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### RESEARCH ARTICLE

#### DISCUSSION ABOUT TREATMENT OF ULCERATIVE COLITIS.

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#### Abstract

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#### Introduction:-

Nearly 4 decades ago, sulfasalazine was the first noncorticosteroid medical therapy approved for the treatment of ulcerative colitis, and the first available aminosalicilate. Over the past 2 decades, a number of other aminosalicilate compounds and formulations have been developed, and aminosalicilates have been established as first-line therapy for mildly to moderately active ulcerative colitis. A large number of clinical trials are evaluating different aminosalicilate therapies in ulcerative colitis, but they differ in study design, dosages, clinical endpoints used, and duration. This report presents a case-based approach to the management of mildly to moderately active ulcerative colitis with aminosalicilate therapies, and reviews the related issues of compliance, chemoprevention, and new aminosalicilate treatments currently under development.

#### Case Presentation:-

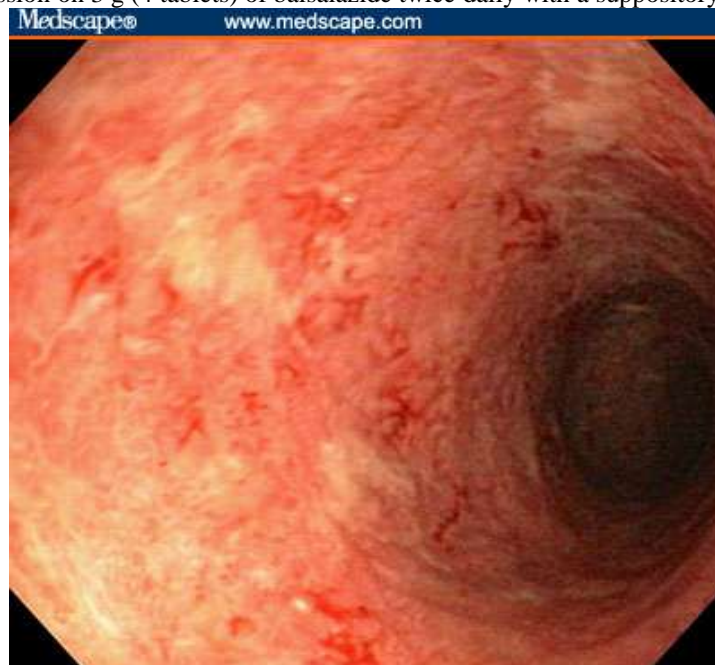
RS is a 34-year-old, female graduate student who presents to the emergency department with 7 days of bloody diarrhea and lower abdominal cramping. She describes up to 10 urgent trips to the bathroom daily and a 5-lb weight loss with dehydration. She denies emesis or extraintestinal manifestations. Laboratory evaluation and abdominal radiographs are significant only for a hemoglobin level of 10.8 g/dL. She is a lifelong nonsmoker and has no history of medical illness or surgeries, denies recent antibiotic or nonsteroidal anti-inflammatory drug use, and has had no known sick contacts or exposure to tainted foods. However, she has experienced increased emotional stress over the past several weeks due to school exams and a tumultuous personal relationship.

The patient is admitted to the hospital for presumed infectious enterocolitis for intravenous hydration, and treated empirically with ciprofloxacin. Stool culture is negative for infection, but fecal leukocytes are present. After 48 hours with minimal response to therapy, she undergoes a flexible sigmoidoscopy and biopsies (Figure 1), which show friable and erythematous mucosa in a diffuse circumferential distribution from the anal verge to the splenic flexure. There are no pseudomembranes. Histologic evaluation reveals acute inflammation without architectural distortion consistent with either acute infectious colitis or new inflammatory bowel disease, favoring ulcerative colitis. However, the patient's symptoms substantially resolve over the next 2 days, and she is discharged with a course of antibiotics. Two days after discharge, she contacts the gastroenterologist to report recurrent bloody diarrhea and abdominal pain.



