

5-ASA Therapy for Successful Ulcerative Colitis Treatment: Optimizing Dosing and Adherence, Determining Meaningful Endpoints

A Review of Selected Presentations
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Target Audience: Gastroenterologists in clinical practice with an interest in caring for patients with ulcerative colitis.

Statement of Need/Program Overview: The abstract meeting monograph will discuss the most recent data emerging within the therapeutic area of 5-ASAs for the treatment of patients with UC. As an abundance of new data has recently come to light in this area, there is a distinct educational need in the community for an updated understanding of the treatment of patients with UC. Throughout the year, various abstracts/posters are presented at major medical meetings that address updates on treatment strategies, comparisons between different therapies, clinical trial data, retrospective data on real-world clinical experience, etc. Unfortunately, physicians at the major meetings cannot attend all of the poster sessions in their therapeutic area. A compendium of abstracts is vital to help disseminate important information on new treatment/management options.

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

1. Describe the class benefits of 5-ASA drugs in the treatment of mild-to-moderate ulcerative colitis.
2. Indicate the efficacy of the 5-ASA delayed-release formulations in the treatment of varying disease manifestations.
3. Review latest data on 5-ASA delayed release formulations for application and optimization in the clinical setting.

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Introduction

Inflammatory bowel disease (IBD) affects between 1 and 2 million persons in the United States, approximately half of whom are diagnosed as having ulcerative colitis (UC).^{1,2} Because there is no cure for UC, treatment is aimed at rapidly treating symptoms and maintaining remission such that the patient's quality of life is significantly improved.³ In addition, an increased risk of colorectal cancer has been linked to both the duration and severity of UC,⁴ thus further highlighting the importance of successful and rapidly acting UC therapy.

The primary approach to treatment of mild-to-moderate UC is oral or rectal 5-aminosalicylate (5-ASA, mesalamine).³ Mesalamine is the 5-amino derivative of salicylic acid and acts as a topical anti-inflammatory agent. Although the exact mechanism of mesalamine is unknown, it is believed that mesalamine blocks the increased production of arachidonic acid metabolites found in patients with IBD by inhibiting cyclooxygenase and lipoxygenase pathways in the bowel mucosa. This subsequently leads to diminished production of prostaglandin and leukotriene synthesis, thereby reducing colonic inflammation. Rectal mesalamine was approved by the US Food and Drug Administration in December 1987 for treatment of active disease, but subsequently a number of oral 5-ASA formulations have become available. These include the prodrugs sulfasalazine, olsalazine (Dipentum), and balsalazide (Colazal); controlled-release mesalamine (Pentasa); and delayed-release mesalamine (Asacol, Lialda). Overall, these oral 5-ASA formulations are safe and effective therapies for UC.

Sulfasalazine is an effective prodrug treatment for mild to moderate UC; however, its use is restricted because of its unfavorable side effects profile. It is composed of sulfapyridine (an antibacterial agent) linked to

5-ASA/mesalamine (an anti-inflammatory agent) through an azo bond. Once sulfasalazine reaches the colon, it is broken down by bacterial azo reductases that cleave the azo bond linking the sulfapyridine and 5-ASA. Sulfasalazine is most effective at high doses (3–6 g/day; 500 mg tablets), but at least 30% of patients report serious side effects at this dosage.⁵

5-ASA formulations without sulfa were developed to limit side effects while delivering effective amounts of 5-ASA to the bowel. Olsalazine is converted to mesalamine in the colon when the azo bond linking its two 5-ASA radicals is broken by bacterial azo reductases.⁶ Olsalazine is indicated for the maintenance of remission (1 g/day in 2 divided doses) in those patients intolerant to sulfasalazine. Balsalazide is given at a dose of 6.75 g/day (equivalent to 2.4 g/day of mesalamine) in 3 divided doses.⁷ Similar to sulfasalazine, balsalazide is comprised of mesalamine azo-bonded to a carrier molecule (4-aminobenzoyl- β -alanine); however, in this drug, the carrier molecule is inert.

Mesalamine is also available in controlled-release and delayed-release formulations. The controlled-release formulation has an ethylcellulose coating that allows water to be absorbed into small beads containing mesalamine.⁸ Water dissolves the 5-ASA, which then diffuses out of the bead, resulting in mesalamine exposure from the stomach through the distal colon. For the treatment of acute disease and induction of remission, controlled-release mesalamine is given in 1 g doses, 4 times per day.⁸ Asacol is a delayed-release mesalamine that is used to both induce and maintain remission of mild-to-moderate UC.⁹ Asacol is coated with an acrylic-based resin that dissolves at a pH of 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory

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action. The indicated dose for mildly to moderately active UC is 2.4 g/day (3 divided doses), with maintenance therapy reduced to 1.6 g/day (divided doses). Lialda is a delayed-release oral tablet with a polymer-coated core that also breaks at a pH of 7 or greater within the terminal ileum.¹⁰ The tablet core contains mesalamine along with hydrophilic and lipophilic excipients that aid in the delayed release and dispersal of 5-ASA. Lialda is approved for once-daily dosing for the induction of remission of mild to moderate UC (2.4 or 4.8 g/day). Unlike Asacol, however, Lialda is not currently approved for maintenance of remission.

