Update on the Optimization of Mesalamine-Based Therapy in the Treatment of Ulcerative Colitis

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Introduction

Incidence and Diagnosis of Ulcerative Colitis

Ulcerative colitis (UC) is a chronic, lifelong, recurrent disease characterized by diffuse mucosal inflammation of the colon. The incidence of inflammatory bowel disease (IBD) varies depending upon the geographic area, with northern countries including the United States, United Kingdom, Norway, and Sweden have the highest rates.[1] Approximately 250,000–500,000 people in the United States are affected by UC, and the annual incidence rate is approximately 2–7 per 100,000 persons.[2] The overall incidence of the disease has remained constant during the last 50 years.[3] The onset of UC is typically between the ages of 15 and 30, but a second peak in incidence is observed between the ages of 60 and 80.[1] The disease rates are similar for men and women. Patients with UC have a higher risk of developing colorectal carcinoma (CRC).[4]

UC typically involves the rectum as well as all or part of the colon and is limited to mucosa and superficial submucosa; deeper layers are unaffected except in fulminant disease. Approximately 40–50% of patients have disease limited to the rectum and rectosigmoid, 30–40% have disease extending beyond the sigmoid but not involving the whole colon, and 20% have a total colitis.[1]

In UC, the crypt architecture of the colon is distorted, and the crypts may be bifid and reduced in number. There is often a gap observed between the crypt bases and the muscularis mucosae. Patients may also have basal plasma cells and multiple basal lymphoid aggregates. In addition, mucosal vascular congestion with edema and focal hemorrhage, as well as an inflammatory infiltrate consisting of neutrophils, macrophages, lymphocytes and plasma cells, is sometimes observed. In these cases the neutrophils can invade the epithelium, usually in the crypts, and give rise to cryptitis and, ultimately, crypt abscesses.[1]

Patient with UC typically present with intermittent bloody diarrhea, rectal urgency, and tenesmus.[5] The extent of colonic involvement can sometimes be predicted by the severity of symptoms exhibited by the patient. For example, more fulminant presentations are frequently associated with pancolitis, severe inflammation, or both.[2] In patients not previously diagnosed with UC, it is important to determine the etiology of their symptoms. Stool examinations for ova and parasites, stool culture, and testing for *Clostridium difficile* toxin may help eliminate other causes of chronic diarrhea. Patients with UC often have elevated measures of markers for systemic inflammation such as erythrocyte sedimentation rate and C-reactive protein. Furthermore, patients with UC may have anemia from chronic blood loss as well as a basic metabolic profile that demonstrates electrolyte abnormalities such as hypokalemia from persistent diarrhea.[6]

Treatment of Ulcerative Colitis

The treatment of UC involves acute management of inflammatory symptoms followed by maintenance of remission. The treatment approach is generally determined by the severity of symptoms.[5,7,8] The current standard of care for induction and maintenance of remission in patients with mild to moderate UC is oral or rectally administered mesalamine (5-aminosalicylic acid, 5-ASA).[9] Patients with proctitis or mild to moderate left-sided disease are typically treated rectally with mesalamine and have an improved and faster response to rectal administration versus oral administration.[10,11] Patients with mild to moderate active pancolitis are treated with oral 5-ASA compounds alone or in combination with enemas, which induces remission or symptomatic improvement in 60% of patients within four weeks.[12] If patients with mild to moderate UC or pancolitis do not respond to 5-ASA compounds, oral corticosteroids and immunosuppressants may be necessary.

Patients with moderate to severe UC are treated with oral or intravenously administered corticosteroids depending upon the severity of their disease; however, long-term therapy is not recommended because of significant side effects.[8] After responding patients are tapered off of corticosteroids, treatment with 5-ASA compounds and possibly oral immunosuppressants is initiated.[2,7] If patients do not respond to intravenous corticosteroids, surgical interventions or intravenous administration of immunosuppressants may be necessary.[7,13]

5-Aminosalicylic Acid

Most patients with UC are treated with 5-ASA compounds for induction and maintenance of remission or prophylaxis depending upon the severity of their disease. Similar to sulfasalazine, mesalamine releases 5-ASA when metabolized but it is better tolerated overall.[14] Mesalamine acts topically from the colonic lumen to suppress the production of numerous proinflammatory mediators. The efficacy of mesalamine is related to its modulation of prostaglandin pathways and inhibition of the production of potent inflammatory cytokines such as interleukin 1

and tumor necrosis factor (TNF).[15] Mesalamine also acts as a cellular antioxidant and free radical scavenger.[16]

Several oral mesalamine formulations that deliver the active moiety to the colon have been developed in recent years, including delayed-release tablets and controlled-release capsules, both of which have proven effective in the induction and maintenance of UC remission.[17,18] These oral formulations of mesalamine require several doses per day with multiple pills. Complicated dosing schedules can interfere with the normal daily activities of the patient, which may ultimately lead to noncompliance with the recommended dose.[19,20]

