Ulcerative Colitis Agents Review

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Ulcerative Colitis Agents Review

FDA-Approved Indications[1,2,3,4,5,6,7,8]

Drug	Manufacturer	Indication(s)	
		Treatment	**Maintenance**
Oral Prodrug Forms			
balsalazide (Colazal®)	generic	Mild to moderately active ulcerative colitis (UC)	--
olsalazine (Dipentum®)	UCB Pharma	--	Maintenance of remission of UC in patients intolerant of sulfasalazine
sulfasalazine (Azulfidine®, Azulfidine EN-tabs®)	generic	Mild to moderately active UC Adjunctive therapy in severe UC	Maintenance of remission of UC
		Other: Enteric-coated tablets are indicated in patients with UC who cannot take uncoated sulfasalazine tablets because of GI intolerance. Treatment of rheumatoid arthritis that has not responded adequately to salicylates or other nonsteroidal anti-inflammatory agents (NSAIDs) Treatment of pediatric patients with polyarticular juvenile rheumatoid arthritis who have not responded adequately to salicylates or other NSAIDs	
Oral Delayed-Release Forms			
mesalamine tablets (Asacol®)	Procter & Gamble	Mild to moderately active UC	Maintenance of remission of UC
mesalamine MMX tablets (Lialda™)	Shire US	Mild to moderately active UC	--
mesalamine capsules (Pentasa®)	Shire US	Mild to moderately active UC	--
mesalamine extended-release capsules (Apriso™)	Salix	--	Maintenance of remission of UC in adults

Drug	Manufacturer	Indication(s)	
Topical Forms			
mesalamine enemas (Rowasa®)*	generic	Mild to moderately active distal UC, proctosigmoiditis, or proctitis	--
mesalamine suppositories (Canasa®)	Axcan Scandipharm	Active ulcerative proctitis	--

*A sulfite-free formulation of Rowasa (sfRowasa®) by Alaven has been approved but is not yet commercially available.

Overview

Ulcerative colitis (UC) is a chronic inflammatory disease primarily affecting the colon and rectum. The disease is characterized by superficial infiltration of the bowel wall by inflammatory white cells, resulting in multiple mucosal ulcerations and crypt abscesses. The lesions are contiguous, typically extending retrograde from the rectum, involving the descending, transverse, or the entire colon. The principal goal of treatment for UC is inducing, then maintaining, remission of the disease.

The predominant symptom of UC is diarrhea which is usually associated with blood in the stool. Bowel movements are frequent but small in volume as a result of rectal inflammation. Other symptoms include fever and pain, which may be in either the lower quadrant or rectum. Systemic features, including fever, malaise, and weight loss are more common if a greater portion of the colon is affected. Elderly patients often complain of constipation rather than diarrhea because rectal spasm prevents passage of stool. The initial attack of UC may be fulminant with bloody diarrhea, but the disease more commonly begins indolently, with non-bloody diarrhea progressing to bloody diarrhea. Ulcerative colitis can present initially with any extent of anatomic involvement ranging from disease confined to the rectum to pancolitis. Most commonly, UC follows a chronic intermittent course with long periods of quiescence interspersed with acute attacks lasting weeks to months. However, a significant percentage of patients suffer a chronic continuous course.[9]

Aminosalicylates are the cornerstone of treatment for mild to moderate active UC with extension proximal to the sigmoid colon.[10] The agents achieve high luminal concentrations of the active component, 5-aminosalicylic acid (5-ASA, mesalamine), while minimizing adverse events due to systemic absorption. Several aminosalicylates are available and differ only in mode of distribution throughout the small intestine and colon.

For active ulcerative proctitis, an effective and rapid acting approach is nightly administration of mesalamine retention enemas or suppositories, often supplemented with an oral aminosalicylate. Corticosteroid enemas can also be used. Another approach to proctitis is administration of an oral aminosalicylate alone, although therapeutic response may not be evident for three to four weeks.[11]

In 2007, the American Academy of Family Physicians (AAFP) released guidelines for the diagnosis and treatment of UC. The guidelines state that the incidence of colon cancer is

increased with UC and achieving remission is critical in order to lower a patient's lifetime risk. According to the AAFP guidelines, 5-ASA (mesalamine) via enema or suppository is first-line for patients with isolated proctosigmoid disease; oral 5-ASA should not be used in these patients. In patients with greater colonic involvement, first-line therapy should include oral mesalamine and oral corticosteroids to maintain remission. To prevent relapse of the disease, patients with UC may be given nonpathogenic *E. coli* instead of 5-ASA. Symptoms refractory to oral mesalamine or oral corticosteroids may be treated with azathioprine or infliximab (Remicade®).[12]

The 2004 Practice guidelines of the American College of Gastroenterology state no difference in efficacy among all available agents exists provided the drug can reach areas affected by disease.[13] All oral agents are effective in maintaining remission of disease. As with acute therapy, remission is more likely to be sustained at higher doses. With distal disease, rectally administered products can maintain remission either alone or in combination with oral agents.