The oral formulations of mesalamine share similar pharmacokinetic profiles. A systemic review of oral mesalamine therapies found that the pharmacokinetic parameters of maximum plasma concentration (C_{max}), time to C_{max} , and area under the plasma concentration versus time curve (AUC) are similar across all formulations.¹¹ All have comparable mesalamine absorption rates (20–30%).^{7–10} The fecal excretion/loss of 5-ASA and N-Ac-5ASA are also similar across drugs.¹¹ Because many of the pharmacokinetic parameters of the oral 5-ASA preparations are similar, other factors should be taken into account when choosing the appropriate therapy.^{11,12}

Rapid symptom relief, improvements in quality of life, and dosing regimen are key factors in determining the optimal therapeutic approach for treating active UC. There are a number of studies demonstrating the efficacy of oral 5-ASA formulations, but the majority involve multiple daily doses of medication. Controlled-release mesalamine has been shown to be safe and effective in studies of active mild to moderate UC at a dose of 4 g/day (1 g 4 times daily), resulting in improvements in physician global assessment (PGA), endoscopic and histologic scores, clinical symptoms, sigmoidoscopic index, and remission.^{8,13} Balsalazide was also proven safe and effective for the treatment of mild to moderate UC.¹⁴ After 8 weeks of treatment, 6.75 g/day (divided dosing) of balsalazide improved rectal bleeding, stool frequency, sigmoidoscopic score, and PGA. In controlled trials of Asacol, rectal bleeding, stool frequency, and sigmoidoscopic improvement were demonstrated at 3 and 6 weeks with a dose of 2.4 g/day (divided dosing).^{15,16} Asacol has also been proven safe and effective for the treatment of moderate UC at the higher dose of 4.8 g/day (divided dosing) in patients with mildly to moderately active UC.^{16,17} In patients with moderate disease, treatment success at 6 weeks was observed in 72% of patients treated with 4.8 g/day, compared to 59% of those that received 2.4 g/day. Asacol has also been shown to induce a marked improvement in quality of life as early as 3 weeks.^{18,19}

Poor adherence is multifactorial; however, in an effort to simplify dosing and perhaps improve patient compliance, therapies for UC are moving toward once-

daily dosing. In controlled trials, once-daily dosing of Lialda was found to be safe and effective for the induction of remission in patients with mild to moderately active UC.^{20,21} In a study comparing once- and twice-daily dosing of Lialda, 29.3% and 34.1% of patients, respectively, achieved clinical and endoscopic remission after 8 weeks of treatment.²⁰

In addition to Lialda, other formulations of mesalamine are now being investigated for use in once-daily dosing for the treatment of active UC. In a recent double-blind controlled phase III trial, the administration of 3 g mesalamine (Salofalk) once daily was compared to 1 g three times per day for patients with active UC.²² At the end of 8 weeks, both treatment groups achieved similar rates of clinical remission (83% and 78%, respectively), indicating that once-daily dosing of mesalamine may be as effective as multiple dosing regimens in inducing remission. More research is needed to determine if other formulations of mesalamine would also be safe and effective with once-daily dosing for active UC.

Therapeutic strategies for the maintenance of remission are focused on sustaining symptom relief and promoting mucosal healing. Asacol (1.6 g/day, divided dosing) has been shown to be effective in maintaining endoscopic remission in 70% of patients.²³ Patient preference for once-daily dosing and long-term adherence to therapy remain issues, particularly in maintenance therapy. Long-term maintenance therapy is essential to prevent flares of disease activity and avoid inflammatory damage to the colon, which significantly increases the risk of colorectal cancer; several studies have shown an increased risk for cancer in those patients with poor compliance to therapy.^{24,25} Currently, Lialda is the only oral mesalamine formulation approved for once-daily dosing, but only for induction of remission. Adequate long-term maintenance data on Lialda are not yet available.

There is growing evidence to suggest that all formulations of mesalamine can be effectively used in once-daily dosing for maintenance of remission. In a phase III trial, investigators found that 2 g of controlled-release mesalamine given once daily or in divided doses were both effective for the maintenance of remission.²⁶ In addition, a pilot study comparing once-daily to multiple-daily dosing of Asacol during the maintenance phase found that by 6 months there were no differences in the number of patients experiencing relapse or in the number of patients that were adherent to the regimens. These studies indicate that once-daily dosing may have similar outcomes to conventional dosing, but more studies are needed.

Mesalamine formulations are safe and effective treatments for UC and there is an increasing emphasis on developing therapeutic approaches to UC that expedite

symptom improvement/resolution, improve long-term remission rates, simplify dosing regimens, and increase patient compliance, with the ultimate goal of improving patient quality of life.

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944 Comparable Pharmacokinetics of Two Delayed Release Formulations of Oral Mesalamine

WJ Sandborn, G Balan, B Kuzmak, SB Hanauer

The first-line therapy for treating mild to moderate UC is 5-ASA. Commercially available delayed-release formulations include Asacol, which was approved in January 1992, and Lialda, which was approved in January 2007. Both Asacol and Lialda are delayed-release tablets with coatings that release mesalamine in the terminal ileum where the pH is greater than 7.^{1,2} Asacol and Lialda both contain mesalamine in the tablet core; however, Lialda also contains hydrophilic and lipophilic excipients.² Asacol and Lialda also differ in their dosing; Asacol is given three times daily (TID) while Lialda is given once per day (QD) for mildly to moderately active UC.^{1,2}

Due to the differences in the tablet core and treatment regimens, the authors of this report sought to evaluate the pharmacokinetics of Lialda QD, Asacol QD, and Asacol TID.³ In this randomized open-label study, 37 healthy volunteers received 2.4 g/day of oral mesalamine for 7 days as follows: two 1.2 g tablets every 24 hours (Lialda QD), six 400 mg tablets every 24 hours (Asacol QD), or two 400 mg tablets every 8 hours (Asacol TID). Plasma samples were taken once daily for 7 days and for 48 hours after the first dose on day 7. Urine samples were collected every 8 hours for 24 hours after the first dose on day 7. The plasma and urine samples were measured using a validated LC-MS/MS assay, and pharmacokinetic parameters were calculated using noncompartmental methods.