Nonadherence to treatment regimens for chronic diseases is common,[21] and because the symptoms of UC are characterized by alternating periods of active flare and quiescence, it is particularly prevalent in this patient population. Studies have reported that during periods of disease quiescence, compliance with 5-ASA dosing regimens is as low as 40%, with patients citing too many pills and inconvenient dosing among their top reasons for noncompliance.[19,22,23] In a study of patients with UC who were in remission and taking maintenance mesalamine, patients who were not adherent with the medication had a more than fivefold greater risk of recurrence than adherent patients.[19]

One formulation of mesalamine utilizes a multi-matrix system (MMX) designed to release 5-ASA gradually throughout the colon, thereby requiring less frequent dosing.[24] Results from recent phase III clinical trials demonstrated that once-daily MMX mesalamine induced remission in over one third of patients with mild to moderate active UC and was generally well tolerated.[25]

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926 Beclomethasone Dipropionate + Mesalamine Enemas for Refractory Ulcerative Proctitis. A Retrospective Analysis[1]

M Guslandi, P Giollo, PA Testoni

Active ulcerative proctitis is generally treated with local administration of either mesalamine or corticosteroids. A meta-analysis of randomized controlled trials of enema/foam beclomethasone dipropionate (BDP), a poorly absorbed glucocorticosteroid that acts as a local anti-inflammatory, versus enema/foam 5-ASA in patients with left-sided mild to moderate distal ulcerative colitis demonstrated equivalent control of UC symptoms.[2] Cessation of rectal bleeding is usually observed within several weeks of treatment initiation, but occasionally patients do not respond; the combination of BDP 3 mg enema and 5-ASA 1 g enema is reportedly more effective than the single agents. Guslandi and colleagues[1] performed a retrospective analysis to establish the therapeutic role of enemas combining BDP and 5-ASA.

Outpatients (aged 29–47 years) with rectal localization of UC treated between January 2003 and December 2006 were retrospectively analyzed. Male (n=20) and female (n=14) patients had experienced a clinical flare-up of the disease during oral maintenance therapy with daily mesalamine (1.6 g). Patients were treated with a BDP (3 g) enema daily for up to 15 days, during which time rectal bleeding persisted for all patients. Subsequently patients in group A (n=16) continued local treatment with BDP and received an increased dose of oral mesalamine (3.2 g) for two weeks. Patients in group B (n=18) maintained the same dose of oral mesalamine (1.6 g), but received a nightly enema combining BDP (3 g) and mesalamine (1.5 g) for two weeks.

Sixteen out of 18 patients in group B (89%) reported cessation of rectal bleeding at the end of the treatment period versus only 5 of 16 patients (31%) in group A (P=.002). Eleven patients from group A were switched to oral corticosteroids at the end of the treatment period due to persistent rectal bleeding.

The results from this retrospective analysis suggest that rectal administration of a combination of BDP and mesalamine is effective in patients who are refractory to BDP alone. Furthermore, the addition of rectal mesalamine to the BDP enema appeared to be more effective than increasing the dose of oral mesalamine in this patient population.

935 MMX™ Mesalamine is Effective for the Maintenance of Remission of Mild-to-Moderate Ulcerative Colitis Irrespective of Patients' Previous Relapse History[4]

WJ Sandborn, R Karlstadt, K Barrett, RE Joseph

939 Once- or Twice-daily MMX™ Mesalamine for the Maintenance of Remission of Mild or Moderate Ulcerative Colitis[5]

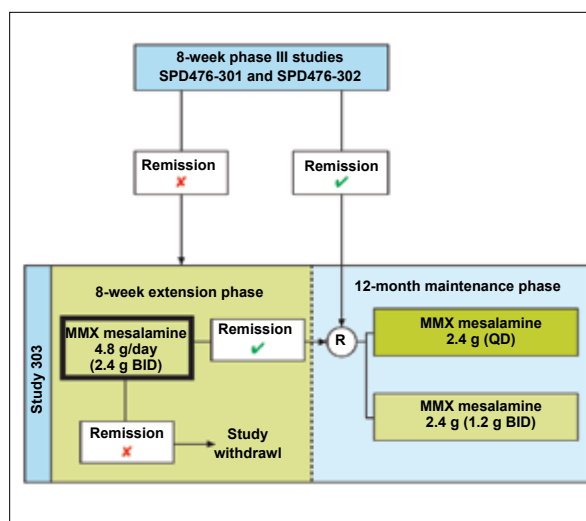R Panaccione, MA Kamm, R Karlstadt, R Diebold, K Barrett, RE Joseph

940 The Effect of Prolonged Therapy with MMX™ Mesalamine in Patients With Acute, Mild-to-Moderate Ulcerative Colitis[6]

GR Lichtenstein, MA Kamm, R Panaccione,
K Barrett, K Lees, RE Joseph

Figure 1. Design of study SPD476-303.

BID=twice daily; QD=once daily; R=randomization.

