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Mild-to-Moderate Ulcerative Colitis: Your Role in Patient Compliance and Health Care Costs

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Target Audience

Managed care pharmacists and other professionals with a focus on improving tangible and intangible outcomes in individuals with ulcerative colitis (no prerequisites required)

Learning Objectives

Upon completion of this activity, participants should be able to

1. describe the impact of patient noncompliance on the course of mild-to-moderate ulcerative colitis (UC);
2. formulate potential strategies that will positively impact patient adherence to UC therapy;
3. delineate the limitations of current treatment approaches for UC and apply new options to disease management; and
4. evaluate the impact of improvement in compliance on socioeconomic and patient outcomes.

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This supplement will discuss the inherent challenges faced by physicians and patients in the treatment of mild-to-moderate ulcerative colitis and will address the role of managed care in improving patient compliance through an increased knowledge of various treatment options.

*A total of 0.10 CEU (1.0 contact hour) will be awarded for successful completion of this continuing education activity (ACPE Program No. 815-999-07-061-H01-P). This educational activity is also accredited for a maximum of 1.0 AMA PRA Category 1 Credit(s)[™]. For faculty disclosures, please see page S11. For accreditation information, please see page S13.

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Mild-to-Moderate Ulcerative Colitis: Your Role in Patient Compliance and Health Care Costs

William N. Tindall, PhD, RPh; John M. Boltri, MD; and Sheila M. Wilhelm, PharmD

ABSTRACT

BACKGROUND: Ulcerative colitis (UC) is a chronic relapsing disease necessitating lifelong treatment. Most patients present with mild-to-moderate disease characterized by alternating periods of remission and clinical relapse. Continued disease progression and relapse of UC over time are associated with an increased risk of colorectal cancer (CRC).

OBJECTIVE: To discuss the latest treatment options for mild-to-moderate UC, to review the current data involving the economics of UC, and to demonstrate the relationship between treatment adherence, clinical relapse, inflammation severity, CRC risk, and treatment outcomes.

SUMMARY: One of the main goals of therapy in UC is to induce and maintain a long-lasting remission of disease to reduce or avoid the high personal and financial costs of relapse. In recent studies, researchers have demonstrated a link between increased colonic inflammation and CRC risk, highlighting the importance of preventing relapse, which can lead to costly surgical procedures and hospital stays and thus increase the cost of treatment 2- to 20-fold. The risk of disease relapse is affected by several factors, of which the most prominent is nonadherence to maintenance therapy. Nonadherence to therapy can be associated with several other factors, including forgetfulness, male sex, complicated dosing regimens, treatment delivery methods (oral vs. rectal), and pill burden.

In the treatment of mild-to-moderate UC, 5-aminosalicylic acid (5-ASA) is the standard first-line therapy and the treatment of choice for maintaining remission of disease. Novel formulations of 5-ASA and newly devised high-dose 5-ASA regimens offer more options for the treatment of UC and thus may lead to improved treatment adherence, longer remission, and improved patient well-being.

CONCLUSION: Periods of remission during UC treatment must be aggressively maintained to prevent relapse and decrease the risk of an unfavorable outcome. By controlling the risks and conditions that lead to therapeutic nonadherence and relapse among patients with UC, clinicians can increase the likelihood of long-term remission and ensure favorable long-term outcomes.

KEYWORDS: Nonadherence, Remission, Relapse, Ulcerative colitis, 5-aminosalicylic acid, Dosing regimens, Compliance, Colorectal cancer risk

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Introduction to Ulcerative Colitis

Ulcerative colitis (UC) is an idiopathic and chronic disease characterized by diffuse inflammation of the colonic mucosa. The occurrence of UC peaks between the ages of 15 and 35 years. This disease is more common in whites than in African Americans or Asian Americans and is 3 to 6 times more common among the Jewish community than among the general population.¹ The mean annual incidence of 6 to 8 cases per 100,000 in Western Europe and the United States has not risen significantly in the past 2 decades.^{2,3}

Although the precise etiology of ulcerative colitis is unknown, it involves a combination of host factors and exogenous components. Results of studies on the rates of UC in monozygotic and dizygotic twins show a clear genetic influence, particularly from major histocompatibility complex class II molecule subtypes such as the DR2 and DRB1 alleles, some of which have been correlated with the severity and extent of disease.⁴ Ulcerative colitis also has been associated with environmental factors such as psychological stress and the use of nonsteroidal anti-inflammatory drugs.⁴

There are several theories about the pathophysiology of UC. Evidence suggests that it is an autoimmune disease related to the function of T cells, macrophages, and other inflammatory cells. One theory is that chronic inflammation in the colonic mucosa is perpetuated by T cells and macrophages that fail to regulate the balance between proinflammatory and anti-inflammatory mediators. For example, the inflamed mucosa of patients with

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UC contains elevated levels of inflammatory cytokines such as interleukin (IL)-1, IL-6, and IL-8, all of which are produced by macrophages and T cells.⁴

Natural History of UC

The most common symptoms of UC are diarrhea and rectal bleeding that are sometimes accompanied by pain. In UC, appropriate therapy is determined by the measurement of clinical features. The commonly used Truelove and Witts categorization stratifies the disease severity. Mild, moderate, or severe designations are based on clinical parameters and laboratory findings, including the number of bowel movements per day (whether or not fever, tachycardia, or anemia are evident) and the sedimentation rate.¹ In general, most patients present with mild-to-moderate disease, and fewer than 10% present with severe disease (defined as ≥ 6 stools daily, fever, anemia, and an erythrocyte sedimentation rate >30 mm/hour). At any point during the course of the disease, 50% of patients are without clinical symptoms, 30% have mild symptoms, and 20% have moderate-to-severe symptoms, with these approximations not having changed significantly over time.⁵ Therefore, this review will focus on patients with mild-to-moderate UC, the most common category.

