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Use of old and new oral 5-aminosalicylic acid formulations in inflammatory bowel disease

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SUMMARY Although sulfasalazine, a 5-aminosalicylic acid (5-ASA) agent, is still the anti-inflammatory agent of choice for ulcerative colitis and Crohn's disease, newer formulations, which release drug to specific regions of the colon for maximal efficacy, also can be appropriate first-line agents. This article reviews recent clinical studies of therapy with older and newer 5-ASA formulations.

KEY POINTS For patients with mildly to moderately active ulcerative colitis or mild Crohn's ileitis, ileocolitis, or colitis who are not allergic to sulfa drugs, sulfasalazine is the drug of choice. Olasalazine is similar in effectiveness to sulfasalazine, and is useful in treating patients allergic to or intolerant of sulfasalazine. The pH-sensitive preparations of mesalamine are useful, although none is more effective than sulfasalazine in patients with mildly to moderately active ulcerative colitis or in maintenance of remission.

Ethylcellulose-coated mesalamine delivers active drug to the proximal small intestine. Even though not approved for Crohn's disease, this formulation may be worthwhile before using steroids because it has fewer adverse effects.

INDEX TERMS: INFLAMMATORY BOWEL DISEASE; AMINOSALICYLIC ACIDS
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INTERNISTS TREATING patients who have inflammatory bowel disease possess an array of potential interventions for this difficult disease, but no cures. Treatment goals focus on diminishing the symptoms and complications, thereby improving quality of life. Conventional medical treatment includes salicylates, notably, different formulations of 5-aminosalicylic acid (5-ASA), in addition to corticosteroids, immunosuppressants, and some antibiotics. Other treatments such as nutrition modifications and surgery are useful in some patients.

New, innovative formulations release 5-ASA in the regions of maximal inflammation; these have been found useful in inducing and maintaining clinical remission of inflammatory bowel disease. This article reviews the indications and use of the oral 5-ASA formulations available in the United States.

EVOLUTION OF TREATMENT

Ulcerative colitis and Crohn's disease are inflammatory bowel diseases of unknown cause charac-

terized by intestinal ulceration with bleeding, diarrhea, and abdominal pain. In ulcerative colitis, the inflammation is limited to the colonic mucosa and has a characteristic endoscopic appearance of superficial ulceration, diffuse and continuous disease extending from the rectum proximally, a distorted mucosal vascular pattern, and a mucopurulent exudate. In contrast, Crohn's disease is heterogeneous, with transmural involvement, discrete serpiginous ulcers, and "skip" areas of inflammation that can affect any segment of the gastrointestinal tract.

Symptoms depend largely on the disease location and the specific intestinal complication (ie, stricture, fistula, inflammatory mass). Both diseases can be accompanied by extraintestinal manifestations. Clinical trials in Crohn's disease are more difficult to perform and to interpret than are trials in ulcerative colitis, because Crohn's disease is more heterogeneous.

Popular treatment for inflammatory bowel disease evolved from empiric observations that were subsequently supported by randomized clinical trials. More recently, drugs were specifically designed to treat particular manifestations of disease by generating a peak effect in the affected regions of the bowel. The most effective treatments for both ulcerative colitis and Crohn's disease are those aimed at diminishing the inflammatory response at the mucosal level.

5-ASA, a potent anti-inflammatory agent, acts locally to decrease the immune response by inhibiting formation of both prostaglandin and leukotriene metabolites. When given orally, 5-ASA is readily absorbed in the proximal intestine, acetylated, and then excreted in the urine before the desired anti-inflammatory effect can be produced. However, innovative delivery systems enable 5-ASA to act locally in the regions of the intestine that are most inflamed.

AZO COMPOUNDS

The formulations of 5-ASA most commonly used in the treatment of inflammatory bowel disease are "azo compounds." These compounds minimize proximal absorption of 5-ASA by linking 5-ASA molecules by an azo bond either to a molecule that serves as a carrier or to another 5-ASA moiety. Only two of such azo compounds are available in the United States: sulfasalazine (Azulfidine) and olsalazine (Dipentum).

