Therapeutic Class Overview
Inflammatory Bowel Disease Agents

INTRODUCTION

- Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms including diarrhea, abdominal pain, bleeding, fatigue, and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic, and lifestyle factors (UpToDate, 2017[b]).
- Complications of IBD include hemorrhoids, rectal fissures, fistulas, peri-rectal and intra-abdominal abscesses, and colon cancer. Possible extra-intestinal complications include hepatobiliary complications, anemia, arthritis and arthralgias, uveitis, skin lesions, and mood and anxiety disorders (Bernstein et al, 2015).
- Ulcerative colitis (UC) and Crohn's disease (CD) are two forms of IBD that differ in pathophysiology and presentation; as a result of these differences, the approach to the treatment of each condition often differs (UpToDate, 2017[a]).
- UC is characterized by recurrent episodes of inflammation of the mucosal layer of the colon. The inflammation, limited to the mucosa, commonly involves the rectum and may extend in a proximal and continuous fashion to affect other parts of the colon. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus (Kornbluth et al 2010, UpToDate 2017[b]).
- CD can involve any part of the gastrointestinal tract and is characterized by transmural inflammation and "skip lesions". Transmural inflammation may lead to fibrosis, strictures, microperforations, and fistulae (UpToDate 2017[b]).
- The immune system is known to play a critical role in the underlying pathogenesis of IBD. It is suggested that abnormal responses of both innate and adaptive immunity mechanisms induce aberrant intestinal tract inflammation in IBD patients (Geremia et al, 2014).
- Precise incidence and prevalence of CD and UC have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggests that the United States (U.S.) incidence rate of UC varies between 2.2 to 14.3 per 100,000 persons and incidence of CD varies from 3.1 to 14.6 per 100,000 persons. Prevalence rate of IBD has been estimated to be as high as 439 per 100,000 persons with as many as 1 to 1.3 million persons in the U.S. suffering from these diseases (Centers for Disease Control [CDC], 2015).
- Some risk factors for IBD include age, gender, race, ethnicity, genetics, smoking status, and dietary considerations.
    - The typical age of onset of IBD is between 15 and 40 years, while a second peak between ages 50 and 80 years has been noted.
    - Caucasians tend to have a higher incidence of IBD compared to Hispanic and Black populations. Additionally, ethnic and racial differences may be related to environmental and lifestyle factors as well as underlying genetic differences.
    - Genetic susceptibility to IBD is not completely understood; however, it is estimated that nearly 10 to 25% of individuals afflicted with IBD have a first-degree relative with IBD.
    - Smoking status affects CD and UC differently, being associated with an increased risk with CD and a decreased risk with UC.
    - Dietary factors have been associated as risk factors since food antigens are believed to activate an immune response. Although specific pathogenic antigens have not been conclusively identified, processed, fried, and sugar-laden foods are associated with an increased risk of developing CD and possibly UC (National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK], 2014).
- The goals for the treatment of IBD include resolution of intestinal inflammation and healing of the mucosa; elimination of symptoms while minimizing side effects; maintenance of corticosteroid-free remission; prevention of complications, hospitalization, and surgery; and maintenance of good nutritional status (Bernstein et al, 2015).
- Current pharmacotherapy for UC consists of four major drug classes: 5-aminosalicylic acid (5-ASA) derivatives, glucocorticoids, immunomodulators (azathioprine, 6-mercaptopurine [6-MP], and methotrexate), and biologic agents (eg, infliximab, infliximab-dyyb, adalimumab, golimumab, vedolizumab) (Micromedex, 2017).
    - Choice of therapy is based on several factors, including disease severity, anatomic extent, and response to prior therapies *(*Kornbluth et al, 2010*).*
    - Inflammation that is distal is limited to below the descending colon and within reach of topical therapy. Inflammation that extends proximal to the descending colon requires systemic medication *(*Kornbluth et al 2010*)*.
- Although the specific Food and Drug Administration (FDA)-approved indications of the oral 5-ASA derivative preparations vary, these agents are used in the treatment and maintenance of remission of UC. The oral 5-ASA

derivatives include balsalazide, mesalamine, olsalazine, and sulfasalazine. Mesalamine is available in several formulations and is also the active component of balsalazide and olsalazine. The newer 5-ASA derivatives, including balsalazide, mesalamine, and olsalazine, were developed to avoid the side effects associated with sulfasalazine while maintaining its overall therapeutic benefits.

