

New Research in Ulcerative Colitis: Optimizing 5-ASA Administration for Efficacy and Adherence

A Review of Selected Presentations from the 74th
American College of Gastroenterology
Annual Scientific Meeting
October 23–28, 2009
San Diego, California

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

Release date: January 2010

Expiration date: January 31, 2011

Estimated time to complete activity: 1.0 hours



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. 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. Assess appropriate use of 5-ASAs in the treatment of patients with UC.
2. Evaluate clinical efficacy of 5-ASAs.
3. Discuss differences in mucosal healing between 5-ASAs.
4. Review the latest dosing strategy data.

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Introduction

Ulcerative colitis (UC) is a chronic bowel disorder characterized by inflammation of the colonic mucosa. The most common symptoms of UC are diarrhea, blood in the stool, and, occasionally, abdominal pain. Other symptoms may include fever, anemia, and weight loss. The annual incidence of UC is estimated at 2–7 per 100,000 people.¹ In the United States, UC is responsible for approximately 20,000 hospitalizations and 250,000 visits to physicians per year.²

Although the pathophysiology of UC is incompletely understood, experts generally agree that a combination of innate and environmental factors produce an inappropriate immune response in a subset of people who are genetically predisposed to the disease. According to epidemiological research, people at higher risk for UC include “westernized” populations, as well as people with high levels of sanitation, white-collar occupations, or diets high in fat. UC is also much more prevalent among whites versus black or hispanic populations.³

UC is categorized according to both symptom severity and the extent of disease. Severity is defined as mild, moderate, severe, or fulminant depending on symptom characterization, the number of stools per day, changes in erythrocyte sedimentation rate, and signs of toxicity.^{1,4} In ulcerative proctitis, inflammation is limited to the rectum, whereas proctosigmoiditis involves inflammation that extends into the rectosigmoid colon. Proctitis and proctosigmoiditis affect approximately 46% of patients with UC.⁵ When inflammation extends to the splenic flexure, the diagnosis is of left-sided disease, which affects 17% of UC patients. In extensive UC, inflammation extends beyond the splenic flexure and may include the entire colon (pancolitis). Pancolitis accounts for approximately 37% of patients with UC.

Current treatment guidelines recommend exclusion of other etiologies of colitis and the use of endoscopy with biopsy and patient assessment to make the diagnosis of UC, and to define the severity and extent of the disease.⁴ Histologic findings for UC include crypt distortion and lymphoid aggregates. The mucosa of patients with UC has a blunted vascular pattern and often appears granular and red. In severe cases, inflammatory polyps may develop.⁶

The main goals of UC management are the treatment of symptoms, the induction of remission, and the prevention of relapse. Mesalamine, or 5-aminosalicylate (5-ASA), is the first-line therapy for achieving and maintaining remission in UC and ulcerative proctitis. Although the mechanism of 5-ASA is not fully understood, researchers believe that it works topically to inhibit inflammatory mediators by blocking transcription factors directly within the colonic mucosa.⁷ In particular, 5-ASA is thought to activate the nuclear peroxisome proliferator-activated receptor α (PPAR α).⁸ Other mechanisms of action for 5-ASA that may cause its anti-inflammatory effects include the inhibition of prostaglandins and leukotrienes.

5-ASA acts topically on the mucosa to reduce inflammation. Rectal therapies deliver mesalamine directly to the rectum and colon, while oral therapies utilize coatings or delayed-release systems to prevent the active drug from being absorbed systemically. Then it reaches the site of inflammation. The amount of active mesalamine that reaches the site of inflammation is a key component in achieving remission. Naganuma and associates⁹ found that higher concentrations of 5-ASA in the colonic mucosa correspond with increased efficacy in treating symptoms. Several formulations of mesalamine rely on coatings that are sensitive to pH levels, releasing 5-ASA when a pH level of 7 or more is reached (usually within the terminal ileum). Other formulations rely on the use of controlled-release ethylcellulose-coated 5-ASA microspheres that are encapsulated in a moisture-sensitive semi-permeable membrane. This membrane is broken down in a time-dependent manner.¹⁰ Multimatrix (MMX) mesalamine is a tablet formulation containing 5-ASA that is suspended in lipophilic and hydrophilic matrices in a pH-dependent coating that delays release until the tablet reaches the terminal ileum.¹¹ Balsalazide is an azo-bonded prodrug that releases 5-ASA when bacterial reductases in the colon release the azo bond, making 5-ASA available to work topically.¹²

Many 5-ASA formulations are administered multiple times per day, in an effort to maintain therapeutically active levels of mesalamine at the site of inflammation. However, evolving data suggest that most 5-ASA formu-

lations, regardless of delivery system, may be effective when given once daily. Although multiple daily dosing strategies are effective, patients often fall short on adherence to multiple dosing regimens. One study found a 40% rate of adherence at 6 months for a 3-times daily dosing regimen of delayed-release 5-ASA.¹³ Low adherence may play a significant role in disease progression, overall morbidity, and quality of life.

For patients whose disease is refractory to 5-ASA therapy, corticosteroids are considered a second-line therapy option for the induction of remission in distal disease. Steroids are associated with high toxicity, particularly when used for longer than 3 months. The immunomodulators 6-mercaptopurine (6-MP) and azathioprine are recommended for patients with refractory disease who fail to improve on 5-ASAs or steroids.⁴ However, the beneficial effect of immunomodulators in UC is less well studied than in Crohn's disease.

