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Treatment Guidelines and Clinical Practice: Optimizing Foundational Therapies for Ulcerative Colitis

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Activity Overview

On April 29, 2008, a roundtable meeting was convened to discuss the optimal use of foundational therapies for ulcerative colitis (UC) as they relate to current treatment guidelines and clinical practice. This supplement summarizes the discussions from this meeting and provides information to extend clinical recommendations from available guidelines and help gastroenterologists in the daily care of their patients.

Target Audience

This activity has been designed to meet the educational needs of gastroenterologists and other clinicians who treat patients with UC.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Define the American College of Gastroenterology (ACG) Practice Guidelines as they relate to the goal of effective management of UC
- Explain how disease activity can affect quality of life for patients with UC
- Evaluate clinical severity and extent of disease in patients with UC
- Compare the dose responses of various currently available formulations of 5-aminosalicylates (5-ASA)
- Identify factors that may differentiate optimal treatment strategies for patients with mild or moderate UC
- Discuss the role of 5-ASA in the treatment of patients who require biologic or immunomodulator therapy
- Define optimal maintenance strategies for patients with UC
- Examine the potential of using 5-ASAs as chemopreventive agents
- Define the role of therapeutic monitoring for patients who are treated with foundational agents
- Design therapeutic strategies to optimize the use of foundational therapies for the management of mild, moderate, or severe UC and reduce the risk of complications in patients with UC

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Treatment Guidelines and Clinical Practice: Optimizing Foundational Therapies for Ulcerative Colitis

Introduction

On April 29, 2008, a roundtable meeting was convened to discuss the optimal use of foundational therapies for ulcerative colitis (UC) as they relate to current treatment guidelines and clinical practice. The faculty addressed a number of clinical considerations, which were discussed within the framework of current clinical practice guidelines for UC. Specific topics included optimal use of oral 5-aminosalicylates (5-ASAs) for induction and maintenance of remission in patients with mild or moderate UC, dose response of 5-ASAs in these patient populations, the role of 5-ASAs in patients who require immunosuppressant or biologic therapies, recommendations for therapeutic monitoring of foundational therapeutic agents, and recommendations for colorectal cancer (CRC) screening in these patients. This supplement summarizes the discussions from this meeting and provides information to extend clinical recommendations from available guidelines and help gastroenterologists in the daily care of their patients.

Table 1. Quality of Evidence Supporting Recommendations of the ACG Clinical Practice Guidelines on UC.[1]

Grade	Evidence
A	Homogenous evidence from multiple well-designed randomized (therapeutic) or cohort (descriptive) controlled trials, each involving a number of participants to be of sufficient statistical power
B	Evidence from at least one large well-designed clinical trial with or without randomization, from cohort or case-control analytic studies, or well-designed meta-analysis
C	Evidence based on clinical experience, descriptive studies, or reports of expert committees

Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): american college of gastroenterology, practice parameters committee. *Am J Gastroenterol.* 2004;99:1371-1385. Reproduced with permission from Blackwell Publishing.

Overview of Ulcerative Colitis Treatment Guidelines

A number of clinical practice guidelines are currently available to guide clinicians in the care of UC patients,[1,2] and a consensus on UC management is soon to be published by the European Crohn's and Colitis Organization (ECCO).[3,4] Practice guidelines developed by both the American College of Gastroenterology (ACG) and the British Society of Gastroenterology grade therapeutic recommendations according to the quality of evidence supporting them. The grading systems in these two sets of guidelines are similar: the strongest evidence (Grade A) is derived from randomized controlled trials, whereas the weakest (Grade C) relies on clinical experience (Table 1).[1,2]

Current practice guidelines reflect important reviews of the evidence regarding individual therapies, but they may be less helpful in determining the therapeutic approach to a specific patient. Dr. Sandborn noted that "the resulting recommendations can be considered a 'one-size-fits-all' approach that serves as a starting place, but don't really tell you how to practice." For example, "the ACG guidelines specify which drugs and doses are effective for first-line therapy, but have not yet incorporated all of the recent data regarding potential dose responses of the 5-ASAs, the idea of treating mild and moderate patients separately, and how to choose a maintenance dose as a consequence of the initial therapy."

Dr. Rubin further noted that, because of the lag time between the final publication of a guideline and the availability of an updated version, it is important to appreciate that guidelines "are representative of, perhaps, a point in time of some opinions and facts that were available at that time" and may not reflect the most current evidence and recommendations.

"These have been important guidelines, but do they really tell us how to treat an individual patient from

Table 2. ACG Classification of Ulcerative Colitis Severity.[1]

Disease Severity	Definition	
	Stool Frequency	***Systemic Signs/ Symptoms***
Mild	<4 stools/day, with or without blood	No systemic signs of toxicity Normal erythrocyte sedimentation rate
Moderate	>4 stools/day	Minimal signs of toxicity
Severe	>6 bloody stools/day	Evidence of toxicity (eg, fever, tachycardia, anemia, or elevated erythrocyte sedimentation rate)
Fulminant	>10 stools/day, with continuous bleeding	Toxicity, abdominal tenderness and distension, need for blood transfusion, colonic dilatation on abdominal plain films

beginning to end? It is important to understand where the data are adequate, definitive, and applicable, but the treating physician must also recognize the gaps within the body of good evidence, what is not reflected in the guidelines, and the questions that remain to be answered as pertains to the treatment of individual patients," summarized Dr. Hanauer.