- Budesonide (UCERIS®) is available in an extended release tablet which delays the release of budesonide until it reaches the site of action. Budesonide is also available as a rectal foam (UCERIS). Budesonide capsules (ENTOCORT® EC) are approved for use for the treatment and maintenance of remission of CD; however, they will not be included in this review.
- Sulfasalazine (AZULFIDINE® EN-tabs) is also FDA-approved for the treatment of rheumatoid arthritis nonresponsive to salicylates and nonsteroidal anti-inflammatory drugs (NSAIDS) and for pediatric polyarticular-course juvenile rheumatoid arthritis.
- Other injectable biologic response modifiers known as monoclonal antibodies (MABs) are also approved to treat UC and/or CD including the tumor necrosis factor (TNF) inhibitors (e.g., CIMZIA [certolizumab pegol], HUMIRA [adalimumab], SIMPONI [golimumab], INFLECTRA [infliximab-dyyb], and REMICADE [infliximab]). In 2014, the alpha-4 beta-7 (α4β7) integrin receptor antagonist, ENTYVIO (vedolizumab) was approved for treatment of moderately to severely active UC and CD in adult patients who have had an inadequate response with, lost response to, or were intolerant to a TNF inhibitor or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. Additional injectable, humanized MABs are being studied for the treatment of various forms of IBD. These are reviewed in the Immunomodulators Class.
- The scope of this review will focus upon the oral and topical agents outlined in Table 1 for their respective FDA-approved, gastrointestinal-related indications.
- Medispan Therapeutic Class: Inflammatory Bowel Agents

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
APRISO® (mesalamine) ER capsule	Salix Pharmaceuticals	10/31/2008	-
ASACOL® HD (mesalamine) DR tablet	various	05/29/2008	✔
AZULFIDINE® (sulfasalazine) tablet	various	06/20/1950	✔
AZULFIDINE EN-tabs (sulfasalazine) DR tablet	various	04/06/1983	✔
CANASA® (mesalamine) rectal suppository	Forest Labs	11/05/2004	-
COLAZAL® (balsalazide) capsule	various	07/18/2000	✔
DELZICOL™ (mesalamine) DR capsule	Warner Chilcott	02/01/2013	-
DIPENTUM® (olsalazine) capsule	Meda Pharmaceuticals	07/31/1990	-
GIAZO® (balsalazide) tablet	Salix Pharmaceuticals	02/03/2012	-
LIALDA® (mesalamine) DR tablet	Shire US, Inc.	01/16/2007	-
PENTASA® (mesalamine) CR capsule	Shire US, Inc.	05/10/1993	-
ROWASA® (mesalamine) rectal enema suspension	various	12/24/1987	✔
sfROWASA® (mesalamine) rectal enema suspension (sulfite-free)	Meda Pharms	06/20/2008	-
UCERIS (budesonide) ER tablet	Salix Pharmaceuticals	01/14/2013	-
UCERIS (budesonide) rectal foam	Salix Pharmaceuticals	10/07/2014	-

CR=controlled release, DR=delayed release, ER=extended release
ASACOL (mesalamine) by Warner Chilcott was discontinued by the manufacturer in the spring of 2013 due to a business decision. A generic is not currently available.