UC is a chronic condition characterized by relapse and remission. In a long-term study of 95 UC patients treated with mesalamine, Bresci and colleagues¹⁴ found that although most of the patients experienced a relapse over the course of 10 years, those who had been diagnosed with distal colitis had a lower rate of relapse than those with more extensive disease. This is contrary to the clinical experience that left-sided colitis may be more difficult to treat.

The ACG treatment guidelines recommend the use of 5-ASA formulations for the maintenance of remission in UC. Steroids are not recommended for maintenance because of their lack of long-term efficacy and their risk of side effects. Azathioprine or 6-MP may be used for maintenance in patients for whom 5-ASA therapy is not sufficient. Patients with moderate or severe refractory disease usually require hospitalization for treatment with intravenous steroids, cyclosporine, or surgical resection of the colon. More recently, anti-TNF biologic therapy has been shown to be effective in patients with refractory disease and it is usually used before cyclosporine in most cases.

Patients with UC carry an increased risk of developing colon cancer, with higher risk for those patients with a long duration of disease and widespread inflammation. The risk may be as high as 18% in patients who have had UC for 30 or more years.¹⁵ Another estimate suggests that the annual incidence of colorectal cancer in UC patients may range from 1 in 500 to 1 in 1,600 persons.¹⁶ The ACG guidelines recommend annual or biannual colonoscopy, with biopsies performed at 10-cm intervals.⁴ Accumulating data suggest that examination via chromoendoscopy may be more effective in identifying dysplasia than traditional white-light endoscopic examination.

Recent research has focused on the use of 5-ASA therapy in chemoprevention. Because 5-ASA therapy reduces the risk of relapse through its anti-inflammatory effects, researchers have postulated that it may also reduce the risk of cancer. A recent meta-analysis found an odds ratio of 0.51 in reducing the risk of cancer and/or dysplasia with the use of 5-ASA therapy.¹⁷

Recently, the American College of Gastroenterology held its 74th Annual Scientific Meeting in San Diego, California. Presenters shared new insights into the efficacy of delayed-release mesalamine and balsalazide, as well as recent findings on gut pH levels of UC patients in relapse and remission. In addition, new information emerged on UC's impact on quality of life, prescribing practices prior to the initiation of immunosuppressive therapy, and patterns of drug adherence among UC patients.

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New Research in Ulcerative Colitis: Optimizing 5-ASA Administration for Efficacy and Adherence

Multiple daily dosing of 5-ASA for UC has been a standard practice since the 1940s. However, these regimens can lead to poor patient adherence. Recently, several 5-ASA formulations have demonstrated non-inferiority to multiple daily dosing, including ethylcellulose-coated microgranules (Pentasa),¹ Multi-Matrix delayed release tablets (Lialda),² and delayed- and extended-release granules (Apriso).³ In the ASCEND I, II, and III trials, a delayed-release 5-ASA formulation (Asacol) was investigated at doses of 2.4 and 4.8 g/day, to optimize therapy in specific patient populations.⁴⁻⁶ This same formulation is currently being evaluated for possible once-daily dosing in the maintenance setting. Two presentations at ACG provided new data on the efficacy of delayed-release 5-ASA.

1185 Once Daily Dosing of Delayed-Release Oral Mesalamine (400 mg Tablet) is as Effective as Twice Daily Dosing for Maintenance of Remission of Ulcerative Colitis: Results of the QDIEM Study

W Sandborn, S Kane, J Korzenik, B Lashner, J Leighton, U Mahadevan, J Marion, M Safdi, C Sninsky, D Ramsey

In the QDIEM trial, Sandborn and colleagues investigated the use of once-daily dosing of delayed-release mesalamine compared with divided dosing in UC patients.⁷ The study was designed to assess the non-inferiority of once-daily versus twice-daily dosing for maintaining clinical remission. Patients who had been maintained on mesalamine doses ranging from 1.6 g/d to 2.4 g/d were randomized to receive either once- or twice-daily regimen of the same overall dose they had been receiving before the study began. Treatments continued for 12 months, with patient visits at 3, 6, and 12 months and a phone call at 9 months. The primary endpoint was the percentage of patients remaining in

remission at month 6 for each dosing arm. Relapse was defined as a Simple Clinical Colitis Activity Index (SCCAI) score of 5 or higher, and remission was defined as a SCCAI score of 2 or less.

Of a total of 1,023 patients who received treatment in this study, 70% received 2.4 g/day, 28% received 1.6 g/day, and 2% received 2.0 g/day. The primary endpoint of remission at 6 months was met with 90.5% and 91.8% of patients dosed once-daily and twice-daily, respectively. The time to relapse was similar in both groups, with a 1.19 hazard ratio (95% confidence interval [CI] 0.77–1.82) between once-daily and twice-daily dosing groups. The number of adverse events was also similar between the two groups. The investigators concluded that once-daily dosing of delayed-release mesalamine was as effective as twice-daily dosing for the maintenance of remission in UC.