Defining Disease Severity and Activity

Clinicians have long characterized UC severity on the basis of symptoms, signs, and laboratory values.[5] In 1955, Truelove and Witts published criteria for classifying UC severity that were based on a qualitative assessment of disease activity.[5] These criteria provided specific descriptions for mild and severe disease, but described moderate disease as an intermediate category between the two extremes of disease activity. Nearly 50 years later, the ACG practice guidelines classified the severity of disease from mild to fulminant/toxic megacolon according to the number of daily stools and signs of systemic toxicity (Table 2).[1]

Although moderate disease has not consistently been considered separately from mild disease,[1,5] population data suggest that most patients present initially with "moderately active" UC (Figure 1).[6] Using a population cohort of 1,161 UC patients in Copenhagen County, Langholz and associates estimated that the majority (71%) of UC patients presented with "moderate to high" disease activity, which was defined as "more than four bowel movements per day and/or daily presence of blood/pus, and/or systemic symptoms."[6] In contrast, 20% of patients presented with "low" activity, and 9.1% presented with fulminant disease during the first year of diagnosis.

Although the ACG practice guidelines provide a framework for classifying disease severity, recent data may help clinicians further characterize patients with moderate UC. Hanauer and colleagues recently performed subgroup analyses on data combined from two multicenter, randomized, double-blind, active controlled studies of similar design (ASCEND I & II) that investigated the efficacy of different dosages of delayed-release mesalamine.[7] Of the 687 patients randomized into these studies, 448 had moderately active UC as defined by a Physician's Global Assessment (PGA) score of 2. Multivariate logistic regression analysis of the patients' demographic and baseline characteristics identified the previous use of two or more UC medications as the only significant predictor of moderately active UC. This finding reflects the concept of refractoriness as it pertains to the disease course, not necessarily point-in-time disease activity.[7]

As defined by UC guidelines, disease activity represents a patient's severity at a particular point in time rather than a "longitudinal grading of severity," as noted by Dr. Rubin. However, disease activity is a dynamic process that changes over time and with various therapies. Data from a Scandinavian cohort of 1,161 patients demonstrate that about half of patients are in remission at any given time, with a 90% cumulative probability of relapse over the 25-year follow-up period.[8]

Dr. Sandborn noted, "What is 'disease activity?' Technically, it refers to what is happening at that snapshot in time. I liken it to the temperature in your house

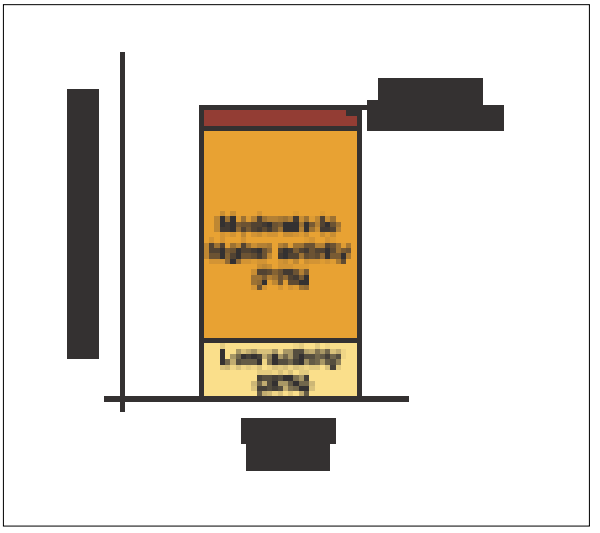

Figure 1. Distribution of disease severity at presentation.[6] UC=ulcerative colitis.

or your car. What does the thermometer say? But that doesn't really tell you how well the patient is responding to first-line or second-line—or third-line—therapy. So it is not a measure of refractoriness (pertaining to the disease course), which is a different concept from disease activity, and those are often mixed together."

Patients may be considered "moderate to severe," but, as Dr. Sandborn pointed out, "what we really mean is moderate and refractory." Dr. Rubin agreed with this concept, emphasizing the significant difference between "a patient classified as having moderately active disease at a single point in time, in contrast to a patient who has had moderately active disease for 6 months and is not responding to therapy."

Considerations in Patient Assessment

Endoscopy

In addition to confirming clinical findings in a patient with suspected UC, endoscopic findings can be useful in characterizing the severity and extent of disease.[1] According to Dr. Sandborn, "endoscopy, and particularly sigmoidoscopy, is substantially an extension of the physical examination and history and should be incorporated frequently into patient assessment." However, the degree to which endoscopic findings should influence treatment decisions remains controversial, particularly when they are incongruent with physical symptoms.

Laboratory Evaluation/Biomarkers

Various noninvasive laboratory markers, or biomarkers, may be useful in evaluating UC patients. The ACG guidelines consider erythrocyte sedimentation rate (ESR) a useful adjunct in differentiating disease severity in UC, with elevated levels more likely reflective of severe disease.[1] C-reactive protein (CRP), an objective marker of inflammation, has been shown to correlate well with disease activity in Crohn's disease.[9] Although more studied in Crohn's disease, CRP may be a useful marker of inflammation in UC patients and is more responsive to change than is ESR. With regard to the use of CRP in outpatients with UC, Dr. Sandborn noted that "the median baseline CRP of the patients receiving infliximab in the ACT 1 and 2 trials was similar to those observed in the Crohn's disease trials, and it decreased after therapy."[10] Given data indicating that CRP is an independent predictor of colectomy in UC patients,[11] CRP may be an important marker in patients with severe disease, as well.

Although not considered definitive information for making diagnostic or clinical decisions, serologic testing for perinuclear antineutrophil cytoplasmic antibodies (pANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA) may be helpful in differentiating between Crohn's disease and ulcerative colitis when other clinical features are not distinguishing.[1] Aside from an association of high ANCA titer with risk of chronic pouchitis,[12] serologic markers may have more prognostic utility in Crohn's disease than in UC.