In patients with severe or refractory UC symptoms, oral corticosteroids are indicated. Corticosteroids, while highly efficacious in short term use, have numerous adverse effects, especially in the elderly, which preclude long-term use.[14] Patients who respond to oral prednisone and can be fully withdrawn from the drug should be maintained on an aminosalicylate. For patients with corticosteroid-dependent or corticosteroid-refractory disease, immunosuppression with azathioprine or mercaptopurine may prevent colectomy.[15] Infliximab, a TNF-inhibitor, is approved for reducing signs and symptoms, achieving clinical remission and mucosal healing, and eliminating corticosteroid use in patients with moderate to severe active UC who fail conventional therapy. Aminosalicylates are the focus of the review.

Pharmacology

The first oral aminosalicylate developed, sulfasalazine, consists of a sulfapyridine carrier moiety linked to 5-ASA via an azo bond.[16] Colonic bacteria cleave the azo bond, converting sulfasalazine into sulfapyridine and 5-ASA moieties.[17] While the sulfapyridine is absorbed and excreted in the urine, the 5-ASA component stays in the colon and is excreted in the feces. Although the specific mechanism is unknown, the intralumenal activity of 5-ASA produces a local therapeutic effect.[18,19] Mucosal production of arachidonic acid metabolites, through cyclooxygenase and lipoxygenase pathways, is increased in patients with chronic inflammatory bowel disease. 5-ASA may decrease inflammation by blocking production of arachidonic acid metabolites in the colon.[20, 21]

Newer oral agents were developed to enhance 5-ASA delivery to the colon and reduce the incidence of adverse events.[22] The formulations fall into three categories: azo-bonded prodrug formulations (Colazal, Dipentum), delayed-release formulations achieved by pH shift (Apriso, Asacol, and Lialda) or controlled-release formulations (Pentasa). The azo-bonded prodrugs are similar to sulfasalazine, and colonic bacteria are required to cleave the azo bond and release the active 5-ASA moiety.[23,24] Effectiveness of delayed and controlled-release formulations may be variable because release of mesalamine is pH-dependent. As a result, early release increases absorption of 5-ASA in the proximal small intestine, increasing systemic exposure to 5-ASA and possible nephrotoxicity.[25] Apriso capsules have the Intellicor extended release delivery technology that combines an enteric pH-dependent coating giving a delayed release starting at a pH of 6.0 followed by a polymer matrix core that provides for extended release.[26] Asacol tablets are coated with a pH-sensitive acrylic polymer which delays the release of 5-ASA. Lialda uses MMX technology, a pH-dependent gastro-resistant coating, to delay the release of 5-ASA from the tablet core to the colon. Pentasa uses a water gradient to release microspheres containing 5-ASA from the capsule.

Mesalamine is available as suppositories (Canasa) and enemas that deliver 5-ASA directly to the site of action. For treatment of ulcerative proctitis, mesalamine suppositories (or corticosteroid foam), which deliver drug to the rectum, are appropriate for disease of up to 20 cm of distal colon. Mesalamine (or corticosteroid) retention enemas, which distribute drug to the left colon, can be used for active disease involving up to 60 cm of distal colon.[27]

Pharmacokinetics[28,29,30,31,32,33,34,35,36,37]

All oral products are designed to release 5-ASA for action in the intestine so absorption is intended to be minimal. Absorbed 5-ASA and its metabolites are excreted in the urine. The majority of 5-ASA remains in the colonic lumen and is excreted in feces. The elimination half-life of 5-ASA ranges from two to 15 hours due to the different formulations of the drugs.

Drug	Delivery Mechanism	Bioavailability (%)
Oral Prodrug Forms		
balsalazide (Colazal)	Delivered to the colon intact then bacteria cleave the compound to release 5-ASA	low and variable
olsalazine (Dipentum)	Rapidly converted in the colon to molecules of 5-ASA by bacteria and the colon's low prevailing redox potential	2.4
sulfasalazine	Metabolized by intestinal bacteria to 5-ASA and sulfapyridine	<15
Oral Delayed-Release Forms		
mesalamine tablets (Asacol)	Acrylic-based resin coating delays 5-ASA release until tablet reaches the terminal ileum and beyond	28
mesalamine MMX tablets (Lialda)	pH-dependent gastro-resistant coating that delays release of 5-ASA until the tablet reaches the colon	21-22
mesalamine capsules (Pentasa)	Ethylcellulose-coated, controlled release formulation releases 5-ASA throughout the intestinal tract	20-30
mesalamine extended-release capsules (Apriso)	Intellicor extended-release delivery technology that combines an enteric pH-dependent coating which provides for a delayed release starting at a pH of 6.0 with a polymer matrix core that enables extended release	21-44
Topical Forms		
mesalamine enemas	Topical administration	10-30
mesalamine suppositories (Canasa)	Topical administration	variable

Contraindications/Warnings[38,39,40,41,42,43,44,45,46]