**Figure 1:-**

At this point in work-up, treatment for presumed ulcerative colitis is initiated with balsalazide 6.75 g daily in 3 divided oral doses along with prednisone at 40 mg orally daily. After only 3 days of treatment, stool frequency had decreased to 3 times daily, with rare blood-tinged stools. Abdominal cramping improves, but still occurs episodically with some tenesmus. The patient suffers from side effects of steroid therapy, including depressed mood and insomnia, which resolve after a taper over the course of 1 month. Due to persistent rectal urgency, an ileocolonoscopy is performed 6 weeks after initial presentation, which shows mild erythema and granularity from the rectum to the sigmoid colon and in the ascending colon (Figure 2). The transverse colonic mucosa and terminal ileum are grossly normal. However, biopsies throughout the colon reveal crypt architectural distortion diffusely. A mesalamine suppository (1000 mg daily) is added for additional topical rectal therapy. Three months later, RS remains in clinical remission on 3 g (4 tablets) of balsalazide twice daily with a suppository 3 days per week.



**Figure 2:-**

**Diagnosis:-**

In a young or middle-aged patient with bloody diarrhea and abdominal pain, infectious and inflammatory causes of colitis are at the top of the differential diagnosis list. Evaluation of such a patient requires a thorough investigation of stool for infection; testing for *Clostridium difficile*, ova, and parasites; and bacterial culture. Routine laboratory studies and abdominal radiographs may be normal or nonspecific, especially if the disease is of limited extent. Computed tomographic (CT) imaging of the abdomen and pelvis with oral and intravenous contrast can identify small and large bowel wall thickening and abdominal abscess, although these findings are also nonspecific.

If symptoms do not resolve after a course of empiric antibiotic therapy, an elective purge-prepared ileocolonoscopy with random biopsies should be performed to evaluate for inflammatory bowel disease. Evaluation of the ileum is imperative to help differentiate ulcerative colitis from Crohn's disease.

The typical endoscopic appearance of mild-to-moderate ulcerative colitis is continuous, circumferential mucosal erythema with mild friability and loss of the normal vascular pattern beginning at the anal verge. Mucosal inflammation is less frequent and less severe in the more proximal colon. The terminal ileum is normal in ulcerative colitis, with the exception of "backwash ileitis," which is characterized by extensive colitis, but instead of focal ulceration in the ileum, there is only erythema and exudate; a patulous ileocecal valve may be present. This condition may be confused with Crohn's ileitis, both grossly and microscopically; therefore, adequate communication from endoscopist to pathologist is essential. Ulcerative colitis can also present with a pattern of left-sided disease with a characteristic "periappendiceal red patch" of cecal inflammation, with grossly and histologically normal intervening mucosa. This presentation may be confused with Crohn's disease, but is thought to be a variant of ulcerative colitis and is of uncertain significance.<sup>[1]</sup>

In addition to ileoscopy, small bowel imaging by CT enteroclysis, magnetic resonance imaging (MRI), video capsule endoscopy, or small bowel follow-through will help in ruling out the presence of small bowel inflammation, ulceration, or stricture, which would suggest Crohn's disease.<sup>[2]</sup> After the diagnosis of ulcerative colitis is confirmed, the choice of initial treatment depends on the severity of symptoms and endoscopic appearance.

**Induction of Remission in Ulcerative Colitis With 5-Aminosalicylic Acid Therapy:-**

The treatment of ulcerative colitis first requires induction of remission, defined clinically as a return to formed stools without blood or urgency. The resolution of rectal urgency and return of the ability of a patient to sense the difference between gas and stool is a reliable clinical indicator of remission. After a successful induction of remission, the second goal of therapy is to prevent relapse over time, or to maintain remission. These intimately related goals may require different medications and doses. The efficacy of oral and rectal formulations of 5-aminosalicylate acid (5-ASA) has been demonstrated in clinical trials as both induction and maintenance agents for mildly to moderately active ulcerative colitis. For extensive colitis (disease extent proximal to the splenic flexure), oral 5-ASA is effective as a single agent, but clinical response is augmented if used in combination with topical rectal 5-ASA. For disease limited to the rectum or left side of the colon, oral 5-ASA therapy is effective, but topical rectal therapy may be used as a single agent if the patient is willing. The first 5-ASA to be introduced into the therapeutic arsenal was sulfasalazine. However, due to side effects associated with the use of sulfasalazine (headache, nausea, diarrhea, and rash), a number of 5-ASA analogs were developed, including mesalamine in various delivery systems, olsalazine, and balsalazide.

