. At each clinical evaluation, patients underwent a physical examination, blood and urine analysis, symptoms assessment, and adverse event review. At the time of final clinical assessment, a sigmoidoscopy was performed and a Physician's Global Assessment (PGA) score was determined. The primary study objective was to assess the long-term safety and tolerability of each of these MMX mesalamine doses.

At study entry, similar proportions of patients in each dosage group were in clinical and endoscopic remission (78.1% for the once daily group and 82.3% for the twice daily group; Figure 1). At the 12-month completion of the study, there was again no significant difference between treatment groups in the proportion of patients who were in clinical and endoscopic remission (64.4% and 68.5%,

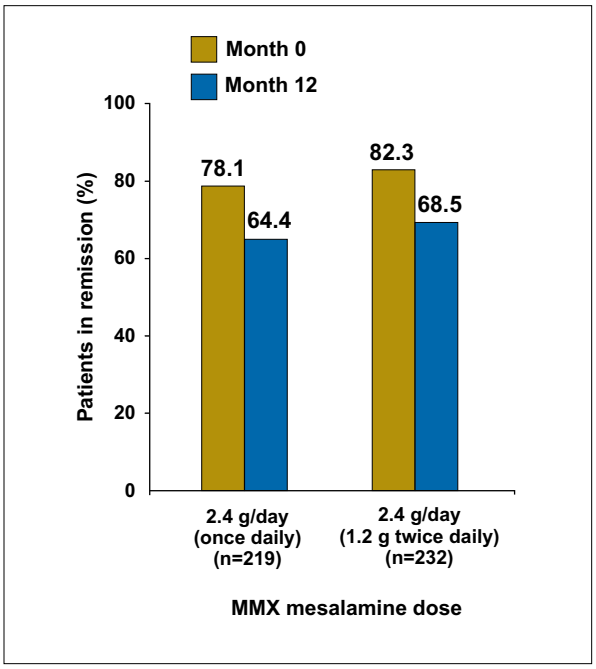

Figure 1. Remission rates at month 0 and month 12 in the efficacy population, following treatment with MMX mesalamine 2.4 g/day given once daily or twice daily.

Adapted from Kamm et al.[16]

respectively). Similar proportions of patients did not experience disease relapse in the once-daily and twice-daily dosage group (88.9% versus 93.2%, respectively).

At the time of entry into this maintenance study, the majority of patients in either the once-daily or twice-daily dosage group had a normal mucosal appearance (66.2% versus 58.6%, respectively), indicated by a sigmoidoscopy score of 0. The remaining patients had a sigmoidoscopy score of 1 (33.8% versus 41.4%, respectively). These sigmoidoscopy scores were largely maintained at month 12. Additionally, the proportion of patients with a sigmoidoscopy score of 0 or 1 was not significantly different between the once-daily or twice-daily group (78.6% versus 78.5%, respectively).

When compared to the intent-to-treat population as a whole, the 89 patients who had not met the strict definition of remission prior to entering this maintenance trial showed a lower 12-month remission rate. However, this remission rate was not significantly different between the dosing groups (52.1% for once daily versus 51.2% for twice daily).

A total of 384 adverse events were reported in 174 (37.9%) patients. There was no significant difference in the proportion of patients reporting an adverse event between the once-daily and twice-daily dosage groups (39.1% versus 36.8%). Most of these adverse events were categorized as mild or moderate in intensity, and the number and types of each event were similar between dosage groups. The most frequent adverse events reported were related to gastrointestinal symptoms. A total of 22 serious adverse events, most frequently gastrointestinal disorders, were recorded in 18 (3.9%) patients. However, only one of these was considered to be possibly or probably related to receiving the study treatment.

The study investigators concluded that both doses of MMX mesalamine were safe and effective as UC maintenance therapy. Importantly, once-daily dosing was not associated with significant decreases in the rate of clinical or endoscopic remission. Because patient compliance often improves with decreased frequency of medication needed during the day, the once-daily administration of MMX mesalamine is a promising strategy for long-term maintenance of UC remission.[15]

Granulated Mesalamine Formulations

In a separate report, Marakhouski and colleagues performed a randomized trial to compare the efficacy of granulated mesalamine with standard delayed-release mesalamine tablets.[19] This was a double-blind randomized study of 233 patients with mild-to-moderate active UC. Patients were randomized to receive 5-ASA either in microgranule (n=115) or tablet (n=118) form. The 5-ASA was initially administered as a dose of 0.5 g three times daily, as this dose has been shown in numerous studies to achieve adequate mucosal 5-ASA concentrations and a satisfactory remission rate. However, after approximately 2 weeks, patients had the option of dose-escalating up to 3 g daily in the event of insufficient response to the initial dosage. This option was allowed in light of the results of several clinical trials showing higher 5-ASA dosages led to increases in efficacy.[20,21] Patients continued 5-ASA therapy for 56 ± 7 days.