(Drugs@FDA, 2017)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
Treatment of mildly to moderately active UC in patients ≥ 5 years of age	✔ (COLAZAL)†	-	✔ (DELZICOL)	-	-

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
Treatment of mildly to moderately active UC in males ages 18 years and older	✔ (GIAZO)‡	-	-	-	-
Treatment of moderately active UC in adults	-	-	✔ (ASACOL HD)*	-	-
Induction of remission in adults with active, mild to moderate UC	-	✔ (UCERIS tablet)	✔ (LIALDA)	-	-
Induction of remission in adults with active mild to moderate distal UC extending up to 40 cm from the anal verge	-	✔ (UCERIS rectal foam)	-	-	-
Maintenance of remission of UC in adults	-	-	✔ (APRISO; DELZICOL; LIALDA)	-	-
Maintenance of remission of UC in patients who are intolerant of sulfasalazine	-	-	-	✔	-
Induction of remission and for the treatment of patients with mildly to moderately active UC	-	-	✔ (PENTASA)	-	-
Treatment of mildly to moderately active ulcerative proctitis	-	-	✔ (CANASA)	-	-
Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis	-	-	✔ (ROWASA; sfROWASA)	-	-
Treatment of mild to moderate UC, and as adjunctive therapy in severe UC	-	-	-	-	✔ (AZULFIDINE; AZULFIDINE EN-tabs**)
Prolongation of the remission period between acute attacks of UC	-	-	-	-	✔ (AZULFIDINE) AZULFIDINE EN-tabs**)
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs [e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs]	-	-	-	-	✔ (AZULFIDINE EN-tabs)
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs	-	-	-	-	✔ (AZULFIDINE EN-tabs)

*Safety and effectiveness of ASACOL HD beyond 6 weeks have not been established.
**AZULFIDINE EN-TABS are specifically indicated in patients with UC who cannot tolerate sulfasalazine tablets due to gastrointestinal intolerance when the gastrointestinal intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites.
†Safety and effectiveness of balsalazide beyond eight weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established.

‡Effectiveness in female patients was not demonstrated in clinical trials. Safety and effectiveness of GIAZO beyond eight weeks have not been established.

(Prescribing information: APRISO, 2016; ASACOL HD, 2016; AZULFIDINE, 2014; AZULFIDINE EN-TABS, 2016; CANASA, 2016; COLAZAL, 2016; DELZICOL, 2016; DIPENTUM, 2014; GIAZO, 2016; LIALDA, 2015; PENTASA, 2015; ROWASA, 2013; sfROWASA, 2013; UCERIS tablet, 2016; UCERIS rectal foam, 2016)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Oral therapy