Approximately 50% to 80% of patients have a relapsing and remitting course of UC that alternates between periods of clinical and endoscopic remission and disease flares of varying severity lasting from 4 to 12 weeks. In 15% to 30% of patients with UC, the disease remains in a constitutively active state during which remission cannot be achieved at all or is achieved only after the administration of large doses of steroids.⁴ In a prospective, longitudinal, multivariate survival analysis of 74 patients with clinically and endoscopically inactive UC, the investigators attempted to find reliable predictors of disease relapse by examining various clinical, biological, and histologic parameters. The results showed that younger age, multiple previous relapses (for women), and basal plasmacytosis evident on rectal biopsy were all independent predictors of early relapse. Basal plasmacytosis is an accumulation of plasma cells extending into the lower third of the lamina propria.⁶ Evidence of plasma cells in this area is indicative of the inflammatory process because, normally, they are not present or are present in very small numbers. Consequently, these results suggest that mucosal healing and the removal of the lymphoplasmacytic infiltrate from the mucosa can reduce the chance of further flaring.

The progression rate for UC is highest during the first year after the disease is diagnosed and remains steady at 5% to 6% during the next 10 years. A population-based, multivariate regression analysis of 1,161 patients with UC in Copenhagen County (Denmark) showed that after 25 years, the probability of further disease progression was 53%.⁷

As the severity of UC increases over time, so do the risks associated with more severe disease. For example, toxic megacolon or treatment-refractory UC are indications for surgery. The

Copenhagen data revealed a high percentage of patients (ranging from 20% to 40%, depending on location, severity, and treatment) who required proctocolectomy during the course of their disease. As the rate of disease progression increased over time, so did the probability of surgery.⁷ These data are supported by another follow-up study in Copenhagen in which researchers examined 783 patients for as long as 18 years.⁵ In this population, the proctocolectomy rate was 9.6% within the first year after diagnosis, 23% after 10 years, and 31% after 18 years.⁵ In other studies, the rates of proctocolectomy were even higher.⁸ In a retrospective study of 1,116 patients, Farmer et al. showed that approximately one third of all patients with UC and nearly two thirds with an initial presentation of pancolitis eventually required surgery.⁸ Because of the risks associated with surgery, however, drug therapy is the preferred therapeutic approach. For example, the cumulative risk of surgical complications 48 months after a proctocolectomy (with ileal pouch-anal anastomosis) was as high as 51%.⁹

The Relationship Between Ulcerative Colitis and Colorectal Cancer

Colorectal cancer (CRC) is one of the most serious potential sequelae of UC. The known risk factors for the development of CRC in patients with UC are an increased severity and longer duration of the disease, evidence of primary sclerosing cholangitis, a family history of CRC, and, possibly, the severity of colonic inflammation over time.¹⁰⁻¹²

Many studies addressing the risk of CRC in UC have shown widely varying results. In a meta-analysis of 116 studies from which the numbers of patients and cancers detected could be extracted, the overall prevalence of CRC among all patients with UC was 3.7%.¹¹ In the 35 studies that included adequate data from patients with total colitis, the overall prevalence was 5.4%, suggesting a link between disease extent and the risk of CRC.¹¹ The overall incidence of cancer in the 41 studies in which researchers reported the duration of colitis was 3 cases per 1,000 person-years duration (PYD).¹¹ In 19 of the studies in which researchers stratified the results into 10-year intervals of disease duration, the incidence was 2 cases per 1,000 PYD for the first decade of illness, 7 per 1,000 PYD for the second decade, and 12 per 1,000 PYD for the third.¹¹ These rates corresponded to the cumulative probability of 2% prevalence by 10 years, 8% by 20 years, and 18% by 30 years.¹¹ Meanwhile, the worldwide annual incidence rate of CRC in the general population is 0.6 cases per 1,000 PYD. Compared with that of the general population, the overall life expectancy of patients with UC is 94.2%,⁴ a difference that is possibly associated with the observed increase in CRC risk.

Although a link between the severity of colonic inflammation and an increase in CRC risk is biologically plausible, until recently, few researchers have demonstrated this association. In a retrospective case-control study of CRC risk in patients with UC, 68 patients with UC and CRC were matched to 136 control

FIGURE 1 5-Aminosalicylic Use and Colorectal Cancer/Dysplasia¹⁷

patients who had long-standing UC without any sign of neoplasia.¹² A univariate analysis of this group showed a significant association between the risk of CRC and colonoscopic inflammation scores (odds ratio [OR]=2.5; $P=0.001$) and histologic inflammation scores (OR=5.1; $P<0.001$).¹²

Although not a causal association, the link between inflammation and CRC risk was notable for what it suggested: that controlling the severity of UC could lower the risk of CRC. A separate analysis of the original matched patient cohort by Rutter et al. supported the original results.¹³ In this study, Rutter et al. examined records of colonoscopic surveillance for a possible correlation between macroscopic colonoscopic lesions and CRC risk. A multivariate analysis of the full cohort showed a significant association between the colonoscopic hallmarks of severe inflammation and CRC risk. For example, symptoms indicative of previous severe inflammation, such as postinflammatory polyps, conferred a greater risk of neoplasia (OR=2.29; $P=0.005$).¹³ Likewise, patients with symptoms indicative of chronically active colitis, such as colonic stricture, were 4 times more likely to have neoplasia (OR=4.22; $P=0.05$).¹³ A normal colonic appearance, however, was associated with a significantly lower risk of neoplasia (OR, 0.38; $P=0.003$), which, at 5 years after a normal colonoscopy, was the same as that among the matched control population.¹³ These results further supported the hypothesis that the severity of UC may influence the risk of CRC.

In view of this evidence, it is not surprising to observe possible chemopreventative effects associated with anti-inflammatory UC therapies, such as 5-aminosalicylic acid (5-ASA), as some researchers have reported. The potentially chemopreventative mechanisms involved may include reduced arachidonic acid metabolism, inactivated reactive oxygen species, increased apoptosis through nuclear factor-kappa B suppression, decreased IL-2 production, and activated peroxisome proliferator-activator receptor gamma.^{14,15} In a case-control study in which researchers compared 102 patients who had CRC with matched control subjects, regularly administered 5-ASA therapy reduced the risk of CRC by 81% in patients with UC.¹⁶ These results have been supported in multiple studies, including a meta-analysis of 9 observational studies (3 cohort, 6 case-control) involving 334 cases of CRC, 140 cases of dysplasia, and a total of 1,932 subjects.^{10,17} A pooled analysis of the collected studies demonstrated a chemopreventative relationship between 5-ASA use and CRC (OR=0.51 [95% confidence interval (CI), 0.38-0.69]; see Figure 1).¹⁷ Other researchers have examined the chemopreventative effects of various doses of 5-ASA. In a case-control study that matched 26 patients who had either CRC ($n=8$) or dysplasia ($n=18$) with 96 control subjects, those who received 5-ASA in doses ≥ 1.2 g/day demonstrated a 72% lower risk of dysplasia or CRC than did other patients.¹⁰

Although the risk of CRC is greater in patients with UC than in the general population, the optimal management of the risk of CRC remains unclear. Studies demonstrating the link between the severity of inflammation and increased CRC risk highlight the importance of tight control over the disease. Because UC is a chronic disease, maintaining long-lasting periods of remission is highly important, especially considering the chemopreventative advantage 5-ASA therapy offers during those periods of remission.