1209 Rapid Symptom Resolution with Delayed-Release Mesalamine 4.8 g/day Compared to 2.4 g/day in Moderately Active Ulcerative Colitis Patients with a History of More Difficult to Treat Disease

W Sandborn, D Ramsey, C Sninsky

Sandborn and associates also provided a retrospective, post-hoc analysis of data from ASCEND I⁴ and ASCEND II⁵ trials. In this analysis, the researchers sought to evaluate the time to resolution of hallmark UC symptoms in 423 patients with moderately active UC with a history of difficult-to-treat disease.⁸ Hallmark symptoms were defined as increased stool frequency and rectal bleeding, and moderately active disease was defined as a score of 2 on the Physician's Global Assessment. For this analysis, difficult-to-treat disease was defined as that previously treated with UC therapies (including oral and rectal 5-ASA, corticosteroids, and immunomodulators).

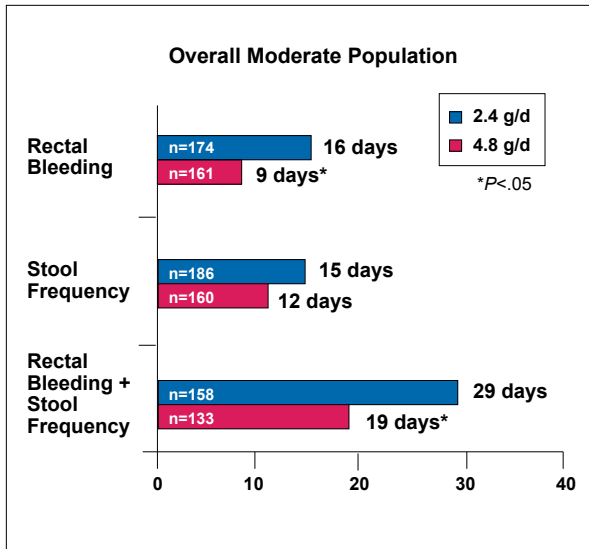


Figure 1. Median time (days) to symptom resolution in the combined populations of moderate-disease patients in the ASCEND I and II trials.

Reproduced from Sandborn et al.⁸

The investigators analyzed data from ASCEND I and II and compared the median time to resolution for delayed-release mesalamine 4.8 g/day compared with 2.4 g/day dosing. The time to resolution was based on the first day of symptom resolution as reported by patients, and resolution was defined as a score of 0 on the Physician's Global Assessment. The mean age of patients randomized to receive 2.4 g/day and 4.8 g/day was 42.6 and 43.4, respectively. The mean UC Disease Activity Index score was 7.3 at the beginning of the study for both study arms.

In the overall population, the median time to resolution of rectal bleeding and improvement in stool frequency was significantly shorter with the 4.8 g/day dose, at 19 days, versus 29 days for the 2.4 g/day dose, ($P<.05$, Figure 1). For rectal bleeding, the median time to resolution was 9 days for the 4.8 g/day dose and 21 days for the 2.4 g/day dose ($P<.05$). For increased stool frequency, the median time to resolution was 10 days for the 4.8 g/day dose and 18 days for the 2.4 g/day dose but it did not reach statistical significance. In patients previously treated with 2 or more UC therapies, the time to resolution was 25 days in patients who received the higher dose, compared with 49 days for those on the lower dose ($P<.05$). In the overall population, the hazard ratio for the resolution of both symptoms was 1.43, whereas in the group previously treated

with 2 or more UC therapies, the hazard ratio was 1.68. The investigators concluded that the magnitude of the dose benefit for 4.8 g/day versus 2.4 g/day was greater in patients with difficult-to-treat disease than in the overall moderate UC population.