A total of 233 patients with mild-to-moderate active UC were recruited to this study. Patients were recruited from 21 centers located across four countries. A clinical evaluation was performed at baseline and 2, 4, 6, and 8 weeks following study initiation.

After approximately 3 weeks, a similar proportion of patients in both the granule group and the tablet group achieved remission (47% versus 42%, respectively; Figure 2). More patients achieved remission after undergoing dose escalation; however, there was still no significant difference between the granule or tablet treatment groups (67% versus 68%, respectively). The noninferiority of the mesalamine granules compared with the tablets was thus determined to be significant.

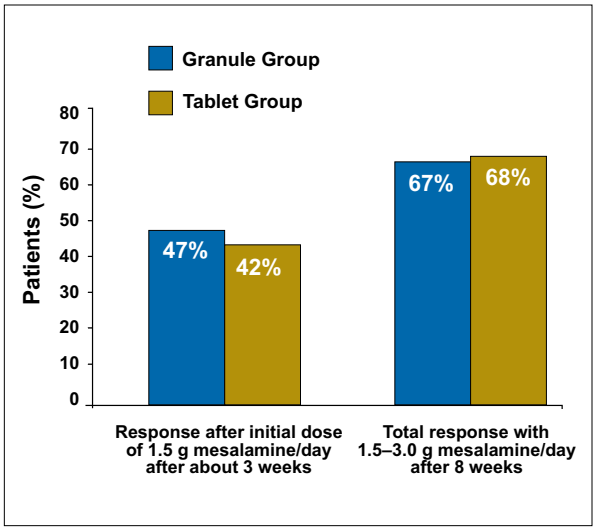

Figure 2. Rates of complete remission in patients with mild to moderately active ulcerative colitis after an initial dose of 1.5 g granulated mesalamine/day and after dose escalation to 3.0 g/day in patients who did not adequately respond to the initial dose.

Adapted with permission from Marakhouski et al.[19]

Patients in both the granule and tablet groups exhibited a similar time to first response (23.5 versus 25.6 days, respectively), a similar rate of endoscopic improvement (84.3% versus 86.4%, respectively), and a similar rate of histological improvement (54.6% versus 57.1%, respectively). Between the two study arms, there was no difference in the proportion of patients exhibiting therapeutic success (80.0% versus 77.8%, respectively) or therapeutic benefit (97.1% versus 96.8%, respectively) after patients were assessed using the PGA.

A similar proportion of patients in both the granule and the tablet groups had to undergo dose escalation (39% versus 45%, respectively). However, the higher dose did produce significantly greater decreases in the UC clinical activity index (CAI) compared to the mean CAI prior to dose escalation ($P<.0001$), regardless of treatment arm.

The CAI score at baseline (≤8 versus >8) and the presence of extraintestinal UC manifestations at baseline (none versus ≥1 symptom) may have impacted the response rate, according to a subgroup analysis. In this analysis, patients with more mild disease activity and no extraintestinal manifestations exhibited the highest rates of response.

The safety profiles of the two 5-ASA delivery systems were also comparable. A similar proportion of patients in the granule group compared with the tablet group experienced 1 or more adverse event (32% versus 36%) or 1 or more potential adverse drug reaction (13% versus 9%). Treatment was discontinued in 5 patients overall (1 patient in the granule group and 4 patients in the tablet group). Reasons for treatment discontinuation included worsening of UC disease (n=2), erythematous rash (n=1), hives (n=1), and nausea (n=1). Two patients in the 5-ASA tablet group experienced a serious adverse event each, both due to worsening of the underlying UC disease.

The non-inferiority of mesalamine granules compared with tablets, as demonstrated in this study, showed that the granulated formulation successfully treated mild-to-moderate UC. The granulated mesalamine was well tolerated, even when dose-escalated. Therefore, this formulation is a safe and effective alternative for induction of response and remission in patients with UC.

In a second study of this 5-ASA formulation, Kruis and colleagues compared once daily dosing of mesalamine granules with a conventional three-times daily dosing.[22] This was a randomized, double-blind, multicenter study that was conducted in 54 centers across 13 countries. The study had a sequential adaptive design, meaning the first interim analysis was planned after 200 intent-to-treat participants had completed the trial. The total planned patient recruitment was 320 patients. All UC medications other than the study drug were stopped at baseline.