Modern Treatment Modalities for Mild-to-Moderate Ulcerative Colitis

The primary goal in the treatment of mild-to-moderate UC is to induce and maintain a clinical and endoscopic remission of inflammation, ideally with therapy that facilitates mucosal healing with the least steroid exposure. First-line treatment for mild-to-moderate UC involves the use of various oral and rectal 5-ASA formulations, such as mesalamine (brand names include Asacol, Canasa, Lialda, Pentasa, and Rowasa), balsalazide (Colazal), olsalazine (Dipentum), and sulfasalazine (Azulfidine En-tabs). Overall, the 5-ASAs are very well-tolerated and effective for both the short- and long-term treatment of UC. As novel formulations of 5-ASAs continue to expand the options for dosing and administration, 5-ASAs remain the gold standard of treatment for mild-to-moderate UC.

Normally, for patients with mild-to-moderate UC, clinicians initiate 5-ASA therapy in a dosage of 2.4 g/day and increase the dosage to a maximum 4.8 g/day only for patients who fail to

respond or have a poor response to treatment.¹⁸ Although higher doses are given to unresponsive patients, the clinical efficacy of a standard initial dose of 4.8 g/day has been mostly unexplored, until recently. To determine whether higher initial doses of 5-ASA would be as safe as lower doses while providing greater efficacy, in 2 randomized, phase 3, multicenter, double-blind, placebo-controlled studies, researchers compared a 4.8-g/day dosage with a 2.4-g/day dosage.¹⁹ In the first of these trials, ASCEND I (Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA), the authors examined patients with mild-to-moderate UC, whereas, in ASCEND II, they focused primarily on patients with moderately active disease. In a pooled analysis of the 2 studies, 423 analyzable patients with moderately active UC were randomly assigned to receive delayed-release oral mesalamine in a dosage of either 4.8 g/day (800-mg tablets) or 2.4 g/day (400-mg tablets) for 6 weeks.¹⁸ The primary efficacy measure of the 2 studies was the percentage of patients who achieved overall improvement or treatment success at the end of the treatment period. Treatment success was defined as either complete remission or a clinical response to therapy, which was defined as an improvement in the baseline physicians' global assessment (PGA) and in at least 1 other physical assessment (e.g., stool frequency, rectal bleeding, patient's functional assessment score [PFA], endoscopy findings) without worsening in any other clinical assessment. Complete remission was defined as complete resolution of all symptoms with all assessment scores (PFA and PGA) equaling 0.¹⁹

A pooled analysis of the ASCEND I and II data showed that the rate of successful treatment was significantly higher among patients given oral mesalamine 4.8 g/day (72%) than among those given 2.4 g/day (58%, $P < 0.05$).¹⁸ The data from ASCEND I alone, however, show that among patients with mild UC, the higher dosage was no more beneficial than the lower dosage. These findings suggest the benefit of the higher dosage would be evident only in patients with moderate UC.^{18,19} In addition, patients taking mesalamine 4.8 g/day demonstrated symptomatic relief significantly more quickly than did patients taking 2.4 g/day. The median time to the resolution of rectal bleeding and a reduction in stool frequency was 19 days among patients given mesalamine 4.8 g/day, compared with 29 days among patients taking 2.4 g/day ($P < 0.05$). Both doses of mesalamine had similar safety profiles, with the frequency and severity of adverse events being comparable.¹⁸ The results of these 2 studies suggest that the use of traditional low-dose 5-ASA induction therapy is best administered only to patients who have mild UC, whereas higher initial doses may be more efficacious in patients with moderate UC.¹⁹

Economics of UC

According to a 1992 study, the total estimated annual medical cost associated with UC was \$0.4 to \$0.6 billion, with a per-patient annual cost of \$1,488.^{20,21} Of this total cost, medical services, such as the diagnostic work-up, outpatient services,

and the cost of medication, accounted for 23.3% (7.8%, 7.1%, and 8.4%, respectively), which is in stark contrast with the 47.1% related to surgical interventions and other associated inpatient services.²⁰ The remainder of the total annual cost (29.6%) is associated with long-term complications due to the expensive extraintestinal manifestations of UC that can include the liver, skin, and musculoskeletal system.²⁰

With surgery and hospitalization accounting for nearly half of the total costs of the treatment of UC, and medication amounting to less than a tenth of that same total, there is an obvious disparity between the cost of controlled disease and the cost of treatment failure. Claims data from a 1-year period revealed that 39% of the total amount paid by providers was incurred by the top (worst affected) 2%, and nearly all of these claims involved hospitalization.²⁰ Although most of the costs reported in the 1992 study were attributable to a small percentage of patients, more than half of the patients in that study accounted for less than 7% of the expenditures incurred, further highlighting the disparity between treatment costs.