Adapted from Panaccione et al.[5]

MMX mesalamine is a novel, high-strength formulation of 5-ASA (1.2 g per tablet) designed to deliver active drug throughout the colon. Two randomized, placebo-controlled phase III clinical trials (SPD476-301 and -302) were performed to compare MMX mesalamine versus placebo for the treatment of active, mild-to-moderate UC.[7,8] In study 301, patients (N=280) with mild to moderately active UC received 4.8 g/day of MMX mesalamine (in two divided doses [n=93] or once daily [n=94]) or placebo (n=93) for 8 weeks. In study 302, patients (N=343) with active, mild to moderate UC received once-daily MMX mesalamine (either 2.4 or 4.8 g/day) or placebo for 8 weeks. In addition, an internal reference arm was included in study 302, in which patients received delayed-release mesalamine 2.4 g/day, given in three divided doses. The primary endpoint for both trials was the percentage of patients in clinical and endoscopic remission, which was defined as a modified UC disease activity index (UC-DAI) score of less than 1 with a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction in sigmoidoscopy score at week 8. Patients with mucosal friability were not regarded as having achieved this endpoint.

The results from study 301 showed that approximately one third of patients receiving either MMX mesalamine 2.4 g twice daily or MMX mesalamine 4.8 g once daily achieved clinical and endoscopic remission at week 8 (34.1% and 29.2%, respectively). A significantly higher proportion of patients receiving MMX mesalamine therapy achieved clinical and endoscopic remission compared with patients receiving placebo (12.9%; *P*<.01). Similar results were observed in study 302, in which a significantly greater proportion of patients receiving MMX mesalamine 2.4 g once daily (40.5%; *P*=.01) and 4.8 g once daily (41.2%; *P*=.007) achieved clinical and endoscopic remission at week 8 compared with patients receiving placebo (22.1%). The clinical and endoscopic remission rate for patients treated with delayed-release mesalamine was not significantly superior to those treated with placebo (32.6% vs 22.1%; *P*=.124) but it should be noted that the study was not powered for head-to-head comparison of the two agents. All active treatments were well-tolerated in both studies.

Patients who did not achieve remission in study 301 or 302 were eligible to receive an additional 8 weeks of therapy with high-dose MMX mesalamine as part of a long-term, open-label study (study 303; Figure 1). Lichtenstein and colleagues[6] investigated the proportion of patients who did not respond to acute treatment with MMX mesalamine in studies 301 and 302 but were able to achieve remission in the 8-week extension study. A total of 304 patients entered the 8-week extension study and received 4.8 g/day of MMX mesalamine (2.4 g twice daily). All patients were included in the efficacy population.

Induction of remission was observed in approximately 60% of patients, and remission rates were similar regardless of the previous treatment received in either study 301 or 302. Remission rates were 61.5% in patients who had previously received MMX mesalamine 2.4 g/day and 60.3% in patients who had received MMX mesalamine 4.8 g/day. The percentage of patients in remission was 57% for those who previously received placebo and 61% for those who previously received delayed-release mesalamine 2.4 g/day. An additional 8 weeks of MMX mesalamine therapy was consequently able to induce stringently defined remission in a large population of patients who initially failed acute treatment.

Patients in remission at the end of study 301, 302, or the 8-week extension phase of study 303 could enter the 303 open-label maintenance phase and receive MMX mesalamine (2.4 g/day) for 12 months (Figure 1). Panaccione and colleagues[5] presented the data from study 303 which assessed the efficacy of MMX mesalamine for maintaining remission in patients with either mild or moderate UC.

Patients were randomized to receive MMX mesalamine 2.4 g once daily or 1.2 g BID. Data were ana-
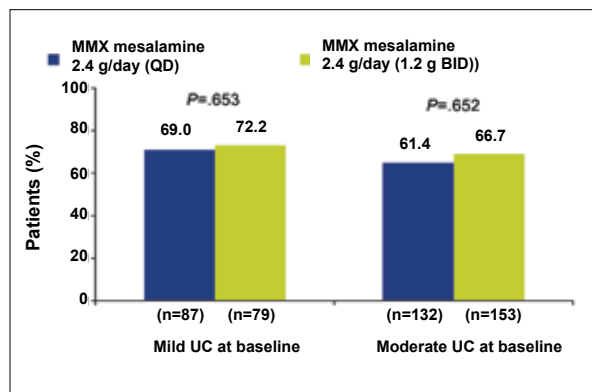
Figure 2. Remission rates after 12 months in patients with mild or moderate disease.

QD=once daily; BID=twice daily; UC=ulcerative colitis.

Adapted from Panaccione et al.[5]

lyzed to assess remission rates by baseline disease severity. Remission was similarly defined in this study as in studies 301 and 302: a modified UC-DAI score of less than 1 with scores of 0 for rectal bleeding and stool frequency, a combined Physician's Global Assessment and sigmoidoscopy score of less than 1, no mucosal friability, and a sigmoidoscopy score reduction of greater than 1 point from baseline. The maintenance phase efficacy population (N=451) consisted of all patients who entered the maintenance phase and received at least one dose of study medication; 166 patients (36.8%) had mild disease and 285 patients (63.2%) had moderate disease at baseline

A total of 459 patients entered the maintenance phase and the majority (79.1%) were exposed to MMX mesalamine for more than 48 weeks (overall mean exposure duration 47.6 weeks). Demographic characteristics were similar in the two dosing groups. Within the efficacy population, 12-month remission rates were 70.5% in patients with mild UC at baseline and 64.2% in patients with moderate UC at baseline. Remission rates were not significantly different in patients receiving MMX mesalamine 2.4 g once daily compared with those receiving MMX mesalamine 1.2 g twice daily (Figure 2). Overall, these results demonstrate that MMX mesalamine 2.4 g/day, whether given as 2.4 g once daily or 1.2 g twice daily, is efficacious for the maintenance of remission in patients with either mild or moderate UC.

