

The following abstracts, from medical journals containing literature on inflammatory bowel disease, were selected for their relevance to this roundtable symposium, and to a managed care perspective.

Overview of Treatments for Ulcerative Colitis and Crohn's Disease

Differentiating and diagnosing ulcerative colitis and Crohn's disease have required reliance on nonspecific clinical and histologic patterns that are often obfuscated by intercurrent infections, iatrogenic events, medication, or surgery. Therapeutic choices are usually determined by the location and severity of disease and response to treatment. In an review of currently available therapeutic options, the author provides a description of current therapy, including indications, usage, limitations, and effectiveness of corticosteroids, aminosalicylates (sulfasalazine and mesalamine), immunomodulatory drugs (azathioprine and mercaptopurine), cyclosporine, methotrexate, antibiotics, nutritional therapy, and supportive therapy (antidiarrheal and antispasmodic drugs, cholestyramine, vitamin supplementation, and antidepressants for chronic pain). In a summary of future therapies, the author outlines prospects that warrant further investigation or modification, including arachidonic acid derivatives, immune-modifying drugs, including lymphocyte apheresis, proinflammatory cytokines, anti-inflammatory cytokines (interleukin-10 or -11) and mediators (interleukin-1 receptor antagonists). A long-term perspective on treatment is required, ie, one that will enhance the mucosal anti-inflammatory effects of inflammatory bowel disease, yet have a minimal systemic impact on the patient.

Hanauer SB. Inflammatory bowel disease: Drug therapy. *N Engl J Med* 1996;334:841-848.

5-ASA Suspension Enema vs Oral SAS

A randomized, double-blind, double-dummy study was conducted to compare treatment response to mesalamine (5-ASA) suspension enema with oral sulfasalazine (SAS) in patients with active mild to moderate distal ulcerative colitis. Patients ages 18 through 65 were enrolled for a 6-week treatment period. At screening, baseline, and at biweekly visits, patients were given 6-mL enemas with either 4 g of 5-ASA or placebo for administration at bedtime and tablets with either 500 mg of SAS or placebo with directions to take 2 tablets qid. A total of 19 patients was assigned to the 5-ASA treatment group; 18 were assigned to SAS treatment. No patient had disease extending to more than 50 cm. Assessments were based on the Disease Activity Index (DAI), Clinical Global Improvement (CGI) scores, and Patient Global Improvement (PGI) scores. Mean DAI scores revealed significant improvement from baseline in both groups. Mean DAI scores revealed that both treatment groups showed significant improvement from baseline. CGI scores showed that 94% of 5-ASA patients were either "Very Much Improved" or "Much Improved" versus 77% of patients in the SAS group. PGI scores also showed greater improvement more quickly in the 5-ASA treatment group than in the SAS group. Adverse events occurred more frequently in the SAS group than in the 5-ASA group, causing 3 SAS patients to withdraw from the study. Rectal administration of 5-ASA was shown to be as effective as oral SAS for active distal ulcerative colitis, and was associated with fewer and more moderate adverse events.

Kam L, Cohen H, Dooley C, et al. A comparison of mesalamine suspension enema and oral sulfasalazine for treatment of active distal ulcerative colitis in adults. *Am J Gastroenterol* 1996;91:1338-1342.

5-ASA Enemas for Distal Ulcerative Colitis

A 4-week, open-label, compassionate-use study was conducted to verify efficacy of 5-aminosalicylic acid (5-ASA) enemas. Patients with mild-to-moderate distal ulcerative colitis (N = 666) were followed. Although 39 of these subjects did not meet selection criteria owing to disease extending beyond 50 cm, presence of Crohn's disease, or colitis of other etiologies, they were included in the study. Previous and/or current medication for most patients included sulphasalazine (81.8%), steroid enemas (76.2%), and systemic steroids (54.8%). One 4 g 5-ASA enema was administered nightly over a 4-week period. Disease activity was assessed at baseline and at 2 and 4 weeks. Improvements were noted in each category, including stool frequency (40.3% at week 2 and 48.6% at week 4), rectal bleeding (62.5% at week 2 and 71.1% at week 4), mucosal appearance (63.8% at week 2 and 76.9% at week 4), physician's overall assessment (54.5% at week 2 and 70.5% at week 4). Patients with disease less than 30 cm showed a significantly greater reduction in disease activity after 2 weeks (44%) compared with patients with disease beyond 30 cm (33.5%). At week 4, improvement increased to 56.8% and 51.2%, respectively, for these patients. Improvements were equally noted in both first-episode and multi-episode patients. 5-ASA enemas were found highly effective for distal ulcerative colitis.