Smoking History

Smoking history may provide useful information, as smoking appears to be protective for UC while increasing the risk for Crohn's disease.[13,14] The ACG practice guidelines address this by recommending that the patient assessment include an inquiry regarding "factors known to exacerbate symptoms of UC (eg, recent or past smoking cessation)." Dr. Rubin explained that "smoking history guides me in the obvious way of understanding the diagnosis. I'm highly suspect of someone who smokes more than a few cigarettes a day and has been carrying a diagnosis of UC. I worry that the patient may have Crohn's colitis and I look for other evidence that this is true." Dr. Hanauer added that "patients who develop UC after they stopped smoking are often the most refractory to medical therapies and are also at greatest risk for developing chronic pouchitis—a double whammy from the standpoint of therapeutic recommendations."

Quality of Life

UC has been shown to have a significant negative impact on patients' quality of life (QoL). Disease-related factors such as extent, severity, and pattern of relapse, as well as treatment-related factors such as side effects of medication and burden of administration, all affect QoL;[15] however, disease activity has been shown to be the most important factor that negatively affects QoL.[15,16]

In addition to objective signs and symptoms, the ACG practice guidelines suggest that patient assessment include attention to extraintestinal manifestations, general health concerns, and QoL issues.[1] Dr. Rubin noted that "during a brief, sometimes rushed clinic visit, patients don't necessarily fully share [with the physician] how this disease affects them, and it's an important issue." Clinicians should take the time to inquire about QoL issues and encourage their patients to share their concerns.

Optimizing 5-ASA Therapy in Mild-to-Moderate UC

Induction Therapy

According to the ACG practice guidelines, the oral 5-ASA agents are first-line therapies for inducing remission in mild to moderate distal and extensive UC.[1] Although the approach to therapy may be guided by disease severity and extent,[1] the initial dose is generally determined by disease severity. The guidelines

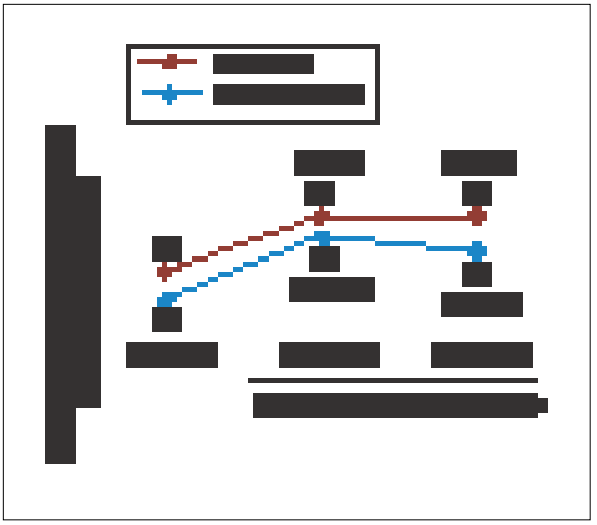

Figure 2. Dose-response of delayed-release mesalamine in patients with active mild to moderate UC.[23,24]

* Remission defined as a Sutherland (UC-DAI) ≤1 with a score of 0 for rectal bleeding and stool frequency, no mucosal friability, and ≥1-point reduction from baseline in sigmoidoscopy score.

Note: *P*-values represent active treatment groups vs placebo. †Lialda.

further indicate that effective doses for patients with mild to moderate disease range from mesalamine 2–4.8 g/day, sulfasalazine 4–6 g/day, balsalazide 6.75 g/day, and olsalazine 1.5–3 g/day.[1] Specific guidance for selecting an initial dose within those dosage ranges is not provided; it is, however, an important consideration given the evidence examining a potential dose-response relationship of these agents.

Is There a Dose-Response With the 5-ASAs? The existence of a dose response with the oral 5-ASAs was first evident in clinical trials of sulfasalazine.[17] Similarly, Levine and coworkers demonstrated a dose-response relationship with balsalazide when a dosage of 6.75 g/day was found superior to 2.25 g/day in 154 patients with active, mild-to-moderate UC.[18]

The dose-response with mesalamine has not been fully characterized as a clear relationship and has not been consistently demonstrated in controlled trials. A dose-response with delayed-release mesalamine was first suggested over 20 years ago, when Schroeder and associates demonstrated 4.8 g/day, but not 1.6 g/day, to be effective in 87 patients with mildly to moderately active UC.[19] In a subsequent trial of 250 patients with mild-to-moderate active disease, both 1.6 g/day and 2.4 g/day were significantly superior to placebo (43% vs 49%), however the higher dose appeared to be more effective in inducing "early stabilization of disease activity."[20] In controlled trials examining controlled-release mesalamine in active UC, a dose of 4 g/day was superior to 2 g/day in one study,[21] but was similar in efficacy to 2 g/day in another trial.[22]

More recently, controlled trials of a once-daily formulation of delayed-release mesalamine did not demonstrate obvious differences in treatment efficacy in patients receiving 2.4 g/day and 4.8 g/day.[23,24] In a randomized, double-blind, controlled trial involving 280 patients with mildly to moderately active UC, the percentage of patients achieving the primary end point (clinical and endoscopic remission at 8 weeks) did not differ between those receiving delayed-release mesalamine 4.8 g/day and 2.4 g/day (29.2% vs 34.1%, respectively, *P*=.485) (Figure 2).[23] Similarly, another double-blind, placebo-controlled trial in 343 patients with active mild-to-moderate colitis failed to demonstrate a difference in efficacy between delayed-release mesalamine 4.8 g/day and 2.4 g/day, as approximately 41% of patients in each dosage group achieved clinical and endoscopic remission at week 8 (Figure 2).[24]