To determine whether a patient's relapse history has an effect on the efficacy of maintenance therapy with MMX mesalamine, Sandborn and colleagues[4] assessed patients from the maintenance phase of study 303 with complete relapse records available for the 2 years prior to enrolling in the parent study (n=438). Of these patients, 290 (66%) achieved remission at 12 months. Approximately 70% of

patients (192/274) who had experienced fewer than 3 relapses in the two years prior to the parent study achieved remission at 12 months. In comparison, 60% of patients (98/164) who had had 3 or more relapses in the two years prior to the parent study achieved remission.

These results suggest that taking into consideration patients' relapse history may help determine whether they have difficult-to-control UC in which long-term remission rates may be reduced. Nonetheless, approximately 60% of patients with a history of increased relapses (>3) in the two years prior to the parent study were able to achieve remission after receiving maintenance therapy with MMX mesalamine (2.4 g/day) for one year. Further studies are required to determine if a higher maintenance dose of MMX mesalamine is necessary in patients who have a history of being prone to relapse.

977 Mesalamine Protects Against Colorectal Cancer in Inflammatory Bowel Disease[9]

J Tang, G Kucera, O Sharif, C Pai, AL Silverman

Individuals with UC are 2-3 times more likely to develop CRC compared to the general population.[10] A meta-analysis of 116 studies from around the world estimated the prevalence of CRC in patients with UC to be approximately 3.7%.[11] CRC risk in IBD is associated with dysplasia, extent of disease, type of therapy, duration of disease, and degree of inflammation. Tang and colleagues investigated the influence of body mass index (BMI), family history of disease, smoking, and treatments received on CRC risk in IBD.[9]

Patients with IBD from the Henry Ford Hospital in Detroit who developed CRC from 1970 to 2005 were included in the study. The cases were matched to controls according to type of IBD, age at diagnosis, sex, race, and extent and duration of disease. BMI, family history of IBD, family history of CRC, smoking, and use of mesalamine, mercaptopurine, folic acid, steroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) were compared. The total cumulative dose and average daily dose were calculated for each prescription drug class. Covariates were compared using chi-square and Student t test. Odd ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression models to examine the relationship between drugs and risk of colorectal cancer.

A total of 30 CRC patients were identified, of whom 25 (16 male, 9 female; mean age 37.8) had UC and 5

(3 male, 2 female; mean age 42.2) had Crohn's disease (CD). A large population of patients (N=1484; 605 UC patients, 879 CD patients) was reviewed to find appropriate controls, and 16 CRC patients (13 UC, 3 CD) were matched to 23 controls (19 UC, 4 CD). The CRC and control patients were similar in BMI (mean, 27.5 vs 25.0), family history of IBD (18.8% vs 8.8% positive history), family history of CRC (18.8% vs 8.8% positive history), and smoking use (66.7% vs 52.2% nonsmoker). There were no significant differences in use of mercaptopurine (6.3% vs 13%), NSAIDs (6.7% vs 21.7%), and steroids (80.0% vs 82.6%).

The results showed that more control patients use folate compared to the CRC patients (56.5% vs 30%; P=.025). In addition, a smaller percentage of CRC patients used mesalamine for UC compared with the control patients (76.9% vs 100%; P=.028). A conditional logistic regression analysis demonstrated that a total mesalamine dose of more than 5,068 g was associated with an 89% reduction in the risk of CRC (OR, 0.11; 95% CI, 0.01–0.91), but a cumulative dose of folate greater than 2,823 mg did not show a significant reduction of CRC risk (OR, 0.47; 95% CI, 0.09–2.50). These results suggest that mesalamine use among UC patients leads to a significant reduction in the risk of developing CRC.

989 Influence of Disease Duration and Severity on Inflammatory Bowels Disease Patients' Medication Preference[12]

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

Inflammatory bowel disease is a lifelong condition that often requires multiple medications to treat flares of disease activity and to maintain remission. Nonadherence to maintenance mesalamine has been reported in up to 60% of patients with quiescent ulcerative colitis.[13] Deconda and colleagues performed a pilot study to investigate if disease severity and duration influences patients' medical or surgical treatment preferences. The goal of the study was to gain an improved understanding of patient preferences in order to better prescribe the appropriate medication to maximize compliance.

A comprehensive questionnaire was administered to 50 consecutive patients with a known diagnosis of IBD who visited the Yale IBD clinic from July to November 2006. Questions asked of patients included demographic information, disease and medication history, treatment preferences (5-ASA compounds, enemas, oral steroids, immunosuppressants, anti-TNF agents, and surgery),

and reasons for medication preferences. The patients were divided into two groups based on disease severity: mild disease (1–3 bowel movements per day, no urgency, occasional blood, and mild pain; n=39) and moderate to severe disease (>5 bowel movements per day with blood, urgency, and interference with daily activities; n=11). In addition, patients were divided into two groups based on disease duration: 10 years or less (n=36) and more than 10 years (n=14).