Sandborn and colleagues found that AUC_{24} , C_{max} , fluctuation index, and half life were similar across all treatments when analyzed by least square geometric means (Table 1). An analysis of the ratio of means found that both QD regimens resulted in a greater AUC and C_{max} than the Asacol TID regimen; however, the differences were not statistically significant. The Asacol TID arm showed less fluctuation relative to the Lialda QD arm. Urinary excretion results suggest that the total systemic absorption was similar among all treatment groups (percent of dose excreted: Lialda QD, 21.3%; Asacol QD, 20.2%; Asacol TID, 17.9%). The authors noted that the treatments in this study were well tolerated, with three adverse events reported in the two Asacol arms (back pain, musculoskeletal stiffness, and pain in extremity) and one adverse event reported in the Lialda arm (pruritus). Based upon the information provided in this study, both Asacol and Lialda had comparable pharmacokinetics when dosed at 2.4 g once daily. The authors concluded that there does not appear to be a difference in the pharmacokinetic release profile of Lialda and Asacol when given once daily; however, the clinical significance of these findings are unknown.

943 Rapid Symptom Resolution With Delayed-Release Mesalamine in Mildly and Moderately Active UC

WJ Sandborn, S Katz, D Ramsey, DH Present

According to the American College of Gastroenterology's UC practice guidelines, the current treatment strategy is to reduce symptoms and mucosal inflammation and

Table 1. 5-ASA Day 7 Pharmacokinetic Parameters – Least Square Geometric Means

Parameter	Lialda QD n=12	Asacol QD n=12	Asacol TID n=13
AUC ₂₄ (ng.hr/mL) (95% CI)	13556 (7616, 24128)	14358 (8132, 25350)	10679 (6168, 18491)
C _{max} (ng/mL) (95% CI)	1553 (857, 2812)	1420 (790, 2550)	1145 (651, 2016)
Fluctuation Index (%) (95% CI)	239.7 (163.4, 351.7)	182.1 (124.8, 265.7)	206.4 (143.3, 297.2)
τ _{1/2} (hr) (95% CI)	10.2 (5.8, 17.9)	9.6 (5.6, 16.5)	8.5 (5.0, 14.7)

5-ASA=5-aminosalicylic acid; AUC₂₄=area under the plasma concentration versus time curve from 0 to 24 hours (total exposure); C_{max}=maximum plasma concentration; CI=confidence interval; fluctuation index=(C_{max} - C_{min})/C_{avg} (peak to trough fluctuation); τ_{1/2}=half life.

The 5-ASA pharmacokinetic parameters were similar across all treatment arms.

Table 2. Median Time to Symptom Resolution

Symptoms	Mild and Moderate UC (median)	Mild UC (median)	Moderate UC (median)
Rectal bleeding*	15 days (95% CI: 10, 18) (n=293)	4 days (95% CI: 3, 5) (n=84)	21 days (95% CI: 17, 28) (n=209)
Stool frequency†	21 days (95% CI: 16, 24) (n=319)	10 days (95% CI: 7, 15) (n=100)	26 days (95% CI: 22, 38) (n=219)

*First day of 3 consecutive days of no visible blood in stools. †First day of 3 consecutive days of normal stool frequency. CI=confidence interval; UC=ulcerative colitis.

maintain remission in order to provide an improved quality of life.⁴ Treatments that provide swift relief of clinical symptoms are crucial for effective patient management. To determine the time to clinical remission in patients with mild to moderate UC treated with Asacol, the current study analyzed data from two clinical trials, ASCEND I and II.⁵ The ASCEND trials were randomized, double-blind, active-controlled, 6-week studies evaluating the efficacy and safety of Asacol 4.8 g/day versus 2.4 g/day for the treatment of mildly or moderately active UC.^{6,7} Sandborn and coworkers focused on data from the 2.4 g/day (two 400 mg tablets TID) active control arm of these trials. Data analysis was limited to those patients who had active UC at baseline, as measured by PGA (mild=1, moderate=2), and who reached clinical remission. Clinical remission was defined as the resolution of rectal bleeding and normalization of stool frequency. The time to clinical remission was

defined as the first day of 3 consecutive days of complete symptom resolution.

Of the 687 patients enrolled in the ASCEND trials, 349 received the 2.4 g/day dose of Asacol. Within this group, 32.4% had mild disease and 67.3% had moderate disease. The median time to clinical remission was 14 days for patients with mild disease (n=108), 39 days for patients with moderate disease (n=225), and 26 days for the combined mild and moderate group (n=333). A detailed analysis of symptom resolution found that the median time to resolution of rectal bleeding was 15, 4, and 2 days for the combined group, the mildly active UC group, and the moderately active UC group, respectively, while the median time to resolution of stool frequency for each group was 21, 10, and 26 days, respectively (Table 2). The authors noted that Asacol was well tolerated, with common adverse events consistent with those described in the current prescribing information.

The results of this study indicate that 2.4 g/day of Asacol (two 400 mg tablets TID) provides quick resolution of rectal bleeding and stool frequency, as well as a short time to clinical remission of disease.

938 Time to Initial Symptom Resolution With MMX Mesalamine Therapy for Active, Mild-to-Moderate Ulcerative Colitis

WJ Sandborn, R Karlstadt, K Barrett, RE Joseph

The aim of the current study was to determine the time to initial resolution of rectal bleeding and a reduction in stool frequency in patients with active, mild to moderate UC treated with Lialda.⁸ Sandborn and colleagues performed a post-hoc analysis of pooled data from two phase III, placebo-controlled, double-blind, double-dummy studies of Lialda.^{9,10} Patients received Lialda 2.4 g/day (either once daily or 1.2 g twice daily), Lialda 4.8 g/day (once daily), or placebo for 8 weeks.