- Multiple systematic reviews have been published evaluating randomized clinical trials of mesalamine products for UC. No significant differences in safety or efficacy between the mesalamine products have been found in the systematic reviews.
  - In a 2013 Cochrane review of 17 randomized clinical trials (N = 2,925), the efficacy and safety of oral mesalamine products used for induction and maintenance of remission of UC were evaluated. The primary outcomes were failure to induce global or clinical remission or improvement, and failure to maintain global or clinical remission (relapse). Products included balsalazide, olsalazine, PENTASA, ASACOL, LIALDA, and three mesalamine products which are not available in the U.S. For the failure to induce global or clinical remission in mild to moderately active UC endpoint, there was no significant difference between the 5-ASA formulations (balsalazide, PENTASA, olsalazine, LIALDA, mesalamine, and 5-ASA micropellets) and the comparator group (ASACOL and two mesalamine formulations) (11 studies, N = 1968, 50% vs. 52%, pooled relative risk [RR] 0.94, 95% confidence interval [CI], 0.86 to 1.02, I^2 = 0%, P = 0.11). For failure to induce global or clinical remission or improvement, a total of eight studies with 1,647 patients were evaluated, and results demonstrated that there was no difference between the 5-ASA products (balsalazide, PENTASA, olsalazine, LIALDA, and 5-ASA micropellets) and the 5-ASA comparators (ASACOL, two mesalamine formulations, and PENTASA) (30% vs. 35%, pooled RR 0.89, 95% CI, 0.77 to 1.01, I^2 = 0%, P = 0.08) using a fixed-effect model. Note that PENTASA was on both sides of the comparison for this endpoint. For the failure to maintain global or clinical or endoscopic remission at 12 months, there was no difference between the 5-ASA formulations (balsalazide, PENTASA, and olsalazine) and the comparators (ASACOL, mesalamine) in five studies (N = 457) (38% vs. 37%, pooled RR 1.01, 95% CI, 0.80 to 1.28, I^2 = 39%, P = 0.95). The incidences of adverse events between the various formulations were not significantly different. Risk of bias was low for most study factors; however, one study was single-blind, and three were open-label. There were numerous products in this systematic review which are not currently available in the U.S. (Feagan et al, 2013).
  - Another systematic review evaluated once daily oral mesalamine compared to conventional dosing regimens of oral mesalamine for induction and maintenance of remission of UC in 11 studies with 4,070 patients. Of the 11 studies, five studies were single-blind, and one study was performed in an open-label manner. Products assessed were LIALDA, ASACOL, PENTASA, and SALOFALK (mesalazine - not available in the U.S.). Failure to induce global or clinical remission was not different between once daily and conventional dosing of mesalamine (three studies, N = 738; pooled RR 0.95, 95% CI, 0.82 to 1.10; I^2 = 0%). No difference was observed between dosing regimens for the failure to maintain global or clinical remission at 12 months (five studies, N = 1,394; pooled RR 0.92, 95% CI, 0.83 to 1.03, I^2 = 40.9%). Rates of medication adherence or adverse events between once daily and conventional dosing regimens of mesalamine were not significantly different. The authors noted that adherence rates in clinical trials may be higher than real world usage (Feagan and MacDonald, 2012).
  - A 2016 Cochrane review of 53 studies with 8,548 patients with UC evaluated the oral 5-ASA preparations and sulfasalazine for the induction of active UC remission. The newer 5-ASA derivatives were “superior” to placebo with 71% of 5-ASA patients failing to enter clinical remission compared to 83% for placebo (11 studies; N = 2,387; RR 0.86, 95% CI, 0.82 to 0.89). No statistically significant differences in efficacy between 5-ASA and sulfasalazine were observed with 54% of 5-ASA-treated patients and 58% of sulfasalazine-treated patients who failed to enter remission (eight studies; N = 526; RR 0.90, 95% CI, 0.77 to 1.04). Adherence did not appear to be enhanced by once daily dosing in the clinical trials; however, it is not known if once daily dosing would improve adherence in the community setting. Failure to enter clinical remission rates were 45% for once daily vs. 48% for conventional dosing regimens (four studies; N = 944; RR 0.94, 95% CI, 0.83 to 1.07). No significant differences among the 5-ASA products for safety and efficacy were found (Wang et al, 2016[a]).
  - In a 2016 Cochrane review of 41 studies with 8,928 patients, all 5-ASA formulations were “superior” to placebo for maintenance of clinical or endoscopic remission of UC. Relapse rates were 41% for 5-ASA-treated patients and 58% for placebo-treated patients (seven studies; N = 1,298; RR 0.69; 95% CI, 0.62 to 0.77). Sulfasalazine was

found to have a statistically significant benefit over 5-ASA in the maintenance of UC when looking at all trials at study endpoint (12 studies; N = 1,655; RR 1.14, 95% CI, 1.03 to 1.27); however, when trials of 12 months or longer were only evaluated, there was no longer a difference between sulfasalazine and 5-ASA (eight studies; N = not reported; RR 1.10, 95% CI, 0.98 to1.23). No significant difference for efficacy was demonstrated between once daily and conventional dosing regimens with 29% of once daily-treated patients relapsed over 12 months vs. 31% of conventionally dosed patients (eight studies; N = 3,127; RR 0.91, 95% CI, 0.82 to 1.01). For adherence, failure to adhere to the regimen was reported in 11% of once-daily-treated patients compared to 9% of patients in the conventional dosing group (six studies; N = 1,462; RR 1.22, 95% CI, 0.91 to 1.64). No significant difference in efficacy was found when comparing the various 5-ASA formulations. Relapse rate was 44% in the 5-ASA group vs. 41% in the 5-ASA comparator group (six studies; N = 707; RR 1.08, 95% CI, 0.91 to 1.28). No statistically significant differences were found for 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 (Wang et al, 2016[b]).

