



Ulcerative Colitis Agents Therapeutic Class Review (TCR)

March 8, 2019

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March 2019

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)	
		Treatment	Maintenance
Oral Prodrug Forms			
balsalazide (Colazal®) ¹	generic, Salix	Mild to moderately active ulcerative colitis (UC) in patients ≥ 5 years	--
balsalazide (Giazo®) ²	Salix	Mild to moderately active UC in male patients ≥ 18 years	--
olsalazine (Dipentum®) ³	Meda/Mylan Specialty	--	Maintenance of remission of UC in patients intolerant of sulfasalazine
sulfasalazine (Azulfidine®, Azulfidine EN-tabs®) ^{4,5}	generic, Pfizer	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 gastrointestinal (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 delayed-release tablets (Asacol® HD) ^{6*}	generic, Allergan	Moderately active UC	--
mesalamine delayed-release capsules (Delzicol®) ^{7†}	Allergan	Mild to moderately active UC in patients ≥ 5 years	Maintenance of remission of UC in adults
mesalamine MMX delayed-release tablets (Lialda®) ⁸	generic, Shire US	Mild to moderately active UC	Maintenance of remission of UC
mesalamine extended-release capsules (Pentasa®) ⁹	Shire US	Mild to moderately active UC	--
mesalamine extended-release capsules (Apriso®) ¹⁰	Salix	--	Maintenance of remission of UC in adults

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)	
		Treatment	Maintenance
Rectal Forms			
budesonide rectal foam (Uceris®) ¹¹	Salix	Mild to moderate active UC extending 40 cm from the anal verge	--
mesalamine enemas (Rowasa®) ¹²	generic, Meda/Mylan	Mild to moderately active distal UC, proctosigmoiditis, or proctitis	--
mesalamine enemas sulfite-free (sfRowasa®) ¹³	Meda/Mylan	Mild to moderately active distal UC, proctosigmoiditis, or proctitis	--
mesalamine suppositories (Canasa®) ¹⁴	generic, Allergan	Active ulcerative proctitis	--
Oral Corticosteroids			
budesonide extended-release tablets (Uceris®) ¹⁵	generic, Santarus	Mild to moderately active UC	--

*Dibutyl phthalate in the enteric coating of Asacol HD delayed release tablets has been replaced by dibutyl sebacate.

†Delzicol delayed-release capsules are bioequivalent to Asacol; however, Delzicol is not AB-rated to Asacol as they are different formulations.

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.

UC affects approximately 1,000,000 people in the United States (US) and the incidence continues to increase worldwide.^{16,17} The Center for Disease Control and Prevention (CDC) estimates the current prevalence of UC at 238 per 100,000 adults.¹⁸ UC may present at any age, but onset typically peaks between 15 and 30 years of age.¹⁹

The predominant symptom of UC is diarrhea, which is usually associated with blood in the stool. Bowel movements are frequent but small in volume due to rectal inflammation.²⁰ Another symptom includes pain in 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 spasms 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. UC can present initially with any extent of anatomic involvement ranging from disease confined to the rectum to the entire large intestine (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.

Aminosalicylates remain first-line treatment options for mild to moderate active UC with 90% of patients treated with this class shortly after disease diagnosis.²¹ Mesalamine agents currently are available in oral and rectal formulations. The rectal products achieve high luminal concentrations of the active component, 5-aminosalicylic acid (5-ASA, mesalamine), while minimizing adverse events from systemic absorption.²² Several aminosalicylates are available and differ only in mode of distribution throughout the small intestine and colon. Second-line therapy with a course of oral or rectal steroids, such as budesonide (Uceris), is indicated for induction therapy in patients with mild to moderate disease who do not respond to oral and rectal mesalamine agents or in patients with moderate to severe disease.²³ Oral and rectal corticosteroids are not intended for maintenance therapy and can lead to serious adverse effects with long-term use.

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.²⁴ 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 3 to 4 weeks.

In patients with severe or refractory UC symptoms, oral corticosteroids are indicated.^{25,26} Corticosteroids, while highly efficacious in short-term use, have numerous adverse effects, especially in the elderly, which preclude long-term use.²⁷ Patients who respond to oral prednisone and can be fully withdrawn from the drug over a period 60 days and should be maintained on an aminosalicylate. For patients with corticosteroid-dependent or corticosteroid-refractory disease, immunosuppression with azathioprine or mercaptopurine may prevent colectomy.²⁸ Several injectable tumor necrosis factor (TNF)-inhibitors (infliximab [Remicade[®]], adalimumab [Humira[®]], and golimumab [Simponi Aria[®]]) are approved for inducing and maintaining clinical response/remission in patients with moderate to severe active UC who fail conventional therapy or who are considered at high-risk for colectomy.^{29,30} Vedolizumab (Entyvio[®]) is an intravenous (IV) integrin receptor antagonist approved for inducing and improving clinical response/remission in patients with moderate to severe active UC who showed an inadequate response to or were intolerant of treatment with a TNF-inhibitor, immunomodulator, or corticosteroid.³¹ The oral Janus kinase inhibitor tofacitinib (Xeljanz[®], Xeljanz XR) is also indicated for moderately to severely active UC.³² These agents are reviewed in a separate therapeutic class review.

The 2013 American Academy of Family Physicians (AAFP) guidelines for the diagnosis and treatment of UC state that the incidence of colon cancer is increased with UC and achieving remission is critical in order to reduce a patient's lifetime risk.³³ The guidelines recommend 5-ASA (mesalamine) via suppository or enema is first-line for patients with proctitis or proctosigmoiditis, respectively; patients unable to tolerate rectally administered 5-ASA therapy may try oral preparations, although response times and remission rates may not be as favorable. Oral 5-ASA is effective in patients with active mild to moderate UC extending from the proximal to the sigmoid colon; a topical 5-ASA may be added if an oral formulation alone is inadequate. A short-term course of oral corticosteroids may be appropriate if oral plus topical 5-ASA therapy is not effective or if a more rapid response is desired. Prednisone is given in dosages of 40 to 60 mg per day, with the full-dose continued until symptoms are completely controlled (usually 10 to 14 days) followed by a gradual taper. Symptoms refractory to oral mesalamine or oral corticosteroids may be treated with IV infliximab (Remicade[®]). A meta-analysis reported no statistically significant effect of azathioprine (Imuran[®]) for active UC and consistent data is lacking that reports adequate effect of azathioprine for preventing relapse. Azathioprine is generally not recommended for active UC; however, it may be considered in patients who require corticosteroids or cyclosporine to

induce remission. The agent that is used to maintain remission is usually the same as that used to achieve remission. To prevent relapse of the disease, the oral probiotics *Lactobacillus* GG and *Escherichia coli* Nissle 1917 have been shown to be effective as 5-ASA. Long-term steroid use is not recommended for chronic maintenance due to significant side effects. Budesonide (Uceris) was first FDA approved in January 2013 and is not specifically addressed in these guidelines. Adalimumab, golimumab, vedolizumab, and tofacitinib were not FDA-approved to treat UC at the time these guidelines were developed.