Sulfasalazine

Introduced over 40 years ago to treat both ulcerative colitis and inflammatory arthritis, sulfasalazine is the most widely used medication for inflammatory bowel disease.

Sulfasalazine consists of a sulfapyridine radical attached to a 5-ASA radical by an azo bond. The sulfapyridine moiety serves as a carrier to deliver the therapeutically active 5-ASA to distal bowel segments.¹

Between 10% and 30% of an ingested dose is absorbed from the upper gastrointestinal tract and is excreted unchanged into the small intestine via the enterohepatic circulation. Fully 90% of the intact sulfasalazine enters the colon, where azo reductase in colonic bacteria cleaves the azo bond and releases both sulfapyridine and 5-ASA into the colonic lumen. Most of the sulfapyridine is absorbed from the colon, metabolized in the liver by acetylation, hydroxylation, and glucuronidation, and excreted in the urine. Most of the 5-ASA remains in the colon, acts locally, is acetylated within the colonic epithelium or by colonic bacteria, and is excreted in the feces. Very little—only 20%—of the 5-ASA is absorbed by the colonic epithelium, acetylated, and excreted in urine.

Sulfasalazine in ulcerative colitis

Sulfasalazine is indicated to treat mildly to moderately active ulcerative colitis, as adjuvant treatment for severe ulcerative colitis, and as maintenance treatment to prolong remission. From 60% to 80% of patients with mildly to moderately active disease can achieve a response with single-drug therapy. The response rate is dose-related, with higher remission rates observed with 6 to 8 grams daily than with 2 to 4 grams daily.^{2,3} However, most patients cannot tolerate higher doses (see below), and a minority are allergic to sulfasalazine. Although improvement can occur soon after sulfasalazine is started, 4 or more weeks may be required to achieve remission.

When ulcerative colitis patients achieve remission with sulfasalazine, maintenance treatment can often prevent relapses. In one study, 70% of such patients taking 2 grams of sulfasalazine daily remained symptom-free for 1 year, compared with 24% of patients randomly assigned to receive placebo.⁴ Maintenance of remission also is dose-dependent, with fewer patients suffering relapses with 4 grams daily than with 1 or 2 grams daily at 6

months in another study.⁵ However, more than one third of patients taking 4 grams daily experience intolerable side effects.

Sulfasalazine in Crohn's disease

Three randomized clinical trials have confirmed the effectiveness of sulfasalazine in treating Crohn's disease. In the National Cooperative Crohn's Disease Study, patients were randomly assigned to receive sulfasalazine, prednisone, azathioprine, or placebo as single-agent therapy for 4 months. Sulfasalazine was effective in patients with Crohn's colitis, but was no better than placebo in patients with ileitis.⁶ The European Cooperative Crohn's Disease Study also found sulfasalazine effective in Crohn's colitis and ileocolitis, but not in ileitis alone.⁷ In a smaller trial, sulfasalazine was effective in patients with Crohn's colitis, as well as those with ileitis alone.⁸

Because Crohn's disease is chronic and recurrent and often requires surgery, it is important to maintain remission or, after surgical resection, to delay recurrence. Both the National Cooperative Crohn's Disease Study and the European Cooperative Crohn's Disease Study found sulfasalazine ineffective as maintenance therapy. The maintenance phases of these trials have been criticized as being too short or involving inadequate doses.⁹ Still, no randomized clinical trial has shown that sulfasalazine adequately maintains remission in Crohn's disease or that it is effective as a steroid-sparing agent.

Side effects of sulfasalazine

Sulfasalazine's high rate of adverse effects limits its use. Up to 30% of patients must decrease their dose or discontinue the medication altogether because of intolerable side effects or allergy (Table 1). Some side effects, such as headache, anorexia, nausea, and vomiting, can be minimized by starting at a low dosage (1 gram daily in divided doses) and increasing the dosage slowly up to 4 to 6 grams daily. Enteric coated preparations may be more tolerable, but cost more (Table 2).