Over time, the severity of disease and the prevalence of surgery increases among patients with UC.⁷ In a 23-year, long-term study of 1,116 patients who had UC, 36.7% eventually required surgery.⁸ Ileoanal anastomosis is the preferred surgical procedure for most patients because, unlike ileostomy, it allows them to have normal bowel movements. This procedure requires 2 to 3 surgeries and hospitalizations, however, with a 6-week convalescence period after each surgery. The direct and indirect costs associated with ileoanal anastomosis are quite significant, with the hospital costs alone equaling \$27,270 for a 2-stage procedure and \$38,184 for a 3-stage procedure. Therefore, to help control the cost of treating UC, clinicians must depend on effective drug therapies that can reduce the necessity for expensive surgery.²²

Although they do not contribute considerably to the cost of treating UC, medications and the formulary management decisions associated with them must be considered carefully. The formulary status of medications used to treat UC can have a potential impact on treatment outcomes, especially given the life-long nature of the disease and its likelihood for relapse. In a survey of the top 25 health maintenance organizations (HMOs), top 10 Medicaid administrations, and top 5 pharmacy benefit management (PBM) companies, the formulary status of various therapies used in the treatment of mild-to-moderate UC were compared (see Table). Asacol, which is on-formulary in 24 of 25 HMOs, 8 of 10 Medicaid administrations, and 4 of 5 PBMs, leads in tier-2/on-formulary access in all 3 managed-market segments. Of all the agents that do not have a generic substitute, Lialda is one of the most restricted agents used in the treatment of mild-to-moderate UC, with tier-2 status in 8 of 25 HMOs, 5 of 10 Medicaid administrations, and 0 of 5 PBMs surveyed.^{23,24}

For this drug class, prior authorization is a common formulary management requirement. Prior authorization for medications

TABLE Formulary Status Analysis:
Number of Managed Care Institutions
Requiring Preauthorization to
Dispense 5-ASA Agents^{23,24}

Drug Name	HMO Rank*	Medicaid Rank†	PBM Rank‡
Delayed-release mesalamine (Asacol)	24	8	4
Controlled-release mesalamine (Pentasa)	20	6	3
Balsalazide disodium (Colazal)	16	6	2
MMX mesalamine (Lialda)	8	5	0
Azathioprine (Imuran) [§]	7	6	1
Mesalamine (Rowasa) enema [§]	7	6	1

Managed market segments analyzed include the top 25 HMOs, the top 10 Medicaid administrations, and the top 5 PBMs.

* In top 25.

† In top 10.

‡ In top 5.

§ Available generically.

HMO=health maintenance organization; PBM=pharmacy benefit management company; MMX=Multi Matrix System

used to treat mild-to-moderate UC was necessary most often for patients insured by Medicaid; in 2 to 4 states, authorization was necessary for all of the therapies addressed in the survey. Among the top 25 HMOs, prior authorization was required only for Colazal (3 HMOs), Imuran (2 HMOs), and Lialda (3 HMOs), whereas among the PBMs, no prior authorization was required for any of the drugs evaluated. In addition, formulary management restrictions do not impose quantity limits or "step edits" for these drugs.²³

Medical insurers and health care providers have become increasingly aware of the disparity between the costs associated with the treatment of UC and the minority of patients who incur most of those costs. Because UC is now understood to increase the risk of morbidity and death in those who suffer the disease, clinicians have begun to understand the importance of disease remission in controlling the outcome of long-term UC and reducing or eliminating the necessity for surgery. During the next 5 to 10 years, drug costs will increase as biologics and newer formulations of existing agents are adopted and included more routinely in current treatment strategies for controlling UC. Yet, despite their increased costs, these therapies have the potential to reduce the overall costs of treating UC by possibly preventing relapse. Overall, the maintenance of remission is vital to controlling UC and its associated risks. Although the cost of controlling UC properly can be significant, the cost of improper treatment is even higher.

■ The Burden of Treatment Adherence

Understanding the financial and clinical importance of maintaining remission in patients who have UC, clinical investigators

have focused on the conditions and factors that lead to relapse. In one prospective study, 99 patients whose UC was currently in remission were observed for a 2-year period during which they underwent evaluations at 6, 12, and 24 months.²⁵ These patients underwent mesalamine therapy to maintain remission and had not demonstrated relapse in the 6 months preceding the trial. The primary outcome of the study was the clinical recurrence of UC, defined as 4 or more bowel movements per day that were associated with urgency, pain, or bleeding. In a multivariate analysis of the data, the 4 factors that were associated with disease recurrence were nonadherence with maintenance therapy (the refilling of less than 80% of the prescribed medication), a shorter duration of disease (<5 years vs. ≥5 years), a shorter length of remission (<12 months vs. ≥12 months), and a positive family history for UC.²⁵

The most significant factor leading to recurrence of disease in the study was nonadherence to therapy.²⁵ The risk of recurrence was 5-fold greater among nonadherent patients than among adherent patients (hazard ratio=5.5; 95% CI, 2.3-13.0; $P<0.001$).²⁵ The rates of adherence were determined from pharmacy records and a validated formula. At 24 months, only 39% of the patients in the study who were nonadherent with their therapy maintained clinical remission, compared with 89% of adherent patients (Figure 2).²⁵

Nonadherence to therapy is a widespread problem in health care today. More than 50% of the 1.8 billion prescriptions written annually are taken incorrectly, and, as a result, 30% to 50% of all prescriptions fail to produce the desired treatment outcome.²⁶ Approximately 10% of all hospitalizations are due to a patient's failure to follow prescribed drug therapy.^{26,27} Patients with UC or Crohn's disease are especially likely to be nonadherent to their therapy.²⁸ In clinical trials, the rate of adherence with mesalamine therapy is as high as 80%, but in prospective, community-based studies, it is much lower, at 40% to 60%, and is often lowest among patients in symptomatic remission. Patients seen in clinical practice are far removed from the highly structured environment of clinical trials that is more conducive to therapeutic adherence.²⁹ Medical recommendations are always easy to follow during the short term but can become burdensome when they are part of a lifelong strategy for the treatment of a chronic disease known to flare unpredictably even when a maintenance treatment regimen is followed. Patients whose disease is in remission are often faced with the difficult choice of either discontinuing their maintenance therapy or continuing the regimen even though it necessitates taking several doses several times a day that may or may not prevent a recurrence of their disease.²⁸

In multiple studies during the past several years, researchers have examined medication nonadherence in patients with UC. Among these is a recent prospective study that examined medication-taking behavior in 115 patients with Crohn's disease and 99 patients with UC. This behavior was assessed via an anonymous questionnaire that focused on prescribed treatments, adherence

behavior, self-medication behavior, and physician confidence. In this study, 56.5% of the patients were prescribed oral mesalamine, and 45% of those patients admitted to forgetting some drug doses during their treatment regimen. In addition, almost 20% admitted to practicing self-medication, often in response to a suspected clinical worsening of their condition or to a desire to avoid requesting sick leave from work.³⁰