The 2019 American College of Gastroenterology (ACG) clinical guidelines state treatment selection for UC should be based on not only inflammatory activity but also disease prognosis.³⁴ In general, mildly active proctitis and distal UC are treated with rectal 5-ASA (Grade: strong, Level of evidence: high or moderate); oral 5-ASA agents are used if needed as add-on for distal UC or to treat extensive disease. In patients with mildly active UC who are intolerant or nonresponsive to 5-ASA, oral budesonide MMX is recommended to induce remission (strong, moderate). Moderately active UC should be treated with oral 5-ASA or budesonide MMX (strong, moderate). In patients with moderately to severely active UC, the ACG recommends induction of remission using systemic corticosteroids, anti-TNF therapy, vedolizumab, or tofacitinib (strong, moderate or high for all). With the exception of corticosteroids, the medication used to induce remission should be continued as maintenance therapy. The ACG states that complimentary therapies such as probiotics, curcumin, and fecal microbiota transplantation (FMT) require further study and clarification of treatment/end points.

The American Gastroenterological Association (AGA) 2019 practice guidelines for the treatment of mild to moderate UC recommend standard-dose mesalamine (2 to 3 g/day) or diazo-bonded 5-ASA (balsalazide and olsalazine) for induction and maintenance treatment in patients with extensive mild to moderate UC (Recommendation strength: strong, Quality of evidence: moderate).³⁵ High-dose oral mesalamine combined with rectal 5-ASA may be required for patients with suboptimal response to standard-dose therapy, or in those with moderate or extensive disease (conditional, moderate [induction]). Oral prednisone or budesonide MMX may be added in those refractory to optimized oral and rectal 5-ASA (conditional, low). Proctosigmoiditis or proctitis can be treated with topical mesalamine rather than oral 5-ASA (conditional, very low); in patients with suboptimal response or intolerance to rectal mesalamine, rectal corticosteroids (enema or foam) may be used (conditional, low). Patients who do not respond adequately to the therapies as outlined above may need to escalate to systemic corticosteroids, immunomodulators, or biologic therapies. The guidelines make no recommendations regarding the use of probiotics, curcumin, and FMT; while they appear to be safe, their use could delay initiation of proven efficacious treatments and potentially lead to worsening symptoms or complications.

PHARMACOLOGY^{36,37,38,39,40,41,42,43,44,45,46,47,48,49,50}

The first oral aminosalicylate developed, sulfasalazine, consists of a sulfapyridine carrier moiety linked to 5-ASA via an azo bond.⁵¹ Colonic bacteria cleave the azo bond, converting sulfasalazine into sulfapyridine and 5-ASA moieties.⁵² 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 intraluminal activity of 5-ASA produces a local therapeutic effect.^{53,54} 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.⁵⁵

Subsequent oral agents were developed to enhance 5-ASA delivery to the colon and reduce the incidence of adverse events.⁵⁶ The formulations fall into 3 categories: azo-bonded prodrug formulations (Colazal, Giazol, Dipentum), delayed-release formulations achieved by pH shift (Apriso, Asacol HD, 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.^{57,58} 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.⁵⁹ 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, with a polymer matrix core that provides an extended release.⁶⁰ Asacol HD tablets are coated with a pH-sensitive acrylic polymer that delays the release of 5-ASA. Lialda uses Multi Matrix System[®] (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.

In December 2012, the FDA issued a final guidance recommending against the use of 2 specific phthalates, dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP), as excipients due to developmental and reproductive toxicants in laboratory animals, potential for being endocrine disrupting, and affecting reproductive and developmental outcomes in humans.^{61,62} These agents are often used as plasticizers in enteric and delayed release coatings of drug products, including a mesalamine delayed-release product (Asacol HD). Two formulations of mesalamine DR, Asacol HD and Delzicol, have been reformulated without DBP; DBP has been substituted with dibutyl sebacate (DBS).

Mesalamine is available as suppositories (Canasa) and enemas that deliver 5-ASA directly to the site of action. For the treatment of ulcerative proctitis, mesalamine suppositories (or corticosteroid foam), which deliver drug to the rectum, are appropriate for the treatment 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 centimeters of distal colon.⁶³ A sulfite-free formulation of mesalamine enema (sfRowasa) has been FDA-approved.⁶⁴

Steroids, such as budesonide ER (Uceris), may suppress autoimmune and inflammatory responses in UC. Budesonide has a high topical glucocorticosteroid activity and substantial first-pass elimination. Uceris is a delayed and extended-release tablet using MMX technology and breaks down at pH \geq 7. Budesonide is available as rectal foam (Uceris rectal foam) and can be used for active mild to moderate distal ulcerative colitis extending up to 40 centimeters from the anal verge.

PHARMACOKINETICS^{65,66,67,68,69,70,71,72,73,74,75,76,77,78,79}

All aminosalicylate oral products are designed to release 5-ASA for action in the intestine; therefore, systemic 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 apparent half-life of 5-ASA can range from 2 to 15 hours due to the different formulations of the drugs.