The ASCEND (Assessing the Safety and Clinical Efficacy of a New Dose of 5-ASA) trials were 6-week, randomized, double-blind trials comparing the efficacy and safety of delayed-release mesalamine 2.4 g/day or 4.8 g/day delivered in 400-mg and investigational 800-mg tablets, respectively. In the ASCEND I trial, 4.8 g/day was not found to be superior to 2.4 g/day in achieving treatment success in the overall population of 301 patients with mild-to-moderate active disease.[25] Subgroup analysis of these data, however, revealed that the higher dose was more effective than the lower dose in the 180 patients with moderate disease, defined as a PGA score of 2 (72% vs 57%, *P*=.0384).[25] A similar difference in efficacy (of 4.8 g/d vs 2.4 g/d) among patients with moderate, but not mild, disease was apparent among the 386 patients observed in the ASCEND II trial.[26] In contrast, the ASCEND III trial showed a numerical advantage, but did not demonstrate a statistically significant difference in efficacy between the two doses in 772 patients with moderate disease (treatment success achieved in 70% and 66% of patients receiving delayed-release mesalamine 4.8 g/day and 2.4 g/day, respectively)[27] (Figure 3).[26,27]

Determining the Optimal Dose of 5-ASA for Induction Two recent subgroup analyses of the three ASCEND trials suggests that there may be a group of patients with difficult-to-treat moderate disease who may benefit from the higher doses. Analysis of the pooled ASCEND I and II populations (N=448 with moderate disease), and a separate analysis of the ASCEND III population, indicated that patients who had previously used two or more UC medications were more likely to benefit from higher

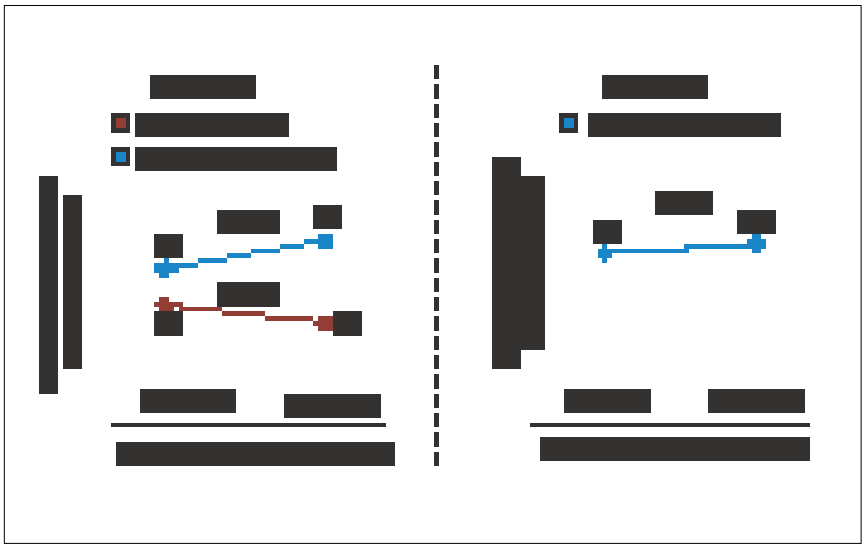

Figure 3. Dose-response of delayed-release mesalamine in mild vs moderate UC.[26,27]

ASCEND II: Treatment success defined as response or remission. Response defined as improvement in PGA and ≥1 other clinical assessment with no worsening in any other clinical assessment. Remission defined as PGA and all clinical assessments = 0.

ASCEND III: Treatment success defined as improvement from baseline at 6 weeks in the PGA (based on clinical assessments of rectal bleeding, stool frequency, and sigmoidoscopy) and no worsening in any of the individual clinical assessments.

*Asacol

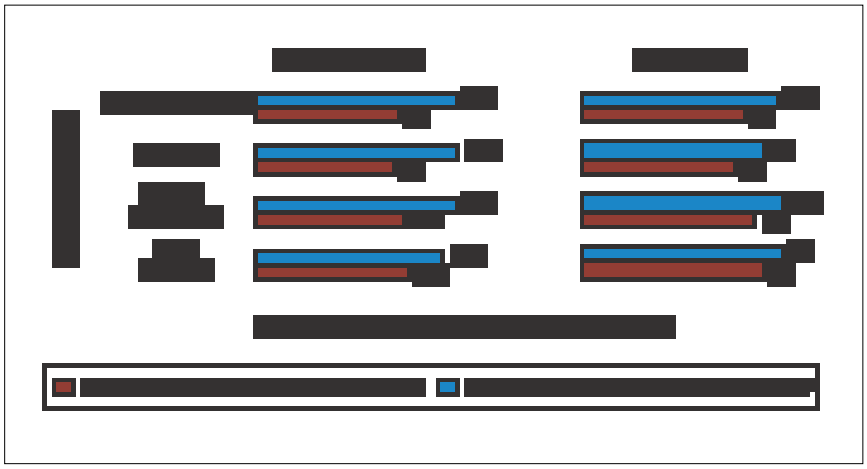

Figure 4. History of more difficult-to-treat disease predicts response to higher dose for moderate UC.[7,27]

*P<.05; †Asacol.

doses (4.8 g/day) of mesalamine (Figure 4).[7,27] Other characteristics associated with greater response to the higher dose were previous use of steroids, rectal therapies, or oral 5-ASAs.[7]

Regarding the evolution of this evidence, Dr. Hanauer stated, "It is reassuring that our clinical or our anecdotal experience has been borne out by the subgroup analyses of the trials, that it is patients who are failing low doses of 5-ASA, patients who have previously been on multiple drug therapies, or patients who have been on steroids that appear to benefit from the higher-dose treatment (up to 4.8 grams) to induce remission."