In another study, investigators examined the adherence rate and the possible risk factors for nonadherence among 94 patients undergoing maintenance therapy for UC that was in clinical remission for longer than 6 months. During a 6-month observation period, patient adherence was determined from computerized pharmacy records and patient inquiry. A patient was nonadherent when he or she consumed less than 80% of the prescription medication dispensed to him or her, as indicated by refill data and patient inquiry. The overall adherence rate was 40%, with only 71% of the prescribed medication dispensed per patient. A stratified analysis and regression modeling revealed that nonadherent patients were more likely to be single and male and have left-sided disease rather than pancolitis. In addition, the risk of nonadherence increased if a history of more than 4 different prescriptions was observed (OR=2.5; 95% CI, 1.4-5.7), whereas the risk of nonadherence decreased if a patient had undergone an endoscopy within the previous 24 months (OR=0.96; 95% CI, 0.93-0.99) or was married (OR=0.46; 95% CI, 0.39-0.57).³¹

The high rate of nonadherence associated with well-tolerated UC therapies such as mesalamine has led investigators to examine the cause of nonadherence. In one study, patients who did not follow their prescribed dosing regimen were asked to give a reason for their nonadherence. Of the 70 patients who responded, 35 (50%) said they forgot to take their medication, 21 (30%) claimed there were too many doses in their regimen, and the remaining 14 (20%) did not believe they needed so much medicine.²⁵ These findings correlated with those from a systemic review of adherence studies that cited full-time employment, age, male sex, and 3-times daily dosing regimens as other possible factors associated with nonadherence with mesalamine-based maintenance treatment of UC.²⁹

The overall impact of nonadherence to therapy in the treatment of UC is significant because such behavior contributes to increased morbidity, reduced quality of life, a suboptimal treatment outcome, increased chance of relapse, and higher overall costs of care. The effects of therapeutic nonadherence on clinical outcomes are clear. In the previously mentioned study, nonadherence was significantly related to the rate of relapse in UC.²⁵ In addition, the same studies demonstrated that the increased inflammation observed during times of relapse can increase the risk of CRC. Therefore, it stands to reason that nonadherence to therapy can increase the risk of CRC. Supporting this theory is a study of 175 patients with UC that demonstrated a significantly increased incidence ($P<0.001$) of CRC during a 10-year period among patients who either were nonadherent to therapy

FIGURE 2 The Impact of Treatment Adherence on Disease Recurrence²⁵

or discontinued their sulfasalazine treatment.²⁹ Only 3% of the patients who continued their sulfasalazine maintenance therapy demonstrated CRC, compared with the 31% of the patients who discontinued their therapy or were nonadherent.²⁹

Nonadherence also leads to higher medical costs. In the United States, nonadherence to all prescribed, long-term therapy costs as much as \$100 billion each year. The direct medical costs amount to \$30 billion dollars, including \$25 billion for hospital admissions and \$5 billion because of unnecessary nursing home placement.²⁷ At \$70 billion, the indirect medical costs represent the bulk of the tab and are primarily due to decreased productivity and premature death. In a recent study of 483 subjects in Germany in which the authors used cost diaries to prospectively evaluate the cost of treating Crohn's disease ($n=241$) and UC ($n=242$) during a 4-week period, 41% of the costs of treating UC were due to direct medical costs, whereas 54% were due to indirect costs.³²

Among patients who undergo initial monotherapy with oral 5-ASA, the average cost of a single case of treatment failure, exclusive of the cost of therapy before or after the treatment failure, exceeds \$11,500 per patient.²² Often, the bulk of this cost is generated by a small number of patients. For example, in a U.K. study in which the authors examined the costs of illness in a cohort of patients with Crohn's disease ($n=172$) or UC ($n=307$) during a 6-month period, only 14% of these patients required hospitalization during that time, yet they accounted for 49% of the total secondary care costs recorded. In comparison with patients whose disease was currently in remission, relapse was

associated with a 2- to 3-fold increase in costs for patients who did not require hospitalization. In the same study, hospitalization was associated with a 20-fold increase in costs.³³ The indirect costs associated with therapeutic nonadherence among patients with UC also have an impact, since nonadherence leads to short-term productivity losses and long-term periods of unemployment that result in decreased earnings.²⁹

In addition to the clinical and financial costs associated with nonadherence, there are personal costs. Because UC is an unpredictable chronic disease that is not controlled consistently by medication, the quality of life among patients who have UC is significantly lower than that among the general population. In a study of 111 patients with UC in which researchers examined the impact of the disease on quality of life, the investigators found that quality of life was minimally affected by a person's age, sex, physiologic markers of disease activity, or anatomic distribution of disease, but they did find a strong association between a patient's symptoms and his or her quality of life.³⁴ The authors of this study concluded that priority should be given to therapies that can prevent the recurrence of symptoms and treat them quickly when they do arise.³⁴

The scope and impact of therapeutic nonadherence is significant, and although many strategies have been devised to increase the rate of adherence, no consensus has been reached concerning the value and long-term efficacy of these approaches.²⁹ In general, therapeutic adherence can be defined as a 2-way relationship between the patient and the physician or health care provider who establishes the dosing regimen. One of the more critical strategies for improving adherence begins with the physician in the establishment of a good therapeutic relationship. By necessity, patients must be active participants in the treatment of their disease and understand what their responsibilities are and how their decisions play a vital role in the courses of their disease.²⁷ The benefit of this approach was demonstrated in a small group of patients who were a part of a larger long-term study³¹ in which investigators examined the effects of therapeutic adherence in the treatment of UC.³⁵ Among this group of 21 patients who were demonstrating nonadherence (defined by a prescription refill rate <75%), the median amount of medication received was 54%. These patients were contacted by their physician, and their prescription refill rates were discussed in accordance with a prepared script. In the discussion, patients were reminded about the benefits of consistent and prolonged therapy and asked to share their reasons for their nonadherent behavior. During the 6 months after the follow-up call, medication consumption increased to 80% in 10 of the 21 patients.³⁵ More important, only 1 of the 10 newly adherent patients experienced a recurrence of disease during that 6-month period, compared with 4 of the 11 patients who remained nonadherent ($P<0.05$). These results suggest that improved adherence and clinical outcomes can be realized through increased support, encouragement, and education of the patient.