The questionnaire was completed by all patients (33 with CD and 17 with UC). The patient population was comprised of 28 women and 22 men with a mean age of 41.5 (±15) years and mean disease duration of 8.8 (±9.6) years. The majority of patients, regardless of disease duration, preferred 5-ASA treatments due to their efficacy and milder side effect profile; however, patients with moderate to severe disease equally preferred anti-TNF agents because of their efficacy (Figure 3). Patients with a history of IBD for more than 10 years were more likely to disfavor surgery compared to patients with IBD for 10 years or less (50% vs 38.9%, respectively). In addition, disfavor of steroids was more common among patients with shorter disease duration than among patients with longer disease duration (38.9% vs 21.4%, respectively). Overall, patients disfavored surgery because of side effects and cost and disfavored steroid treatment because of side effects.

In conclusion, disease severity appeared to influence the choice of preferred medication, whereas disease duration appeared to influence disfavored medications. Irrespective of the duration of the disease, treatment with 5-ASA was the first choice of patients.

995 Long-Term Safety of 5 Aminosalicylates (Mesalamine) in the Treatment of Inflammatory Bowel Disease[14]

CD Trivedi, S Mithani, E Chichili, D Xing, KM Das

Because of their limited absorption, their short-term side-effect profile of 5-ASA compounds has been excellent[15]; however, there has never been a systematic review of a large database of patients who have been on 5-ASA medications for a prolonged period of time. In this study, Trivedi and colleagues evaluated the safety of high-dose, chronic use of 5-ASA to identify any adverse events, particularly focusing on nephrotoxicity and hematologic side effects.

The authors retrospectively reviewed the charts of colitis patients followed at the Crohn's and Colitis Center of NJ between 1985 and 2007. For each patient
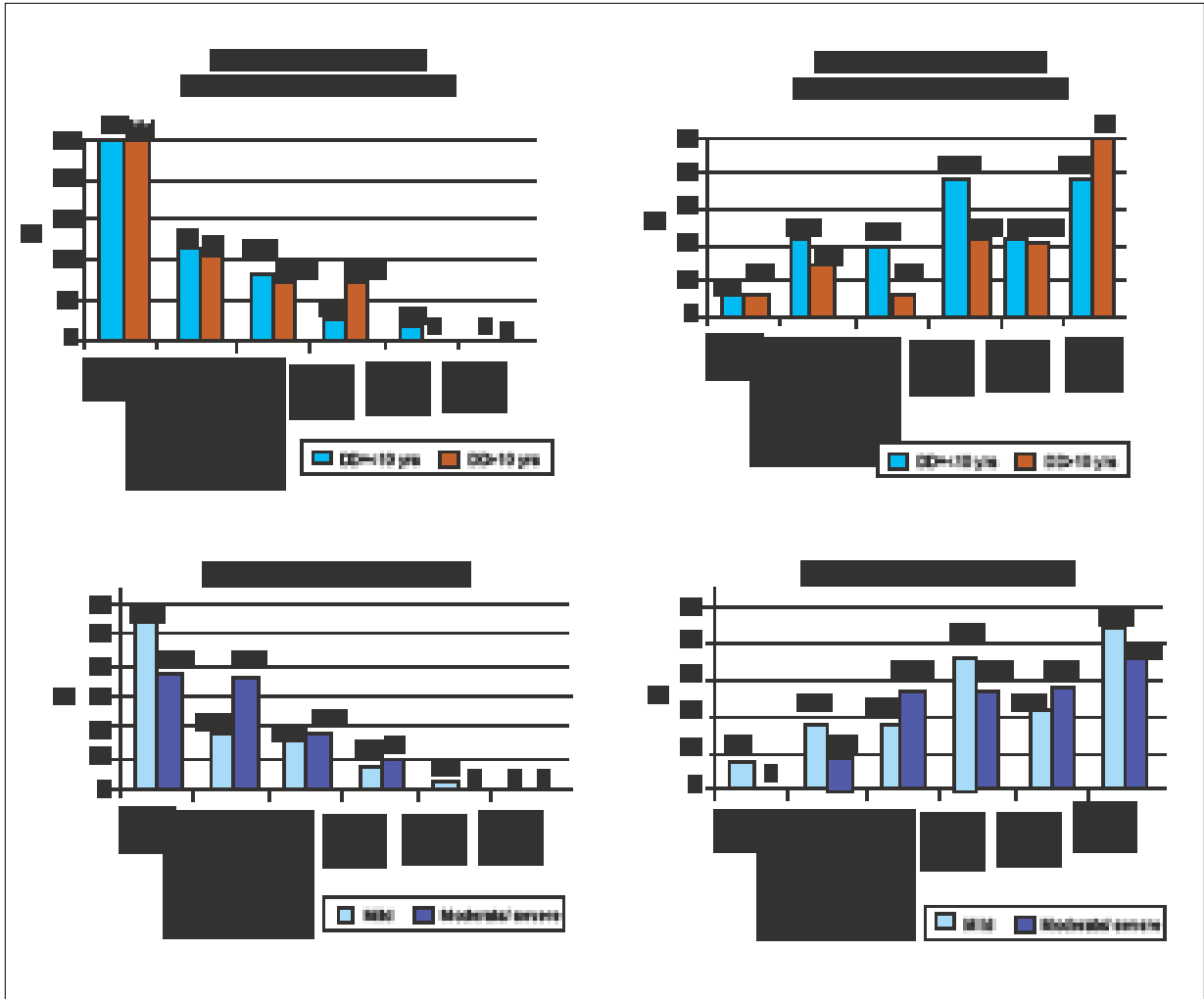
Figure 3. Effect of disease duration and disease severity on patient preference in ulcerative colitis treatment method. Adapted from Deconda et al.[12]