Pharmacokinetics

Drug	Delivery Mechanism	Bioavailability (%)
Oral Prodrug Forms		
balsalazide (Colazal, Giazio)	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 (Azulfidine, Azulfidine En-Tabs)	Metabolized by intestinal bacteria to 5-ASA and sulfapyridine; site of delivery is the colon Azulfidine En-Tabs contain a cellulose acetate phthalate coating that retards disintegration in the stomach	< 15
Oral Delayed-Release Forms		
mesalamine delayed-release tablets (Asacol HD)	Acrylic-based resin coating delays 5-ASA release until tablet reaches the terminal ileum and beyond; pH dependent release at pH \geq 7	20–25
mesalamine delayed release capsules (Delzicol) [†]	Capsules contain acrylic based resin, Eudragit S (methacrylic acid copolymer type B, NF), which delays 5-ASA release until capsule reaches the terminal ileum and beyond; pH dependent release at \geq pH 7	28
Oral Delayed-Release Forms (continued)		
mesalamine MMX tablets (Lialda)	pH dependent polymer film breaks down at pH \geq 6.8, in terminal ileum where mesalamine begins to be released from tablet core; tablet core has hydrophilic and lipophilic excipients that provide an extended release of mesalamine	21–22
mesalamine extended release 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 a delayed release starting at a pH of 6 with a polymer matrix core that enables extended release	21–44
Rectal Forms		
budesonide rectal foam (Uceris)	Rectal Administration	60
mesalamine enemas (Rowasa, sfRowasa)	Rectal administration	10–30
mesalamine suppositories (Canasa)	Rectal administration	variable
Oral Corticosteroids		
budesonide extended release tablets (Uceris)	pH dependent enteric coated delayed release tablets with a polymer coating that dissolves at pH \geq 7 with an extended release tablet core	10–20

[†] Delzicol 400 mg capsules are bioequivalent to Asacol 400 mg tablets. Two Delzicol 400 mg capsules have not been shown to be bioequivalent to 1 Asacol HD 800 mg tablets.

CONTRAINDICATIONS/WARNINGS^{80,81,82,83,84,85,86,87,88,89,90,91,92,93,94}

Aminosalicylates are contraindicated in patients with salicylate hypersensitivity. Hypersensitivity reactions to mesalamine (Apriso, Asacol HD, Delzicol, Lialda, Pentasa) may include myocarditis or pericarditis. Sulfasalazine is also contraindicated in patients with sulfonamide hypersensitivity, porphyria, and intestinal or urinary obstruction. Budesonide ER (Uceris) is contraindicated in patients hypersensitive to budesonide or any excipients in of the product.

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 performed 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.

Sulfasalazine should be given with caution to patients with severe allergic conditions or bronchial asthma. Serious skin reactions, including exfoliative dermatitis, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN), have been reported. Drug rash with eosinophilia and systemic symptoms (DRESS) have also been reported, and early manifestations such as fever or lymphadenopathy may be present even though rash is not. If such signs or symptoms are present, the patient should be evaluated immediately and sulfasalazine should be discontinued if there is no alternative etiology. Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

SJS and DRESS have also been reported with the mesalamine-containing products Lialda and Pentasa.

Renal impairment has been reported in patients taking products that contain or are converted to mesalamine. Evaluate renal function prior to initiation of therapy and periodically thereafter. Patients with pyloric stenosis may have prolonged gastric retention of oral mesalamine and balsalazide, which could delay the release of drug in the colon. The risks and benefits of using mesalamine delayed-release products should be evaluated in patients with known renal impairment of taking nephrotoxic drugs. There have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Lastly, mesalamine, balsalazide, and olsalazine have been associated with an acute intolerance syndrome that may be difficult to distinguish from a UC flare. These symptoms may abate once the agent is discontinued.

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. A sulfite-free mesalamine enema (sfRowasa) is available; it is proposed to be safe for use in patients with sulfite allergy.

Chronic glucocorticosteroid use may cause hypercorticism, adrenal suppression, and can reduce the response of the hypothalamus-pituitary adrenal (HPA) axis to stress, such as surgery. Patients who are switched from glucocorticosteroids with greater systemic effects may undergo withdrawal, including acute adrenal suppression or benign intracranial hypertension. Consequently, adrenocortical function should be monitored and the dose of the high potency glucocorticosteroid should be reduced cautiously. Glucocorticoids can also suppress the immune system causing increased susceptibility to infection. Consequently, exposure to transmissible diseases should be avoided and corticosteroid use in patients with active or quiescent tuberculosis infection or untreated fungal, bacterial, or systemic viral or parasitic

infections should be done cautiously, if at all. Liver dysfunction may decrease elimination and increase bioavailability resulting in increased toxicity. Caution should be observed in patients with hypertension, diabetes, osteoporosis, peptic ulcer, glaucoma or cataracts, or with a family history of diabetes or glaucoma, or with any other condition where glucocorticoids may have unwanted effects.

Mesalamine, a metabolite of sulfasalazine, may spuriously elevate test results for urinary normetanephrine when measured by liquid chromatography with electrochemical detection when testing for pheochromocytoma.

Two mesalamine-containing medications, Lialda and Pentasa, have updated warnings of photosensitivity reactions for patients who have pre-existing skin conditions such as atopic dermatitis and atopic eczema.

DRUG INTERACTIONS^{95,96,97,98,99,100,101,102,103,104,105,106,107,108,109}

CYP3A4 inhibitors: Concomitant oral administration of budesonide ER (Uceris) and ketoconazole causes an 8-fold increase in the systemic exposure to oral budesonide ER. If treatment with inhibitors of CYP3A4 activity (e.g., ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, erythromycin) is indicated, prior discontinuation of budesonide ER should be considered. Ingestion of grapefruit juice (which predominantly inhibits intestinal mucosal CYP3A4), increased systemic exposure for oral budesonide ER about 2-fold. Consequently, ingestion of grapefruit or grapefruit juice should be avoided with budesonide ER administration. Similarly, the inhibitors of CYP3A4 previously noted, may increase systemic budesonide concentrations and should be avoided with budesonide rectal foam.

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

Drugs that alter gastric pH: Mesalamine extended-release capsules (Apriso) depend on pH for dissolution of the coating of the granules; therefore, concomitant use with antacids should not occur. Dissolution of the coating of budesonide ER (Uceris) is pH dependent. Consequently, drug release and absorption may be altered when budesonide ER is used with drugs that raise gastric pH (e.g., proton pump inhibitors [PPIs], histamine 2- [H2]-blockers, and antacids).