Most of sulfasalazine's side effects are caused by the sulfapyridine moiety, especially in patients with the genetic trait for slow hepatic acetylation.¹⁰ Sulfasalazine is a competitive inhibitor of folic acid absorption; therefore, patients taking sulfasalazine should take at least 0.4 mg of supplemental folic acid daily. Serious side effects, such as toxic epidermal necrolysis, acute pancreatitis, acute hepatitis, acute

TABLE 1
SIDE EFFECTS OF SULFASALAZINE
BY FREQUENCY OF OCCURRENCE

Common (30% to 35%)
Headache
Anorexia
Nausea, vomiting
Dyspepsia
Oligospermia
Less common (3% to 4%)
Heinz body hemolytic anemia
Rash
Pruritus
Urticaria
Uncommon (< 1.5%)
Transverse myelitis
Seizures
Peripheral neuropathy
Hearing loss
Tinnitus
Hepatitis
Pancreatitis
Bloody diarrhea
Abdominal pain
Aplastic anemia
Megaloblastic anemia
Methemoglobinemia
Erythema multiforme
Epidermal necrolysis
Anaphylaxis
Myocarditis
Arthralgia
Alopecia
Interstitial nephritis
Nephrotic syndrome
Hematuria
Proteinuria
Pneumonitis with or without eosinophilia
Fibrosing alveolitis
Pleuritis

fibrosing alveolitis, tracheolaryngitis with bronchospasm, neutropenia, agranulocytosis, or allergic reactions (manifested by fever, skin rash, arthralgias, and lymphadenopathy) are rare and require discontinuation of the drug.

Olsalazine

Olsalazine is composed of two 5-ASA radicals linked by an azo bond. Only a small amount of an ingested dose is absorbed from the small bowel, and most reaches the colon intact, where bacterial reduction splits the azo bond and releases two molecules of 5-ASA.

Olsalazine is similar in effectiveness to sulfasalazine in treating active ulcerative colitis and Crohn's colitis and in maintaining remission in ulcerative colitis. It is most useful in patients allergic

TABLE 2
COSTS OF 5-AMINOSALICYLIC ACID DRUGS

Drug	Price per 100 units*	Unit dose, mg	Unit doses per day
Azo compounds			
Sulfasalazine (generic)	\$19.60	500	4–8
Sulfasalazine (Azulfidine)	\$25.10	500	4–8
Sulfasalazine (Azulfidine EN)	\$33.20	500	4–8
Olsalazine (Dipentum)	\$79.90	250	4
pH-sensitive preparation			
Mesalamine, polymer-coated (Asacol)	\$76.80	400	6
Delayed-release preparation			
Mesalamine, ethylcellulose-coated (Pentasa)	\$45.50	250	16

*Average wholesale price in US dollars, July 1995

to or intolerant of sulfasalazine.^{11–13} More than 80% of patients who cannot tolerate sulfasalazine can tolerate olsalazine.

Up to 17% of patients experience a nonbloody diarrhea caused by increased secretion of fluid in the small bowel (Table 3), and approximately 5% of patients have to discontinue treatment because of it. This effect is dose-related and can be minimized to about 2% of patients by giving the medication with meals.¹⁴

pH-SENSITIVE PREPARATIONS

Several 5-ASA preparations have an acrylic-based resin coating that dissolves at a critical pH. These drugs are as effective as sulfasalazine in maintaining remission in patients with ulcerative colitis, and they are effective, safe, and well tolerated in patients who cannot tolerate sulfasalazine.^{15–17}

The only such preparation available in the United States is Asacol—mesalamine (a 5-ASA congener) coated with methacrylic acid copolymer B (Eudragit-S), which dissolves at pH 7 or greater. After ingestion, the preparation begins to dissolve in the distal terminal ileum, but most of the mesalamine is released in the colon.¹⁸ Other pH-sensitive preparations (not available in the United States) are coated with a different resin (Eudragit-L), which dissolves at pH 6, thereby releasing me-

salamine more proximally in the terminal ileum as well as in the colon.