(N=214) they calculated equivalent mesalamine dose, duration of exposure to medication, and adverse events occurring during the course of their follow up. Within this patient group, 63% (134/214) were exposed to 5-ASA for over 12 months and 92% (198/214) required an average mesalamine maintenance dosage greater than that approved by the FDA.

To assess kidney function, serum creatine levels were examined. Twelve patients (6 UC and 6 CD) had elevated concentrations of serum creatine (>1.2 mg/dL); one third of these patients were on no other medications and had no concomitant illnesses accounting for renal disease. Glomerular filtration rates were calculated for these patients with the Modification of Diet in Renal Disease study equation; the values ranged from 69.24 to

85.06 mL/min/1.73 m^2, suggesting a mild reduction in glomerular filtration or stage II kidney disease.

In addition to kidney function, hematologic parameters were assessed. Sixteen patients were found to have leukopenia, 12 of whom were concomitantly on mercaptopurine or azathioprine and required dosage modification to prevent worsening of leukopenia. Four patients taking only 5-ASA medications (2 on sulfasalazine and 2 on mesalamine) developed leukopenia. These findings were independent of the average daily 5-ASA dose or duration of exposure.

In this first report regarding the long-term safety of 5-ASA treatments, these medications were found to be safe at an average dose of up to 3.17 g/day over a period of 80 months. A small percentage of patients had evidence of

Table 1. Incidence of Renal Insufficiency and Leukopenia with 5-ASA Medications

	Number of patients (N)	Average daily mesalamine dose, g/day (SEM)	Average duration of exposure to mesalamine, months (SEM)
Ulcerative colitis	95	3.11 (0.13)	43.08 (4.52)
Patients with Cr ≥1.2 mg/dL	6	2.53 (0.40)	52.83 (31.53)
Patients with WBC ≤4K	7 (4 taking concomitant 6MP)	2.57 (0.39)	81.29 (20.40)
Crohn's disease	110	3.17 (0.09)	35.77 (3.41)
Patients with Cr ≥1.2 mg/dL	6	2.89 (0.29)	24.33 (6.76)
Patients with WBC ≤4K	9 (8 taking concomitant 6MP)	3.26 (0.22)	53.22 (10.67)
Indeterminant Colitis	9	2.98 (0.28)	21.67 (7.49)
Patients with Cr ≥1.2 mg/dL	0	N/A	N/A
Patients with WBC ≤ 4K	0	N/A	N/A

Cr=creatine; SEM=standard error of measurement; WBC=white blood cells.

Data from Trivedi et al.[14]

stage II kidney disease and leukopenia of unknown etiology; however, none had clinically significant worsening of renal disease or leukopenia requiring cessation of 5-ASA therapy. Periodic monitoring of serum creatine and complete blood count are warranted during long-term treatment with 5-ASAs.

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Commentary

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The long-term treatment of UC continues to present a challenge in a subset of patients, highlighting the importance of further refining treatment methods and optimizing the administration of the medical therapies at our disposal. Given the lifelong therapy required in the majority of patients, mesalamine preparations represent our safest treatment option. Research into novel formulations and schedules of administration of mesalamine are ongoing and should continue in order to maximize the benefit and improve the outcomes obtainable with these drugs.

Ulcerative proctitis presents a unique challenge in the treatment of active disease, often requiring rectal administration of therapy to achieve remission. A recent meta-analysis examined the efficacy of combination therapy with beclomethasone dipropionate (BDP), a poorly absorbed glucocorticosteroid that acts topically as an anti-inflammatory while avoiding the adverse effects associated with systemic steroid treatment. The efficacy of BDP, in the form of a foam enema, was initially examined versus 5-ASA administered in a similar manner, and combined administration of BDP and 5-ASA, by Mulder and associates. The efficacy in patients with active UC symptoms was equal among treatment options, thus setting the stage for Guslandi and colleagues' retrospective evaluation of patients with ulcerative proctitis, treated between 2003 to 2006.

The authors evaluated patients treated with BDP (3 g) enemas for 15 days versus those taking combination BDP and mesalamine. The results of their study showed a greater cessation of bleeding at the end of therapy among those taking the combination therapy, suggestive of a greater level of efficacy. Study of this novel approach should be further pursued, although BDP is not currently available in the United States.