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.

Nephrotoxic Agents, Including non-steroidal anti-inflammatory drugs (NSAIDs): Mesalamine use with known nephrotoxic agents may increase the risk of renal reactions and mesalamine related adverse effects.

Azathioprine or 6-mercaptopurine: Mesalamine use with azathioprine or 6-mercaptopurine may increase the risk for blood disorders.

ADVERSE EFFECTS^{110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126}

Drug	Abdominal pain	Diarrhea	Fever	Headache	Nausea	Rash	Vomiting
Oral Prodrug Forms							
balsalazide (Colazal)	6–13 (3)	5–9 (3)	2–6 (0)	8–15	4–5	nr	4–10
balsalazide (Giazo)	nr	3.7 (0)	nr	nr	nr	nr	nr
olsalazine (Dipentum)	10.1 (7.2)	5.9–17 (4.8-6.7)	< 1	5 (4.8)	5 (3.9)	2.3 (1.4)	1
sulfasalazine (Azulfidine)	reported	reported	less common	more common	more common	less common	more common
sulfasalazine (Azulfidine En-tabs)	8	reported	reported	9	19	13	8
Oral Delayed-Release Forms							
mesalamine delayed-release tablets (Asacol HD)	2.3	1.7	rare	4.7	2.8	reported	1.4
mesalamine MMX tablets (Lialda)	< 1	< 1	reported	3.4–5.6 (0.6)	nr	< 1	< 1
mesalamine extended release capsules (Pentasa)	1.1–1.7 (4)	3.5 (7.5)	0.9 (1.2)	2.2 (3.5)	1.8–3.1	1.3 (1.2)	1.1–1.5
mesalamine extended release capsules (Apriso)	5 (3)	8 (7)	reported	11 (8)	4 (3)	reported	nr
Rectal Forms							
budesonide rectal foam (Uceris)	nr	nr	nr	nr	2 (1)	reported	nr
mesalamine enemas (Rowasa)	8.1 (7.8)	2.1 (3.1)	3.2 (0)	6.5 (12.5)	5.8 (9.4)	2.8 (3.1)	< 1
mesalamine enemas sulfite-free (sfRowasa)	8.1 (7.8)	2.1 (3.1)	3.2 (0)	6.5 (12.5)	5.8 (9.4)	2.8 (3.1)	< 1
mesalamine suppositories (Canasa)	5.2	3.1	1.2 (0)	14.4	3.1	1.2 (0)	< 1
Oral Corticosteroids							
budesonide ER tablets (Uceris)	3.9 (1.9)	nr	nr	11.4 (10.5)	5.1 (4.3)	nr	nr

Adverse effects are reported as a percentage. Incidences reported for placebo group are shown in parentheses. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Adverse event rates with Delzicol are not available as approval was based on bioequivalence to Asacol and the data from the Asacol safety and efficacy studies.

Clinical tolerance of 3 aminosalicylate preparations [mesalamine (Asacol), olsalazine (Dipentum), and balsalazide] was assessed in a consecutive series of 43 patients with inflammatory bowel disease

intolerant to sulfasalazine.¹²⁷ Ninety-one percent of patients were able to tolerate at least 1 of the 3 preparations. Clinical tolerance of mesalamine (63%), olsalazine (70%), and balsalazide (70%) was similar. The most common adverse effects associated with the preparations were gastrointestinal in nature; diarrhea was a problem in 5 patients during treatment with olsalazine and 3 each while on mesalamine and balsalazide. Allergic reactions to aminosalicylates were uncommon; of 10 patients with rash following sulfasalazine, only 1 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 1 of the 4 aminosalicylates, and adverse effects of sulfasalazine are multifactorial in etiology. Some adverse effects are due to the parent molecule, and some to 1 of its 2 metabolites, 5-ASA and sulfapyridine.

Renal impairment and injury including nephropathy, acute and chronic interstitial nephritis, and rarely, renal failure, have been reported in patients taking products that contain or are converted to mesalamine. In addition, exacerbation of UC symptoms has been reported upon initiation of therapy with Asacol HD as well as other mesalamine products. These symptoms usually abate once Asacol HD is discontinued. Patients with pyloric stenosis may have prolonged gastric retention of Asacol HD tablets, which could delay release of mesalamine in the colon. Lastly, there have been reports of hepatic failure in patients with pre-existing liver disease who have been administered mesalamine. Several other post-marketing adverse effects have been reported with various mesalamine formulations, including nephrogenic diabetes insipidus, intracranial hypertension, lupus-like syndrome, hypersensitivity pneumonitis, and interstitial lung disease.

The sulfite-free mesalamine enema (sfRowasa) is proposed to cause less bowel irritation than the original Rowasa enema formulation.

In a pooled analysis of the two phase 3 clinical trials, there were no clinically significant differences in glucocorticoid-related adverse events between budesonide ER (Uceris) 9 mg and placebo at 8 weeks.

In the use of budesonide rectal foam, no clinically significant differences were reported in the overall percentage of glucocorticoid related adverse effects between budesonide foam and placebo in the course of 2 placebo-controlled trials at 6 weeks of therapy. Common adverse reactions (incidence \geq 2%) included decreased blood cortisol, adrenal insufficiency, and nausea.

SPECIAL POPULATIONS^{128,129,130,131,132,133,134,135,136,137,138,139,140,141,142}

Pregnancy

Olsalazine (Dipentum), budesonide ER (Uceris), and budesonide rectal foam (Uceris) are Pregnancy Category C. Sulfasalazine (Azulfidine), balsalazide tablets (Giazo), and mesalamine (Lialda, Pentasa) are Pregnancy Category B. There have been case reports of neural tube defects (NTDs) in infants born to mothers exposed to sulfasalazine during pregnancy. The role of sulfasalazine in these NTDs has not been established; however, oral sulfasalazine inhibits the absorption and metabolism of folic acid, which may interfere with folic acid supplementation.