Deaths associated with administration of sulfasalazine have been reported. Deaths occurred from hypersensitivity reactions, agranulocytosis, aplastic anemia, other blood dyscrasias, renal and liver damage, irreversible neuromuscular and central nervous system changes, and fibrosing alveolitis. Complete blood counts, as well as urinalysis with careful microscopic examination, should be done frequently in patients receiving sulfasalazine. Oligospermia and infertility have been observed in men treated with sulfasalazine; however, withdrawal of the drug appears to reverse the effects.[47]

Aminosalicylates are contraindicated in patients with sulfonamide hypersensitivity. Sulfasalazine is also contraindicated in patients with salicylate hypersensitivity, porphyria, urinary tract infections, and in women who are breastfeeding. Mesalamine enemas (Rowasa Rectal Suspension Enema) contain potassium metabisulfite, a sulfite which may cause life-threatening allergic-type reactions including anaphylaxis. Sulfite sensitivity is more frequent in asthmatic patients or atopic non-asthmatic persons. Overall prevalence of sulfite sensitivity in the general population is not known, but probably low.[48]

Drug Interactions[49,50,51,52,53,54,55,56,57]

Antacids: Mesalamine extended-release capsules (Apriso) depend on pH for dissolution of the coating of the granules so concomitant use with antacids should not occur.

Digoxin: Sulfasalazine,, in doses more than 2 g daily, reduces the oral absorption of digoxin by 25 percent. It is unclear if other aminosalicylates have any significant effect on digoxin absorption.

Folic acid: Sulfasalazine can inhibit the absorption of folic acid; supplementation of folic acid may be required.

Phenytoin: Sulfasalazine can displace highly protein-bound drugs such as phenytoin.

Warfarin: Salicylates may displace warfarin from protein binding sites leading to hypoprothrombinemia. This dose-related interaction has been reported with olsalazine and sulfasalazine.

Adverse Effects[58,59,60,61,62,63,64,65,66,67,68]

Drug	Abdominal pain	Diarrhea	Fever	Headache	Nausea	Rash	Vomiting
Oral Prodrug Forms							
balsalazide (Colazal)	6	5-7	2-4	8-11	5-10	<2	4-7
olsalazine (Dipentum)	10.1	2.5-17	<1	5	5	2.3	1
sulfasalazine (Azulfidine)	more common	rare	less common	more common	more common	less common	more common
Oral Delayed-Release Forms							
mesalamine tablets (Asacol)	13-18	7-9	6-10	16-35	13-15	6	1-5
mesalamine MMX tablets (Lialda)	<1	<1	nr	5.6	nr	<1	<1
mesalamine capsules (Pentasa)	1.1	3.5	0.9	2.2	3.1	1.3	1.1
mesalamine extended-release capsules (Apriso)	5	8	nr	11	4	nr	nr
Topical Forms							
mesalamine enemas (Rowasa)	8.1	2.1	3.2	6.5	5.8	2.8	<1
mesalamine suppositories (Canasa)	5.2	3.1	1.2	14.4	3.1	1.2	<1

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Clinical tolerance of three aminosalicylate preparations [mesalamine (Asacol), olsalazine (Dipentum), and balsalazide] was assessed in a consecutive series of 43 patients with inflammatory bowel disease intolerant to sulfasalazine.[69] Ninety-one percent of patients were able to tolerate at least one of the three preparations. Clinical tolerance of mesalamine (63 percent), olsalazine (70 percent) and balsalazide (70 percent) was similar. The most common adverse effects associated with the preparations were gastrointestinal in nature; diarrhea was a problem in five patients during treatment with olsalazine and three each while on mesalamine and balsalazide. Allergic reactions to aminosalicylates were uncommon; of ten patients with rash following sulfasalazine, only one developed a rash with mesalamine. Results of this study indicate the vast majority of patients with inflammatory bowel disease can be managed with at least one of the four aminosalicylates and side effects of sulfasalazine are multifactorial in etiology. Some are due to the parent molecule, and some to one of its two metabolites, 5-ASA and sulfapyridine.

Special Populations[70,71,72,73,74,75,76,77]

Pediatrics

Safety and efficacy of olsalazine (Dipentum) were compared to sulfasalazine over three months in a multicenter, randomized, double-blind study of 56 children with mild to moderate UC.[78] Twenty-eight children received 30 mg/kg/day of olsalazine (maximum of 2 g/day) and 28 received 60 mg/kg/day of sulfasalazine (maximum of 4 g/day). After three months, 39 percent of olsalazine-treated patients were asymptomatic or clinically improved, compared to 79 percent of sulfasalazine-treated patients (p=0.006). In addition, 10 of 28 patients on olsalazine versus one on sulfasalazine required prednisone because of lack of response or worsening of colitis (p=0.005). The dose of olsalazine used in the trial was equivalent to a standard dose of sulfasalazine, but fewer patients on olsalazine improved and a greater number had progression of symptoms when compared to sulfasalazine. Adverse effects were frequent in both groups; a clinically significant difference was not detected.