Maintenance Therapy

The ACG practice guidelines consider the oral 5-ASAs effective for maintaining remission in mild-to-moderate distal and extensive disease, with benefits noted from sulfasalazine dosages ranging from 2 to 4 g/day and mesalamine dosages of up to 4 g/day.[1] However, the optimal 5-ASA dose for maintaining remission in mild or moderate UC remains uncertain.

Regarding the maintenance of mild or moderate UC with 5-ASA, Dr. Sandborn noted that "it is very difficult to unlink induction (dose) from maintenance (dose)." A reasonable approach may be to stratify the dosage at the induction phase (as discussed above) and then continue the dose for maintenance.

In 2005, Sandborn and colleagues reviewed the medical records of 411 UC patients who had experienced a disease flare that had been successfully treated with delayed-release mesalamine. One year after induction, nearly 80% of patients with moderate or severe disease

who maintained the mesalamine dose used for induction were rated as having a normal PGA, compared with 53% of those whose maintenance dose was reduced.[28] Thus, in that retrospective study, maintaining the same dose of mesalamine used to induce remission significantly increased the likelihood of receiving a "normal" PGA one year after induction.

The induction regimen that was used plays an important role in determining the maintenance regimen for a given patient. For example, in patients with distal colitis who were initially treated with a rectal 5-ASA formulation, Dr. Rubin noted that "despite the benefit of combined therapy for maintenance, most patients don't find that to be convenient and are less willing to adhere to such a regimen. So when I have discontinued mesalamine suppositories or enemas, it is the same as reducing the dose of 5-ASA by 1 to 4 g/day, and I am committed to increasing or maintaining these patients on higher daily oral doses" Dr. Sandborn agreed that "maximizing oral therapy is a more practical scenario for the long term" in patients who are unable to tolerate the withdrawal of rectal therapy. Patients who required steroids for induction may also need higher doses of 5-ASAs to maintain remission.

Although the efficacy of 5-ASA maintenance in patients who received induction therapy with azathioprine (AZA)/6-mercaptopurine (6-MP) or biologic agents remains uncertain, the growing body of evidence demonstrating chemoprotective effects of 5-ASAs[29] suggests that it is reasonable to continue these agents in patients who are receiving immunosuppressant or biologic therapy, in order to reduce the likelihood of CRC. Although a significant chemoprotective effect has not been demonstrated in all studies,[30] a meta-analysis of 9 studies involving 1,932 UC patients found that 5-ASA use conferred a 49% protection rate against CRC and CRC/dysplasia.[29] Given these findings, Dr. Sandborn noted that "when I add an immunosuppressive or biologic, as soon as the patient is in remission and off steroids, I reduce the 5-ASA dose to 1.2–2.4 g and administer it once a day for the purpose of potential chemoprevention."

An additional consideration for continuing 5-ASA maintenance in patients receiving concomitant thiopurines is the potential for the 5-ASAs to reversibly inhibit thiopurine methyltransferase (TPMT), a key enzyme in thiopurine metabolism.[31,32] Concomitant use of oral 5-ASAs with these agents has been reported to result in higher concentrations of 6-thioguanine (6-TGN) and consequent bone marrow suppression.[31,33] Observational studies examining this interaction have reached varying conclusions,[34,35] whereas prospective intervention trials measuring 6-TGN levels have generally found that the addition of an oral 5-ASA agent increased 6-TGN levels to varying degrees.[31,36,37] "Given an average 20% difference in AZA/6-MP metabolite concentration," observed Dr. Sandborn, "there will be instances where it could have either a clinical effect or a toxicity effect, but most of the time it won't. Other than being aware of this modest drug interaction, I think you probably just deal with the azathioprine as you ordinarily would for monitoring and dose adjustments."

Considerations in Treatment Outcomes

Quality of Life

Given its significant impact on patients with UC, QoL is frequently a secondary end point of interest in UC clinical trials.[15,38] In fact, as Dr. Hanauer pointed out, "quality of life is one of the most important aspects of treatment from a patient's perspective."

Large randomized controlled trials have demonstrated significant improvements in QoL with both mesalamine[15,39] and infliximab[38] in UC patients. Analyzing data from the Active Ulcerative Colitis 1 and 2 (ACT 1 and 2) trials, Feagan and coworkers found that infliximab therapy was associated with significant improvements in health-related QoL as determined by Inflammatory Bowel Disease Questionnaire (IBDQ) scores as well as the physical and mental component summaries of the Short Form 36 (SF-36).[38] Further, the benefit in QoL observed with infliximab maintenance therapy was sustained through 1 year.

At least two controlled trials have demonstrated the ability of mesalamine to improve QoL in UC patients.[15,39] Robinson and colleagues found that 8 weeks of treatment with controlled-release mesalamine 2 g and 4 g daily was superior to placebo in improving function-related QoL parameters, including 5 clinical symptoms and 7 general life capabilities ($P<.05$).[39] In an analysis of the combined ASCEND I and II trials, Irvine and associates used the IBDQ to assess the impact of delayed-release mesalamine on QoL in patients with UC. The results showed that delayed-release mesalamine significantly improved QoL in patients with mildly and moderately active UC, and this improvement was evident in as early as 3 weeks.