Robinson MG. Efficacy of 5-aminosalicylic acid enemas in the treatment of distal ulcerative colitis. *Can J Gastroenterol* 1990;4:468-471.

Efficacy and Safety of 5-ASA Enemas Assessed

Patients with ulcerative colitis (N = 153) with involvement of up to 50 cm of distal colon were enrolled in a 6-week, double-blind study to confirm the efficacy and safety of 4-g 5-aminosalicylic acid (5-ASA) enemas. Patients were randomized to receive either active medication (n = 76) or placebo (n = 77). Concurrent use of oral steroids or sulfasalazine was allowed in some patients. A disease activity index (DAI) assessed four variables: stool frequency, rectal bleeding, sigmoidoscopic appearance of mucosa, and physician's assessment of disease severity. A statistically significant reduction in bleeding occurred within 3 days of enema treatment with 5-ASA. The mean DAI for patients decreased 55% for patients receiving 5-ASA and 22% for patients on placebo. The number of previous episodes, duration of current episode, or duration of disease had no effect on the response to treatment. More patients on placebo (11) than on 5-ASA (9) reported side effects. However, side effects in both groups were insignificant. Response to treatment was unaffected by concurrent use of sulfasalazine, but concurrent steroid therapy markedly reduced the response to 5-ASA. Efficacy (a statistically significant reduction in bleeding) was noted within 3 days of treatment with 5-ASA.

Sutherland LR, Martin F, Greer S, et al. 5-aminosalicylic acid enema in the treatment of distal ulcerative colitis, proctosigmoiditis, and proctitis. *Gastroenterol* 1987;92:1894-1898.

Treating Primary Sclerosing Cholangitis

Although the efficacy of ursodeoxycholic acid (ursodiol) for the treatment of primary sclerosing cholangitis has not been proved, it is widely used for this purpose. In a study by Lindor et al on ursodiol for primary sclerosing cholangitis, ursodiol was reported to significantly improve the results of biochemical tests, but it had no beneficial effect on the clinical endpoints of the study: time to treatment failure and survival without liver transplantation. Ursodiol also did not improve symptoms or histologic liver findings. Lack of progress in treating this disease include a poor understanding of causative factors, inability to make an early diagnosis, and lack of clinical trials using varying drug combinations to determine more effective treatment. The author recommends that (1) patients with inflammatory bowel disease be screened annually with measurements of serum alkaline phosphatase, aminotransferases, or both, to determine if histologic findings are consistent with primary sclerosing cholangitis and to consider enrolling patients in treatment trials; (2) a panel of experts convene to establish diagnostic criteria that include biochemical, serologic, and histologic factors; (3) treatment trials include patients with early disease who do not have radiographic finding; (4) studies be conducted in which combinations of different classes of drugs are used; and (5) endpoints be refined to include normalization of blood-test results and reduction in portal inflammation and bile-duct necrosis to establish efficacy.

Kaplan MM. Toward better treatment of primary sclerosing cholangitis, editorial. *N Engl J Med* 1997;336:719-721.

Quantitative Study of Enema Distribution

A study was conducted to verify a technique for labeling 5-ASA with a technetium-99m label (^{99m}Tc) in vitro and to quantify the distribution of [^{99m}Tc]5-ASA in the colon of patients with left-sided ulcerative colitis over a 4-hour period. The in vitro study confirmed that only minimal amounts of radioactivity were absorbed from the gastrointestinal tract. Eight patients were then studied in whom active left-sided ulcerative colitis was confirmed through colonoscopy. Patients underwent three scintigraphic studies within 7 days, during which they received an enema of 4 g of 5-ASA radiolabeled with 150 mCi of ^{99m}Tc . 5-ASA reached the ascending colon in four patients, the transverse colon in two, and the descending colon in two. Initially, nearly 40% of the 5-ASA was detected in the sigmoid and descending colon. Within 60 minutes, over 50% of the enema had reached beyond the rectum in five of eight patients. Within 1 to 4 hours, the amount reached a maximum of 60% in these locations. The spread of the enema to or beyond the diseased area was noted during the study period. Colonic distribution of [^{99m}Tc]5-ASA was reproducible when measured in the same patients on different days. Radiation dosimetry calculations indicated that the lower large intestine received 171 mrad and the total body received 2 mrad/150 mCi following rectal administration.

Vitti RA, Meyers F, Knight LC, et al. Quantitative distribution of radiolabeled 5-aminosalicylic acid enemas in patients with left-sided ulcerative colitis. *Dig Dis Sci* 1989;34:1792-1797.