The intent-to-treat population contained a total of 517 patients: 172 received 2.4 g/day Lialda, 174 received 4.8 g/day Lialda, and 171 received placebo. The authors assessed the resolution of symptoms (ie, rectal bleeding, high stool frequency, and both combined).^{9,10} Time to initial symptom resolution was defined as the time between the first dose of study medication and the first day of symptom resolution. The median time to initial resolution of symptoms (combined stool frequency and rectal bleeding) was 25 days in the 2.4 g/day group, 26 days in the 4.8 g/day group, and 44 days in the placebo group (Kaplan-Meier log-rank test: $P=.0001$). The median time to initial resolution of rectal bleeding alone was 7 days in the 2.4 g/day group, 8 days in the 4.8 g/day group, and 16 days in the placebo group ($P<.0001$), while the median time to initial normalization of stool frequency alone was 19 days in the 2.4 g/day group, 20 days in the 4.8 g/day group, and 34 days in the placebo group ($P=.0001$).

The authors concluded that, for most patients, either the 2.4 g/day or 4.8 g/day dose of Lialda provides relief from the major symptoms of UC (rectal bleeding and high stool frequency) within weeks of starting the medication. The majority of patients receiving either dose of Lialda experienced resolution of both major symptoms within 4 weeks of the initiation of therapy, compared to more than 6 weeks with placebo treatment.

942 Rapid Clinical Remission Is Significant for the Well-Being of Ulcerative Colitis Patients Treated With Delayed-Release Mesalamine

EJ Irvine, S Magowan, M Pasquale, S Katz

The rapid resolution of UC symptoms has a profound influence on a patient's quality of life and overall satisfaction with therapeutic interventions. A previous study demonstrated that treatment of mildly to moderately active UC with Asacol 2.4 g/day can induce clinical remission in a median of 26 days.⁵ While information regarding symptom resolution is important in determining optimal treatment options, there are relatively few studies examining other quality-of-life benefits.

To address this question, Irvine and coworkers used the Inflammatory Bowel Disease Questionnaire (IBDQ) to quantify the improvement in social, emotional, systemic, and bowel domains associated with clinical remission (rectal bleeding and stool frequency scores both =0) at 3 weeks.¹¹ Data were analyzed from patients in the combined active control arm (Asacol 2.4 g/day) of the ASCEND I and II trials who completed the IBDQ at 3 weeks after initiation of therapy ($n=274$).^{6,7} The IBDQ is comprised of 32 questions grouped into 4 domains: bowel symptoms, systemic symptoms, emotional factors, and social factors. IBDQ scores range from 32 to 224, with higher IBDQ scores indicating better quality of life.^{12,13} Changes in IBDQ scores from baseline to 3 weeks of treatment were compared between responders (patients that achieved clinical remission at 3 weeks) and nonresponders (patients who did not achieve remission at 3 weeks).

Mean baseline scores between responders and nonresponders were comparable except in the bowel domain, where the mean baseline responder score was higher than the mean baseline nonresponder score (44.7 vs 41.3, respectively). Upon treatment with 2.4 g/day of Asacol for 3 weeks, the total change in the IBDQ score was 24% for responders and 18% for nonresponders ($P<.05$; Figure 1). There were significant improvements for the responders compared to the nonresponders in the emotional and bowel domains ($P<.05$); improvements in the social and systemic domains were not significantly different between groups. In addition, IBDQ scores for the responders were sustained through 6 weeks of therapy. These changes in IBDQ scores led the authors to conclude that rapid induction of clinical remission significantly improves the well-being of UC patients.

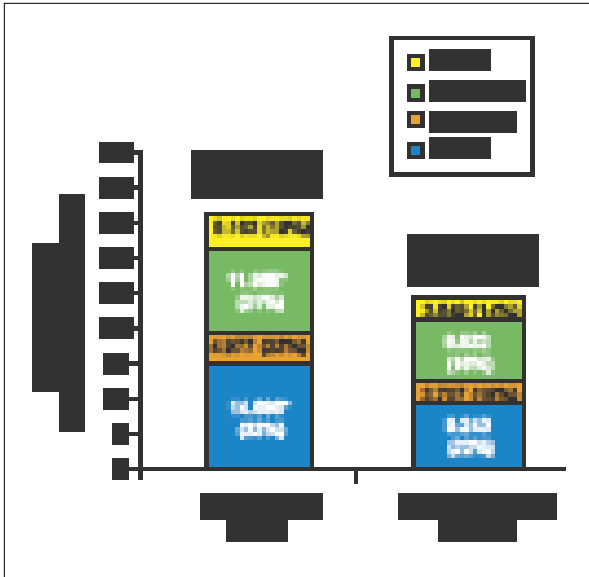


Figure 1. Change in Inflammatory Bowel Disease Questionnaire (IBDQ) score from baseline to three weeks.

* $P < .05$ (responders compared to nonresponders).