1199 Daily Dosing of Delayed Release Mesalamine Prior to Immunosuppressive Use

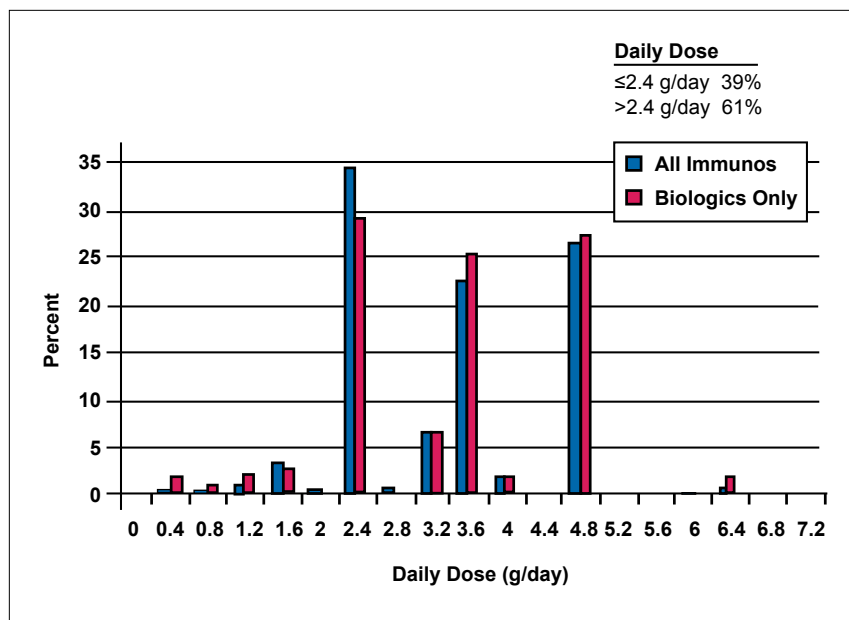
S Katz, M Pasquale

Clinical practice guidelines recommend the use of 5-ASAs at doses up to 4.8 g/day.⁹ When 5-ASA does not provide patient improvement, additional therapies such as corticosteroids and immunosuppressives are recommended. In this study, Katz and Pasquale investigated the use of 5-ASA therapy before the initiation of immunosuppressives, in order to determine whether patients were maximizing their use of available 5-ASA doses before resorting to immunosuppressive therapy, which requires increased monitoring and is associated with greater risk of adverse effects.¹⁰ The investigators analyzed data from two medical claims databases from 2000–2007 and included in their analysis patients who had been diagnosed with UC for at least 30 days prior to their use of immunosuppressives, and who had been enrolled continuously for 12 months. Patients who had received at least 2 prescriptions for delayed-release mesalamine prior to their first use of an immunosuppressive therapy were eligible for analysis. Researchers determined the most recent dose of delayed release mesalamine that was filled prior to each patient's first dose of immunosuppressive therapy. Immunosuppressives included in the analysis were infliximab, adalimumab, azathioprine, cyclosporine, 6-mercaptopurine, and methotrexate.

Among 2,599 patients included in the analysis, 96% filled a prescription for an oral, nonbiologic immunosuppressive agent and 4% received a biologic. The mean and median daily doses of delayed-release mesalamine were 3.48 g/day and 3.6 g/day, respectively. However, 39% of all patients in the study had been taking delayed-release mesalamine at a most recent daily dose of 2.4 g/day or lower (Figure 2). For these patients, their dose had not been stepped-up to the recommended 4.8 g/day before the initiation of immunosuppressive therapy. The investigators concluded that, despite recommendations in clinical guidelines, patients are not maximizing their use of available 5-ASA therapies before initiating immunosuppressive therapy. Katz and Pasquale suggested that future research focus on the drivers of this behavior, as well as the medical and economic consequences of underutilization of 5-ASA therapy.

Figure 2. Delayed release mesalamine daily dosing prior to immunosuppressive use.

Reproduced from Katz and Pasquale.¹⁰



1184 Patient Perceptions of the Impact of Ulcerative Colitis in Daily Life

S Katz, M Hershberger

UC has a significant impact on patients' quality of life (QoL). Several studies have sought to define the predictors of QoL in UC patients, in an effort to improve treatment success.¹¹ A recent study found that patients in remission had significantly higher QoL scores than those with active disease.¹²

Katz and Hershberger conducted a survey of 722 UC patients to evaluate the symptoms of UC and the impact of UC on a series of QoL attributes.¹³ Between August 2007 and August 2008, the researchers performed online interviews with patients aged 18 and older who treated their condition with a prescription medication. Patients rated the impact of UC on a series of QoL attributes on a scale of 1 (no impact) to 5 (severe impact).

The majority of patients interviewed—65%—were female. Fifty-three percent were between the ages of 35 and 54, 69% were married, and 87% were Caucasian. Forty-seven percent of the patients interviewed reported that they had been diagnosed with UC for 3 or more years. Approximately half of the respondents reported 3–10 UC flares over the previous 2 years, with the most frequent symptoms including abdominal cramping/pain (72%), urgent need to go to the bathroom (66%), and increased frequency of bowel movements (66%). Rectal bleeding and a change in bowel movement patterns each occurred in 50% of those surveyed.

Katz and Hershberger found that, among QoL factors, UC had the greatest impact on patients' personal life, with 55% of respondents reporting a moderate or severe (scored as a 4 or 5) impact. For 49% of participants, UC had a moderate/severe impact on work life, and 39% reported that UC had a moderate/severe impact on interactions with friends and family members.

According to the investigators, this study highlights the dramatic impact of UC on a patient's personal life, their ability to function at work, and their interactions with friends and family. The authors conclude that health care practitioners should strive to improve patients' QoL by aggressively treating active UC symptoms and maintaining remission.

1224 Colonic pH Differs Depending on the Activity of Ulcerative Colitis (UC): Report of Two Patients with pH Measurements Over Time

D Rubin, S Gavzy, C Chapman, A Bunnag, A Mikolajczyk, B Surma

Several studies have documented the variations in colonic pH in UC patients and healthy volunteers and have suggested that these variations may play a role in the success of treatment regimens. In an earlier study, Rubin and colleagues found that the pH in the colon was more acidic than previously described in a separate study of healthy volunteers.^{14,15} In this study, Rubin and colleagues fol-

Table 1. Mean pHs of Active and Quiescent Disease by GI Location

Location	Patient 1		Patient 2	
	pH (active)	pH (quiescent)	pH (active)	pH (quiescent)
Proximal small bowel	5.49	5.26	6.13	5.88
Middle small bowel	6.71	6.88	6.83	7.07
Distal small bowel	7.04	7.24	6.92	7.47
Proximal colon	6.22	6.82	5.44	7.36
Distal colon	6.84	9.77	5.3	7.73

Data from Rubin et al.¹⁶

lowed two patients with mildly to moderately active UC in order to better understand how colonic pH varies with disease activity.¹⁶ The patients, both of whom had endoscopic, histologic, and clinical diagnoses of long-standing UC, were recruited while their disease was active, and followed until they achieved clinical remission. During the active and remitted phases, patients underwent total gut pH, pressure, and temperature measurements using SmartPill pH, a device normally used for gastroparesis but recently also used in the UC population.¹⁵ The study required that no acid-blocking agents be used and a standardized diet was utilized.