A total of 381 UC patients were randomized 1:1 to two treatment arms, receiving either once daily or three times daily dosing of the mesalamine granules. A double-dummy design was used to maintain double-blind status. For example, patients in the once daily group took 3 g mesalamine in the morning, and 1 g placebo each at noon and at night, while patients in the three times daily group administered 1 g mesalamine plus 2 g placebo in the morning, and 1 g mesalamine each at noon and at night. The study treatment duration was 8 weeks, during which clinical visits occurred every 2 weeks. In addition to normal clinical assessment, clinic visits at baseline and 8 weeks included both endoscopy and histology evaluations as well. No significant differences were observed in the baseline characteristics of the treatment groups in these patients.

The primary study endpoint was the proportion of patients who achieved clinical remission, defined as a CAI of 4 or lower, at the end of the study. Secondary study endpoints were also assessed, including clinical improvement (≥1 point decrease in CAI from baseline), and endoscopic remission, assessed as an endoscopic index (EI) score of less than 4.

Among the intent-to-treat population, 79.1% and 75.7% achieved clinical remission in the once daily and three times daily treatment groups, respectively. Because the rate of clinical remission was so similar between the treatment arms, the study authors concluded the two

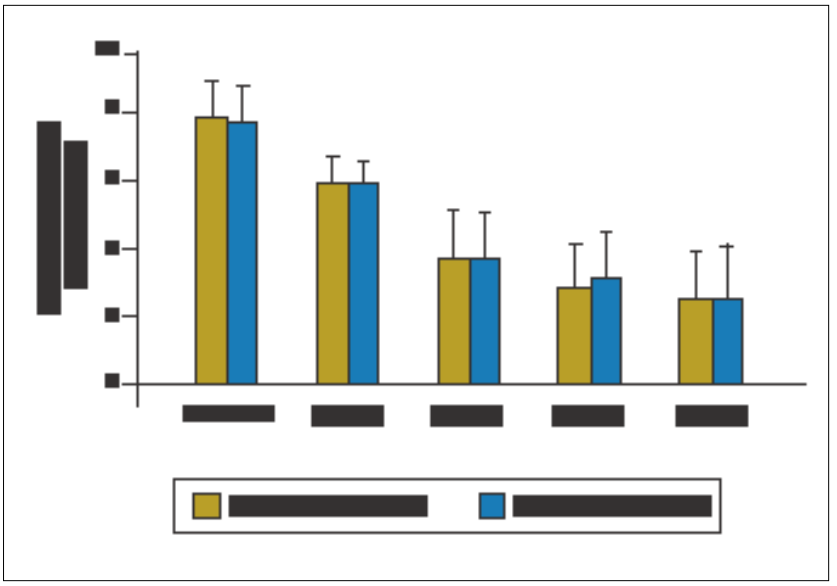

Figure 3. Mean Crohn's Activity Index (CAI) scores as measured during the study of two different doses of granulated mesalamine (intention to treat population).

Adapted from Kruis et al.[22]

treatment regimens were non-inferior (P<.0001). The time course and mean change from baseline of the CAI score also did not differ significantly between treatment arms over the study period (Figure 3).

Although neither gender nor disease duration (≤5 years versus >5 years) significantly affected the rate of clinical remission between the treatment groups, baseline severity did show some importance. Within the once daily treatment arm, significantly more patients with mild disease at baseline achieved clinical remission compared to patients with moderate disease (85% versus 69%, respectively, P=.0067). Additionally, significantly more patients in the once-daily arm with distal disease achieved remission compared to those with proximal disease (86% versus 72%, respectively, P=.0247), suggesting the disease location was also important. However, previous maintenance therapy with 5-ASA had no affect on the rate of achieving clinical remission in this study.

Secondary endpoints did not differ significantly between the treatment arms. Patients in the once daily and three times daily arms showed a similar median time to first symptom resolution (12 versus 16 days). These patients also showed similar rates of endoscopic remission (71% versus 70%) and histologic remission (35% versus 41%). When surveyed, the vast majority of patients (82%) stated they would prefer a once daily dosing regimen, whereas 2% preferred a three times daily regimen and 15% claimed no preference.