Sulfasalazine is approved for use in patients six years of age and older. Balsalazide is approved for use in patients five years of age and older. Other products have not been studied sufficiently in pediatric populations.

Pregnancy

Olsalazine (Dipentum) is Pregnancy Category C. All other agents in this category are Pregnancy Category B.

Renal Impairment

Reports of renal impairment, including minimal change nephropathy, and acute or chronic interstitial nephritis have been associated with the mesalamine products and prodrugs of mesalamine. For patients with known renal dysfunction, caution should be exercised and patients should be properly monitored.

Phenylketonuria (PKU)

Caution should be taken when mesalamine ER (Apriso) is administered to patients with phenylketonuria because each capsule contains aspartame equivalent to 0.56 mg of phenylalanine.

Dosages

Drug	Adults	Pediatrics	Availability
Oral Prodrug Forms			
balsalazide (Colazal)	2.25 g three times daily for eight to twelve weeks	Children 5 to 17 yrs 2.25 g three times daily for eight weeks OR 750 mg three times daily for eight weeks	750 mg capsule
olsalazine (Dipentum)	0.5 g twice daily	--	250 mg capsule
sulfasalazine	Treatment: 3 to 4 g daily in evenly divided doses with dosage intervals not exceeding eight hours Maintenance: 2 g daily	Children 6 yrs and older Treatment: 40 to 60 mg/kg/day divided into three to six doses Maintenance: 30 mg/kg/day divided into four doses	500 mg tablet 500 mg enteric coated delayed-release tablet
Oral Delayed-Release Forms			
mesalamine tablets (Asacol)	Initial dose: 0.8 g three times daily for six weeks Maintenance dose: 1.6 g per day in divided doses for six months	--	400 mg delayed-release tablet
mesalamine MMX tablets (Lialda)	2.4 g or 4.8 g (two to four tablets) once daily with a meal for up to eight weeks	--	1.2 g delayed-release tablet
mesalamine capsules (Pentasa)	1 g four times a day for up to eight weeks	--	250 mg, 500 mg controlled-release capsules
mesalamine extended-release capsules (Apriso)	1.5 g once daily in the morning with or without food	--	0.375 mg extended-release capsules

Balsalazide capsules may be opened and sprinkled on applesauce; contents may be chewed.

Drug	Adults	Pediatrics	Availability
Topical Forms			
mesalamine enemas (Rowasa)	4 g (60 mL) rectally at bedtime (and retained for a minimum of eight hours) for three to six weeks	--	4 g/60 mL enema
mesalamine suppositories (Canasa)	1 g daily at bedtime (and retained for a minimum of one to three hours) for three to six weeks	--	1,000 mg suppositories

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

mesalamine delayed release (Asacol) 4.8 g/day versus 2.4 g/day

Delayed-release oral mesalamine 2.4 g/day to 4.8 g/day has been shown to be effective in treating mild to moderately active UC; but, it is unknown whether an initial dose of 4.8 g/day is more effective than 2.4 g/day in patients with mild to moderately active UC and in a subgroup with moderate disease.[79] A six-week, multicenter, randomized, double-blind, controlled trial assessing the safety and clinical efficacy of a new dose (ASCEND I) of medication randomly assigned 301 adults with mild to moderate active UC to delayed-release oral mesalamine 2.4 g/day (400 mg; n=154) or 4.8 g/day (800 mg; n=147). Primary efficacy endpoint was overall improvement defined as complete remission or response to therapy from baseline to week 6. Primary safety end points were adverse events and laboratory evaluations. Treatment success was not statistically different between the groups at week six; 51 percent of the group who received 2.4 g/day and 56 percent of the group who received 4.8 g/day reached the efficacy endpoint (p=0.441). In the moderate disease subgroup however, the higher initial dose was more effective (57 versus 72 percent in the 2.4 versus 4.8 g/day groups, respectively) (p=0.0384). Both regimens were well tolerated. In conclusion, the initial 4.8 g/day dose may be better reserved for patients with moderate disease.

Treatment success with any product is often dose-related, as seen in other studies such as ASCEND II, where overall improvement was significantly more likely with higher doses of mesalamine.[80]

balsalazide (Colazal) versus mesalamine controlled-release (Pentasa)

In a double-blind trial, 133 patients with UC in remission were randomized to receive balsalazide 1.5 or 3 g twice daily or mesalamine controlled-release 0.5 g three times daily.[81] Efficacy was measured by clinical activity index, endoscopy score, and histological score at 26 weeks. Balsalazide 3 g twice daily produced a significantly higher clinical remission rate (77.5 percent) than both lower dose balsalazide (43.8 percent) and mesalamine controlled-release (56.8 percent). The respective times to relapse were 161 days for high-dose balsalazide, 131 days for low-dose balsalazide (p=0.003 compared to high-dose balsalazide), and 144 days for mesalamine controlled-release (p=NS compared to high-dose balsalazide). Pairwise contrasts of the final endoscopic score demonstrated a significant difference (p=0.005) between the two balsalazide treatment groups while differences among either of these two groups and mesalamine controlled-release were not statistically significant. All three treatments were well tolerated.