The first patient followed was a 39-year-old male with left-sided colitis diagnosed 12 years previously, maintained on delayed-release mesalamine at a dose of 4.8 g/day. The second patient was a 29-year-old male with pancolitis who had been diagnosed 8 years previously. He was maintained on 4.8 g/day of delayed-release mesalamine and 2.5 mg/kg/d of azathioprine. Over the course of the study period, both patients experienced a clinically mild relapse (with Simple Clinical Colitis Activity Index [SSCAI] scores of 2 and 3 for patients 1 and 2, respectively), and were successfully treated with corticosteroids. After the induction of remission (defined as an SSCAI score of 0), the patients were maintained with the same pre-relapse regimen they had followed before. pH measurements during remission were obtained after 7 and 8 months of stable disease for patients 1 and 2, respectively.

In both patients, the colonic pH rose substantially between active inflammation and subsequent remission (Table 1). According to the investigators, these case studies may have implications for future therapy and for the potential modifications of drug delivery systems during active and quiescent phases of UC.

1235 Lumenal pH and Transit Time in Patients with Quiescent Ulcerative Colitis (UC) Resembles that of Healthy Controls

D Rubin, S Gavzy, C Chapman, A Mikolajczyk, B Surma

Although there is limited information about variations in colonic pH in healthy versus UC-affected subjects, studies in healthy volunteers have shown that the mean ileal pH is 7.45 (range 7.3–7.6), and that the mean proximal and distal colon pH is 6.14 (5.7–6.8) and 6.87 (6.1–7.2), respectively.¹⁷ Researchers have postulated that variations in colonic pH levels may play a key role in the success of UC treatment.¹⁴

In a second study using the SmartPill pH, Rubin and colleagues measured pH levels and gut transit times in 8 patients in clinical remission, in order to better understand the variations in pH measurements associated with the activity of the disease.¹⁸ Patients with an established diagnosis of UC (made by clinical, endoscopic, and histologic means) were recruited. Clinical remission was defined according to the ACG Practice Guidelines,⁹ and wherever possible the researchers confirmed the presence of histologic and mucosal healing. Using the SmartPill pH, the investigators measured total gut pH, pressure, and temperature. As in the previous SmartPill pH study, a standardized diet was employed, and patients were forbidden to take acid-blocking agents. The researchers measured gut transit based on standard changes in pressure and pH associated with known locations in the bowel.

Of the 8 patients who completed the study, 5 were male, with median disease duration of 12.5 years. Four patients had extensive UC or pancolitis and 4 had left-sided colitis. The mean pH for the proximal and distal colons was 6.36 and 7.21, respectively. The investigators found that there were no significant differences in pH or transit time based on the extent of the disease, and that

the colonic pH in UC patients in remission appears to be similar to that of previously reported values in healthy volunteers. The authors concluded that their findings of higher pH in patients in remission compared with that of active UC patients may lead to future improvements in optimal drug delivery for UC treatment.

1172 The Effect of High-Dose Balsalazide on the Modified Sutherland Ulcerative Colitis Activity Index in Patients with UC

A Safdi

Balsalazide is an azo-bonded prodrug that works independently of pH levels, releasing 5-ASA when it comes in contact with bacteria found in the colon, thus increasing 5-ASA concentration at the colonic mucosa.¹⁹ In some patients with active UC whose colonic pH may not reach 7, balsalazide may be more effective than pH 7-dependent formulations. In this study, Safdi evaluated the effects of balsalazide in inducing remission in patients with mild-to-moderate UC who had previously failed pH 7-dependent 5-ASA therapy.²⁰

The study included patients with mild-to-moderate UC who had failed at least 8 weeks of mesalamine therapy and who had modified Sutherland Ulcerative Colitis Activity Index (UCAI) scores of 4–10, with scores of 1 or more for rectal bleeding, mucosal appearance, and physician rating of disease activity. The primary endpoint after 8 weeks of therapy was the percentage of patients who achieved remission (defined as a modified Sutherland UCAI score of 0 for rectal bleeding, 0 for stool frequency, and 1 or less for physician rating of disease activity). Patients received three 0.75 g balsalazide capsules 3 times daily (tid) for the first 2 weeks. If remission was not achieved at weeks 2, 4, or 6 of the study, the dose was increased by 1 capsule tid, with a maximum dose increase to 6 capsules tid. Patients who did achieve remission with the starting dose were maintained at that level for the duration of the study.

By the end of the 8-week study period, 47% of the patients enrolled in the study experienced symptomatic remission, with a median modified Sutherland UCAI score of 0 (range, 0–2). Patients who did not achieve remission had a median total score of 6 (range, 3–9). For patients who achieved remission, the median maximum dose was the starting dose (3 capsules tid, range 3–6), whereas the median maximum dose for those not achieving remission was 6 capsules tid (range, 4–6).

In this study, balsalazide effectively induced remission in patients whose UC had not responded

to pH 7-dependent mesalamine. Safdi suggested that pH 7-dependent mechanisms of 5-ASA delivery may cause a lack of efficacy in certain individuals because of increased fecal wasting. He concluded that switching patients to an azo-bonded delivery system may lead to expeditious symptom resolution and should be considered in patients who are refractory to pH-dependent formulations.