The labeling for balsalazide (Colazal) and mesalamine (Delzicol, Rowasa, sfRowasa) have been updated based on the Pregnancy and Lactation Labeling Rule (PLLR). All state that there are no adequate and well-controlled studies in pregnant women; therefore, the drug should only be used during pregnancy if clearly needed. The labeling for mesalamine (Asacol HD, Canasa) advises data are insufficient to inform of drug-associated risks in pregnant women.

Pediatrics

Sulfasalazine is approved for use in patients ≥ 6 years of age. Mesalamine (Delzicol) is indicated for treatment of mild to moderate active ulcerative colitis in children age ≥ 5 years, but is not indicated for maintenance therapy. Efficacy of mesalamine suppositories (Canasa) was not demonstrated in a 6-week open-label study in patients 5 to 17 years of age with ulcerative proctitis (n=49). Balsalazide 750 mg, (Colazal), is approved for use in patients ≥ 5 years of age, whereas balsalazide 1 gm (Giazo) is only approved in male patients age ≥ 18 years. Other products have not been sufficiently studied in pediatric populations.

Safety and effectiveness of oral budesonide ER (Uceris) as well as budesonide rectal foam (Uceris) have not been established in pediatric patients. Glucocorticosteroids, such as budesonide, may cause a reduction of growth velocity.

Product labeling for olsalazine (Dipentum) state that safety and effectiveness of in a pediatric population have not been established. However, in a 3-month double-blind, randomized trial that compared olsalazine to an equivalent dose of sulfasalazine in 56 children with mild to moderate UC, fewer patients on olsalazine improved and a greater number had progression of symptoms. Adverse effects were similar between the groups. For more detail of this study see the Clinical Trials section of this class review.

Geriatrics

Reports from uncontrolled clinical studies and postmarketing reporting systems suggested a higher incidence of blood dyscrasias (e.g., neutropenia and pancytopenia) in patients ≥ 65 years old who were taking mesalamine-containing products. Caution should be taken to closely monitor blood cell counts during therapy.

Clinical studies of budesonide ER (Uceris) and budesonide rectal foam (Uceris) did not include sufficient subjects aged ≥ 65 years to determine whether they respond differently in younger subjects. In general, budesonide ER should be used cautiously in elderly patients due to the potential for decreased hepatic, renal, or cardiac function, and concomitant disease.

Hepatic Impairment

Patients with moderate to severe liver disease should be monitored for increased signs and/or symptoms of hypercorticism with budesonide ER (Uceris).

Gender

In a pivotal trial, effectiveness of balsalazide tablets (Giazo) was not demonstrated in female patients and pooled data revealed that female patients experienced adverse effects more often than male patients. Reasoning for the difference in treatment effect has not been determined. Lack of effect in females is not reported in the labeling for balsalazide capsules (Colazal); although, adverse effects such as abdominal pain, fatigue, and nausea were reported more frequently in women than in men.

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^{143,144,145,146,147,148,149,150,151,152,153,154,155,156,157}

Drug	Adults	Pediatrics	Availability
Oral Prodrug Forms			
balsalazide (Colazal)	2.25 g (3 capsules) 3 times daily with or without food for 8 to 12 weeks; total daily dose: 6.75 g	Children 5 to 17 years: 2.25 g (three 750mg capsules) 3 times daily for 8 weeks OR 750 mg (1 capsule) 3 times daily for 8 weeks*	750 mg capsule
balsalazide (Giazo)	3.3 g (3 tablets) twice daily with or without food for up to 8 weeks; total daily dose: 6.6 g	--	1.1 g tablet
olsalazine (Dipentum)	0.5 g (2 capsules) twice daily	--	250 mg capsule
sulfasalazine (Azulfidine, Azulfidine EN-tabs)	Initial: 3 to 4 g (6 to 8 tablets) daily in evenly divided doses with dosage intervals not exceeding 8 hours Maintenance: 2 grams daily	Children ≥ 6 years: Initial: 40 to 60 mg/kg/day divided into 3 to 6 doses Maintenance: 30 mg/kg per day divided into 4 doses	500 mg tablet 500 mg enteric coated delayed-release tablet
Oral Delayed-Release Forms			
mesalamine delayed-release tablets (Asacol HD) [†]	1.6 g (2 tablets) 3 times daily for 6 weeks [‡] ; total daily dose: 4.8 g; take on an empty stomach ≥ 1 hour before and 2 hours after a meal	--	800 mg delayed-release tablet
mesalamine delayed-release capsules (Delzicol) [†]	Initial: 0.8 g (2 capsules) 3 times daily with or without food for 6 weeks Maintenance: 1.6 g (4 capsules) daily in 2 to 4 divided doses for 6 months [§]	Children ≥ 5 years: Initial: weight-based up to a maximum of 2.4 g/day with or without food; twice daily dosing for 6 weeks Maintenance: not indicated	400 mg delayed-release capsule
mesalamine MMX tablets (Lialda)	Initial Therapy: 2.4 g or 4.8 g (2 to 4 tablets) once daily with food for up to 8 weeks [¶] Maintenance: 2.4 g (2 tablets) once daily with food [§]	--	1.2 g delayed-release tablet

* Balsalazide capsules (Colazal) may be opened and sprinkled on applesauce; contents may be chewed.

[†]Asacol HD and Delzicol have been formulated without dibutyl phthalate (DBP).

[‡] Safety and efficacy of mesalamine delayed-release (Asacol HD) past 6 weeks of treatment of UC have not been established.

[§] Mesalamine DR (Delzicol): swallow whole, do not chew, crush or break; for patients unable to swallow capsules whole, open the number of capsules required for the dose and swallow the contents whole.

[¶] Safety and efficacy of mesalamine MMX extended-release (Lialda) longer than 8 weeks of treatment of UC have not been established.