Two large meta-analyses from the Cochrane database have been updated for 2006, comparing a delayed-release pH-dependent mesalamine formulation, an immediate-release moisture-dependent mesalamine formulation, and prodrugs that require intestinal flora to release 5-ASA (olsalazine and balsalazide) with sulfasalazine (also a prodrug requiring bacterial enzymes for release) and placebo for the attainment of clinical remission.<sup>[3,4]</sup> As a group, the 5-ASAs were found to be significantly more effective than placebo for induction of remission, and within the limits of this analysis, there was no significant difference between the efficacy of sulfasalazine and the other 5-ASA therapies. For maintenance of remission, 5-ASAs were again found to be superior to placebo, but sulfasalazine was modestly more effective than the other 5-ASA therapies (odds ratio [OR], 1.29; 95% confidence interval [CI], 1.05-1.57). Of importance, the benefit of sulfasalazine was limited by dose-dependent side effects, which led to discontinuation.

Despite several trials reporting disparate findings, a trend toward dose response is present for disease response with mesalamine up to 4.8 g daily.<sup>[5-7]</sup> In contrast, maintenance therapy with mesalamine is effective at doses above 800

mg/day, with no clear dose response, although many clinicians recommend a 5-ASA dose for maintenance that is similar to the induction dose.<sup>[8-10]</sup>

### **Combination Oral and Topical 5-ASA Therapy Is Better Than Either Therapy Alone:-**

A fundamental principle of 5-ASA therapy is delivery of the drug to the site of disease. Therefore, a number of topical therapies have been developed and studied; in fact, remission of distal ulcerative colitis can be maintained with topical treatment alone. Daily (500 mg) and every-other-day (1000 mg) administration of mesalamine suppositories was more effective than placebo in maintaining remission in patients with mild-to-moderate ulcerative proctitis at 1 and 2 years.<sup>[11,12]</sup> Several studies, including a meta-analysis published in 2000, confirmed the efficacy of 5-ASA in an enema formulation in both inducing and maintaining remission in left-sided ulcerative colitis (defined as distal to the splenic flexure).<sup>[13-16]</sup> The addition of topical 5-ASA to oral therapy increases mucosal levels of mesalamine by 3-fold in the descending colon and over 20-fold in the rectum.<sup>[17]</sup> Moreover, it has been demonstrated repeatedly that the combination of 5-ASA in oral and enema formulations is superior to either therapy alone in inducing and maintaining remission of extensive colitis.<sup>[13-18]</sup>

### **Safety of 5-ASA Therapy:-**

As a class, 5-ASA therapy is considered exceptionally safe. The side-effect profiles of mesalamine and balsalazide are similar to placebo, whereas olsalazine and sulfasalazine are associated with an increased incidence of treatment withdrawal due to adverse events.<sup>[3,4]</sup> Sulfasalazine commonly causes headache, rash, and nausea, which are dose-related and may be due to the sulfa moiety, whereas olsalazine may have a side effect of dose-related diarrhea.<sup>[3,4]</sup> Although reported and concerning, the risk for interstitial nephritis, pancreatitis, and other rare events is low for all of the aminosalicylates. Nonetheless, current guidelines do suggest "periodic" renal function assessment while on 5-ASA therapy. In our practice, this is done every 3-6 months.<sup>[19,20]</sup>