Dr. Rubin noted that "UC is a disease that affects the bowel and social functioning to a greater degree than other chronic illnesses. We've learned that therapies that adequately control the disease also significantly improve quality of life."

Should Asymptomatic Patients Be Treated to Endoscopic Remission?

The ability to achieve and/or maintain mucosal healing in UC patients has been demonstrated with a number of agents, including corticosteroids,[5] delayed-release

mesalamine,[24,40] and infliximab.[10] However, as Dr. Rubin observed, "the definition of mucosal healing varies among clinical trials and often isn't held to the most rigorous standard of what we would consider to be a normal intact mucosa but allows some degree of inflammation."

Although it has long been believed that an effective therapy for UC should control symptoms as well as restore and maintain the integrity of the bowel mucosa,[41] the clinical relevance of mucosal healing remains uncertain. Several studies suggest that endoscopic and histologic healing may have protective effects against dysplasia[42-44] and recent data have associated mucosal healing with reduced risk of future colectomy in UC patients.[45] However, until data are sufficient to characterize the impact of mucosal healing on short- and long-term outcomes in UC, Dr. Sandborn believed that it would be impractical, difficult, and expensive to "insist on routine endoscopic exams to assure remission."

Therapeutic Monitoring and Screening Practices in Ulcerative Colitis

5-ASAs

The oral 5-ASA agents have been associated infrequently with nephrotoxicity, occurring at an estimated mean rate of 0.26% per patient-year.[46,47] Although reported most frequently within the first 12 months of use, nephrotoxicity related to 5-ASA use has also been reported to occur after several years of use. Withdrawal of therapy leads to recovery of renal function in most cases,[47] but 5-ASA–related nephrotoxicity may be irreversible.[46]

Although the approved labeling for the various oral 5-ASA agents recommends periodic monitoring of renal function,[22,48-51] the optimal monitoring schedule is not specified in the product labeling or in the ACG practice guidelines.[1] Dr. Rubin commented, "I monitor renal function (blood urea nitrogen and creatinine) at baseline, before starting therapy, and then twice a year using a basic metabolic panel (BMP)." Several authors recommend obtaining serum creatinine measurements at baseline, periodically during the first year, and once yearly thereafter.[46,47] Because other complications associated with 5-ASAs (eg, hepatitis, pancreatitis, pericarditis, pneumonitis) are extremely rare, no specific monitoring strategies have been recommended; however, clinicians should be aware of them.

Corticosteroids

The ACG guidelines address the fact that corticosteroids can cause emotional and psychiatric disturbances, and are associated with significant toxicities (that can involve nearly every organ system and many metabolic activities) including infections, ocular complications, metabolic disease, hyperglycemia, sodium and fluid retention, and hypokalemia.[1] "When I start a patient on steroids," Dr. Rubin explained, "I always discuss that it's a risky therapy for a variety of reasons and that we use them only short term, and I emphasize to clinician colleagues the importance of up-front communication with patients about these issues." Because the development of metabolic bone disease is a significant concern in IBD patients, the ACG and American Gastroenterological Association (AGA) recommend dual energy x-ray absorptiometry (DXA) bone testing for patients with a number of risk factors for osteoporosis (eg, smoking, low body mass, sedentary lifestyle, hypogonadism, family history, nutritional deficiencies).[1,52] Whether or not a baseline DXA scan should be obtained in all UC patients on steroids is uncertain. Dr. Sandborn noted that "although I don't routinely obtain a baseline bone density in everyone who is prescribed what's intended to be a 2–3-month course of steroids, I wouldn't argue with anyone who says you should do that. It may be the right thing to do."

Thiopurines

The biologic activity of the thiopurines (AZA/6-MP) is attributed primarily to the accumulation of intracellular 6-TGNs, which are associated with both the therapeutic benefit and myelotoxicity (ie, leukopenia, anemia, thrombocytopenia, pancytopenia) associated with these agents.[53,54] The formation of 6-TGNs is inversely related to the activity of TMPT,[55] an enzyme that is controlled by a common genetic polymorphism and varies widely between individuals. Approximately 89%, 11%, and 0.3% of Caucasian subjects have high, intermediate, and undetectable TPMT activity, respectively.[56] Because individuals with genetic polymorphisms resulting in intermediate or low TMPT activity may accumulate 6-TGNs and develop leukopenia,[57,58] prospective TPMT genotyping has been proposed as a means of identifying patients at risk for thiopurine-related bone marrow toxicity or adjusting the dose based on the patient's pharmacogenetic profile.[55] Additionally, thiopurine metabolite (6-TGN, 6-methylmercaptopurine [6-MMP]) monitoring has been suggested as a means for individualizing thiopurine therapy in order to optimize clinical benefit while minimizing toxicity.[55]

Despite retrospective data supporting the use of prospective TPMT genotyping/phenotyping and metabolite monitoring,[32,55] the ACG practice guidelines state that prospective studies are needed before the routine use of these assays can be recommended.[1] In contrast, the AGA does recommend measuring TPMT at baseline.[52] Measuring TPMT activity in patients before initiating thiopurine therapy "would reduce the frequency of leukopenia by about 25%," estimated Dr. Sandborn. "If the patient is

homozygous low for TPMT activity, I usually don't treat [him or her] with thiopurines. If [he or she is] intermediate, I reduce the dose by about 50%, which is going to mean AZA 1 mg/kg, whereas if they have normal TPMT activity, I give them AZA 2 mg/kg. I'm going straight to my target dose based on their TPMT." These tests may help guide therapy; however, the ACG (and the AGA) guidelines continue to emphasize the importance of traditional routine monitoring of complete blood counts (CBC), liver laboratory tests, and clinical response to thiopurine therapy.[1,52]