Dosages (continued)

Drug	Adults	Pediatrics	Availability
Oral Delayed-Release Forms (continued)			
mesalamine extended-release capsules (Pentasa)	1 g (2 to 4 capsules) 4 times a day for up to 8 weeks	--	250 mg, 500 mg extended-release capsules
mesalamine extended-release capsules (Apriso)	1.5 g (4 capsules) once daily in the morning with or without food ^{**}	--	0.375 g extended-release capsules
Rectal Forms			
budesonide rectal foam (Uceris)	1 metered dose (2 mg) rectally twice daily for 2 weeks followed by 1 metered dose once daily for 4 weeks	--	2 aerosol canisters each containing 14 metered doses delivering 2 mg per actuation with 28 PVC applicators
mesalamine enemas (Rowasa)	4 g (60 mL) rectally at bedtime (and retained for a minimum of 8 hours) for 3 to 6 weeks	--	4 g/60 mL enema (7 and 28 unit packages) Kits include the suspension and cleansing wipes
mesalamine enemas sulfite-free (sfRowasa)	4 g (60 mL) rectally at bedtime (and retained for a minimum of 8 hours) for 3 to 6 weeks	--	4 g/60 mL enema (7 and 28 unit packages)
mesalamine suppositories (Canasa)	1 g rectally at bedtime (and retained for a minimum of 1 to 3 hours) for 3 to 6 weeks	--	1,000 mg suppositories
Oral Corticosteroids			
budesonide ER tablets (Uceris) ^{††}	9 mg once daily in the morning with or without food for up to 8 weeks	--	9 mg enteric coated delayed- and extended-release tablets

^{||} Mesalamine capsules (Pentasa): capsules may be swallowed whole or capsule may be opened and the contents sprinkled onto applesauce or yogurt. The entire contents should be consumed immediately. Capsules and contents must not be crushed or chewed.

^{**} The duration of mesalamine Intellicor extended-release (Apriso) use for maintaining remission of UC beyond 6 months has not been evaluated.

^{††} Budesonide ER (Uceris): swallow whole, do not chew, crush or break.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved 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% 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.

The safety and efficacy of Delzicol is based on the Asacol clinical trials.¹⁵⁸ Asacol has since been removed from the market, but studies including Asacol are included below because Asacol served as an active comparator for subsequent products.

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.¹⁵⁹ Patients were randomized to receive balsalazide 6.75 g/day or mesalamine delayed-release 2.4 g/day for 12 weeks. After 2, 4, and 12 weeks, symptom control was greater in the balsalazide group. Remission rate after 12 weeks of therapy was 62% with balsalazide and 37% with mesalamine delayed-release. Median time to first day of complete relief of symptoms was 10 days for the balsalazide group and 25 days for the mesalamine delayed-release group. Adverse effects occurred in 48% of patients treated with balsalazide and 71% of those treated with mesalamine delayed-release.

A randomized, double-blind, double-dummy, parallel-group, dose-response study was performed comparing balsalazide 2.25 g or 6.75 g daily and delayed-release mesalamine 2.4 g daily.¹⁶⁰ Medication was administered for 8 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 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 2-week sigmoidoscopic score for patients treated with balsalazide (55% versus 29%; $p=0.006$). 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 8 weeks of double-blind treatment with balsalazide 2.25 g or mesalamine 0.8 g, each given 3 times daily.¹⁶¹ Overall, 46% of balsalazide-treated and 44% 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% of balsalazide- and 64% of mesalamine-treated patients reported at least 1 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 2 Asacol products.¹⁶²

balsalazide (Giazo) versus placebo

A double-blind, placebo-controlled, multicenter trial was conducted in 250 male and female adult patients with mild to moderate active UC.¹⁶³ Patients were randomized 2:1 to receive 8 weeks of treatment with either balsalazide 3.3 g twice daily or placebo. Disease activity was assessed using a modified Mayo Disease Activity Index (MMDAI). The primary efficacy endpoint was the proportion of patients that achieved clinical improvement and improvement in the rectal bleeding subscale of the MMDAI at the end of 8 weeks of treatment. Clinical improvement was defined as having both a ≥ 3 point improvement from baseline in the MMDAI score and ≥ 1 point improvement from baseline in the rectal bleeding sub score. At total of 55% of patients experienced clinical improvement with balsalazide compared to 40% on placebo, ($p=0.0237$). This difference in clinical improvement was completely due to improvement in males (57% improved with balsalazide versus 20% with placebo). There was no significant difference in the percentage of females with clinical improvement (54% versus 58% with balsalazide versus placebo, respectively).

budesonide extended-release tablets (Uceris) versus placebo and budesonide

This was a randomized, double-blind, placebo-controlled study in 461 adults with active, mild to moderate UC, defined as an Ulcerative Colitis Disease Activity Index (UCDAI) of ≥ 4 and ≤ 10 and histology consistent with active UC.¹⁶⁴ Budesonide ER 9 mg and budesonide ER 6 mg (not approved in the US) were compared with, another brand of budesonide 9 mg (as reference) not approved for the treatment of UC, and compared to placebo. The primary endpoint was induction of remission after 8 weeks and remission was defined as a UCDAI score of ≤ 1 , with sub scores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a ≥ 1 point reduction in an endoscopy-only score. At the end of 8 weeks 17.4% in the budesonide ER 9 mg group, 8.3% in the budesonide ER 6 mg group, 12.6% in the budesonide 9 mg group, and 4.5% of placebo, were in remission. The difference in remission rate for budesonide ER 9 mg versus placebo was 12.9% (95% confidence interval [CI], 4.6 to 21.3, $p<0.025$).

budesonide extended-release tablets (Uceris) versus placebo and mesalamine

This was a randomized, double-blind, placebo-controlled study in 509 adult patients with active, mild to moderate UC.^{165,166} Budesonide ER 9 mg and budesonide ER 6 mg (not approved in the US) was compared with mesalamine DR 2.4 g (as reference), and to placebo. The primary endpoint was induction of remission after 8 weeks. Remission was defined as a UCDAI score of ≤ 1 , with sub scores of 0 for rectal bleeding, stool frequency, and mucosal appearance and with a ≥ 1 point reduction in an endoscopy-only score. At the end of 8 weeks 17.9% of patients administered budesonide ER 9 mg, 13.2% in the

budesonide ER 6 mg arm, 12.1% in the mesalamine DR 2.4 g arm, and 7.4% of placebo patients, were in remission. The difference in remission rate for budesonide ER 9 mg compared to placebo was 10.4% (95% CI, 2.2 to 18.7, $p < 0.025$). Adverse events occurred at similar rates among groups.