A similar percentage of patients in each treatment arm experienced a treatment-emergent adverse event (29% and 32% for once daily and three times daily, respectively). The most frequently reported adverse events were headache, UC disease worsening, and nasopharyngitis, and most were mild or moderate in intensity. Severe intensity adverse events occurred in 7 and 3 patients in the once daily and three times daily arms, respectively; the most common adverse event of severe intensity was worsening of UC. No serious adverse event that occurred was thought to be related to study drug.

Because of the non-inferiority of the once daily schedule of granulated mesalamine determined in this study, the investigators concluded that this more convenient schedule was a safe and effective alternative for the administration of this 5-ASA formulation. Therefore, the once daily regimen was found to be a viable alternative for clinicians to prescribe in order to increase patient adherence to 5-ASA medication.

In a third study evaluating the granulated formulation of mesalamine, Kruis and colleagues conducted a randomized, double-blind trial with two goals.[23] First, they sought to determine the optimal dosage of mesalamine for the induction of remission of mild-to-moderate disease. Second, they evaluated the efficacy and safety of granulated mesalamine. This was a multi-center study which recruited participants from several sites across Austria, Germany, Hungary, and Israel. Only patients with mild-to-moderate UC, defined as a CAI of between 6–12 and an endoscopic index of 4 or greater, were included. Patients had to have had a UC flare with at least 1 previous episode or persistent bloody diarrhea within 14 days of study entry.

A total of 321 patients were randomized to separate treatment arms in which they received a different dose of granulated mesalamine: either 0.5 g three times daily (1.5 g daily), 1.0 g three times daily (3.0 g daily), or 1.5 g three times daily (4.5 g daily). No concurrent UC

medication was allowed throughout the study period. The treatment period continued over 8 weeks, during which patients underwent clinic evaluations at baseline and every 2 weeks thereafter. The efficacy of treatment was evaluated by calculating the CAI at each clinical evaluation. The primary study endpoint was to determine the number of patients who achieved clinical remission over the 8 week period, defined as a CAI of 4 or less. Secondary efficacy endpoints included endoscopic remission, histologic improvement, clinical improvement, life quality index, and PGA.

The proportion of patients achieving clinical remission was 50%, 66%, and 55% in the 1.5 g daily, 3.0 g daily, and 4.5 g daily treatment arms, respectively (Figure 4). Although the difference between the 4.5 g daily and the 1.5 g daily groups was not statistically significant, the difference between the 3.0 g daily and 1.5 g daily groups did reach statistical significance (P=.014). Similarly, more patients in the 3.0 g daily group exhibited clinical improvement compared with the lowest or highest dosage groups. The number of patients experiencing clinical improvement, defined as either a CAI of 4 or less or achieving a 3 point or greater decrease in CAI from baseline, in the 1.5 g daily, 3.0 g daily, and 4.5 g daily groups was 64%, 75%, and 66%, respectively.

Among patients achieving remission, the mean time to the first response, calculated as the time interval between the first dose of study medication and the first point at which a CAI of 4 or less was assessed, was similar among the 1.5 g daily, 3.0 g daily, and 4.5 g daily treatment arms (27.5, 26.5, and 21.5 days, respectively).

A subgroup analysis found that both disease severity and disease duration significantly affected clinical response to therapy. A significantly superior rate of remission was noted in patients with milder disease, defined as a CAI of 8 or less at baseline, compared with patients with more severe (CAI >8) disease (62% versus 49%, P=.016). Patients with a longer disease history (>5 years) also exhibited a significantly superior rate of remission compared with patients with a shorter (≤5 years) disease history (64% versus 51%, P=.019). The highest rates of remission occurred in patients with proctosigmoiditis, compared with left-sided or pancolitis; however, this difference did not achieve statistical significance.

The 3.0 g daily group exhibited a superior rate of endoscopic improvement compared with the lowest and highest doses (53%, 84%, 70% for 1.5 g daily, 3.0 g daily, and 4.5 g daily treatment groups; P≤.0001 for comparison between 1.5 g and 3.0 g daily groups; P=NS for comparison between 3.0 g and 4.5 g daily groups). The proportion of patients experiencing histological improvement was generally lower, and no significant differences

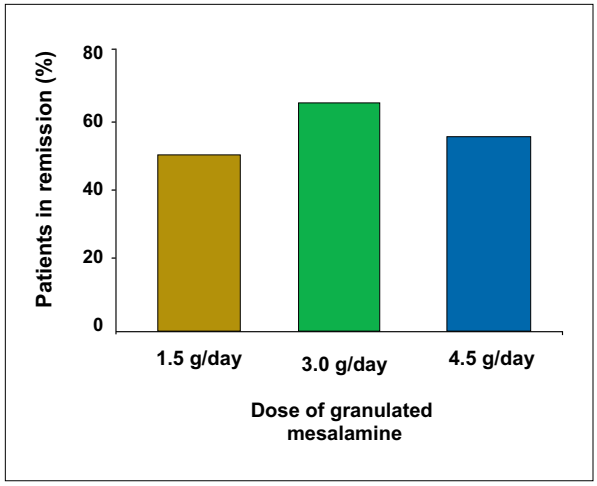

Figure 4. Proportion of patients achieving clinical remission with three different doses of granulated mesalamine.