### **Compliance With Chronic Therapy in Ulcerative Colitis:-**

The administration of 5-ASA therapy — whether in oral or topical form — usually requires between 4 and as many as 16 tablets or capsules divided into daily dosing regimens. As with other chronic diseases requiring maintenance therapy, compliance with the prescribed medical regimen is a challenge. Although compliance in clinical trials, which involve a highly selected and motivated patient group, is greater than 80%, much lower rates were seen in community-based, "real-world" studies (40% to 60%).<sup>[21-23]</sup> Despite the proven efficacy and safety of rectally administered 5-ASA, patients have demonstrated lower compliance rates with topical compared with oral therapy.<sup>[22]</sup> Noncompliance results in an increased risk for disease relapse,<sup>[21,24]</sup> a diminished quality of life,<sup>[7,25,26]</sup> and a possible increase in the risk for colorectal cancer.<sup>[27]</sup> Therefore, successful management of patients with ulcerative colitis requires treatment strategies that encourage and confirm compliance with the prescribed therapeutic plan. In recent years, a 1-g suppository and 500-mg moisture-dependent mesalamine capsules were approved for use in the United States for the treatment of mildly to moderately active ulcerative colitis.

### **Chemoprevention: The Role of 5-ASA?**

Colorectal cancer remains a significant cause of morbidity and mortality in patients with ulcerative colitis; the risk for this complication increases with longer duration of disease and greater extent of organ involvement, among other risk factors. The 5-ASA agents have been suggested to have chemopreventive properties because of their structural and partial functional relationship with aspirin.<sup>[28]</sup> Retrospective case-control and cohort studies, conducted primarily at referral-based centers, suggested that the chemopreventive benefit is significant, whereas larger population-based and administrative claims studies with limited pharmacy and clinical data did not confirm these results.<sup>[29-32]</sup> A 2005 meta-analysis of 9 observational studies identified a significant risk reduction associated with 5-ASA therapy, with the OR for dysplasia and colorectal cancer combined (ie, combined endpoint) at 0.51 (95% CI, 0.37-0.69) in patients with ulcerative colitis.<sup>[27]</sup> A dose response occurred with longer use and higher daily dosing of 5-ASA, but the risk for dysplasia alone was not affected by 5-ASA therapy; however, only two of the studies provided information to allow for analysis of this endpoint. As one of this report's co-authors has written previously, an appropriately powered observational or randomized-controlled trial to better answer the question of whether there is a protective association between 5-ASA use and colorectal cancer or dysplasia is unlikely to occur due to prohibitive costs and ethical issues related to withholding 5-ASA therapy in ulcerative colitis patients in order to study cancer outcomes.<sup>[33]</sup> Although the existing evidence for the association is promising but inconclusive, the potential benefit is based on good clinical rationale, and given the excellent safety profile of this class of drugs, will likely encourage compliance with long-term prescribed therapy.

**New 5-ASA Formulations:-**

Higher dose, pH-dependent mesalamine tablets and balsalazide capsules have been developed and are now in development and under review, although the pH-dependent 800-mg mesalamine tablets are already available in Canada. Novel delivery systems and higher dosing formulations of 5-ASA are also in development. These include the once-daily oral multimatrix (MMx) 5-ASA (SPD476) formulation<sup>[34,35]</sup>; a twice-daily oral micropellet formulation<sup>[36]</sup>; a once-daily, slow-release suppository formulation<sup>[37]</sup>; and a 5-ASA rectal gel that treats the left colon and in early trials is preferred by patients over existing 5-ASA enema preparations.<sup>[38,39]</sup>

A new MMx formulation of mesalamine (SPD476; MMX mesalamine)<sup>[40,41]</sup> is now undergoing clinical trials. The double matrix is composed of mesalamine embedded in lipophilic microparticles that are dispersed throughout a hydrophilic matrix, and is developed to deliver 1.2 g of 5-ASA per tablet. The tablet is coated with a polymer film with pH-dependent dissolution. Resistant to gastric digestion, the coating begins to dissolve in the terminal ileum at a more neutral pH. As the hydrophilic matrix erodes, the 5-ASA diffuses out of the lipophilic matrix, providing even drug distribution from the ascending colon to the rectum. Pranter and colleagues<sup>[34]</sup> conducted an 8-week double-dummy study involving 79 patients with left-sided colitis; subjects received either 1.2 g SPD476 3 times daily or a 4-g mesalamine enema. There were similar rates of clinical and endoscopic remission for patients treated with SPD476 and mesalamine enema. The compliance rate for patients in the MMx group was 97%. Despite a high dropout rate and small sample size, this early clinical trial served as the basis for a larger multicenter phase 3 trial that was presented in abstract form during Digestive Disease Week 2006.<sup>[35]</sup> In this study, a statistically significantly greater percentage of subjects (with mild-to-moderate ulcerative colitis) who received 2.4 g/day or 4.8 g/day of the MMx formulation achieved remission compared with placebo: 37.2% and 35.1% vs 17.5%, respectively ( $P < .001$ ). No significant dose response was seen in the 2 treatment groups. There have been no head-to-head trials comparing SPD476 with other oral 5-ASA preparations.