budesonide (Uceris) plus oral mesalamine versus placebo plus oral mesalamine

A randomized, double-blind, placebo-controlled, multicenter trial assessed the efficacy and safety of budesonide multimatrix for induction of remission in 510 adults with mild to moderate ulcerative colitis (UC) refractory to mesalamine therapy.¹⁶⁷ Patients were randomized to either once daily oral budesonide 9 mg or placebo for 8 weeks. Patients also continued baseline treatment with oral mesalamine ≥ 2.4 g/day. An intention-to-treat (ITT) analysis was used and found that clinical and endoscopic remission was achieved by the end of 8 weeks in 13% of patients receiving budesonide compared to 7.5% of patients receiving placebo ($p = 0.049$). In patients receiving budesonide versus placebo, more patients achieved endoscopic remission (20% versus 12.3%, respectively; $p = 0.02$) and histological healing (27% versus 17.5%, respectively; $p = 0.02$). However, clinical remission as measured by UC disease activity index rectal bleeding and stool frequency subscale scores of 0 was similar in both groups ($p = 0.7$). Adverse effect rates were similar between the budesonide group and placebo (31.8% versus 27.1%; $p = 0.02$).

budesonide rectal foam (Uceris) versus placebo

Two randomized, double-blind, placebo-controlled, multicenter trials evaluated 546 adults with active mild to moderate distal UC.^{168,169} For these trials oral and rectal corticosteroids, as well as rectal 5-ASA products were prohibited during the course of the trials, but allowed as rescue therapy. Oral 5-ASA products were allowed at doses ≤ 4.8 g/day. Patients were randomized to 267 subjects to budesonide rectal foam and the remaining 279 subjects to placebo. During each trial patients received budesonide rectal foam 2 mg or placebo twice daily for 2 weeks followed by 2 mg doses once daily for an additional 4 weeks. In each of the 2 trials, the primary endpoint was the proportion of patients who were in remission after 6 weeks of treatment with remission defined as a decrease or no change in the stool frequency subscore from baseline, a rectal bleeding subscore of 0, and an endoscopy score of 0 or 1. In each trial, a higher proportion of patients in the budesonide rectal foam group than in the placebo group were in remission at Week 6, (38.3% and 44% versus 25.8% and 22.4%, 95% CI) and had a rectal bleeding subscore of 0, (46.6% and 50% versus 28% and 28.6%, 95% CI) at Week 6.

mesalamine delayed-release granules (Apriso) versus placebo

Mesalamine delayed-release granules were evaluated in a double-blind, placebo-controlled trial of patients with UC in remission who took mesalamine delayed-release granules 1.5 g ($n = 209$) or placebo ($n = 96$) once-daily for up to 6 months.¹⁷⁰ The percentage of relapse-free patients at month end of treatment was higher with mesalamine than placebo (78.9% versus 58.3%; $p < 0.001$) in the intent-to-treat (ITT) population. Significant differences ($p \leq 0.025$) favoring mesalamine were observed for most secondary endpoints including improvement in rectal bleeding, physician's disease activity rating, stool frequency, patients classified as a treatment success, and relapse-free duration. For the mesalamine delay-release granules-treated group, 31.1% of patients withdrew from the study; UC relapse was the cause for 19.6% ($n = 41$) of patients. For the placebo-treated group, 49% patients ($n = 47$) withdrew from the study; 39.6% of patients ($n = 38$) withdrew due to UC relapse. The incidence of adverse events was similar between groups. This study was sponsored by the manufacturer of Apriso, Salix Pharmaceuticals.

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

A 6-week, multicenter, randomized, double-blind, active-control study (ASCEND III) was conducted to assess the non-inferiority of mesalamine delayed release high dose (Asacol HD) 4.8 g/day to mesalamine delayed release (Asacol) 2.4 g/day in 772 patients with moderately active UC.¹⁷¹ The primary endpoint was overall improvement at Week 6 as defined by the Physician's Global Assessment (PGA) (based on clinical assessments of rectal bleeding, stool frequency, and sigmoidoscopy) with no worsening in any individual clinical assessment. The primary objective of non-inferiority was met when 70% (273 of 389) of patients who received mesalamine 4.8 g/day achieved treatment success at week 6 compared to 66% (251 of 383) of patients receiving mesalamine 2.4 g/day. In addition, 43% of patients receiving the higher dose of mesalamine achieved clinical remission at Week 6 compared to 35% of patients receiving the lower dose of mesalamine (p=0.4). A therapeutic advantage was observed for those patients who were previously treated with corticosteroids, oral mesalamine, rectal therapies, or multiple UC medications. Both regimens were well tolerated with similar adverse events.

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 8 weeks.¹⁷² 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 8 weeks of treatment. Clinical and endoscopic remission at week 8 was achieved by 34.1% and 29.2% of the mesalamine MMX delayed-release 2.4 g/day and 4.8 g/day groups, respectively, versus 12.9% 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 8-week, double-blind, multicenter trial was conducted in 340 patients with active, mild to moderate UC comparing mesalamine MMX delayed-release 2.4 g/day or 4.8 g/day, mesalamine delayed-release 2.4 g/day given in 3 divided doses, or placebo.¹⁷³ The primary endpoint was proportion of patients in clinical and endoscopic remission. Remission was measured by a modified UC disease activity index of ≤ 1 with rectal bleeding, stool frequency scores of 0, no mucosal friability, and a ≥ 1 point reduction in sigmoidoscopy score from baseline. Patients treated with mesalamine MMX delayed-release experienced significantly greater clinical and endoscopic remission rates by Week 8 versus placebo (2.4 g/day = 40.5%; 4.8 g/day = 41.2%; placebo = 22.1%). The remission rate for mesalamine delayed-release was not significantly greater than placebo (32.6%; p=0.124). All active treatments were well-tolerated.