989 Influence of Disease Duration and Severity on Inflammatory Bowel Disease Patients' Medication Preference

D Deconda, T Taddei, HL Miller, JH Cho, D Proctor

In the United States, approximately 169,000 hospitalizations and 825 deaths per year are attributable to IBD.¹⁴ Due to the seriousness of these chronic diseases, ongoing drug therapy is necessary to induce and maintain remission as well as to treat flares. In an effort to improve treatment recommendations, Deconda and colleagues aimed to determine if the severity and duration of IBD alters patients' treatment preferences.¹⁵

To address this aim, 50 consecutive IBD patients visiting the Yale IBD clinic from July to November 2006 were asked to fill out a questionnaire regarding demographics, disease and medication history, and treatment preferences (5-ASA, enemas, oral steroids, immunosuppressants, anti-tumor necrosis factor [TNF] agents, and surgery). The patients were divided into groups based upon disease severity (mild: 1–4 bowel movements per day, no urgency, rare blood, and mild pain; or moderate/severe: ≥ 5 bowel movements per day with blood, urgency, and interference with daily activities) or disease duration (< 10 years vs ≥ 10 years). Of the patients completing the survey, 33 had Crohn's disease and 17 had UC, with a

mean disease duration of $8.8 (\pm 9.6)$ years. Approximately 50% of patients with mild disease preferred treatment with 5-ASA, while those patients with moderate/severe disease preferred either 5-ASA (36.4%) or anti-TNF agents (36.4%). Of those patients that had a disease duration of 10 years or less, surgery (38.9%) and oral steroids (38.9%) were the most disfavored treatment options. Overall, patients across all groups preferred treatment with 5-ASA due to efficacy and mild adverse events; however, those patients with more severe disease also favored more aggressive treatments such as anti-TNF therapy.

945 Previous History of Steroid Use Does Not Preclude Treatment With Mesalamine in Ulcerative Colitis

S Katz, BR Yacyshyn, DL Ramsey, GR Lichtenstein

Because of the serious adverse effects associated with steroids, their use is tapered once clinical improvement of moderate UC has occurred. It is unknown whether patients with moderately active UC who were previously treated with steroids can be subsequently treated with a high dose of 5-ASA. The investigators of the current study sought to determine the effect of high-dose delayed-release oral mesalamine (4.8 g/day) in patients previously treated with steroids.¹⁶ They performed an analysis of data from the ASCEND I and II trials, focusing on patients with moderately severe UC that had previously received oral or intravenous (IV) steroid therapy.^{6,7}

A total of 137 patients with moderate UC, a known treatment outcome, and a history of previous therapy with oral or IV steroids were identified. The data from these patients were analyzed to evaluate treatment success, mucosal healing, and improvement in individual clinical assessments 6 weeks after the initiation of mesalamine treatment. Seventy-nine percent of the patients receiving high-dose mesalamine (4.8 g/day) achieved treatment success compared to 52% of the patients receiving 2.4 g/day mesalamine ($P < .01$). Treatment success was defined as improvement in PGA, improvement in at least one clinical assessment (stool frequency, rectal bleeding, patient's functional assessment, or sigmoidoscopy), and no worsening in any of the remaining clinical assessments. Mucosal healing, as defined by an endoscopy subscore of 0 or 1, was achieved in 85% of patients receiving 4.8 g/day compared with 65% of patients receiving 2.4 g/day ($P < .05$). Patients receiving the higher mesalamine dose also showed significantly greater improvements in PGA, rectal bleeding, and sigmoidoscopy

compared to patients receiving the lower dose ($P < .05$; Figure 2). The authors noted that the high dose of mesalamine was well tolerated with adverse events comparable to the lower dose.

This study supports a role for delayed-release mesalamine in the treatment of UC patients with moderately active disease who have been previously treated with steroids. Overall in these patients, the 4.8 g/day dose was more efficacious than the 2.4 g/day dose. The authors concluded that a previous history of steroid use does not preclude treatment with mesalamine, and UC patients previously treated with oral or IV steroids respond better to higher initial doses of mesalamine.

935 MMX™ Mesalamine Is Effective for the Maintenance of Remission of Mild-to-Moderate Ulcerative Colitis Irrespective of Patients' Previous Relapse History

WJ Sandborn, R Karlstadt, K Barrett, RE Joseph

937 Long-Term Remission Rates in Patients With Mild-to-Moderate Ulcerative Colitis Who Require an MMX™ Mesalamine Dose Increase to Induce Initial Remission

SB Hanauer, MA Kamm, R Diebold, K Barrett, RE Joseph

Two randomized, controlled, 8-week, phase III trials, studies 301 and 302, demonstrated the efficacy of Lialda

for the induction of clinical and endoscopic remission of UC in patients with active, mild to moderate disease.^{9,10} Study 303 offered an 8-week, high-dose (2.4 g two times daily [BID]) extension period for those patients that did not achieve remission in studies 301 and 302, followed by a 12-month maintenance phase (Lialda 2.4 g QD or 1.2 g BID) for patients who achieved remission in any of the 3 studies.

In the first report, Sandborn and colleagues performed an analysis of data from study 303 to determine the effect of patients' prior relapse history on the efficacy of maintenance therapy with Lialda.¹⁷ Of the 459 patients that entered the 12-month maintenance phase of study 303, 438 patients had complete relapse records prior to enrollment in the studies. Of these 438 patients, 205 entered the maintenance phase from the 8-week extension and 233 entered directly from studies 301 and 302.

Analysis of the data found that 66.2% of the patients ($n=290$) were in remission at the end of the 12-month maintenance phase. Patients with a history of 3 or more relapses in the 2 years prior to entering the parent studies had a lower remission rate than patients with a history of less than 3 relapses (59.8% vs 70.1%, respectively). The authors concluded that relapse history may help identify patients in whom long-term remission rates may be reduced; they added that further studies are needed to determine if a higher maintenance dose of mesalamine is necessary in patients who are prone to relapse.