1272 Factors Affecting Persistence with Mesalamine Therapy: Results from a Large Pharmacy Database

S Kane, M Sumner, D Solomon, M Jenkins

Low patient adherence to UC therapies is a complex challenge facing physicians who treat this population. Researchers estimate that adherence among UC patients is similar to that of other populations of chronic disease sufferers, with 20–50% of patients failing to follow their prescribed course of treatment.²¹ A recent analysis found that patients who do not comply with maintenance therapy have a 3-fold higher risk of experiencing UC flares than those who are compliant.²² Previous studies of UC patients have highlighted some of the factors that influence patient persistence.²³

In order to examine the patterns of persistence in a group of patients receiving 5-ASA therapies, Kane and colleagues performed a study analyzing prescription refill records of 44,191 patients starting a course of treatment with the following therapies: MMX mesalamine, delayed-release mesalamine, controlled-release mesalamine, olsalazine capsules, or balsalazide.²⁴ Patients, who began therapy between March and September 2007, were followed over 18 months. Persistent patients were defined as those who refilled their prescriptions within a time frame of up to double the duration of the prescription.

Across all groups studied, persistence decreased over time. Patients receiving MMX mesalamine had higher persistence at 3 months (60%) and 18 months (13%) than patients receiving delayed-release mesalamine (41% at 3 months; 5% at 18 months), controlled-release mesalamine (41% and 6%), balsalazide (43% and 6%), or olsalazine (35% and 6%). In all treatment groups, males were more persistent than females, and patients younger than 17 years old were more persistent than older patients. The most persistent subgroup was the group of patients aged 41–55 years old who received MMX mesalamine (62% at 3 months). The most persistent subgroup by prescriber was the group prescribed MMX mesalamine by internists (60%, 22% and 16% at 3, 12, and 18 months, respectively.)

The investigators concluded that lower pill burdens, once-daily dosing, and patient satisfaction may all play roles in encouraging persistence in the UC population. The overall low rates of persistence among this population, however, combined with variation by prescriber and decreases over time, indicate that novel intervention strategies are still necessary to maximize the potential benefit of UC therapies.

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Commentary

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Over 40 years ago, when 5-ASAs were first prescribed for ulcerative colitis (UC) in the form of sulfasalazine, standard practice was to administer them in 3–4-times-daily regimens. After the development of sulfasalazine, it was determined that this drug acted as a prodrug and bacterial reductases released the 5-ASA to work topically in the colon. Sulfapyridine, which is linked to 5-ASA with an azo bond, was later determined to be the moiety responsible for most of the side effects and little or any of the therapeutic benefit. Thus, sulfasalazine had to be given in this manner because patients could not tolerate the side effects of nausea, headache, and dyspepsia that a single 2–4 g dose caused. It eventually became standard practice to give all 5-ASA formulations 3 or 4 times a day in order to optimize efficacy. Evidence is slowly developing to demonstrate that the only reason for this separation may have been the mitigation of the side effects profile of the sulfa prodrug.

The QDIEM study examines more directly the question of efficacy of once-daily versus twice-daily regimens in the maintenance setting of UC, utilizing a delayed-release formulation of 5-ASA at a range of daily doses. Delayed-release mesalamine was originally approved for three-times-daily administration, but it is most commonly administered twice a day by most practicing physicians to improve overall compliance, hence the comparison to twice a day and not three times per day. The authors found that time to relapse was virtually identical in patients taking a single daily dose or a split dose. Overall remission rates at 6 months were 90.5% in patients dosed once daily and 91.8% in those dosed twice daily. Thus, this study of over 1,000 patients clearly demonstrates, for the first time with this particular mesalamine preparation, that once-daily maintenance therapy is effective and split dosing provides no added advantage during maintenance therapy. This finding can be added to growing evidence suggesting that all 5-ASA formulations can be effectively dosed once daily for maintenance, providing an important advantage in our effort to improve patient adherence to 5-ASA maintenance regimens.

The ASCEND I and II studies considered another aspect of therapy, the amount of active 5-ASA adminis-

tered daily, in order to further optimize outcomes in the induction phase. These were exploratory studies, designed to define the difference in overall response among patients with mild-to-moderately active disease, who received 2.4 g/day versus 4.8 g/day of delayed-release mesalamine, utilizing a novel, 800 mg tablet formulation.

In the early interim analysis of ASCEND I, it appeared that only patients with moderate disease were more likely to benefit from the higher dose. This finding influenced the design of ASCEND II, which, instead of mixing mild and moderate patients, looked at patients with moderate disease only, to confirm the added benefit of the higher dose in these patients. Our post-hoc analysis of pooled results from moderate patients in ASCEND I and II looked at the time to resolution of rectal bleeding and improvement in stool frequency. In this analysis, the 4.8 g/day group saw improvement of both factors after 19 days, whereas the 2.4 g/day group required 29 days to resolve rectal bleeding and improve stool frequency. This was a statistically significant difference. Looking at each symptom alone, both resolution of rectal bleeding and improvement in stool frequency were achieved more quickly with the 4.8 g/day dose. This illustrates that there is a group of patients with moderately active disease who will achieve remission more quickly with the 4.8 g/day dose of delayed-release mesalamine. The subset of patients that were more likely to respond to the higher dose were those with previous mesalamine exposure, those who had previously taken rectally-administered therapy, and those that had previously been treated with steroids.