Asacol in ulcerative colitis

In the United States, Asacol is indicated in the treatment of mildly to moderately active ulcerative colitis. The recommended dosage is 2.4 grams daily in divided doses for 6 weeks. In other countries, such as Canada, it is also indicated for maintaining remission, and the recommended dosage is as high as 4.8 grams daily.

In one study, 87 patients with mildly to moderately active ulcerative colitis were randomly assigned to receive 1.6 or 4.8 grams of Asacol daily or placebo for 6 weeks.¹⁹ More patients experienced clinical improvement with the 1.6-mg daily dose than with placebo, but this trend was not statistically significant. However, at a dose of 4.8 grams daily, Asacol induced complete remission in 24% and partial remission in 50% of patients ($P < .0001$ compared with placebo). Tolerance for the drug was excellent; adverse reactions limited therapy in only 4% of the patients. In uncontrolled trials, as many as 78% of patients with mildly to moderately active ulcerative colitis entered remission with Asacol.²⁰

Asacol in Crohn's disease

Most of the information on the use of Asacol for active Crohn's disease comes from open-label studies, in which approximately two thirds of patients taking an average daily dose of 2.4 grams improved, as compared with 80% of patients taking an average daily dose of 3.2 grams of sulfasalazine.^{21,22}

In a randomized, placebo-controlled, multicenter trial, Crohn's disease patients in remission between 3 months and 2 years were given either Asacol 800 mg three times daily or placebo. The risk of relapse decreased significantly in treated patients with ileitis, previous bowel resection, or prolonged prestudy remission.²³ More recently, in a multicenter randomized clinical trial, patients were assigned to re-

ceive either Asacol 800 mg three times daily or placebo within 2 weeks of their first intestinal resection for Crohn's disease.²⁴ Recurrence was defined endoscopically. Patients taking Asacol had significantly lower recurrence rates at 6, 12, and 24 months than patients taking placebo. The medication was well tolerated and was discontinued in only two (4%) of 47 patients.

DELAYED RELEASE PREPARATION

Because the azo compounds and the pH-sensitive preparations release most of the 5-ASA in the colon and only a small amount in the terminal ileum, they have little therapeutic use in Crohn's disease of the more proximal small intestine. An ethylcellulose-coated mesalamine formulation (Pentasa), available in the United States, has been designed to release approximately 50% of the mesalamine into the small intestine and the rest into the colon. The controlled release of mesalamine does not appear to be affected by rapid intestinal transit or colonic resection.^{25,26}

Although currently approved only for "the induction of remission and for the treatment of patients with mildly to moderately active ulcerative colitis," this formulation offers an attractive alternative to treat patients with inflammatory bowel disease proximal to the colon.

Pentasa in ulcerative colitis

In a dose-ranging study, 375 patients with mildly to moderately active ulcerative colitis were randomly assigned to receive placebo or Pentasa (1, 2, or 4 grams daily) for 8 weeks.^{27,28} Patients were stratified according to extent of disease. The response to Pentasa was dose-dependent, with an effective dose being 2 to 4 grams daily as a single agent regardless of previous steroid use or extent of disease. In another large multicenter trial in active ulcerative colitis, 251 patients were randomly assigned to receive either placebo or Pentasa (2 or 4 grams daily) for 8 weeks.²⁹ The medication significantly reduced both patient symptoms and histological grade.

Pentasa also is effective in maintaining remission in ulcerative colitis. In a double-blind randomized trial, 75 patients were assigned to receive either Pentasa (1.5 grams daily) or sulfasalazine (3 grams daily) for 1 year.³⁰ Remission was maintained in 63% of patients at 6 months and in 54% at 1 year in the Pentasa group, compared with 72% at 6 months and

TABLE 3
SIDE EFFECTS OF 5-AMINOSALICYLIC ACID
BY FREQUENCY OF OCCURRENCE

Common
Diarrhea (3.5%)
Olsalazine secretory diarrhea (2% to 17%)
Less common (2% to 4%)
Nausea
Headache
Uncommon (< 1.5%)
Rash
Pruritus
Abdominal pain
Nausea
Vomiting
Bloating
Fatigue
Lethargy
Depression
Arthralgia
Arthritis
Myalgia

46% at 1 year in the sulfasalazine group. These differences were not statistically significant. Two patients in the sulfasalazine group were withdrawn because of severe side effects, and another had transient increases in serum urea, creatinine, and lactic dehydrogenase. No adverse effects were reported in the Pentasa group.