The likelihood of adherence also can be increased through the simplification of treatment. Less intrusive drug delivery systems and more convenient dosing regimens have led to improved patient adherence in the treatment of a number of disorders, including hypertension, diabetes, osteoporosis, angina pectoris, and human immunodeficiency virus infection,^{26,27,29} and recent data suggest similar results in the treatment of UC as well.^{36,37} Whenever less intrusive drug delivery methods are considered for the treatment of mild-to-moderate UC, the question of oral versus rectal delivery of 5-ASA arises. Enema preparations of 5-ASA are the gold standard in the treatment of left-sided UC. In comparison with oral formulations of 5-ASA, the rectal formulations are more efficacious in resolving symptoms and inducing remission, but despite this superior efficacy, most patients prefer the oral formulations to the rectal ones, and the compliance data reflect this. In a pilot study of 79 patients with active, mild-to-moderate, left-sided UC, the overall rate of adherence to oral 5-ASA treatment was 97%, versus 87.5% with rectal 5-ASA.³⁶

Long-acting drug formulations and once-daily dosing regimens represent the easiest approach to encouraging therapeutic adherence. Results of multiple studies have shown an association between both a lower pill burden and once-daily dosing with improved adherence.^{26,27} In a UC pilot feasibility study, investigators compared the rate of adherence associated with an oral once-daily dosing regimen with the rates associated with an oral 2- or 3-times-daily dosing regimen among patients whose disease was currently in remission.³⁷ Twenty-two patients with mild-to-moderate UC were randomly assigned to either once-daily treatment ($n=12$) or conventional treatment (2-3 daily doses, $n=10$) and underwent assessments at 3 and 6 months that addressed disease activity, treatment adherence, medication consumption rates, and satisfaction with treatment. At 3 months, neither treatment group demonstrated disease relapse, but although all 12 patients assigned to once-daily treatment were adherent to their therapy, only 7 of 10 patients assigned to conventional treatment were adherent ($P=0.04$). After 6 months of treatment, one patient from each group demonstrated clinical relapse (neither patient was adherent to his or her treatment), and 75% of patients assigned to once-daily treatment, versus 70% of those assigned to conventional treatment, were adherent with their therapy ($P=0.8$; note this finding is insignificant). At the end of the treatment period, the average amount of medication consumed was 90% of the prescribed dose among patients assigned to once-daily treatment and 76% of the prescribed dose among those assigned to conventional treatment ($P=0.07$). When surveyed about their satisfaction with treatment, 83% of the patients assigned to once-daily treatment reported being "very satisfied" with their treatment regimen, compared with 60% of those assigned to conventional treatment ($P=0.18$). Until recently, the treatment of UC with 5-ASA required 3 daily doses or more; however, the US Food and Drug Administration's

(FDA's) approval of Multi Matrix System (MMX) mesalamine (Lialda) marked the availability of a formulation of 5-ASA that could be administered once daily. In view of the trends observed in this study³⁷ and of the recent availability of therapies that allow once-daily treatment of mild-to-moderate UC, larger studies will be necessary to determine the impact of these new regimens on both treatment adherence and the duration of remission.

Although the benefits of once-daily dosing should be obvious, this comparison trial does point to a possible disadvantage with the simplified regimen that clinicians should consider when determining the appropriate dosing regimen for a particular patient who has UC. Although once-daily dosing can improve adherence because a single daily dose is easier to remember, if a patient still forgets to take a dose of a once-daily formulation, he or she will miss 24 hours of therapy instead of the 8 or 12 hours that would be missed during conventional regimens requiring 2 or 3 daily doses. Therefore, the clinician must understand that adherence to therapy will always be determined by the willingness of a patient to take the treatment administered. Simplifying the administration by reducing the dosing frequency or improving the delivery method will only facilitate adherence, not guarantee it.

Adherence to therapy can also be improved through routine pill checks and, possibly, the use of managed care databases to monitor compliance. Because most cases of nonadherence arise involuntarily, routine pill checks can provide clues to any specific barriers that may prevent a patient from following his or her regimen or otherwise make the therapy difficult. By asking patients to bring in their prescription drugs, a physician can inspect the amounts of medication present and open a dialogue with the patients about their medication-taking behavior.^{27,38} Managed care organizations can also help improve adherence through the development of databases (specifically from pharmacy benefit manager data) that enable clinicians to track lapses in their patients' prescription refills or to determine which patients may benefit from more education about the advantages of therapeutic adherence.²⁷

Overall, the chronic and unpredictable nature of UC, combined with noncurative treatments that must be taken even during asymptomatic periods of remission, makes adherence to UC therapy a difficult task. Despite the well-documented medical, financial, and personal consequences of nonadherence, it still occurs in an alarming percentage of the patient population. Several of the conditions that lead to nonadherence in the treatment of UC can be effectively controlled, such as the pill burden and inconvenient administration or dosing regimens. Patient interaction and education can also improve adherence rates. Indeed, along with the numerous methods available for identifying and improving treatment adherence in UC patients, a multifaceted approach that focuses on patient empowerment is necessary to ensure optimal treatment outcomes.