A twice-daily prolonged-release micropellet formulation of mesalamine produced a comparable response to a 4-times daily prolonged-release tablet in 227 patients with mild-to-moderate ulcerative colitis. There was no difference in side effects and patients preferred twice-daily dosing.<sup>[36]</sup> A study by Lamet and colleagues<sup>[37]</sup> of 99 patients with ulcerative proctitis found that once-daily dosing of a 1-g extended-release mesalamine suppository was equivalent to a 500-mg twice-daily suppository for the induction of remission, with similar side effects. Finally, a 2-g gel formulation of rectal mesalamine provided similar efficacy to standard mesalamine foam enema for induction of remission at 4 weeks in mild-to-moderate left-sided ulcerative colitis with clinical, endoscopic, and histologic remission rates of 75%, 52%, and 30%, respectively. One hundred three patients were randomized and investigators were blinded to treatment. The foam enema was associated with a statistically significant increase in bloating (50% vs 26%), discomfort with administration (48% vs 26%), and difficulty with retention (25% vs 6%) compared with the rectal gel.<sup>[38,39]</sup>

**Beyond 5-ASA:-**

Although many patients with mildly to moderately active ulcerative colitis will achieve and maintain remission on 5-ASA therapy, patients with more extensive disease and more severely active disease will require additional treatment, and if they are not already doing so, should see a gastroenterologist. Such options include corticosteroids, thiopurine analogs, antitumor necrosis factor (TNF) therapy, and colectomy. The thiopurine analogs (6-mercaptopurine and azathioprine) are effective for steroid sparing and probably for maintenance of remission, but may take up to 3 months to work; therefore, corticosteroids may be necessary in the interim. Approximately 10% of patients will have problems with side effects of nausea, headaches, and idiosyncratic pancreatitis.<sup>[42]</sup> Unlike the 5-ASA agents, both azathioprine and 6-mercaptopurine require regular laboratory testing for leukopenia and hepatitis, which may be reduced with pretesting and knowledge of an individual's thiopurine methyltransferase activity. When thiopurines fail to induce or maintain remission, anti-TNF therapy with infliximab is more effective than placebo for inducing and maintaining remission, on the basis of the results from 2 large, multicenter, placebo-controlled trials.<sup>[43]</sup> Although beneficial, infliximab is costly and carries a risk for hypersensitivity reactions.<sup>[44,45]</sup> Failure of medical therapy or steroid dependence is an indication for total colectomy with either end ileostomy or ileoanal anastomosis.<sup>[1]</sup>

**Concluding Remarks:-**

After 40 years, the 5-ASA agents continue to serve as the "workhorse" for the treatment of mildly to moderately active ulcerative colitis. They are effective both for inducing and maintaining remission, with systemic and/or topical administration. Overall, there is little difference in efficacy between the 5-ASA compounds, but compliance

with the chronic regimen and the number of pills remain significant challenges to effective long-term therapy. It is anticipated that in the near future, longer-acting 5-ASA and novel delivery systems will improve our control of ulcerative colitis.

**Footnotes:-**

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**Patient consent:-** Obtained.