Pentasa in Crohn's disease

In a double-blind, placebo-controlled, dose-response study, Pentasa was found both effective and safe in patients with Crohn's ileitis, ileocolitis, or colitis.³¹ Initial open-label studies on the use of this formulation (1.5 grams daily) in patients with active Crohn's disease suggested a beneficial effect, and studies comparing 1.5 grams daily of Pentasa with 3 grams daily of sulfasalazine have shown similar effectiveness. However, a placebo-controlled study in patients with mildly to moderately active Crohn's disease showed a beneficial effect for this drug at 1.5 grams daily that was not statistically significant.³²

In a double-blind, placebo-controlled, dose-response study, 310 patients with mildly to moderately active Crohn's disease were stratified according to disease location and randomly assigned to receive either placebo or Pentasa at 1, 2, or 4 grams daily for 16 weeks.³³ Compared with placebo, Pentasa had a significant beneficial effect at 4 grams daily, but not at 1 or 2 grams daily. Forty-three percent of patients receiving 4 grams daily were in remission at 16

weeks, and 64% had improved by at least 50 points in the Crohn's Disease Activity Index, signifying an excellent, although not necessarily complete, response. This trial showed that Pentasa is safe and effective at a dose of 4 grams daily as a single agent in the treatment of mildly to moderately active Crohn's disease of the ileum and colon.

Symptomatic relapses in Crohn's disease occur at a rate of 40% to 70% over 18 to 24 months. Only one controlled trial has shown sulfasalazine beneficial in maintaining remission in patients with Crohn's disease. Corticosteroids are not indicated for maintaining remission because they have significant side effects and do not prevent recurrence. In an open-label, multicenter trial, 134 patients with Crohn's disease in remission were given Pentasa at a dosage that did not exceed 4 grams daily for 1 year.³³ At the end of the study, 79% of the patients remained in remission, and 72% maintained remission continuously after 12 months of therapy. Furthermore, this trial also showed a steroid-sparing effect in those patients with active disease who were taking steroids at the time of enrollment.

Further support for the use of Pentasa to maintain remission in selected patients with Crohn's disease comes from a double-blind, placebo-controlled, multicenter trial in which 161 patients were stratified according to duration of remission and subsequently randomly assigned to receive either placebo or Pentasa (2 grams daily) for 2 years.³⁴ Patients given Pentasa within 3 months of achieving remission stayed well significantly longer than did patients in the placebo group. There were no significant side effects. While there is no agreement as to whether patients with Crohn's disease in remission should receive maintenance treatment with Pentasa, it is not unreasonable to offer it, albeit at a considerable cost, to improve the odds of maintaining remission.

There is good evidence that Pentasa delivers active drug to the proximal small intestine.³⁵ There is also some evidence that patients with mildly to moderately active Crohn's disease improve with Pentasa at a dose of 4 grams daily. Even though not yet FDA-approved for Crohn's disease, this formulation may be worthwhile before one resorts to steroids because it has fewer adverse effects.

As for maintenance treatment, Pentasa has prolonged remissions in at least some patients with Crohn's disease, namely those with ileitis or recent medically induced remissions.³⁶

RECOMMENDATIONS

The choice of medication for either Crohn's disease or ulcerative colitis depends largely on disease extent, location, and severity. Treatment can be divided into two phases: induction of remission and maintenance of remission.

For patients with mildly to moderately active ulcerative colitis or mild Crohn's ileitis, ileocolitis, or colitis who are not allergic to sulfa drugs, sulfasalazine is the drug of choice at 3 grams or more daily for active disease and 2 grams daily to maintain remission.

We recommend folic acid supplements (at least 0.4 mg daily) for patients taking sulfasalazine to counter sulfasalazine's competitive inhibition of folic acid absorption.