balsalazide (Colazal) versus mesalamine delayed-release (Asacol)

A double-blind study compared the effectiveness of balsalazide and mesalamine delayed-release in the treatment of 101 patients with active moderate-to-severe UC.[82] Patients were randomized to receive balsalazide 6.75 g/day or mesalamine delayed-release 2.4 g/day for 12 weeks. After two, four, and 12 weeks, symptom control was greater in the balsalazide group. Remission rate after 12 weeks of therapy was 62 percent with balsalazide and 37 percent with mesalamine delayed-release. Median time to first day of complete relief of symptoms was ten days for the balsalazide group and 25 days for the mesalamine delayed-release group. Adverse effects occurred in 48 percent of patients treated with balsalazide and 71 percent of those treated with mesalamine delayed-release.

A randomized, double-blind, double-dummy, parallel group dose-response study was performed comparing balsalazide 2.25 or 6.75 g daily and delayed-release mesalamine 2.4 g daily.[83] Medication was administered for eight weeks to 154 patients with active, mild-to-moderate UC, the majority of who were relapsing. High dose balsalazide was superior to low dose in rectal bleeding, stool frequency, sigmoidoscopic score, and Physician's Global Assessment (PGA). The only significant difference observed between high-dose balsalazide and mesalamine delayed-release was more rapid onset of action as determined by a better two-week sigmoidoscopic score for patients treated with balsalazide (55 versus 29 percent; p=0.006). Balsalazide 6.75 g daily was well tolerated, and the safety profile did not differ significantly from either balsalazide 2.25 g daily or mesalamine delayed-release 2.4 g daily.

A total of 173 patients with active, mild-to-moderate UC were randomized to eight weeks of double-blind treatment with balsalazide 2.25 g or mesalamine 0.8 g, each given three times daily.[84] Overall, 46 percent of balsalazide- and 44 percent of mesalamine-treated patients achieved symptomatic remission at endpoint. Although the median time to symptomatic remission was shorter with balsalazide (25 days) than with mesalamine (37 days), the difference was not clinically significant. Significantly more balsalazide-treated patients showed improvement in sigmoidoscopic score (p=0.002), stool frequency (p=0.006), rectal bleeding (p=0.006), and physician global assessment scores (p=0.013) by 14 days compared to mesalamine-treated patients. The difference between groups in improved sigmoidoscopic score was significant at day 28 (p=0.002). By day 56 and at endpoint, no significant differences

between groups were detected. During the treatment period, 54 percent of balsalazide- and 64 percent of mesalamine-treated patients reported at least one treatment-emergent adverse event. The most common adverse events affected the gastrointestinal tract or the central and peripheral nervous systems.

The mesalamine delayed-release (Asacol) product used in the studies was manufactured and marketed by Smith Kline & French in the United Kingdom, rather than the Procter & Gamble product used in North America. Although the significance is not known, data are available from comparative *in vitro* dissolution studies to suggest slight differences exist between the two Asacol products.[85]

olsalazine (Dipentum) versus sulfasalazine (Azulfidine)

A randomized, double-blind, six-month study compared three doses of olsalazine (0.5, 1.25, and 2 g daily) and sulfasalazine 2 g daily for maintenance of remission in 162 patients with UC.[86] Using intention-to-treat analysis, failure rates of the different treatment groups were not significantly different (36, 49, and 24 percent for 0.5, 1.25 and 2 g olsalazine daily and 32 percent for 2 g sulfasalazine daily). Olsalazine and sulfasalazine showed a tendency towards lower failure rates in extended disease (28 percent) than in distal disease (44 percent). Withdrawal rate due to adverse effects was four percent with the most frequent single event being diarrhea, which occurred only in patients treated with olsalazine (2.5, 5.2, and 11.7 percent for daily olsalazine doses of 0.5, 1.25, and 2 g, respectively).

A randomized, double-blind trial compared the relapse-preventing effects of olsalazine and sulfasalazine in patients with UC over 12 months.[87] A total of 227 patients received either olsalazine 500 mg twice daily or sulfasalazine 1 g twice daily. A total of 197 patients completed the trial. Relapse rate after 12 months in the olsalazine group was 46.9 percent versus 42.4 percent in the sulfasalazine group (95% confidence interval (CI), -9 to 18 percent). Equal numbers of patients in each group withdrew from the trial because of adverse effects.

mesalamine MMX delayed-release tablets (Lialda) versus placebo

A randomized, double-blind, parallel-group, placebo-controlled trial was conducted in 280 patients with active, mild to moderate UC over eight weeks.[88] Patients received mesalamine MMX delayed-release 1.2 g twice daily, 4.8 g once daily, or placebo. The primary efficacy endpoint was percentage of patients in clinical and endoscopic remission after eight weeks of treatment. Clinical and endoscopic remission at week eight was achieved by 34.1 percent and 29.2 percent of the mesalamine MMX delayed-release 2.4 g/day and 4.8 g/day groups, respectively, versus 12.9 percent of placebo patients. Mesalamine MMX delayed-release tablets given once or twice daily were well tolerated and, compared with placebo, demonstrated efficacy for induction of clinical and endoscopic remission in mild to moderately active UC.