Adapted from Kruis et al.[23]

were noted among the treatment groups (42%, 56%, and 63% for 1.5 g daily, 3.0 g daily, and 4.5 g daily groups, respectively). The life quality index improved among all three treatment groups.

A total of 14 serious adverse events occurred in 12 patients over the study; 7 of these events were hospitalizations due to progression of UC disease. The study medication was discontinued due to adverse events in 27 patients, most frequently (n=19) because of worsening of UC or UC-related symptoms. A similar proportion of patients reported 1 or more adverse event among the three treatment groups (63%, 61%, and 58% in the 1.5 g daily, 3.0 g daily, and 4.5 g daily, respectively). The most frequent adverse event reported overall was headache.

Previously, both a dose-response relationship and a superiority of high-dose treatment were observed for 5-ASA.[21,24,25] Interestingly, this study did not find either to occur with the doses of granulated mesalamine used. The study authors therefore recommended that the lowest effective dose be used, and in the event of lack of response to this dose, alternative treatment strategies be attempted.

Study of Simulated Mesalamine Release

Because 5-ASA is locally active within the intestinal tract, its release profile is a dominant factor in determining adequate local bioavailability, and thus efficacy. In order to approximate the changing environment of the gastrointestinal tract, Schellekens and colleagues developed a novel dissolution method termed the gastroin-

Table 1. Release Rates During Different Phases of Mesalamine Administration (Standardized Dose of 500 mg)

Adapted from Schellekens et al.[26]

	Release rate (mg/min per phase)			
	I	II	III	IV
Granulated mesalamine tablet	0.0	4.3	0.8	0.0
Granulated mesalamine sachet	0.1	1.2	2.5	0.4
Delayed-release mesalamine	0.0	3.3	2.2	0.2
Controlled-release mesalamine tablet	2.1	0.5	0.6	0.1
Controlled-release mesalamine sachet	2.8	0.6	0.6	0.2

testinal simulation system (GISS).[26] The GISS allowed these researchers to vary four key parameters—transit time, pH, osmolality, and agitation—important for the release of 5-ASA compounds throughout the intestine. They then used the GISS to evaluate the release kinetics of several modified-release 5-ASA formulations, including granulated mesalamine tablets, granulated mesalamine sachets, delayed-release mesalamine, controlled-release mesalamine tablets, and controlled-release mesalamine sachet.

During the GISS test, each 5-ASA agent was exposed to four dissolution phases meant to simulate four consecutive phases of the gastrointestinal tract. The GISS began with a simulation of the stomach for 2 hours, followed by 2-hour exposure in a simulation of the jejunum, 0.5 hour exposure to an environment simulating the distal ileum, and culminating in a 1.5-hour exposure to a simulation of the proximal colon. Biorelevant media were used to achieve each phase specification. A switch solution was applied at the end of each phase to adjust the environment, including both pH and osmolality, to the required composition of the subsequent phase. The release profile of each 5-ASA agent was then determined throughout each phase in the GISS by spectrophotometrically measuring the concentration of the compound. The rate of 5-ASA release was calculated as the amount of agent released in each phase divided by the residence time.

Overall, the investigators found that the release profile of each 5-ASA agent corresponded to the technological formulation applied to that agent (Table 1). Agents with a pH-sensitive coating, including granulated mesalamine tablets and sachets, and delayed-release mesalamine, did not release any 5-ASA in the low pH simulated stomach phase. Conversely, both time-delayed formulations of 5-ASA, the controlled-release tablets and controlled-release sachets, released up to 70% 5-ASA during the 2-hour stomach simulation. 5-ASA release by controlled-release mesalamine in the simulated stomach phase occurred at a rate 3 to 5 times faster than that observed in the simulated small and large intestine phases. The authors concluded that the amount of 5-ASA that was released from the controlled-release sachets and tablets was related to the gastric transit time and the amount of time spent exposed to the simulated stomach environment. The majority of 5-ASA was released from the controlled-release formulation before the simulated colon was ever reached.