Colorectal Cancer Screening

Surveillance colonoscopy remains a key strategy for the secondary prevention of CRC. The ACG practice guidelines recommend annual or biannual surveillance colonoscopy, with multiple biopsies at regular intervals for all patients with left-sided disease or pancolitis, beginning 8 to 10 years after the onset of colitis.[1] For patients with UC and primary sclerosing cholangitis (PSC), however, colonoscopic surveillance should begin as soon as these coexisting diagnoses are established.[1] Dr. Rubin added that patients who had proctitis "deserve a colonoscopy after 8 years, as well, to make sure disease progression has not occurred. So I would actually say everyone gets a screening exam at year 8 to restage the extent of their disease." Given the increased risk of CRC associated with family history,[42,59] it may be reasonable to survey patients with a positive family history more often, but it is uncertain if surveillance should begin sooner in these patients compared with the general UC population.

The frequency of colonoscopy varies based on factors such as duration and extent of disease, age, family history, and presence of PSC.[1] Although a typical subsequent screening interval in patients with no dysplasia at the first endoscopy may be 1 to 2 years, it is reasonable to modify the screening interval based on how well-controlled the disease has been and the compounded risk factors. Factors such as PSC and a history of sporadic adenoma, for example, should prompt more frequent surveillance. Alternative strategies to colectomy are being explored for selected patients with adenomatous lesions (discreet polypoid dysplasia), and Dr. Sandborn believes that this population needs very close follow-up: "After finding dysplasia of some type, if colectomy is not performed, I would re-endoscope the patient within 3–6 months, and I would almost certainly do chromoendoscopy with dye spray or narrow band imaging with the next endoscopy." The understanding regarding degree of inflammation as a risk for neoplasia in colitis may lead to modified follow-up of patients as well, but currently it is unclear how this will factor in future surveillance guidelines. In the meantime, "it is reasonable to identify patients for more frequent surveillance based on the severity of inflammation during their previous examination; however, specific guidelines have not been forthcoming" noted Dr. Rubin.

The ACG practice guidelines further recommend that random biopsies for dysplasia be obtained at every 10 cm of mucosa,[1] with extra focus on nodules, masses, or strictures. This standard has not changed since the guidelines were published, although Dr. Rubin suggested adding "irregular mucosa" to the list of findings worthy of extra focus. "And I don't mean just inflamed mucosa, of course, but irregular in comparison to the surrounding inflamed mucosa."[60]

Conclusion

Several sets of clinical practice guidelines are currently available for assisting clinicians in the care of UC patients. Although these guidelines provide evidence-based recommendations for clinical practice, they may be less helpful in individualizing the approach to therapy for given patients.

The ACG guidelines stratify UC severity—and subsequent treatment recommendations—according to various clinical symptoms and signs of systemic toxicity. In clinical practice, endoscopic findings and biomarkers (CRP, ESR) may also be helpful in defining disease severity. Although not consistently separated from mild disease, moderate disease may constitute the largest segment of the UC population.

The ACG clinical practice guidelines outline a general management approach to UC based on the anatomic extent and severity of disease. Although the oral 5-ASAs are effective and remain first-line therapy for induction of remission in mild-to-moderate UC, the evolution of data regarding a dose response of these agents suggests that patients with mild and moderate disease may require different therapeutic approaches. Whereas patients with mild disease tend to respond well to conventional 5-ASA doses (ie, 2.4 g/day delayed-release mesalamine), recent data demonstrate the existence of subgroups of patients with more difficult-to-treat, moderate disease that may benefit from higher doses (ie, 4.8 g/day delayed-release mesalamine). Patients more likely to benefit from the higher dose include those who do not respond to low doses of 5-ASAs, those who have received multiple drug therapies, or those who have required corticosteroids.

Although the oral 5-ASAs are also considered effective for maintaining remission in mild to moderate UC, the optimal maintenance dose of these agents remains uncertain. The maintenance regimen is likely to be influenced by the induction regimen, with higher doses of 5-ASAs considered reasonable for patients who required corticosteroids for induction and patients with distal

disease who have recently been withdrawn from rectal therapy. Given recent evidence suggesting their chemoprotective properties, many clinicians continue 5-ASAs in patients receiving immunosuppressants or biologic agents in an attempt to reduce the risk of CRC.

Specific monitoring strategies addressed by the ACG clinical practice guidelines include obtaining a baseline DXA scan for patients at risk for osteoporosis who are to receive corticosteroids and routine CBCs and liver function tests for patients receiving thiopurines. Although the ACG guidelines do not recommend the routine use of TPMT and thiopurine metabolite assays, measuring TPMT activity prospectively can reduce the incidence of leukopenia associated with these agents (and TPMT measurement is advocated by the AGA). Due to the rare development of nephrotoxicity associated with the oral 5-ASAs, baseline and periodic monitoring of renal function is advised for patients receiving these agents.

Surveillance colonoscopy remains a key strategy for the secondary prevention of CRC, although the frequency of examinations and optimal screening interval may vary based on a number of patient factors (ie, family history, presence of PSC, history of dysplasia or sporadic adenomas, activity of disease).

Although several questions regarding the optimal management of UC remain, the discussions summarized in this supplement expand the information provided in current practice guidelines by drawing on the collective experience of clinicians who are involved in clinical research and in the daily care of UC patients.