mesalamine MMX delayed-release tablets (Lialda) versus mesalamine delayed-release tablets (Asacol)

An eight-week, double-blind, multicenter trial was conducted in 340 patients with active, mild-to-moderate ulcerative colitis comparing mesalamine MMX delayed-release 2.4 g/day or 4.8 g/day, mesalamine delayed-release 2.4 g/day given in three divided doses or placebo.[89] The primary endpoint was proportion of patients in clinical and endoscopic remission. Remission was measured by a modified UC disease activity index of less than or equal to one with rectal bleeding, stool frequency scores of zero, no mucosal friability, and a greater than or equal to one point reduction in sigmoidoscopy score from baseline. Patients treated with mesalamine

MMX delayed-release experienced significantly greater clinical and endoscopic remission rates by week eight versus placebo (2.4 g/day = 40.5 percent; 4.8 g/day = 41.2 percent; placebo = 22.1 percent). The remission rate for mesalamine delayed-release was not significantly greater than placebo (32.6 percent; p=0.124). All active treatments were well-tolerated.

Summary

The active ingredient of the aminosalicylates, mesalamine (5-ASA), is available as both delayed-release tablets (Asacol) and controlled-release capsules (Pentasa). A third delayed-release dosage form of mesalamine (5-ASA) is also available, using MMX technology (Lialda). The newest extended-release capsule form of mesalamine (5-ASA) called Apriso is now available that uses the Intellicor technology. Although very few significant studies directly compare the dosage forms, the drugs have similar efficacy.

Due to the addition of the 500 mg capsule of mesalamine controlled-release (Pentasa), daily pill burden has decreased from 16 to eight. Mesalamine controlled-release (Pentasa) is dosed four times a day using eight capsules, and mesalamine delayed-release (Asacol) is dosed three times a day using six tablets. Mesalamine MMX delayed-release (Lialda) is dosed once daily using two to four tablets. Mesalamine Intellicor extended-release (Apriso) is dosed once daily using four capsules. Relative tolerability and compliance must be considered in evaluation of the oral mesalamine preparations.

Safety and efficacy of mesalamine MMX extended-release (Lialda) past eight weeks of treatment of UC have not been established. The duration of Apriso use for maintaining remission of UC beyond six months has not been evaluated.

Balsalazide (Colazal) is indicated for UC treatment. Olsalazine (Dipentum) is indicated for UC maintenance. Balsalazide (Colazal) differs from olsalazine (Dipentum) only in that balsalazide (Colazal) appears to have a more rapid onset of effect; it may also be slightly more effective in left-sided disease. The tolerance of olsalazine (Dipentum) is often limited by a high rate of secretory diarrhea.

The adverse effect profile for sulfasalazine is less favorable than newer agents especially at higher doses. Patients with disease affecting the distal portion of the colon should use a rectal preparation either alone or in combination with oral therapy. Enemas and suppositories may provide quicker response time as well as less frequent dosing compared to oral therapy. Rectally administered mesalamine (generic, Rowasa enemas, Canasa suppositories) has a specific role as a non-oral treatment of distal UC, proctosigmoiditis, and proctitis.

References

[1] Colazal [package insert]. Raleigh, NC; Salix Pharmaceuticals, Inc.; May 2008.
[2] Dipentum [package insert]. Rochester, NY; UCB Pharma Limited; December 2006.
[3] Azulfidine [package insert]. Kalamazoo, MI; Pharmacia & Upjohn; August 2006.
[4] Asacol [package insert]. Cincinnati, OH; Procter & Gamble Pharmaceuticals; October 2007.
[5] Lialda [package insert]. Wayne, PA; Shire US; January 2007.
[6] Pentasa [package insert]. Newport, KY; Shire US; January 2007.
[7] Rowasa [package insert]. Marietta, GA; Alaven Pharmaceutical; May 2008.
[8] Canasa [package insert]. Birmingham, AL; Axcan Scandipharm; May 2008.
[9] Stenson WF. Ulcerative Colitis: Clinical Findings and Natural History. Cecil Textbook of Medicine. 2002.
[10] http://www.aafp.org/afp/20071101/1323.html. Accessed January 15, 2009.
[11] Stenson WF. Ulcerative Colitis: Clinical Findings and Natural History. Cecil Textbook of Medicine. 2002.
[12] Langan RC, Gotsch PB, Krafczyk MA, et al. Ulcerative colitis: diagnosis and treatment. Am Fam Phys. 2007; 76(9): 1323-1330.
[13] Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice

Parameters Committee. Am J Gastroenterol. 2004; 99(7):1371-1385.
[14] Stein RB, Hanauer SB. Comparative tolerability of treatments for inflammatory bowel disease. Drug Saf. 2000; 23:429-448.
[15] Pardi DS, Loftus EV, Camilleri M. Treatment of inflammatory bowel disease in the elderly: an update. Drugs Aging. 2002; 19:355-363.
[16] Stein RB, Hanauer SB. Comparative tolerability of treatments for inflammatory bowel disease. Drug Saf. 2000; 23:429-448.
[17] Dipentum [package insert]. Rochester, NY; UCB Pharma Limited; December 2006.
[18] Schroder H, Campbell DES. Absorption, metabolism and excretion of salicylazosulfapyridine in man. Clin Pharmacol Ther. 1972; 13:539–551.
[19] Kahn AK, Piris J, Trulove SC. An experiment to determine the active therapeutic moiety of sulfasalazine. Lancet. 1977; 2:892–895.
[20] Colazal [package insert]. Raleigh, NC; Salix Pharmaceuticals, Inc.; May 2008.
[21] Asacol [package insert]. Cincinnati, OH; Procter & Gamble Pharmaceuticals; October 2007.
[22] Stein RB, Hanauer SB. Comparative tolerability of treatments for inflammatory bowel disease. Drug Saf. 2000; 23:429-448.
[23] Chan RP, Pope DJ, Gilbert AP, et al. Studies of 2 novel sulfasalazine analogs, ipsalazide and balsalazide. Dig Dis Sci. 1983; 28:609-615.
[24] Peppercorn MA, Goldman P. The role of intestinal bacteria in the metabolism of salicylazosulphapyridine. J Pharmacol Exp Ther. 1972; 181:555-562.
[25] Schreiber S, Hamling J, Zehnter E, et al. Renal tubular dysfunction in patients with inflammatory bowel disease. Gut. 1997; 40:761-766.
[26] Apriso [package insert]. Morrisville, NC; Salix Pharmaceuticals, Inc.; October 2008.
[27] Stenson WF. Ulcerative Colitis: Clinical Findings and Natural History. Cecil Textbook of Medicine. 2002.
[28] Colazal [package insert]. Raleigh, NC; Salix Pharmaceuticals, Inc.; May 2008.
[29] Asacol [package insert]. Cincinnati, OH; Procter & Gamble Pharmaceuticals; October 2007.
[30] Pentasa [package insert]. Newport, KY; Shire US; January 2007.
[31] Rowasa [package insert]. Marietta, GA; Alaven Pharmaceutical; May 2008.
[32] Canasa [package insert]. Birmingham, AL; Axcan Scandipharm; May 2008.
[33] Dipentum [package insert]. Rochester, NY; UCB Pharma Limited; December 2006.
[34] Azulfidine [package insert]. Kalamazoo, MI; Pharmacia & Upjohn; August 2006.
[35] Azulfidine EN-tabs [package insert]. Kalamazoo, MI; Pharmacia & Upjohn; August 2006.
[36] Lialda [package insert]. Wayne, PA; Shire US; January 2007.
[37] Apriso [package insert]. Morrisville, NC; Salix Pharmaceuticals, Inc.; October 2008.
[38] Colazal [package insert]. Raleigh, NC; Salix Pharmaceuticals, Inc.; May 2008.
[39] Dipentum [package insert]. Rochester, NY; UCB Pharma Limited; December 2006.
[40] Azulfidine [package insert]. Kalamazoo, MI; Pharmacia & Upjohn; August 2006.
[41] Asacol [package insert]. Cincinnati, OH; Procter & Gamble Pharmaceuticals; October 2007.
[42] Lialda [package insert]. Wayne, PA; Shire US; January 2007.
[43] Pentasa [package insert]. Newport, KY; Shire US; January 2007.
[44] Rowasa [package insert]. Marietta, GA; Alaven Pharmaceutical; May 2008.
[45] Canasa [package insert]. Birmingham, AL; Axcan Scandipharm; May 2008.
[46] Apriso [package insert]. Morrisville, NC; Salix Pharmaceuticals, Inc.; October 2008.
[47] Azulfidine EN-tabs [package insert]. Kalamazoo, MI; Pharmacia & Upjohn; August 2006.
[48] Rowasa [package insert]. Marietta, GA; Alaven Pharmaceutical; May 2008.
[49] Colazal [package insert]. Raleigh, NC; Salix Pharmaceuticals, Inc.; May 2008.
[50] Pentasa [package insert]. Newport, KY; Shire US; January 2007.
[51] Rowasa [package insert]. Marietta, GA; Alaven Pharmaceutical; May 2008.
[52] Canasa [package insert]. Birmingham, AL; Axcan Scandipharm; May 2008.
[53] Asacol [package insert]. Cincinnati, OH; Procter & Gamble Pharmaceuticals; October 2007.
[54] Dipentum [package insert]. Rochester, NY; UCB Pharma Limited; December 2006.
[55] Azulfidine EN-tabs [package insert]. Kalamazoo, MI; Pharmacia & Upjohn; August 2006.
[56] Lialda [package insert]. Wayne, PA; Shire US; January 2007.
[57] Apriso [package insert]. Morrisville, NC; Salix Pharmaceuticals, Inc.; October 2008.
[58] Colazal [package insert]. Raleigh, NC; Salix Pharmaceuticals, Inc.; May 2008.
[59] Pruitt R, Hanson J, Safdi M, et al. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. Am J Gastroenterol. 2002; 97:3078-3086.
[60] Pentasa [package insert]. Newport, KY; Shire US; January 2007.
[61] Rowasa [package insert]. Marietta, GA; Alaven Pharmaceutical; May 2008.
[62] Canasa [package insert]. Birmingham, AL; Axcan Scandipharm; May 2008.
[63] Asacol [package insert]. Cincinnati, OH; Procter & Gamble Pharmaceuticals; October 2007.
[64] Pruitt R, Hanson J, Safdi M, et al. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. Am J Gastroenterol. 2002; 97:3078-3086.
[65] Dipentum [package insert]. Rochester, NY; UCB Pharma Limited; December 2006.
[66] Kruis W, Judmaier G, Kayasseh L, et al. Double-blind dose-finding study of olsalazine versus sulphasalazine as maintenance therapy for ulcerative colitis. Eur J Gastroenterol Hepatol. 1995; 7:391-396.
[67] Azulfidine EN-tabs [package insert]. Kalamazoo, MI; Pharmacia & Upjohn; August 2006.
[68] Lialda [package insert]. Wayne, PA; Shire US; January 2007.
[69] Giaffer MH, O'Brien CJ, Holdsworth CD. Clinical tolerance to three 5-aminosalicylic acid releasing preparations in patients with inflammatory bowel disease intolerant or allergic to sulphasalazine. Aliment Pharmacol Ther. 1992; 6:51-59.