Rectal Absorption Study of 5-ASA

A study was performed to determine peak plasma levels and urinary excretion capabilities of 5-aminosalicylic acid (5-ASA) following administration as a high-dosage enema. Three separate experiments were conducted: the first on patients with ulcerative colitis in remission to study the relationship of absorption to the volume and concentration of 5-ASA; a second on patients with active left-sided disease to determine the absorption of 5-ASA in the presence of active inflammation; and a third on patients with proctitis, sigmoiditis, and in patients with splenic involvement to determine if 5-ASA would accumulate in the blood following daily enemas. Following rectal administration, absorption of 5-ASA was found variable. Mean peak plasma concentrations of 5-ASA were greater than those noted following administration of oral sulphasalazine and 5-ASA as a slow-release preparation, but were lower than those noted following oral administration of 4 g 5-ASA for tuberculosis. Concentrations were significantly lower when compared with the therapeutic range of salicylates. Negligible levels of total 5-ASA were recorded after 24 hours, possibly owing to evacuation by patients immediately following the experiment. Urinary recovery in 24-hour urine was 19% (ranging from 10% to 37%) in patients with disease in remission, and 10% (ranging from 2% to 18%) in patients with active disease. High dosage enemas of 5-ASA were determined suitable for topical treatment of ulcerative colitis provided renal function is normal. However, it is recommended that renal function tests be conducted serially to monitor for possible nephrotoxicity.

Campieri M, Lanfranchi GA, Boschi S, et al. Topical administration of 5-aminosalicylic acid enemas in patients with ulcerative colitis. Studies on rectal absorption and excretion. *Gut* 1985;26:400-405.

Distribution of 5-ASA Enema

The distribution of intrarectally administered 5-aminosalicylic acid (5-ASA), designed to simulate nocturnal administration, was studied on 3 consecutive days in 8 patients (5 women and 3 men, ages 18 to 48) with active distal ulcerative colitis extending 12 to 40 cm from the anal verge. Supine anterior and posterior images of radiolabeled enema were obtained at 0, 30, 60, 120, and 240 minutes. Variations from day to day were insignificant. Mesalamine enema was initially confined to the rectum. At 1 hour, isotope had moved toward the descending colon. At 2 hours, it was distributed between the rectum and descending colon. At 4 hours, it had migrated to the splenic flexure. The 60-mL, 5-ASA enema distributed itself from the rectum to the splenic flexure in patients with segmental colitis of the sigmoid and descending colon. Medication remained most highly concentrated in the sigmoid colon throughout the study. After 4 hours, 38% had migrated to the descending colon, supporting the use of intrarectally administered 5-ASA enema for segmental colitis of the sigmoid and descending colon.

Chapman NJ, Brown ML, Phillips SF, et al. Distribution of mesalamine enemas in patients with active distal ulcerative colitis. *Mayo Clin Proc* 1992;67:245-248.

5-ASA Suppositories

A double-blind, randomized, placebo-controlled trial was conducted over a period of 2 weeks on 40 patients (21 male and 19 female) with active hemorrhoid disease. Patients were evenly divided and randomized to receive one 5-aminosalicylic acid (5-ASA) (500 mg) suppository bid for 2 weeks or one placebo suppository bid for the same period of time. Concurrent treatment for hemorrhoids was prohibited. After 2 weeks, 75% of patients in the 5-ASA group were in remission or had improved, whereas only 40% of patients in the placebo group showed improvement. In the 5-ASA group, pain, bleeding, mucus and tenesmus was reduced in 70%, 78%, 70%, and 79% of patients, respectively. In the placebo group, percentage of improvement in these categories was 35%, 16%, 33%, and 33%, respectively. A total of 70% of patients in the 5-ASA group showed improvement or were in remission, but only 35% of patients in the placebo group showed improvement. For all parameters, both clinical and endoscopic, 5-ASA suppositories were significantly more effective than placebo and had lessened the intensity of all symptoms and significantly decreased congestion of the hemorrhoidal plexus.

Gionchetti P, Campieri M, Belluzzi A, et al. 5-ASA suppositories in hemorrhoidal disease. *Can J Gastroenterol* 1992;6:18-20.

CME QUESTIONS: TEST #0397S5

Instructions

After reading this Special Report, select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is one hour. CME credits are distributed on a yearly basis.