It is my personal opinion that the results from the combined trials (ASCEND I and II) are being misinterpreted by some gastroenterologists. The post-hoc analysis draws an important distinction from the results of the ASCEND I and II trials as a whole, where no statistically significant difference was found between 2.4 and 4.8 g, in a mixed cohort of patients with mild and moderately active disease. Here, it is clear that specific groups of patients are going to do better on the higher dose. It also suggests that if any patient is not responding to 2.4 g, they should be tried on 4.8 g daily, because patients that are refractory to the lower dose are the ones who were seen

to respond to 4.8 g in this post-hoc analysis. In addition, separate studies have demonstrated that patients with left-sided UC respond better to combined oral and topical mesalamine. Thus, in order to define a patient as a 5-ASA failure, they need to be tried on the maximum dose of drug.

Unfortunately, as Drs. Katz and Pasquale illustrate, this is not currently the standard practice. In these authors' observational study, looking at medical claims databases from 2000 to 2007, they simply asked what dose of mesalamine the patients were on before they were started on immunomodulator therapy. The authors found that among 39% of patients, the dose of 5-ASA was at 2.4 g/day when they were switched, suggesting that 5-ASA had not been maximally optimized. This, despite the fact that current guidelines suggest an increase to 4.8 g/day, as well as adequate time to respond, before starting immunomodulator therapy.

Stepping up from 5-ASA to immunomodulator therapy incurs increased risks and requires increased physician monitoring. The adverse effects of immunomodulators include possible nausea, vomiting, abnormal liver tests, arthralgias and 5% of patients may develop pancreatitis. In the long term, 1 in 2000 patients may develop lymphoma. Patients receiving immunomodulators require weekly monitoring initially even if patients are determined to have a normal thiopurine methyltransferase (TPMT) metabolizer status and gradually decreased to every 3 to 4 months if stable. All of these factors make the decision to switch a significant one for patients.

Further, a trial of maximal 5-ASA dosing can be attempted without the need for further, expensive laboratory studies. In the use of immunomodulators, patients require gradual dose titration and/or TPMT and 6-thioguanine (6TG) testing to optimize therapy. These tests are often not reimbursed by insurers but without them, the time to response to azathioprine and 6-mercaptopurine can be significantly delayed beyond the typical 8–12 weeks.

Drs. Katz and Hershberger illustrate the importance of inducing a complete remission in their survey on QOL as it is affected by active UC. They found that approximately half of patients that were interviewed had experienced 3–10 UC flares over the previous 2 years. They found abdominal discomfort, urgency, and increased bowel frequency reported among 60% of patients, suggesting a lack of adequate control and remission. The need for better, faster disease control could be seen in that over half of the respondents reported moderate to severe impact on their personal life and ability to work. We, as physicians, must do a better job of asking our patients about their QOL and optimizing their therapy, which requires a trial of maximum 5-ASA dosing in patients

who do not have adequate control and aggressive efforts to achieve real remission before the need to step up to immunomodulator or anti-TNF therapy.

Rubin and colleagues conducted intraluminal pH studies within the small intestine and colon, using the SmartPill, in a few patients to address the ongoing question of how best to deliver orally administered 5-ASA and achieve maximum topical exposure to the mucosa. The efficacy of pH-dependent formulations of 5-ASA can be affected by small intestinal and colonic pH, which can in turn be affected by a variety of factors including disease activity, diet, and other medications. These authors found that when their patients experienced a disease flare requiring steroids, the colonic pH rose substantially between active inflammation and subsequent remission. This might suggest the possibility that the medicines may need a different release pH for treatment of active disease and during maintenance. Adjusting the pH of the eudragit 5-ASA coating to tailor it to active-disease or maintenance patients may be one way to improve overall response.

We know that the colonic environment of UC patients varies from healthy controls for a variety of reasons. Transit may be faster in some patients with active disease and now we see that pH may be different as well. However, the other factors mentioned above, including diet and other medications, may require further individualization of pH formulations to truly optimize response.

Dr. Safdi looked at patients who had been on pH-dependent 5-ASA formulations and who had failed 8 weeks of therapy. The patients were switched to balsalazide, another prodrug with an azo bond that links an inactive metabolite to mesalamine. The bond is broken in the colon when it is exposed to bacterial reductases, allowing free mesalamine to work topically. What Dr. Safdi found in switching patients after 8 weeks was that by the end of the study, 47% of the patients had experienced symptomatic remission with balsalazide.

Another scenario may have been to separate the group into two arms and continue the pH-dependent mesalamine in some of them, while switching the others to balsalazide. This would account for the potential group who may require more than the standard 4–6 weeks to respond to therapy. In addition, in a cohort of patients initially failing balsalazide, a similar result might be seen if they were switched to delayed-release 5-ASA.

Dr. Sunanda Kane has conducted a variety of important studies looking at 5-ASA compliance/adherence/persistence. In this study, she and her colleagues looked at a database of over 44,000 UC patients and analyzed their prescription refill records. They looked at compliance/adherence/persistence in patients that were getting once-daily MMX mesalamine, multiple doses per day of delayed-release mesalamine, or other types of mesalamine, as well

as balsalazide. When they looked across all groups, they found that persistence decreased over time and patients receiving MMX mesalamine had the highest persistence at 3 months and 18 months. This is important, particularly in light of the QDIEM results, which illustrate the ability to effectively administer a once-daily dose of delayed-release mesalamine in the maintenance period. However, even when once daily MMX mesalamine was utilized, 40% of patients were not taking their drug after 3 months. At 18 months, more than 80% were not taking it. The slight improvement seen with the once-daily formulation is really a negligible issue when so many patients were shown to be nonadherent across all of the formulations.