For patients allergic to sulfa drugs or who cannot tolerate sulfasalazine, the new preparations of 5-ASA are useful, although none is more effective than sulfasalazine in patients with mildly to moderately active ulcerative colitis or in maintenance of remission.³⁷

Olsalazine, Asacol, and Pentasa are similar in effectiveness to sulfasalazine, and are useful in treating patients allergic to or intolerant of sulfasalazine.

Pentasa delivers active drug to the proximal small intestine. There is some evidence that patients with mildly to moderately active Crohn's disease improve with this formulation at a dose of 4 grams daily. Even though not approved for Crohn's disease, this formulation may be worthwhile before using steroids because it has fewer adverse effects.

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REFERENCES

1. Azad Kahn AK, Piris J, Truelove SC. An experiment to determine the active therapeutic moiety of sulfasalazine. *Lancet* 1977; 2:892-895.
2. Dick AP, Grayson MJ, Carpenter RG, Petrie A. Controlled trial of sulfasalazine in the treatment of ulcerative colitis. *Gut* 1964; 5:437-442.
3. Klotz U, Maier K, Fischer C, Hientel K. Therapeutic efficacy of sulfasalazine and its metabolites in patients with ulcerative colitis and Crohn's disease. *N Engl J Med* 1980; 303:1499-1502.
4. Misiewicz JJ, Lennard-Jones JE, Connel AM, et al. Controlled trial of sulphasalazine in maintenance therapy for ulcerative colitis. *Lancet* 1965; 1:185-188.