■ A New Option in the Treatment of Mild-to-Moderate UC

In an attempt to improve therapeutic adherence rates in the treatment of UC, researchers have developed new once-daily formulations of mesalamine such as MMX mesalamine (Lialda). Approved by the FDA for the induction of remission in patients with active mild-to-moderate UC, MMX mesalamine utilizes a novel and unique drug delivery system that combines multiple release mechanisms to ensure extended 5-ASA drug delivery to the entire colon and rectum. A gastroresistant coating on MMX mesalamine delays initial release of 5-ASA until the pill reaches the terminal ileum, where it is exposed to a pH $\geq$ 7. Once the outer coating dissolves, the hydrophilic matrix swells upon exposure to intestinal fluid and forms a viscous gel that eventually can break away from the pill core, releasing 5-ASA throughout the colon and rectum. It is believed that the pieces of hydrophilic matrix could adhere to the mucosal wall, increasing exposure, but this has not been proven conclusively.³⁹ The lipophilic matrix of MMX mesalamine is interspersed with 5-ASA within the hydrophilic matrix, which creates a partly hydrophobic environment that slows penetration of aqueous fluids to the tablet core. This process is expected to slow drug dissolution and provide further extended release of active 5-ASA, potentially prolonging the therapeutic activity of the medication.³⁹

The efficacy and safety of MMX mesalamine was demonstrated in 2 randomized, phase 3, global, double-blind, double-dummy, parallel-group, placebo-controlled trials examining patients with acute mild-to-moderate UC. The first of these trials (SPD476-301) compared the efficacy and safety profiles of 2 dosing regimens of MMX mesalamine with those of placebo. Two-hundred eighty patients were administered either 1 tablet of MMX mesalamine 1.2 g twice daily (n=93), 4 tablets of MMX mesalamine 1.2 g once daily (n = 94), or placebo (n = 93). The primary efficacy measure of the study was the percentage of patients demonstrating remission after 8 weeks of treatment. Remission was defined by a modified Ulcerative Colitis Disease Activity Index (UCDAI) $\leq$ 1, a score of 0 for rectal bleeding and stool frequency, and at least a 1-point reduction from baseline in the sigmoidoscopy score. In this study, the UCDAI was modified to be more stringent than the standard system by adjusting the sigmoidoscopic scoring system so that patients with any mucosal friability could not demonstrate remission.³⁹

After 8 weeks of treatment, both doses of MMX mesalamine were significantly more effective than placebo in inducing remission. Clinical and endoscopic remission was demonstrated by 34.1% of the patients taking MMX mesalamine 2.4 g/day and 29.2% of the patients taking 4.8 g/day, compared with 12.9% of patients taking placebo.³⁹ Furthermore, the frequency of treatment-emergent adverse events did not differ significantly between the treatment groups. A small number of patients (n=7) experienced serious adverse events (SAEs).³⁹ With the exception

FIGURE 3 302 MMX Mesalamine Trial:
Patients in Remission at Week 8⁴⁰

The MMX mesalamine 2.4 g/day dose is not statistically significant compared with the MMX mesalamine 4.8 g/day dose.

MMX=Multi Matrix System; NS=not significant vs. placebo; QD=once daily; TID=3 times a day.

of 2 cases of pancreatitis caused by mesalamine hypersensitivity, most of these events were not related to the study medication. Both cases of pancreatitis were completely resolved after the discontinuation of study medication. In addition, 90% of patients in the safety population of the study were adherent to therapy (that is, they took between 80% and 120% of their assigned study medication).³⁹

In the second pivotal trial of MMX mesalamine (SPD476-302), researchers compared the efficacy and safety profiles of 2 dosing regimens of MMX mesalamine with those of placebo.⁴⁰ Three hundred forty-three patients with active mild-to-moderate UC were administered either 2 tablets of MMX mesalamine 1.2 g once daily (n=84), 4 tablets of MMX mesalamine 1.2 g once daily (n=85), 2 tablets of delayed-release mesalamine 400 mg 3 times daily (n=86), or placebo (n=86).⁴⁰ This trial also included an active-comparator group who received delayed-release oral mesalamine. The primary efficacy measure of the study was the same as that in the first pivotal trial, focusing on the number of patients who demonstrated remission after 8 weeks of treatment.⁴⁰ The results were similar to those of the first pivotal trial; both doses of MMX mesalamine were significantly more effective than placebo in inducing remission (see Figure 3).⁴⁰ Clinical and endoscopic remission was demonstrated by 40.5% of the patients taking MMX mesalamine 2.4 g/day ($P=0.01$) and 41.2% of the patients taking MMX mesalamine 4.8 g/day ($P=0.007$); however, the remission rate among the comparator arm given delayed-release mesalamine (32.6%) was not

statistically significant ($P=0.124$ vs. placebo).⁴⁰ As was observed in the first pivotal trial, the frequency of treatment-emergent adverse events did not differ significantly between the treatment groups. Five patients experienced SAEs, but none of these events was considered to be related to study medication.⁴⁰

In the pivotal trials (SPD476-301 and SPD476-302), MMX mesalamine was efficacious and safe in inducing remission of active mild-to-moderate UC.^{39,40} In a 12-month open-label extension (SPD476-303), patients who achieved remission in the pivotal trials could opt to receive maintenance therapy with MMX mesalamine 2.4 g/day (given once daily or as 1.2 g twice daily).⁴¹ At 12 months, remission rates for the patients were scored according to the same remission criteria used in the pivotal trials. More than two thirds of the patients who met the remission criteria at baseline remained in remission at 12 months. The mean rate of adherence to treatment was 98.7%.⁴¹ Overall, MMX mesalamine is an effective therapy for inducing and maintaining remission in patients with UC and may help improve treatment adherence.

During the past 50 years, 5-ASA agents have been the standard therapy for the treatment of UC. During this time, the drug has demonstrated its value as a chemopreventative agent and an effective treatment for mild-to-moderate UC, especially during periods of disease remission. With the emergence of newer 5-ASA formulations, such as MMX mesalamine, that require a less complicated, once-daily dosing regimen, the rate of therapeutic adherence is expected to increase. In light of such advances, the future of this long-standard therapy looks promising.

On the Horizon

The new therapeutic options in development for the treatment of UC are not limited solely to novel formulations of 5-ASA. The approval of infliximab for the treatment of Crohn's disease and moderate-to-severe UC, for example, heralds the arrival of a new wave of biologic therapies. Alternate tumor necrosis factor inhibitors such as adalimumab and certolizumab pegol, currently undergoing clinical investigation, have thus far demonstrated efficacy in Crohn's disease.⁴² Other biologics undergoing clinical evaluation in the treatment of UC include inhibitors of adhesion molecules such as MLN02 and alicaforsen, the anti-CD3 antibody visilizumab, and the anti-IL-2 receptor antibody daclizumab.⁴³ These novel agents may have a significant impact on the treatment of UC, since, by sustaining remission and preventing relapse, they can potentially reduce the necessity or costs of hospitalization or surgery and the risk of adverse outcomes such as CRC. The currently available data demonstrate both the importance of maintaining a long-lasting remission of disease and the link between therapeutic nonadherence and relapse. As the new treatments for UC emerge, further investigation will eventually reveal the best among them for ensuring optimal outcomes in the treatment of UC.