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**References:-**

1. 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. Abstract
2. Mackalski BA, Bernstein CN. New diagnostic imaging tools for inflammatory bowel disease. Gut. 2006;55:733-741. Abstract
3. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006;(2):CD000544.
4. Sutherland L, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2006;2:CD000543.
5. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. N Engl J Med. 1987;317:1625-1629. Abstract
6. Levine DS, Riff DS, Pruitt R, et al. A randomized, double blind, dose-response comparison of balsalazide (6.75 g), balsalazide (2.25 g), and mesalamine (2.4 g) in the treatment of active, mild-to-moderate ulcerative colitis. Am J Gastroenterol. 2002;97:1398-1407. Abstract
7. Hanauer SB, Sandborn WJ, Kornbluth A, et al. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. Am J Gastroenterol. 2005;100:2478-2485. Abstract
8. An oral preparation of mesalamine as long-term maintenance therapy for ulcerative colitis. A randomized, placebo-controlled trial. The Mesalamine Study Group. Ann Intern Med. 1996;124:204-211. Abstract
9. Kruis W, Schreiber S, Theuer D, et al. Low dose balsalazide (1.5 g twice daily) and mesalazine (0.5 g three times daily) maintained remission of ulcerative colitis but high dose balsalazide (3.0 g twice daily) was superior in preventing relapses. Gut. 2001;49:783-789. Abstract
10. Paoluzi OA, Iacopini F, Pica R, et al. Comparison of two different daily dosages (2.4 vs. 1.2 g) of oral mesalazine in maintenance of remission in ulcerative colitis patients: 1-year follow-up study. Aliment Pharmacol Ther. 2005;21:1111-1119. Abstract
11. Marteau P, Crand J, Foucault M, Rambaud JC. Use of mesalazine slow release suppositories 1 g three times per week to maintain remission of ulcerative proctitis: a randomised double blind placebo controlled multicentre study. Gut. 1998;42:195-199. Abstract
12. Hanauer S, Good LI, Goodman MW, et al. Long-term use of mesalamine (Rowasa) suppositories in remission maintenance of ulcerative proctitis. Am J Gastroenterol. 2000;95:1749-1754. Abstract
13. Safdi M, DeMicco M, Sninsky C, et al. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. Am J Gastroenterol. 1997;92:1867-1871. Abstract
14. Hanauer SB. Dose-ranging study of mesalamine (PENTASA) enemas in the treatment of acute ulcerative proctosigmoiditis: results of a multicentered placebo-controlled trial. The U.S. PENTASA Enema Study Group. Inflamm Bowel Dis. 1998;4:79-83. Abstract
15. Cohen RD, Woseth DM, Thisted RA, Hanauer SB. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. Am J Gastroenterol. 2000;95:1263-1276. Abstract