1. **Which of the following statements is true?**
 - a) assessment of the mucosal extent of ulcerative colitis is sufficient to determine initial therapy
 - b) only patients with fulminant pancolitis will have systemic involvement
 - c) treatment of ulcerative colitis can be determined only after the assessment of the extent, the severity of inflammation, and the systemic burden on the patient
 - d) left-sided ulcerative colitis involves more of the mucosa than does pancolitis
 - e) none of the above

2. **Barium enemas:**
 - a) have no role in evaluation of IBD or in cancer surveillance
 - b) provide accurate assessment of extent of disease and severity of inflammation
 - c) are more sensitive and specific than endoscopy for evaluation of ulcerative colitis
 - d) provide the best opportunity for taking biopsies
 - e) are the procedure of choice for cancer surveillance in IBD

3. **In a patient with persistent diarrhea, with or without blood:**
 - a) an immediate referral to a gastroenterologist is required
 - b) treatment with empirical antibiotics should be started immediately
 - c) an infectious etiology should first be ruled out
 - d) testing for *C. difficile* toxin is contraindicated
 - e) flexible sigmoidoscopy should be performed immediately

4. **Oral steroids are appropriate therapy for:**
 - a) mild-to-moderate distal colitis
 - b) refractory proctitis or proctosigmoiditis
 - c) mild-to-moderate proctitis
 - d) long-term management of Crohn's disease
 - e) patients presenting with bloody diarrhea

5. **An oral aminosalicylate, such as sulfasalazine:**
 - a) is the most effective treatment for ulcerative colitis
 - b) is the least expensive treatment for ulcerative colitis
 - c) is the least toxic treatment for ulcerative colitis
 - d) is the only option for maintenance therapy of ulcerative colitis
 - e) may improve compliance over rectal therapies for some patients

6. **Rectal mesalamine:**
 - a) is the least expensive treatment for ulcerative colitis
 - b) is the most toxic treatment for ulcerative colitis
 - c) is the least effective treatment for ulcerative colitis
 - d) is an effective treatment for left-sided ulcerative colitis and proctosigmoiditis
 - e) is contraindicated for maintenance therapy of ulcerative colitis

7. **Colectomy is recommended:**
 - a) only if high-grade dysplasia is found
 - b) in all patients with left-sided colitis of 15 years' duration
 - c) in all patients with pancolitis of 8 to 10 years' duration
 - d) if any dysplasia is found
 - e) as a cure for Crohn's disease

8. **Colonoscopy for cancer surveillance in ulcerative colitis should be carried out:**
 - a) annual after 8 years of disease
 - b) every 2 to 3 years between 8 and 20 years of disease, and more frequently thereafter
 - c) annually following initial diagnosis
 - d) every 2 to 3 years following initial diagnosis
 - e) only in patients over the age of 50 who are disposed to get polyps

(CME QUESTIONS CONTINUED ON NEXT PAGE)

<p>AMA/CME TEST FORM AJMC Test #0397S5</p> <p>Inflammatory Bowel Disease: A Managed Care Perspective</p> <p><i>Application for 1 Credit Hour of AMA Category I</i></p> <p>(Test valid through May 31, 1998. No credit will be given after this date.)</p>	<p>Please circle your answers:</p> <p>1. a b c d e</p> <p>2. a b c d e</p> <p>3. a b c d e</p> <p>4. a b c d e</p> <p>5. a b c d e</p> <p>6. a b c d e</p> <p>7. a b c d e</p> <p>8. a b c d e</p> <p>9. a b c d e</p> <p>10. a b c d e</p>	<p>(PLEASE PRINT CLEARLY)</p> <p>Name _____</p> <p>Address _____</p> <p>City _____</p> <p>State/Zip _____</p> <p>Phone # _____</p> <p>Please enclose a check for \$10, payable to American Medical Publishing, LLC, and mail with this form to:</p> <p style="text-align: center;">The AJMC CME Test American Medical Publishing 1816 Englishtown Road, Suite 101 Old Bridge, NJ 08857</p>
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CME QUESTIONS: TEST #0397S5

(continued from page S48)

9. **The stapled ileoanal colectomy procedure:**
- a) can be done as a single-stage operation in several cases
 - b) requires a temporary ileal diversion
 - c) leaves the patient with a permanent ileostomy
 - d) results in poorer sphincter control than the mucosectomy procedure
 - e) is the only appropriate procedure for patients with limited disease
10. **Sclerosing cholangitis:**
- a) is a contraindication for liver transplantation
 - b) is the result of hepatotoxic medications
 - c) is the principal hepatobiliary complication for IBD
 - d) can be diagnosed easily with ultrasound
 - e) all of the above

PROGRAM EVALUATION

Johns Hopkins University School of Medicine and Long Island Jewish Medical Center would like to have your opinion. Please fill out the questionnaire below, tear off along the dotted line, and mail along with your AMA/CME test form. We thank you for your evaluation, which is most helpful.

On the whole, how do you rate the information presented in the article?

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Is the information presented useful in your practice?

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