MMX mesalamine is a relatively new formulation of oral mesalamine. Two randomized, phase III, multicenter studies, Studies 301 and 302, compared active therapy at doses of 2.4 g daily and 4.8 g daily to placebo. Study 301 also had an active comparator arm, utilizing 2.4 grams of delayed-release mesalamine. An extremely rigorous endpoint utilizing a modified UCDAI and a component of mucosal healing that did not allow for mucosal friability was utilized in these studies. An additional study, Study 303, was conducted to examine 8-week, open-label extension treatment in patients who responded but did not achieve the strict definition of remission in Studies 301 and 302. It found that additional therapy may be necessary to achieve complete remission and should be pursued in patients responding to initial induction therapy.

Patients achieving remission in all three studies were offered further open-label maintenance dosing of 2.4 g of MMX mesalamine daily for an additional 12 months. This study was undertaken primarily to examine the safety of long-term MMX administration. However, the data accrued could also be utilized to examine this agent's efficacy in the maintenance of remission. Twelve-month remission rates were 70.5% for patients with mild UC at baseline and 64.2% for patients with moderate disease at baseline. These results are particularly important in that past studies of delayed-release mesalamine have shown difficulty in controlling mild disease to a significant degree.

Historically, patients with prior relapses have been perceived as less likely to achieve remission and often require corticosteroids in the escalation of therapy. Therefore, another subanalysis of the MMX studies looked at patients' relapse history to see if this factor had any affect on the ability of MMX mesalamine to maintain remission. Patients in the 303 maintenance study, who had relapse records available for 2 years prior to study, were assessed. It was demonstrated that a history of prior relapse had no bearing on their response to current medical therapy. Of patients with a history of relapses greater than 3 in the 3 years prior to study, 60% were able to maintain remission on MMX mesalamine for 1 year.

Patients with UC are at higher risk for the development of CRC. However, a recent meta-analysis by Velayos and colleagues suggests that UC patients taking mesalamine reduce the risk of developing CRC by approximately 50%. In an effort to confirm these findings, Tang and associates from the Henry Ford Hospital in Detroit looked at 35 years of mesalamine use at their institution in patients matched appropriately for other CRC risk factors to determine if individual patients in the study garnered any chemopreventive benefit from mesalamine as well as assessing what other factors had the greatest impact on likelihood of disease development. Although BMI was not found to affect risk, family history of CRC did. Further, logistic regression analysis demonstrated that cumulative mesalamine doses of over 5 g daily lowered risk by 89%.

Prior studies examining this question have simply defined the use or nonuse of medication. This is the first to look at estimated cumulative lifetime doses and suggest that a mean total mesalamine dose can be designated to associate with cancer reduction. Further, the fact that mesalamine could be associated with reduced CRC incidence, whereas other effective therapies, including 6MP and steroid administration, could not, suggests a direct chemopreventive effect rather than a secondary effect of inflammation control. Several questions remain, however. Is there a plateau in terms of the dose-response relationship? Does topical, rectally administered mesalamine therapy provide the same chemopreventive benefit? A multitude of different mechanisms has been suggested as the key to mesalamine's chemopreventive properties, including free radical scavenging and inhibition of TNF-alfa. Pinpointing the specific pathway of prevention may be our next avenue of research.

Data to date show that patients with active disease are more likely to take medication as prescribed than those with quiescent disease. Nonadherence to mesalamine therapy has been reported by Kane and colleagues in up to 60% of patients when in remission. Deconda and associates designed their pilot study to assess disease severity and duration as influencing factors on patients' medical or surgical treatment preferences and adherence levels. They found that overall, mesalamine was the first choice of most patients but that disease severity and duration could affect patient attitudes in terms of risk tolerance and desire for more aggressive forms of therapy. If the adverse event profile of a medication is significant, patients may not be willing to take it. It is important to understand the relationship between disease severity and patients' risk acceptance. This understanding and decision-making process in partnership with patients augments the physician-patient relationship and gains invaluable trust for the physician.

Trivedi and colleagues' institutional experience of over 20 years provides long-term data on the affect of mesalamine on potential adverse-event–related parameters, including kidney function as measured by serum creatine levels, estimated glomular filtration rate, and incidence of leukopenia. Over an average duration of 80 months, the incidence of adverse events was of uncertain significance and, in most instances, could be related to disease-associated symptoms or cotherapy with 6MP. No earlier trials have examined long-term use of mesalamine to this extent. Phase III trials generally do not last longer than 12 months. Thus, this important contribution to the literature confirms the long-term safety of mesalamine to go with our documented knowledge of short- and medium-term use.

All of these studies add to the already persuasive data regarding the ongoing role of mesalamine formulations as the safest and potentially most beneficial choice for patients with mild-to-moderate UC. Clearly, these benefits are estimable and justify further research in order to continually optimize the role of these agents in the control of active disease, maintenance of remission, and potential chemoprevention of CRC.

Suggested Reading

Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol.* 2005;100:1345-1353.