The greatest lesson to be seen from this analysis is that once patients achieve initial remission, their adherence to therapy falls dramatically. We might consider factors of once-daily administration, overall efficacy, side effects, and cost, but we need to find other factors and other methods to improve persistence across the board.

In this regard, education is crucial. Patients need to understand that they have a chronic disease without a cure and that the disease will come back without continuous maintenance therapy. Many physicians use Dr. Kane's graph illustrating her finding that if patients do not take 80% of their medicine, they are likely to experience flare. The Crohn's and Colitis Foundation of America is a tremendously helpful organization that also provides materials to underscore the importance of adherence to therapy.

Finally, we need to see our patients more frequently. Instead of scheduling visits once a year when patients are in remission, it may be important that we see them on a more frequent basis to underscore the importance of taking their medication.

Another possible tool for future use will be the electronic pharmacy report, which will tell us if patients are not taking their medication. This could trigger a call from the physician to remind patients to take their medicine. An automatically generated e-mail message could also provide reminders. Whatever solution we envision for the future, it remains clear that the adherence to therapy is the ultimate hurdle to truly optimizing 5-ASA therapy in UC patients.

Suggested Reading

Sandborn WJ, Regula J, Feagan BG, et al. Delayed-release oral mesalamine 4.8 g/day (800-mg tablet) is effective for patients with moderately active ulcerative colitis. *Gastroenterology*. 2009;137:1934-1943.

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New Research in Ulcerative Colitis: Optimizing 5-ASA Administration for Efficacy and Adherence

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

1. Approximately how many hospitalizations each year are attributed to UC in the United States?
 - a. 20,000
 - b. 10,000
 - c. 30,000
 - d. 40,000
2. In the United States, the incidence of ulcerative colitis is ____ per 100,000 people per year.
 - a. 2–7
 - b. 8–12
 - c. 1
 - d. 13–18
3. True or False? In the QDIEM study, once-daily dosing of delayed-release mesalamine (400 mg tablet) was as effective as twice-daily dosing for the maintenance of UC remission.
 - a. True
 - b. False
4. In the analysis of ASCEND I and II by Sandborn and colleagues, which of the following was considered a hallmark symptom of UC?
 - a. Abdominal cramping
 - b. Rectal bleeding
 - c. Bowel urgency
 - d. Vomiting
5. In the ASCEND I and II analysis, patients previously treated with 2 or more UC therapies experienced a median time to resolution of ____ days while on the higher (4.8 g/d) dose, versus ____ days for those on the lower (2.4 g/d) dose.
 - a. 15, 22
 - b. 20, 32
 - c. 25, 49
 - d. 30, 50
6. Among 2,599 patients included in Katz and Pasquale's analysis of claims data, what was the median daily dose of delayed-release mesalamine prior to the initiation of immunosuppressive therapy?
 - a. 4.5 g/day
 - b. 2.7 g/day
 - c. 3.6 g/day
 - d. 3.3 g/day
7. In Katz and Hershberger's survey of 722 UC patients, what was the most frequent symptom reported by patients who experienced a UC flare?
 - a. Abdominal pain/cramping
 - b. Rectal bleeding
 - c. Change in bowel movement patterns
 - d. Urgent need to go to the bathroom
8. True or False? In Rubin's study of colonic pH in two patients whose pH was measured during active and remittent UC stages, the colonic pH dropped substantially between active inflammation and subsequent remission.
 - a. True
 - b. False
9. In a second study measuring pH in 8 patients in remission for UC, the mean pH for the proximal and distal colons was 6.36 and ____, respectively.
 - a. 7.42
 - b. 6.20
 - c. 7.21
 - d. 6.56
10. In Safdi's trial of patients who had failed mesalamine therapy, what percentage achieved remission after 8 weeks of balsalazide therapy?
 - a. 47%
 - b. 31%
 - c. 56%
 - d. 35%

Evaluation Form New Research in Ulcerative Colitis: Optimizing 5-ASA Administration for Efficacy and Adherence

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. 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 rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives

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

- | | |
|---|-------------------|
| 1. Assess appropriate use of 5-ASAs in the treatment of patients with UC. | 1 2 3 4 5 |
| 2. Evaluate clinical efficacy of 5-ASAs. | 1 2 3 4 5 |
| 3. Discuss differences in mucosal healing between 5-ASAs. | 1 2 3 4 5 |
| 4. Review the latest dosing strategy data. | 1 2 3 4 5 |

Based upon your participation in this activity, choose the statement(s) that apply:

- I gained new strategies/skills/information that I can apply to my area of practice.
- I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____

What barriers do you see to making a change in your practice? _____

Which of the following best describes the impact of this activity on your performance?

- I will implement the information in my area of practice.
- I need more information before I can change my practice behavior.
- This activity will not change my practice, as my current practice is consistent with the information presented.
- This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

The content presented:

- | | |
|---|-------------------|
| Enhanced my current knowledge base | 1 2 3 4 5 |
| Addressed my most pressing questions | 1 2 3 4 5 |
| Promoted improvements or quality in health care | 1 2 3 4 5 |
| Was scientifically rigorous and evidence-based | 1 2 3 4 5 |
| Avoided commercial bias or influence | 1 2 3 4 5 |

Would you be willing to participate in a post-activity follow-up survey? Yes No

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

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

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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For Physicians Only: I certify my actual time spent to complete this educational activity to be: _____

- I participated in the entire activity and claim 1.0 credits.
- I participated in only part of the activity and claim _____ credits.