In the second report, Hanauer and colleagues examined long-term remission rates in patients who required Lialda dose escalation—from 2.4 g/day in studies 301 and 302 to 4.8 g/day in the 8-week extension study—to induce remission.¹⁸ Of the patients that received 2.4 g/day of Lialda as induction therapy in studies 301

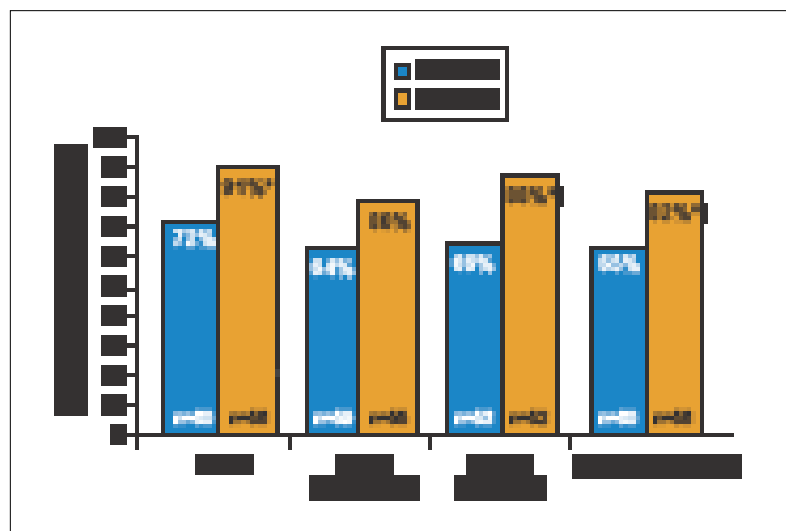


Figure 2. Improvement at week 6 in moderate ulcerative colitis patients previously treated with steroids.

* $P < .05$ stratified by protocol using Cochran-Mantel Haenszel test.

PGA=physician global assessment.

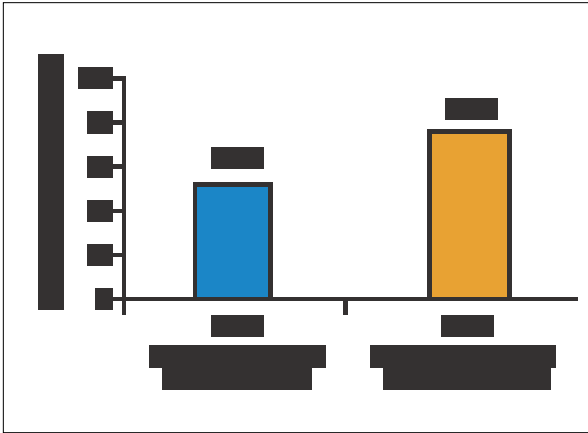


Figure 3. Remission rates after 12 months for patients who received MMX mesalamine 2.4 g/day as induction therapy.

and 302, a total of 132 entered the 12-month maintenance phase. This group was comprised of 79 patients who entered directly from studies 301 and 302 and 53 patients who entered after the 8-week high-dose extension phase. The authors found that patients who directly entered the maintenance phase had higher remission rates at 12 months than patients who entered via the 8-week extension phase (Figure 3). These data suggest that maintenance therapy with 2.4 g/day of Lialda is more effective in those patients that did not require a high-dose extension period to induce remission. The authors add that those patients that fail to enter remission without high-dose therapy may represent a subgroup of patients that will require a higher maintenance dose of mesalamine; however, further study is required.

941 Predictors of 5-ASA Prescription Persistence During the Chronic Phase in Patients With Ulcerative Colitis

S Kane, S Magowan, N Accortt, D Brixner

Previous studies have shown that there is a 40% decline in 5-ASA prescription refill rates 3 months into treatment of UC.¹⁹ Adherence to medication is complicated and multifactorial and the identification of risk factors associated with poor compliance may facilitate long-term patient management. In the present study, Kane and colleagues sought to identify predictive factors for 5-ASA nonpersistence (defined as no 5-ASA refill at 12 months) in patients with UC.²⁰ The authors conducted a retrospec-

Table 3. Significant Factors for Not Refilling 5-aminosalicylic acid (5-ASA) at 12 Months

Parameters	Odds ratio	P-value
Increased risk of not refilling		
Gastrointestinal hospitalization (6.3%)	1.59	.02
Mail order of 3-month script (16.5%)	1.50	.001
Comorbid conditions (per illness)	1.04	<.0001
Age (per 1 year increase)	1.01	.02
Decreased risk of not refilling		
Use of rectal 5-ASA (16.7%)	0.63	.0004
Switched to a different 5-ASA (7.7%)	0.53	.0008

Parentheses denote the percentage of total study population with specific characteristics.

tive cohort study using health service utilization records from a large research database. Study subjects were individuals older than 18 years of age diagnosed with UC and prescribed 5-ASA who had refilled their prescription at 3 months. Parameters of interest were captured from the 3-month time point until the 12-month time point and compared between those patients who did and did not refill their prescriptions at 12 months (+30 days). Logistic regression modeling was used to identify independent predictors of nonrefill behavior.

A total of 2,044 UC patients prescribed 5-ASA were included in the analysis; of these patients, 920 (45%) did not refill their 5-ASA prescriptions at 12 months. The investigators found that gastrointestinal (GI) hospitalization, mail order prescription fulfillment, comorbid illness, and older age were associated with nonpersistence (Table 3). Gender, psychiatric history, steroid or immunomodulator use, number of GI office visits, and non-UC concomitant medications were not found to be significant risk factors for nonpersistence. In addition, use of rectal 5-ASA formulations and switching from a different formulation were both associated with better persistence.

The authors noted that there are many contributing factors to persistence of 5-ASA maintenance therapy, adding that those factors differ somewhat from those of the acute phase.²¹ They suggest that knowledge of the factors related to persistence of maintenance therapy can help optimize patient management.