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Notes

Posttest Questions *Please print your answers in the area provided below (Certificate information.)*

1. Ulcerative colitis (UC) practice guidelines developed by the American College of Gastroenterology (ACG) and the British Society of Gastroenterology consider the strongest evidence for clinical recommendations to be derived from

   a. Meta-analyses
   b. Randomized controlled trials
   c. Descriptive studies
   d. Case-control analytic studies

2. The current ACG clinical practice guidelines on UC define disease severity on which of the following parameters?

   a. Clinical symptoms and signs of systemic toxicity
   b. Smoking status
   c. Anatomic extent of disease
   d. All of the above

3. Which of the following statements regarding disease activity in UC is/are true?

   a. Refractoriness is a concept pertaining to disease course rather than disease activity
   b. UC activity is dynamic and changes over time
   c. Population data suggest that about half of UC patients are in remission at any given point in time
   d. All of the above

4. Which of the following statements regarding the use of biomarkers in UC is/are true?

   a. Serologic markers (pANCA, ASCA) are widely believed to have more prognostic utility in UC than in Crohn's disease
   b. ESR is more responsive to change in UC patients than is CRP
   c. CRP has been found to be an independent predictor of colectomy
   d. All of the above

5. Recent studies examining the dose-response of the oral 5-ASAs

   a. Have consistently demonstrated a statistically significant benefit of higher-dose (4.8 g/day) versus lower-dose (2.4 g/day) mesalamine for the treatment of mild to moderate UC
   b. Have demonstrated that patients with mild disease respond better to higher-dose mesalamine
   c. Suggest the existence of a subgroup of difficult-to-treat patients with moderate disease who may benefit from higher doses of mesalamine
   d. All of the above

6. Patients who are likely to need higher doses of oral 5-ASAs to maintain remission include

   a. Patients who required delayed-release mesalamine 2.4 g/day to achieve remission
   b. Patients with distal disease who have been withdrawn from rectal therapy
   c. Patients with mild disease
   d. All of the above

7. Which of the following statements regarding the role of oral 5-ASAs as maintenance therapy is/are true?

   a. 5-ASAs may be continued for their chemoprotective benefits in patients receiving immunosuppressants or biologics
   b. 5-ASA may inhibit TPMT activity, resulting in higher 6-TGN concentrations in patients receiving thiopurines
   c. Lower doses (1.6–2.4 g/day) appear to be sufficient for providing chemoprotective benefit
   d. All of the above

8. Which of the following statements regarding therapeutic monitoring in UC is/are true?

   a. TPMT measurement and metabolite monitoring are recommended to replace traditional CBC monitoring for evidence of bone marrow suppression in patients receiving thiopurines
   b. The estimated rate of nephrotoxicity with the oral 5-ASAs is 7.5% per patient-year
   c. Renal function should be monitored periodically in patients receiving oral 5-ASAs
   d. All of the above

9. Which of the following medications has/have been studied and reported to improve quality of life in patients with UC?

   a. Delayed-release mesalamine
   b. Controlled-release mesalamine
   c. Infliximab
   d. All of the above

10. Key strategies for surveillance colonoscopy include

    a. Annual or biannual surveillance colonoscopy for all patients with left-sided disease or pancolitis beginning 8 to 10 years after the onset of colitis
    b. Beginning surveillance as soon as coexisting diagnoses of UC and primary sclerosing cholangitis are made
    c. Varying the frequency of colonoscopy based on patient factors such as duration and extent of disease, age, family history, and presence of primary sclerosing cholangitis
    d. All of the above

Activity Evaluation Treatment Guidelines and Clinical Practice: Optimizing Foundational Therapies for Ulcerative Colitis

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EVALUATION

1. Please rate how well the following learning objectives were achieved. **Poor** **Excellent**

Participants should be able to:

• Define the American College of Gastroenterology (ACG) Practice Guidelines as they relate to the goal of effective management of ulcerative colitis (UC)	1	2	3	4	5
• Explain how disease activity can affect quality of life for patients with UC	1	2	3	4	5
• Evaluate clinical severity and extent of disease in patients with UC	1	2	3	4	5
• Compare the dose responses of various currently available formulations of 5-aminosalicylates (5-ASA)	1	2	3	4	5
• Identify factors that may differentiate optimal treatment strategies for patients with mild or moderate UC	1	2	3	4	5
• Discuss the role of 5-ASA in the treatment of patients who require biologic or immunomodulator therapy	1	2	3	4	5
• Define optimal maintenance strategies for patients with UC	1	2	3	4	5
• Examine the potential for 5-ASAs as chemopreventive agents	1	2	3	4	5
• Define the role of therapeutic monitoring for patients using foundational agents	1	2	3	4	5
• Design therapeutic strategies to optimize the use of foundational therapies for the management of mild, moderate, or severe UC and reduce the risk of complications for patients with UC	1	2	3	4	5

2. This activity was fair, balanced, and free of commercial bias. ✹ Yes ✹ No

If you felt the activity was biased, please explain: _____

3. Overall comments: _____

_____

4. What questions do you still have? _____

_____

5. Suggested topics and/or speakers you would like for future activities: _____

_____

6. This educational activity has contributed to my professional effectiveness and improved my ability to do the following:

	Strongly Disagree				**Strongly Agree**
• Identify patients for treatment	1	2	3	4	5
• Treat/manage patients	1	2	3	4	5
• Improve standard of care	1	2	3	4	5

7. After participating in this activity, will you make any changes in your practice? ✹ Yes ✹ No

(If yes, please explain.) _____

_____

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