[70] Colazal [package insert]. Raleigh, NC; Salix Pharmaceuticals, Inc.; May 2008.
[71] Dipentum [package insert]. Rochester, NY; UCB Pharma Limited; December 2006.
[72] Azulfidine [package insert]. Kalamazoo, MI; Pharmacia & Upjohn; August 2006.
[73] Asacol [package insert]. Cincinnati, OH; Procter & Gamble Pharmaceuticals; October 2007.
[74] Lialda [package insert]. Wayne, PA; Shire US; January 2007.
[75] Pentasa [package insert]. Newport, KY; Shire US; January 2007.
[76] Rowasa [package insert]. Marietta, GA; Alaven Pharmaceutical; May 2008.
[77] Canasa [package insert]. Birmingham, AL; Axcan Scandipharm; May 2008.
[78] Ferry GD, Kirschner BS, Grand RJ, et al. Olsalazine versus sulfasalazine in mild to moderate childhood ulcerative colitis: results of the Pediatric Gastroenterology Collaborative Research Group Clinical Trial. J Pediatr Gastroenterol Nutr. 1993; 17(1):32-38.
[79] Hanauer SB, Sandborn WJ, Dallaire C, et. Al. Delayed-release oral mesalamine 4.8 g/day (800 mg tablets) compared to 2.4 g/day (400 mg tablets) for the treatment of mildly to moderately active ulcerative colitis: The ASCEND I trial. Can J Gastroenterol. 2007; 21(12):827-34.
[80] 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(11):2478-2485.
[81] Kruis W, Schreiber S, Theuer D. Low dose balsalazide (1.5 g twice daily) and mesalamine (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.
[82] Green JR, Lobo AJ, Holdsworth CD, et al. Balsalazide is more effective and better tolerated than mesalamine in the treatment of acute ulcerative colitis. Gastroenterology. 1998; 114:15-22.
[83] 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.
[84] Pruitt R, Hanson J, Safdi M, et al. Balsalazide is superior to mesalamine in the time to improvement of signs and symptoms of acute mild-to-moderate ulcerative colitis. Am J Gastroenterol. 2002; 97:3078-3086.
[85] Procter & Gamble Pharmaceuticals. Data on file.
[86] Kruis W, Judmaier G, Kayasseh L, et al. Double-blind dose-finding study of olsalazine versus sulphasalazine as maintenance therapy for ulcerative colitis. Eur J Gastroenterol Hepatol. 1995; 7:391-396.
[87] Kiilerich S, Ladefoged K, Rannem T, et al. Prophylactic effects of olsalazine v sulphasalazine during 12 months maintenance treatment of ulcerative colitis. The Danish Olsalazine Study Group. Gut. 1992; 33(2):252-255.
[88] Lichtenstein GR, Kamm MA, Boddu P, et al. Effect of once or twice daily MMX mesalamine for the induction of remission of mild to moderately active ulcerative colitis. Clin Gastroenterol Hepatol. 2007; 5(1):95-102.
[89] Kamm MA, Sandborn WJ, Gassull M, et al. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. Gastroenterology. 2007; 132(1):66-75.