A 6 month, randomized, double-blind, active-control, multicenter trial was conducted to assess the non-inferiority of once-daily mesalamine MMX (Lialda) 2.4 g/day compared with twice-daily mesalamine delayed-release (Asacol) 1.6 g/day in 826 patients with UC in maintaining endoscopic remission after 6 months.¹⁷⁴ At 6 months, 83.7% and 77.8% of patients receiving mesalamine MMX in the per-protocol and ITT populations, respectively, maintained endoscopic remission compared with 81.5% and 76.9% of patients receiving mesalamine delayed-release (95% CI for difference -3.9%, 8.1% [for the per protocol

population, PP]). Time to relapse was not significantly different between the 2 treatment groups (log-rank test, $p=0.5116$ [PP population]).

olsalazine (Dipentum) versus sulfasalazine (Azulfidine)

A randomized, double-blind, 6-month study compared 3 doses of olsalazine (0.5 g, 1.25 g, and 2 g daily) and sulfasalazine 2 g daily for maintenance of remission in 162 patients with UC.¹⁷⁵ Using intention-to-treat analysis, failure rates of the different treatment groups were not significantly different (36%, 49%, and 24% for 0.5 g, 1.25g, and 2 g olsalazine daily and 32% for 2 g sulfasalazine daily). Olsalazine and sulfasalazine showed a tendency towards lower failure rates in extended disease (28%) than in distal disease (44%). Withdrawal rate due to adverse effects was 4% with the most frequent single event being diarrhea, which occurred only in patients treated with olsalazine (2.5%, 5.2%, and 11.7% for daily olsalazine doses of 0.5 g, 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.¹⁷⁶ 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% versus 42.4% in the sulfasalazine group (95% CI, -9 to 18). Equal numbers of patients in each group withdrew from the trial because of adverse effects.

olsalazine (Dipentum) versus sulfasalazine (Azulfidine) in pediatrics

Safety and efficacy of olsalazine (Dipentum) were compared to sulfasalazine over 3 months in a multicenter, randomized, double-blind study of 56 children with mild to moderate UC.¹⁷⁷ 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 3 months, 39% of olsalazine-treated patients were asymptomatic or clinically improved, compared to 79% of sulfasalazine-treated patients ($p=0.006$). In addition, 10 of 28 patients on olsalazine versus 1 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.

META-ANALYSIS

A meta-analysis was performed that included randomized controlled trials of at least 6 months duration evaluating oral 5-aminosalicylic (ASA) therapy for treatment of patients with remitted ulcerative colitis compared with placebo, sulfasalazine, or other 5-ASA formulations.¹⁷⁸ The analysis was based on a literature search for relevant data through July 2015 using MEDLINE, EMBASE, Cochrane Library, review articles, and conference proceeding information. The primary outcome was the failure to maintain clinical or endoscopic remission. A total of 41 studies (8,928 patients) were included; a majority were rated as low risk of bias. 5-ASA was significantly superior to placebo for maintaining clinical or endoscopic remission. A total of 41% of patients treated with 5-ASA relapsed compared to 58% of placebo-treated patients (RR, 0.69; 95% CI, 0.62 to 0.77). Trends showing statistically greater efficacy with higher doses of 5-ASA of 1 to 1.9 g/day (RR, 0.65; 95% CI, 0.56 to 0.76) and the > 2 g/day subgroups (RR, 0.73; 95% CI, 0.6 to 0.89) were found. Sulfasalazine was significantly superior to 5-ASA for maintenance of remission; 48% of patients treated with 5-ASA relapsed compared to 43% of sulfasalazine-treated patients (RR, 1.14; 95% CI, 1.03 to 1.27). A GRADE analysis indicated that the overall quality of the evidence for the

primary outcome for the placebo and sulfasalazine-controlled studies was high. Once daily and conventionally dosed 5-ASA were similar for efficacy and adherence. In addition, no difference was found for efficacy among the various 5-ASA formulations (RR, 1.08; 95% CI, 0.91 to 1.28). A pooled analysis of 2 studies showed no statistically significant difference in efficacy between balsalazide 6 g and 3 g/day; 1 study found balsalazide 4 g to be superior to 2 g/day. There were no statistically significant differences in the incidence of adverse events between 5-ASA and placebo, 5-ASA and sulfasalazine, once daily and conventionally dosed 5-ASA, 5-ASA and comparator 5-ASA formulations, and 5-ASA dose ranging studies. However, trials comparing 5-ASA and sulfasalazine may have been biased, favoring sulfasalazine, since most trials included patients with known tolerance to sulfasalazine which may have minimized sulfasalazine related adverse events.

SUMMARY

Relative tolerability and compliance must be considered in evaluation of the oral mesalamine preparations. Due to the addition of the 500 mg capsule of mesalamine controlled-release (Pentasa), daily pill burden has decreased from 16 to 8. Mesalamine controlled-release (Pentasa) is dosed 4 times a day using 8 capsules and mesalamine delayed-release (Delzicol) is dosed 3 times a day using 6 capsules. Another formulation of mesalamine delayed-release (Asacol HD) is available at a higher strength that also allows for 3 times daily dosing using 6 tablets. One Asacol HD 800 mg tablet has not been shown to be bioequivalent to two Delzicol 400 mg capsules; therefore, substitution should not occur. Mesalamine MMX delayed-release (Lialda) is dosed once daily using 2 to 4 tablets. Mesalamine Intellicor extended-release (Apriso) is dosed once daily using 4 capsules. Use of mesalamine Intellicor extended-release (Apriso) and mesalamine MMX delayed-release tablets (Lialda) beyond 6 months has not been evaluated for maintaining remission of UC.

Balsalazide (Colзал, Gіazo) is indicated for UC treatment, while olsalazine (Dіpentum) is indicated for UC maintenance. Balsalazide (Colзал, Gіazo) differs from olsalazine (Dіpentum) in that balsalazide (Colзал, Gіazo) appears to have a more rapid onset of effect; it may also be slightly more effective for left-sided disease. The tolerance of olsalazine (Dіpentum) 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, sfRowasa enemas, Canasa suppositories) has a specific role as a non-oral treatment of distal UC, proctosigmoiditis, and proctitis. The sulfite-free mesalamine enema (sfRowasa) was FDA-approved as a formulation revision with a new trade name. It is proposed to cause less bowel irritation and to be safe for use by patients with sulfite allergy; however, this has yet to be demonstrated clinically.

Aminosalicylates remain first-line treatment options for mild to moderate active UC. Extended-release budesonide (Uceris) oral and rectal foam offer alternatives for induction of remission in mild to moderate UC, but they, along with systemic corticosteroids, should not be used in maintenance of remission.

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