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Mild-to-Moderate Ulcerative Colitis: Your Role in Patient Compliance and Health Care Costs

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- What percentage of patients with ulcerative colitis present to their doctor with severe disease?
 - Fewer than 10%
 - 10% to 30%
 - 30% to 60%
 - 60% to 90%
 - More than 90%
- Over the course of ulcerative colitis, what percentage of patients will have to undergo proctocolectomy at some point?
 - 0% to 20%
 - 20% to 40%
 - 40% to 60%
 - 60% to 80%
 - 80% to 100%
- Colorectal cancer risk is increased in patients with ulcerative colitis. Which of the following is not considered a possible risk factor?
 - A family history of colorectal cancer
 - Primary sclerosing cholangitis
 - Increased severity of disease
 - Shorter duration of disease
 - The severity of colonic inflammation

4. In multiple studies, researchers have demonstrated the chemopreventative effects of 5-ASA therapy on colorectal cancer risk. The administration of 5-aminosalicylic acid (5-ASA) in a dose ≥ 1.2 g/day was associated with what percentage reduction in the odds of dysplasia or colorectal cancer?
 - a. 0% to 20%
 - b. 20% to 40%
 - c. 40% to 60%
 - d. 60% to 80%
 - e. 80% to 100%
5. Which of the following was associated with the highest costs regarding the treatment of ulcerative colitis?
 - a. Diagnostic work-up
 - b. Outpatient services
 - c. Surgical interventions
 - d. Extraintestinal manifestations of ulcerative colitis
 - e. Medication costs
6. In examining the direct costs associated with ulcerative colitis, what is the average cost of a single case of oral 5-ASA treatment failure (as initial monotherapy)?
 - a. Less than \$2,000 USD
 - b. \$2,000 to \$5,999 USD
 - c. \$6,000 to \$10,000 USD
 - d. More than \$10,000 USD
7. In clinical trials, more than 80% of patients with ulcerative colitis who were given 5-ASA compounds were adherent to their treatment regimen. What percentage of patients in community-based studies were adherent to 5-ASA maintenance therapy?
 - a. 0% to 20%
 - b. 20% to 40%
 - c. 40% to 60%
 - d. 60% to 80%
 - e. 80% to 100%
8. Which of the following is associated with decreased quality of life in patients with ulcerative colitis?
 - a. Age
 - b. Sex
 - c. Physiologic markers of disease activity
 - d. Anatomic distribution of disease
 - e. Patient symptoms
9. What is the most common reason for nonadherence to 5-ASA treatment?
 - a. Forgetfulness
 - b. Inconvenient dosing regimen
 - c. Drug-related adverse events
 - d. Lack of efficacy
 - e. Remission of disease
10. Which of the following is associated with the highest risk of relapse of ulcerative colitis?
 - a. Length of remission
 - b. Disease duration
 - c. Nonadherence to therapy
 - d. Positive family history
11. What was found to be the optimal 5-ASA dose for achieving treatment success in the recent ASCEND I and ASCEND II (Assessing the Safety and Clinical Efficacy of a New Dose) trials that examined the optimal dosing of 5-ASA in the treatment of moderate ulcerative colitis?
 - a. 1.2 g/day
 - b. 2.4 g/day
 - c. 4.8 g/day
 - d. 6.0 g/day
 - e. 7.2 g/day

Mild-to-Moderate Ulcerative Colitis: Your Role in Patient Compliance and Health Care Costs

Method of Participation

There are no fees for participating in and receiving credit for this activity. During the period of September 1, 2007 (release date), through September 30, 2008 (expiration date), participants must (1) read the entire supplement; (2) complete the posttest, credit application, and evaluation form; and (3) either send the completed forms to MEC or complete the activity online.

Medical Education Collaborative

By mail: 651 Corporate Circle, Suite 104 / Golden, CO 80401

By fax: (303) 420-3259

To complete this activity online, please visit www.amcp.org (Learning Center/Online CE), where you will access the posttest, credit application, and evaluation form.

The estimated time to complete this activity is 1 hour. A statement of credit will be issued only upon receipt of a completed posttest (with a score of 70% or better), credit application, and evaluation form. Statements of credit will be mailed within 6 to 8 weeks for faxed forms and issued immediately online.

For questions regarding the accreditation of this activity, please contact Medical Education Collaborative at (303) 420-3252.

POSTTEST ANSWERS

1	2	3	4	5	6	7	8	9	10	11

CREDIT APPLICATION

Please print clearly, as illegible applications will result in a delay.

Name: _____ Profession: _____

License #: _____ State of License: _____

Address (if business, please include floor and/or department):

City: _____ State: _____ Zip: _____

Please check which credit you are requesting:

☐ ACCME

☐ ACPE

Date of Participation: _____ Number of Hours (Max. 1.0 hours): _____

Signature: _____

Name: _____

EVALUATION

I. Please evaluate this educational activity by checking the appropriate box:

	Excellent	Very Good	Good	Fair	Poor
Faculty					
Content					
How well did this activity avoid commercial bias and present content that was fair and balanced?					
What is the likelihood that you will change the way you practice on the basis of what you learned in this activity?					
Overall, how would you rate this activity?					

II. Course Objectives

Were the following overall course objectives met? <i>At the conclusion of this activity, are you able to:</i>	Yes	Somewhat	No
• Describe the impact of patient noncompliance on the course of mild-to-moderate ulcerative colitis (UC)			
• Formulate potential strategies that will positively impact patient adherence to UC therapy			
• Delineate the limitations of current treatment approaches for UC and apply new options to disease management			
• Evaluate the impact of improvement in compliance on socioeconomic and patient outcomes			

III. Additional Questions

a. Do you believe future activities on this subject matter are necessary or important to your practice?

☐ Yes ☐ No

b. What is your preferred learning method? (Check all that apply)

☐ Local meetings ☐ Symposia at national meetings
☐ Online programs ☐ Print materials
☐ CD-ROMs

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

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

e. Additional comments

[illegible]

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