Mulder CJ, Fockens P, Meijer JW, et al. Beclomethasone dipropionate (3 mg) versus 5-aminosalicylic acid (2 g) versus the combination of both (3 mg/2 g) as retention enemas in active ulcerative proctitis. *Eur J Gastroenterol Hepatol.* 1996;8:549-553.

Sandborn WJ, Kamm MA, Lichtenstein GR, Lyne A, Butler T, Joseph RE. MMX Multi Matrix System mesalazine for the induction of remission in patients with mild-to-moderate ulcerative colitis: a combined analysis of two randomized, double-blind, placebo-controlled trials. *Aliment Pharmacol Ther.* 2007;26:205-215.

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Notes

Update on the Optimization of Mesalamine-Based Therapy in the Treatment of Ulcerative Colitis

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

1. Of UC patients, approximately___% have disease encompassing the entire length of colon.

   a. 10 b. 20
   c. 30 d. 35

2. Guslandi and colleagues performed a retrospective analysis which demonstrated that _____ of patients receiving enemas with combined BDP and mesalamine reported cessation of rectal bleeding at the end of two weeks compared with ____ of patients receiving local BDP alone.

   a. 75%, 43% b. 89%, 31%
   c. 40%, 55% d. 95%, 20%

3. In study SPD476-301, which compared MMX mesalamine with placebo for the treatment of active mild to moderate UC, approximately what percentage of patients receiving MMX mesalamine (either 2.4 g BID or 4.8 g once daily) achieved clinical and endoscopic remission at week 8?

   a. one third b. two thirds
   c. one fourth d. three fourths

4. In study SPD476-301, which compared MMX mesalamine with placebo for the treatment of active mild to moderate UC, approximately what percentage of patients receiving once-daily MMX mesalamine (either 2.4 g/day or 4.8 g/day) achieved clinical and endoscopic remission at week 8?

   a. 25% b. 70% c. 33% d. 40%

5. Lichtenstein and colleagues found that approximately ____ of patients who did not respond to acute MMX mesalamine treatment experienced induction of remission during an additional 8 weeks of high-dose MMX mesalamine (4.8 g/day) therapy.

   a. 33% b. 45% c. 60% d. 72%

6. Tang and colleagues investigated the influence of multiple factors on CRC risk in patients with IBD and found that _____ use among UC patients leads to a significant reduction in the risk of developing CRC.

   a. Folate
   b. NSAIDs
   c. Mesalamine
   d. Steroids

7. According to meta-analysis by Eaden and colleagues, the prevalence of CRC among UC patients is approximately ____%.

   a. 3.7 b. 6.5
   c. 7.9 d. 8.8

8. True or False: According to Deconda and associates, patients with IBD, regardless of disease duration, preferred mesalamine treatment versus other medical and surgical options.

   a. True b. False

9. In a retrospective analysis of the long-term safety of 5-ASA medications, evidence of stage II kidney disease and _____ was found in a small percentage of patients with IBD.

   a. Anemia b. Leukopenia
   c. Liver damage d. Heart disease

10. Based on the results of this study, Trivedi and associates recommend periodic testing of serum creatine levels and ____ in patients receiving long-term 5-ASA therapy.

    a. C-reactive protein
    b. erythrocyte sedimentation rate
    c. complete blood count
    d. electrolytes

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Evaluation Form

Initial release date: March 15, 2008; material expires one year from release date: March 15, 2009.

Please complete the CME post-test, the certificate request form, and this evaluation form and return to:
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This activity is designated for 1.0 *AMA PRA Category 1 Credit(s)™*. In order to receive your CME credit(s), you are requested to review the material in full and take the post-test on page 15. Once you have completed the quiz, please note in the space provided on the certificate request form the amount of time it took you to complete the entire activity, including the post-test.

Thank you for completing the evaluation form. Your evaluation of the activity and comments are important to us and will remain confidential.

Please answer the following questions by circling the number that best reflects your view.
(Scale: 1 = poor; 2 = fair; 3 = satisfactory; 4 = good; 5 = excellent)

1. Please rate how effectively you are able to:

a. Describe the use of 5-ASA formulations in the current treatment of ulcerative colitis.　　1　2　3　4　5

b. Discuss latest data pertaining to the use of new 5-ASA formulations to further optimize UC therapy.　　1　2　3　4　5

c. Summarize possible research directions for the development of new 5-ASA regimens or formulations.　　1　2　3　4　5

2. Activity/Topic:

a. The extent this program met your continuing professional development goals　　1　2　3　4　5
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c. The overall format of the activity　　1　2　3　4　5
d. The applicability/usefulness of the material to your practice　　Not in practice ☐　　1　2　3　4　5

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Too basic ☐　　　　Appropriate ☐　　　　Too complex ☐

4. Do you feel that the activity was objective, balanced, and free of commercial bias?　Yes　　No

　　If no, why? _____

5. Based on this activity, how might you change your practice management or patient care?

_____

6. Please list any speakers and/or topics you would like in future programs.

_____

7. Would a periodic review of this or related material be appropriate?　　　Yes　　No

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