16. Piodi LP, Ulivieri FM, Cermesoni L, Cesana BM. Long-term intermittent treatment with low-dose 5-aminosalicylic enemas is efficacious for remission maintenance in ulcerative colitis. *Scand J Gastroenterol.* 2004;39:154-157. Abstract
17. Frieri G, Pimpo MT, Palumbo GC, et al. Rectal and colonic mesalazine concentration in ulcerative colitis: oral vs. oral plus topical treatment. *Aliment Pharmacol Ther.* 1999;13:1413-1417. Abstract
18. Marteau P, Probert CS, Lindgren S, et al. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut.* 2005;54:960-965. Abstract
19. Ransford RA, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut.* 2002;51:536-539. Abstract
20. Van Staa TP, Travis S, Leufkens HG, Logan RF. 5-Aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. *Gastroenterology.* 2004;126:1733-1739. Abstract
21. Kane S, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med.* 2003;114:39-43. Abstract
22. Kane SV, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalamine in quiescent ulcerative colitis. *Am J Gastroenterol.* 2001;96:2929-2933. Abstract
23. Levy RL, Feld AD. Increasing patient adherence to gastroenterology treatment and prevention regimens. *Am J Gastroenterol.* 1999;94:1733-1742. Abstract
24. Bresci G, Parisi G, Bertoni M, Capria A. Long-term maintenance treatment in ulcerative colitis: a 10-year follow-up. *Dig Liver Dis.* 2002;34:419-423. Abstract
25. Janke KH, Klump B, Gregor M, Meisner C, Haeuser W. Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis.* 2005;11:272-286. Abstract
26. Saibeni S, Cortinovis I, Beretta L, et al. Gender and disease activity influence health-related quality of life in inflammatory bowel diseases. *Hepatogastroenterology.* 2005;52:509-515. Abstract
27. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and metaanalysis of observational studies. *Am J Gastroenterol.* 2005;100:1345-1353. Abstract
28. Eaden J. Review article: the data supporting a role for aminosalicylates in the chemoprevention of colorectal cancer in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2003;18(suppl2):15-21.
29. Bernstein CN, Blanchard JF, Metge C, Yogendran M. Does the use of 5-aminosalicylates in inflammatory bowel disease prevent the development of colorectal cancer? *Am J Gastroenterol.* 2003;98:2784-2788.
30. Eaden J, Abrams K, Ekbom A, Jackson E, Mayberry J. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther.* 2000;14:145-153.
31. Rubin DT, LoSavio A, Huo D, Yadron N, Hanauer SB. Use of 5-ASA is associated with decreased risk of dysplasia and colorectal cancer in ulcerative colitis. *Clin Gastroenterol Hepatol.* In press.
32. van Staa TP, Card T, Logan RF, Leufkens HG. 5-Aminosalicylate use and colorectal cancer risk in inflammatory bowel disease: a large epidemiological study. *Gut.* 2005;54:1573-1578. Abstract
33. Rubin DT, Lashner BA. Will a 5-ASA a day keep the cancer (and dysplasia) away? *Am J Gastroenterol.* 2005;100:1354-1356.
34. Prantera C, Viscido A, Biancone L, Francavilla A, Giglio L, Campieri M. A new oral delivery system for 5-ASA: preliminary clinical findings for MMx. *Inflamm Bowel Dis.* 2005;11:421-427. Abstract
35. Sandborn WJ, Kamm MA, Lichtenstein GR, et al. Combined data from two pivotal, randomized, placebo-controlled, phase-III studies show that SPD476, a novel mesalamine formulation given once or twice daily is effective for the induction of remission of mild-to-moderate ulcerative colitis. *Gastroenterology.* 2006;130:A813.
36. Farup PG, Hinterleitner TA, Lukas M, et al. Mesalazine 4 g daily given as prolonged-release granules twice daily and four times daily is at least as effective as prolonged-release tablets four times daily in patients with ulcerative colitis. *Inflamm Bowel Dis.* 2001;7:237-242. Abstract
37. Lamet M, Ptak T, Dallaire C, et al. Efficacy and safety of mesalamine 1 g HS versus 500 mg BID suppositories in mild to moderate ulcerative proctitis: a multicenter randomized study. *Inflamm Bowel Dis.* 2005;11:625-630. Abstract
38. Aumais G, Lefebvre M, Massicotte J, et al. Pharmacokinetics and pilot efficacy of a mesalazine rectal gel in distal ulcerative colitis. *Drugs R D.* 2005;6:41-46. Abstract
39. Gionchetti P, Ardizzone S, Benvenuti ME, et al. A new mesalazine gel enema in the treatment of left-sided ulcerative colitis: a randomized controlled multicentre trial. *Aliment Pharmacol Ther.* 1999;13:381-388. Abstract

40. Lichtenstein G. SPD476 is a novel, once-daily, high-dose, effective and well tolerated 5ASA formulation for the induction of remission of mild-to-moderate ulcerative colitis: a phase III study. *Am J Gastroenterol.* 2005;100:A21.
41. Kamm M. Comparison of the efficacy and safety of SPD476, a novel, once-daily, high dose formulation of mesalamine, and Asacol with placebo for the induction of remission of mild-moderate ulcerative colitis: a phase III study. *Am J Gastroenterol.* 2005;100:A22.
42. Ardizzone S, Maconi G, Russo A, Imbesi V, Colombo E, Bianchi Porro G. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut.* 2006;55:47-53. Abstract
43. Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med.* 2005;353:2462-2476. Abstract
44. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol.* 2003;98:1315-1324. Abstract
45. Colombel JF, Loftus EV Jr, Tremaine WJ, et al. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience. *Gastroenterology.* 2004;126:19-31. Abstract