Schellekens and colleagues further used the GISS to determine the in vitro colon selectivity of each 5-ASA agent, expressed as the colon released percentage of the total quantity released (CRP-TQR). This was calculated as the amount of 5-ASA released during the fourth phase of the GISS as a percentage of the total release of 5-ASA during all four GISS phases. The authors concluded that the in vitro colon selectivity for all of the evaluated 5-ASA formulations was poor. The CRP-TQR was as low as 0% for the granulated mesalamine tablet. The controlled-release tablet and sachet, as well as delayed-release tablets, exhibited similar CRP-TQR (3.3%, 4.7%, and 3.8%, respectively). The granulated mesalamine sachet had the highest CRP-TQR, 14.8%, but this was still considered by the investigators to be relatively low. The authors concluded that the data from this study corroborated previously published studies which showed the colon selectivity of these agents was relatively low.[27,28]

Based on the results of this study, the authors concluded that in the setting of inflammation limited to the distal parts of the colon, the granulated mesalamine sachet was the optimal formulation to allow the most 5-ASA agent to reach the site of inflammation. In the event of inflammation occurring in the more proximal portions of the intestine, the authors determined that granulated mesalamine tablets or delayed-release mesalamine tablets were the preferred formulation of 5-ASA, as they exhibit low release in the stomach but rapid and substantial release in the proximal intestine.

Cost Effectiveness of High-Dose Mesalamine

The phase III trials ASCEND I and ASCEND II together showed that doubling the dose of delayed-release mesalamine significantly improved its efficacy in mod-

erate UC without an increase in adverse events.[29,30] A pooled analysis of these two trials found that 72% of patients who received 4.8 g/day delayed-release mesalamine exhibited a treatment response, compared with only 58% of patients who received 2.4 g/day, a statistically significant difference ($P<.05$).[31] Although these results clearly demonstrate the improved clinical efficacy of increased delayed-release mesalamine dosage, there are few data on the cost-effectiveness of this treatment. Buckland and colleagues sought to evaluate the cost-effectiveness of the high-dose delayed-release mesalamine used in these studies (4.8 g/day of 800 mg delayed-release mesalamine) compared with the conventional delayed-release mesalamine dose (2.4 g/day of 400 mg) in the treatment of moderate UC.[32]

The authors generated a decision tree analytical model, which incorporated treatment algorithms from both the British Society of Gastroenterology guidelines and published treatment regimens.[14,33] This decision tree model allowed the study investigators to evaluate each treatment by incorporating the probabilities of an event occurring based on a course of treatment. A hypothetical cohort of 1,000 patients entered this decision tree model by receiving either high-dose or standard-dose delayed-release mesalamine. These patients could experience either treatment success, denoted by either a remission or a partial response, or a treatment failure. In order to achieve remission, the hypothetical patients progressed down different treatment arms of the decision tree. Patients who did not require further drug treatment were assumed to receive maintenance 5-ASA treatment. To determine the cost-effectiveness of therapy, the decision tree model considered both drug costs as well as costs of other resources associated with either high-dose or standard-dose delayed-release mesalamine. A cost-utility analysis was generated by mapping the clinical benefit achieved over the duration of the decision tree model with quality-of-life data. A 12-week time period was used to generate the cost-effectiveness analysis, as it was assumed this time period could successfully capture all of the treatment-associated costs and health benefits after a single moderately severe UC flare.

Base-case analysis of the 12-week treatment modality showed an average cost savings of £93 ($137) per patient treated with high-dose mesalamine (average of $3,526 per patient receiving high-dose mesalamine compared with $3,663 per patient receiving standard dose mesalamine). Patients receiving high-dose mesalamine experienced 0.0016 more QALYs compared with those receiving standard-dose mesalamine. Therefore, high-dose mesalamine was found to be superior in both improving the amount of QALYs as well as yielding less cost. The authors further showed that 72% of all simulations found high-dose mesalamine to be cost-effective when considering the commonly used threshold of £30,000 ($44,400)/QALY.

Importantly, the higher treatment success of high-dose versus standard-dose mesalamine projected by the decision tree model (72% versus 58%, respectively, $P<.05$) predicted that 10% fewer patients would require surgery (9% versus 10%, respectively) and 9% fewer patients would require hospitalization while receiving intensive IV steroid or cyclosporine therapy (20% versus 22%, respectively).