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Commentary

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Two main paradigms have emerged in defining success of UC therapy. The first and more conventional is one of clinical remission, defined as symptom relief (cessation of rectal bleeding and diarrhea) and improved quality of life.¹⁻⁴ The second designates mucosal healing as the necessary key to clinical improvement as well as lowered rates of complication, cessation of disease progression, and possible protection from the development of dysplasia and/or carcinoma.⁵⁻⁷

Experienced clinicians measure therapeutic successes by clinical improvement/remission and, to some degree, mucosal healing but these endpoints are often vaguely defined and certainly differ among clinical trials.^{8,9} Multiple activity indices have evolved since the first randomized clinical trial for UC.¹⁰ These disease activity scores

usually include symptomatic, laboratory, and endoscopic criteria.^{8,11} Few physicians use activity indices (eg, Mayo score, UCDAI) in their daily practice outside of clinical trials and no one score has been accepted as the validated standard instrument.⁸ It has been demonstrated that endoscopic findings contribute less than 4% to the overall evaluation of patients in clinical practice.¹¹ Nonendoscopic indices (eg, Seo Index, Simple Clinical Colitis Activity Index [SCCAI]) permit greater patient participation, due to less time lost from the workplace as well as allowing for less discomfort and risk.^{12,13} The dilemma for the clinician resides not only in choosing among these nonendoscopic indices but in their lack of biopsy screening for dysplasia. It remains unclear whether better patient screening compliance with nonendoscopic activity indices is worth the missed opportunity to survey for neoplasia.

Despite these limitations in assessing outcome, 5-ASA agents have consistently shown themselves to be the workhorse among pharmaceutical options in inducing and maintaining remission in UC patients with mild to moderately active disease. Even in patients unfortunate

enough to develop CRC that goes undetected for as long as 2 years, the use of 5-ASA therapy lowers the rate of cancer mortality, particularly in adherent patients on regularly scheduled maintenance dosing but also those taking intermittent or episodic 5-ASA, when compared to infrequent use of these agents (HR=0.1, 95% CI, 0.01–0.04; HR=0.3, 95% CI, 0.1–0.8, for regular and intermittent use, respectively).¹⁴

Considering that the population of UC patients in a community gastroenterology practice is comprised of 71% with moderate and 20% with mild activity, symptom relief can be effectively achieved in the majority of these populations with 5-ASAs.¹⁵ Studies of delayed-release mesalamine (Asacol, 2.4 g/day) demonstrate improvement in rectal bleeding and stool frequency in 64% and 55% of patients respectively at three weeks and 77% and 70% of patients at six weeks.¹⁶ Success as measured by these parameters can be expected in 76% and 70% of patients with pancolitis, respectively, within 6 weeks of therapy and 76% and 74% of patients with left-sided disease. Even in the very difficult-to-treat cohort of patients with isolated proctitis, response to oral therapy was 83% in terms of improvement in rectal bleeding and 57% in improvement of stool frequency.^{17,18} This impressive evidence demonstrates that oral therapy alone can be effective without recourse to topical rectal administration.

Rapid symptom resolution has also been achieved with delayed-release 5-ASA therapy. The median time to clinical remission, defined as the first of 3 consecutive days of complete resolution of stool frequency and rectal bleeding, was 26 days in mildly and moderately active UC patients combined. The median time to clinical remission occurred sooner in the mild group (14 days) than in the moderate group (39 days).¹⁹ This would be anticipated based on disease severity. Another formulation of delayed-release mesalamine, Lialda, produced similar results for initial resolution of symptoms (25 days at 2.4 g/day) using a less stringent criterion of the first day of symptom resolution (rather than the first of 3 consecutive days of complete symptom resolution) in a combined mild/moderate UC population.²⁰

Quality-of-life issues have recently received the attention and credence similar to more conventional measures of efficacy (ie, clinical improvement/remission, endoscopic and mucosal healing). Current ACG guidelines include QOL assessments and suggest a more comprehensive evaluation of the impact of therapy by including patients' physical, emotional, and social functions during periods of ill health.^{3,21} Of the validated instruments for assessment, the Inflammatory Bowel Disease Questionnaire (IBDQ) is specifically attuned to disease-related dysfunction in IBD patients.²² Thirty two questions subgrouped into bowel symptoms, sys-

temic symptoms, and emotional and social function are scored such that higher scores predict better QOL and an increase of 16–20 points over time indicates clinically significant improvement. Scores ranging from 170 to 190 indicate disease remission.^{2,9} A shorter version has been validated and is useful for outpatient evaluation, requiring approximately 20 minutes to complete.²³

Recent experience from the ASCEND I and II trials measured IBDQ at 3 weeks after introduction of therapy (Asacol, 2.4 g/day). At 3 weeks, total IBDQ score improved by 24% for responders (patients achieving clinical remission at 3 weeks while receiving delayed-release mesalamine) compared to 18% in nonresponders ($P = .0024$). Also at 3 weeks, improvement for responders was significantly greater than that for non-responders within the emotional and bowel domains of the scoring system. Greater improvement was also noted in the social and systemic domains for responders versus non-responders, although not statistically significant. Domain scores for responders continued to improve after the first 3 weeks of therapy and were sustained through 6 weeks of therapy.²⁴

Longterm compliance with the prescribed dose of mesalamine remains a major obstacle, considering the 40% decline in mesalamine prescription refill rates after 3 months of UC therapy. Nonpersistent refill behavior in the maintenance phase of therapy has most often been noted in patients with prior hospitalizations for GI disease, use of a mail-order pharmacy, and in older patients with multiple comorbid conditions.²⁵ This demographic is decidedly different from the noncompliant patients seen in the induction of remission phase of active disease treatment, where noncompliant patients tend to be single, unmarried, and male.²⁶ New evidence shows that once-daily dosing with either Asacol (six 400 mg tablets) or Lialda (two 1.2 g tablets) has comparable pharmacokinetic behavior in terms of total systemic absorption (AUC, C_{max}), half-life, and fluctuation indices.²⁷ Given this similar pharmacokinetic data, delayed-release mesalamine and other 5-ASA formulations may conceivably be dosed once daily. These observations may contribute to a greater level of compliance without fear of excessive systemic absorption.