5. Azad Khan AK, Howes DT, Peres J, Truelove S. Optimum dose of sulfasalazine for maintenance treatment of ulcerative colitis. *Gut* 1980; 21:232-240.
6. Summers RW, Switz DM, Sessions JT, et al. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979; 77:847-869.
7. Malchow H, Ewe K, Brandes JW, et al. European Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1984; 86:249-266.
8. Van Hees PAM, Van Lier HJJ, Van Elteren PH, et al. Effect of sulfasalazine in patients with active Crohn's disease: a controlled double-blind study. *Gut* 1981; 22:404-409.
9. Goldstein F, Thornton JJ, Abramson J. Comments on National Cooperative Crohn's Disease Study. *Gastroenterology* 1980; 78:1647-1648.
10. Das KM, Eastwood MA, McManus JP, Sircus W. Adverse reactions during salicylazosulfapyridine therapy and the relation with drug metabolism and acetylator phenotype. *N Engl J Med* 1973; 289:491-495.
11. Selby WS, Barr GD, Ireland A, Mason CH, Jewell DP. Olsalazine in active ulcerative colitis. *Br Med J* 1985; 291:1373-1375.
12. Meyers S, Sachar DB, Present DH, Janowitz HD. Olsalazine sodium in the treatment of ulcerative colitis among patients intolerant of sulfasalazine: a prospective, randomized, placebo-controlled, double blind, dose-ranging clinical trial. *Gastroenterology* 1987; 93:1255-1262.
13. Rijk MCM, van Lier HJ, van Tongeren JH. Relapse-preventing effect and safety of sulfasalazine and olsalazine in patients with ulcerative colitis in remission: a prospective double-blind, randomized multicenter study. *Am J Gastroenterol* 1992; 87:438-442.
14. Courtney MG, Nunes DP, Bergin CF, et al. Randomized comparison of olsalazine and mesalazine in the prevention of relapses in ulcerative colitis. *Lancet* 1992; 339:1279-1281.
15. Dew MJ, Hughes PJ, Harries AD, et al. Maintenance of remission in ulcerative colitis with oral preparation of 5-aminosalicylic acid. *Br Med J* 1982; 285:1012.
16. Habal FM, Greenberg GR. Treatment of ulcerative colitis with oral 5-aminosalicylic acid including patients with adverse reactions to sulfasalazine. *Am J Gastroenterol* 1988; 83:15-19.
17. Dew MJ, Harries AD, Evans BK, et al. Treatment of ulcerative colitis with oral 5-aminosalicylic acid in patients unable to take sulfasalazine. *Lancet* 1983; 2:801. Letter.
18. Dew MJ, Ryder REJ, Evans N, Evans BK, Rhodes J. Colonic release of 5-aminosalicylic acid from an oral preparation in active ulcerative colitis. *Br J Clin Pharmacol* 1983; 16:185-186.
19. Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. *N Engl J Med* 1987; 317:1625-1629.
20. Faber SM, Korelitz BI. Experience with Eudragit-S-coated mesalamine (Asacol) in inflammatory bowel disease. *J Clin Gastroenterol* 1993; 17:213-218.
21. Beck IT, Hudacin J, Paterson WG, Depew WT, Simon JB, Groll A. Mesalazine in the treatment of active Crohn's disease. *Can J Gastroenterol* 1988; 2:63A-70A.
22. Faber SM, Korelitz BI. Experience with Asacol in the treatment of IBD: a review of 66 patients. *Gastroenterology* 1990; 98:A168. Abstract.
23. Prantera C, Pallone F, Brunetti G, Cottone M, Miglioli M, The Italian IBD Study Group. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. *Gastroenterology* 1992; 103:363-368.
24. Caprilli R, Andreoli A, Capurso L, et al. Oral mesalazine (5-aminosalicylic acid, Asacol) for the prevention of post-operative recurrence of Crohn's disease. *Aliment Pharmacol Ther* 1994; 8:35-43.
25. Christensen LE, Slot O, Sanchez C, et al. Release of 5-aminosalicylic acid from Pentasa during normal and accelerated intestinal transit time. *Br J Clin Pharmacol* 1987; 23:365-369.
26. Bondesen S, Tage-Jensen U, Jacobsen O, et al. 5-Aminosalicylic acid in patients with ileo-rectal anastomosis: a comparison of the fate of sulfasalazine and Pentasa. *Eur J Clin Pharmacol* 1986; 31:23-26.
27. Hanauer S, Schwartz J, Roufail W et al. Dose-ranging study of oral mesalamine capsule (Pentasa) for active ulcerative colitis. *Gastroenterology* 1989; 98:A195. Abstract.
28. Hanauer S, Beshears L, Wilkinson C, et al. Induction of remission in a dose-ranking study of oral mesalamine capsules (Pentasa). *Gastroenterology* 1990; 98:A174. Abstract.
29. Miner P, Nostrant T, Wruble L, et al. Multicenter trial of Pentasa for active ulcerative colitis. *Gastroenterology* 1991; 100:A231. Abstract.
30. Mulder CJJ, Tytgat GNJ, Weterman IT, et al. Double-blind comparison of slow-release 5-aminosalicylate and sulfasalazine in remission maintenance in ulcerative colitis. *Gastroenterology* 1988; 95:1449-1453.
31. Singleton JW, Hanauer SB, Gitnick GL, et al. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. *Gastroenterology* 1993; 104:1293-1301.
32. Rasmussen SN, Lauritsen K, Tage-Jensen U, et al. 5-Aminosalicylic acid in the treatment of Crohn's disease: a 16-week double-blind, placebo-controlled multicenter study with Pentasa. *Scand J Gastroenterol* 1987; 22:877-883.
33. Hanauer SB, Krawitt EL, Robinson M, et al. Long-term management of Crohn's disease with mesalamine capsules. *Am J Gastroenterol* 1993; 88:1343-1351.
34. Gendre JP, Mary JY, Florent C, et al. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. *Gastroenterology* 1993; 104:435-439.
35. Larouche J, Morais J, Picard M, et al. Bioavailability of Pentasa in patients with Crohn's disease of the small intestine. *Gastroenterology* 1994; 106:A718. Abstract.
36. Steinhart AH, Hemphill DJ, Greenberg GR. Sulfasalazine and mesalazine for the maintenance therapy of Crohn's disease: a meta-analysis. *Gastroenterology* 1994; 106:A778. Abstract.
37. Sutherland LR, May GR, Shaffer EA. Sulfasalazine revisited: A meta-analysis of 5-aminosalicylic acid in the treatment of ulcerative colitis. *Ann Intern Med* 1993; 118:540-549.

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