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Commentary

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Recent studies from the European literature have described several novel approaches to research in optimizing strategies for 5-ASA therapy in UC. The studies summarized herewith examine a range of endpoints and treatment scenarios that add to our understanding of novel mesalamine formulations and dosing strategies, as they relate to clinical, histologic, and endoscopic response and remission. Cost-effectiveness data and gastrointestinal simulation models provide further reinforcement of efficacy findings as well as provocative data for discussion and future research.

Kamm and associates conducted a multicenter, open-label trial of over 450 patients to evaluate the efficacy of the MMX mesalamine formulation in inducing and further maintaining remission of mild-to-moderate UC. This trial was unique in its examination of both response and maintenance endpoints in a single cohort of patients. The authors showed that patients who received 2.4 g of MMX mesalamine, given as either a single daily dose or a divided dose of 1.2 g twice daily, were able to achieve and maintain remission effectively. The once-daily dose was non-inferior to the twice-daily regimen, demonstrating that it is a viable strategy for maintenance, with the potential to improve adherence among patients receiving long-term treatment. This study was designed to be open-labeled, making it somewhat less rigorous than a blinded, placebo-controlled trial. However, the multinational, multicenter nature of the trial makes for greater generalizability in terms of what is seen in actual clinical practice, as opposed to more stringently designed trials that have been conducted in the past.

Marakhouski and colleagues compared the novel granulated mesalamine formulation to standard delayed-release mesalamine in a double-blind, randomized, non-inferiority trial of patients with mild to moderately active UC. Although the initial dosing regimen for the granulated formulation was somewhat low (0.5 g, tid), there was an option to escalate to a total of 3 g daily after 2 weeks, in patients without adequate response. This design is relevant to clinical practice as patients often start at a lower dose and then escalate to achieve efficacy, as has been seen in marketing surveys assessing gastroenterologists' practices in use of mesalamine for patient treatment.

At 3 weeks, findings of both safety and efficacy were similar in the two groups, thus demonstrating the noninferiority of the granulated formulation versus the delayed release, which is generally considered the industry standard.

The first study by Kruis and colleagues considered a once-daily strategy of dosing 3 g of the novel granulated mesalamine versus the same dose divided into a thrice-daily regimen. All patients received active therapy or placebo three times a day to blind them to the treatment arms and were evaluated via office visit every 2 weeks. Histology was taken at baseline and at 8 weeks. No initial difference was seen between the two groups in the primary and secondary endpoints of clinical and endoscopic remission, respectively. This was once again a noninferiority study where the endpoint was achieved successfully, demonstrating both efficacy and safety of the once-daily strategy for granulated mesalamine, similar to that seen in earlier studies of MMX.

The second study by Kruis was a dose finding study to determine the optimal thrice-daily regimen for the induction of UC remission in active disease. Patients received three-times-daily doses of 0.5 g, 1.0 g, or 1.5 g for a total of 1.5 g, 3.0 g, or 4.5 g daily. No other medication was permitted over the 8-week study period, in which the investigators monitored the number of patients achieving remission.

Results were somewhat unexpected in that the rate of remission seen with the lowest dose (1.5 g daily) did not reach statistical significance versus the highest dose (4.5 g daily). However, the 3 g daily dose did show significant clinical benefit versus the other two doses. This is somewhat atypical for mesalamine formulations. Other studies, such as the ASCEND studies of delayed-release mesalamine, have looked at only two doses (2.4 g vs 4.8 g daily), and have seen no significant benefit from the higher dose in all comers. However, in ASCEND, secondary analyses considering disease severity, disease duration, and history of prior medication revealed these to be mitigating factors affecting response to the higher dose and a dose-response was seen in these harder-to-treat patients. Thus, these findings with granulated mesalamine suggest a dose-response as would be seen in the standard fashion when comparing 1.5 g and 3 g. The 4.5 g dose may provide a saturable, maximal dose effect, over which there is no clinical benefit. This is a new concept that requires direct testing through the definition of subgroups with more refractory disease and longer disease duration and multivariate logistic regression analysis to see how the different doses affect these populations. Based on the current study, we should assume that 1.5 g

is too low a dose for induction of remission and that 3 g daily is the reasonable dose to try initially. Further study may ultimately show a place for 4.5 g daily in specific patients with more difficult-to-treat disease.