What have we learned about 5-ASA in 2007 that is clinically relevant?

- 5-ASA remains an effective therapy for induction and maintenance of remission of mild-to-moderate UC.²⁸
- The similarity of pharmacokinetic profiles among various oral 5-ASA formulations suggest that all of these formulations can be effectively dosed once daily.²⁵ Further controlled clinical studies are needed.

- Rapid symptom relief has been demonstrated with several 5-ASA formulations, although it has been defined differently in different studies (1 day versus first of 3 consecutive days of symptom relief).
- Quality of life scores correlate well with the significant rapid clinical remission seen with Asacol.²⁴
- A prior history of steroid use does not preclude a retreat of 5-ASA treatments.²⁹ Greater treatment success (79%) has been reported with the elevated (4.8 g daily) dose of Asacol versus 52% with 2.4 g daily, in previous steroid users.²⁹ Patients taking steroids may be more difficult to treat and thus need higher initial doses of 5-ASA to achieve remission.
- Although a prior relapse on 5-ASA does not preclude a retreat of 5-ASA, a history of three or more relapses is associated with a lower remission rate.²⁸ Given that patients with a more frequent relapse history may be more difficult to treat, a trial of longer duration of treatment and a higher 5-ASA dose may be required to induce and maintain remission.
- There is a different demographic of patients who are non-compliant with 5-ASA prescription refills in the maintenance phase of UC management.²⁷ Once-daily dosing may improve adherence and fears of excessive absorption are dispelled by recent pharmacokinetic studies. Whether the emphasis on once-daily dosing versus multiple doses per day truly effects compliance to therapy remains subject to debate.³⁰
- The role of 5-ASA as a chemoprotective agent against CRC, either by suppressing inflammation or as a novel anti-proliferative agent, seems plausible but further study is needed.^{14,31}

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5-ASA Therapy for Successful Ulcerative Colitis Treatment: Optimizing Dosing and Adherence, Determining Meaningful Endpoints

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

- _____ is associated with a high number of adverse events, which may limit its usage as a successful treatment for mild to moderate UC.
 - Sulfasalazine
 - Asacol
 - Lialda
 - Pentasa
- Once-daily dosing of mesalamine is approved for _____.
 - maintenance of remission
 - induction of remission
 - both induction and maintenance
- True or false? A study by Sandborn and colleagues found that once-daily dosing of Lialda or Asacol exhibited similar pharmacokinetic profiles.
 - True
 - False
- An analysis of the ASCEND trials by Sandborn and colleagues found that when treated with 2.4 g/day of Asacol, the median time to resolution of mild and moderate UC was _____ days.
 - 5
 - 14
 - 26
 - 39
- In a post-hoc analysis of data from clinical trials of Lialda, Sandborn and colleagues found that the median time to resolution of mild to moderate UC symptoms was less than _____ week(s).
 - 1
 - 2
 - 3
 - 4
- Based upon data collected from the control arm of the ASCEND trials, Irvine and colleagues found that treatment with Asacol resulted in significant improvement in the _____ domain(s) of the IBDQ.
 - emotional factors
 - bowel symptoms
 - systemic symptoms
 - emotional factors and bowel symptoms
- A report by Deconda and colleagues found that patients with mild IBD preferred which of the following treatment options?
 - 5-ASA
 - Anti-TNF agents
 - Steroids
 - Surgery
- Data presented by Katz and colleagues indicates that Asacol _____ g/day is more efficacious than _____ g/day for the treatment of moderate UC in patients previously on steroid therapy.
 - 2.4; 4.8
 - 4.8; 2.4
 - 1.6; 2.4
 - 2.4; 1.6
- A post-hoc analysis performed by Sandborn and colleagues found that among patients who have a history of at least 3 relapses, approximately _____ are likely to be in remission up to 1 year later when treated with 2.4 g/day MMX mesalamine maintenance therapy.
 - 50%
 - 60%
 - 70%
 - 80%
- A report by Kane and colleagues found that _____, GI hospitalization, mail order prescriptions, and older age are risks for nonpersistence of 5-ASA maintenance therapy.
 - gender
 - psychiatric history
 - comorbid illness
 - steroid use

Evaluation Form: 5-ASA Therapy for Successful Ulcerative Colitis Treatment: Optimizing Dosing and Adherence, Determining Meaningful Endpoints

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

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

Extent to Which Program Activities Met the Identified Objectives

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

- | | | | | | |
|--|---|---|---|---|---|
| 1. Describe the class benefits of 5-ASA drugs in the treatment of mild-to-moderate ulcerative colitis. | 1 | 2 | 3 | 4 | 5 |
| 2. Indicate the efficacy of the 5-ASA delayed-release formulations in the treatment of varying disease manifestations. | 1 | 2 | 3 | 4 | 5 |
| 3. Review latest data on 5-ASA delayed-release formulations for application and optimization in the clinical setting. | 1 | 2 | 3 | 4 | 5 |

Overall Effectiveness of the Activity

The content presented:

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

Impact of the Activity

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

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

Additional comments about this activity. _____

Follow-up

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

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

If you wish to receive acknowledgment for completing 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. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-test/Evaluations by Course" and search by project ID 5131. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Request for Credit

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City, State, Zip _____

Telephone _____ Fax _____ E-mail _____

Signature _____ Date _____

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.