The study by Schellekens and associates helps to explain the variable dissolution among mesalamine formulations as well as among doses of a single formulation. As an example, patients have observed whole delayed-release mesalamine capsules in their stools. Explanations for this phenomenon range from variable pH in the ileum to differing pH in patients with active colitis to variability in the coating of the capsules themselves. By simulating transit in the different parts of the gastrointestinal tract, these authors demonstrate the theoretical release of drug as it would occur in healthy individuals. My concern with this article is that it takes what is essentially an in vitro study and attempts to apply it clinically. pH levels, as well as motility, differ among patients with IBD and should be factored in this analysis. Although this study provides an interesting first step, further investigation should be undertaken via scintigraphy to track the release and transit of mesalamine as should stool sampling via unprepped colonoscopy, in order to take this concept from bench to bedside in applicable patients.

Buckland and colleagues noted the results of the phase III ASCEND I and ASCEND II trials and applied them to show that doubling the dose of delayed-release mesalamine, from 2.4 g to 4.8 g, significantly improves overall efficacy in patients with moderate disease, without imparting a higher rate of adverse events. Utilizing a decision-tree model based on recommendations from British guidelines and treatment algorithms, they created a hypothetical cohort of 1,000 patients to receive either high-dose (4.8 g) or standard-dose (2.4 g) mesalamine. Based on 12 weeks of treatment, they found a cost saving via quality of life years for patients taking high-dose mesalamine, compared to the standard dose.

The comparison made in this study assumes that all patients with moderate disease take the high-dose mesalamine or that they all take the standard dose of delayed-release mesalamine. Further study of patient subsets in ASCEND I and II, as well as the further findings of ASCEND III, address the question of what patients with moderate disease derive the most benefit from increased dosing. Based on these findings, clinicians do not use the high dose in all of their patients with moderate disease. It may be that an even greater cost benefit than is seen here could be realized if patients with a long history of disease or who are refractory to other medications are selected for comparison. If this study were modeled as such, these patients would account for a much greater cost savings. Patients with moderate UC who are still steroid-naïve and who have disease confined to the left side of the colon may not benefit from the higher dose and are far less likely to realize benefit, in terms of either cost or efficacy.

Notes

Novel Formulations and Dosing Strategies for 5-ASA

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

1. Which of the following is NOT a strategy used to alter the pharmacological properties of 5-ASA?

   a. Azo-bond with a carrier molecule
   b. pH-dependent release
   c. Time-dependent release
   d. Pegylated 5-ASA

2. Which of the following is an example of a 5-ASA molecule with both pH-dependent and time-dependent release properties?

   a. Delayed-release mesalamine
   b. Controlled-release mesalamine
   c. Olsalazine
   d. MMX mesalamine tablets

3. In a clinical study conducted by Kamm and colleagues, a once-daily administration of 2.4 g/day MMX mesalamine resulted in _____ compared with twice-daily MMX.

   a. a similar rate of clinical and endoscopic remission
   b. a significantly higher rate of clinical and endoscopic remission
   c. a significantly lower rate of clinical and endoscopic remission
   d. a significantly higher rate of adverse events

4. A randomized trial by Marakhouski and colleagues showed that mesalamine granules were _____ compared with mesalamine tablets.

   a. significantly more effective for induction of remission
   b. non-inferior for induction of remission
   c. significantly less effective for induction of remission
   d. significantly less effective for maintenance of remission

5. In the trial by Marakhouski and colleagues, _____ of patients achieved remission in the group treated with granulated mesalamine.

   a. 35%
   b. 38%
   c. 47%
   d. 52%

6. In a randomized study by Kruis and colleagues, _____ of patients receiving a once daily dose of granulated mesalamine achieved clinical remission.

   a. 52.4%
   b. 68.3%
   c. 70.4%
   d. 79.1%

7. A separate randomized trial by Kruis and colleagues found a _____ dose of granulated mesalamine produced the highest rate of clinical improvement and remission.

   a. 1.5 g daily
   b. 3.0 g daily
   c. 4.2 g daily
   d. 4.5 g daily

8. Which of the following was NOT a parameter that could be varied in the GISS developed by Schellekens and colleagues?

   a. Transit time
   b. pH
   c. Osmolality
   d. Bacterial concentration

9. Using the GISS, Schellekens and colleagues found that the controlled-release formulations of mesalamine released up to____% of 5-ASA in the stomach.

   a. 45
   b. 55
   c. 60
   d. 70

10. Buckland and colleagues found that _____ was cost-effective in 72% of the simulations they performed.

    a. MMX mesalamine
    b. granulated mesalamine
    c. low-dose mesalamine
    d. high-dose mesalamine

Evaluation Form: Novel Formulations and Dosing Strategies for 5-ASA

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.

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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 UC.	1	2	3	4	5
2. Review 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. Summarize the current evidence regarding the efficacy of novel granulated mesalamine formulations.	1	2	3	4	5

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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
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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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