  - A meta-analysis of 10 studies that evaluated mesalamine once daily vs. multiple daily dosing regimens in 3,410 patients with quiescent UC was conducted to determine the efficacy in preventing a relapse. The intention to treat analysis found that mesalamine once daily (26.3%) was as effective as multiple daily doses (26.5%) (eight studies, RR 1.00, 95% CI, 0.89 to 1.12, I^2 = 41%, P = 0.105). An analysis of the efficacy of once daily vs. multiple daily dosing of mesalamine for inducing remission in active UC found that remission was not observed in 29.8% of patients on once daily mesalamine and 37.8% of patients receiving multiple daily doses. The risk of failure to achieve remission was higher with multiple daily doses (two studies, RR 0.80; 95% CI, 0.64 to 0.99, I^2 = 21.6%, P = 0.259). When evaluating the same outcome on a per-protocol analysis, there was no significant difference between the two groups. No significant differences in adverse events were observed between the two groups (Tong et al, 2012).
  - In another 2012 meta-analysis, 9 of 10 studies included in the Tong et al analysis were evaluated by another group (Zhu et al, 2012). There were no significant differences for once daily compared to more frequent dosing (twice or three times daily) of mesalamine for UC for the maintenance of clinical remission, endoscopic remission, maintenance of combined clinical and endoscopic remission, and the overall incidence of adverse events.

- A Cochrane review evaluated oral budesonide for induction of remission in UC. A total of six studies (N = 1,808) were evaluated. Budesonide MMX 9 mg was superior to placebo for inducing remission at eight weeks (15% vs. 7%, respectively; 3 studies, N = 900; RR 2.25, 95% CI, 1.50 to 3.39; moderate quality of evidence). An analysis of two studies with budesonide MMX 6 mg showed that it was not superior to placebo for induction of remission (11% vs. 6%, respectively; two studies, N = 440; RR 1.80, 95% CI, 0.94 to 3.42; low quality of evidence). Budesonide (ENTOCORT EC) was significantly less likely to induce clinical remission than oral mesalamine after eight weeks (one study, N = 343; RR 0.72, 95% CI 0.57 to 0.91; moderate quality of evidence). However, another study discovered no difference in remission rates between budesonide MMX 9 mg and mesalamine (one study; N = 247; RR 1.48, 95% CI 0.81 to 2.71; low quality of evidence). In a comparison of the two budesonide formulations, there was no difference in remission rates between budesonide MMX 9mg and budesonide 9 mg (one study, N = 212; RR 1.38, 95%CI, 0.72 to 2.65; low quality of evidence). More studies are needed to compare budesonide to other UC therapies (Sherlock et al, 2015).
- ASACOL (mesalamine) is not currently available; however, efficacy data of DELZICOL was based on clinical trial data with ASACOL (DELZICOL prescribing information, 2015).

<u>Topical therapy</u>

- According to a meta-analysis comparing rectal 5-ASA therapy to either placebo or other active agents for the treatment of distal disease, rectal 5-ASA was superior to placebo and rectal corticosteroids. Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement (Marshall et al, 2010). A 2012 smaller meta-analysis found that rectal 5-ASA therapy was superior to placebo and similar to oral 5-ASA on rates of symptomatic remission and endoscopic remission. No dose response relationship for 5-ASA enemas or other rectal dosage forms has been observed (Marshall et al, 2012).
- A meta-analysis found greater efficacy with topical mesalamine than placebo for the prevention of relapse of disease activity in quiescent UC, with a number needed to treat of three. Time to relapse was longer with topical mesalamine in the two trials, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy (Ford et al, 2012[b]).
- Budesonide rectal foam was compared to placebo in two randomized, Phase 3 trials in patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis. Compared to placebo, a significantly greater proportion of patients receiving budesonide rectal foam experienced remission, resolution of rectal bleeding, and endoscopic improvement at week six (P < 0.05 for all comparisons in both trials) (Sandborn et al, 2015).

Oral vs. topical mesalamine

- A meta-analysis found combined oral and topical 5-ASA therapy to be superior to oral 5-ASA therapy for induction of remission in mild to moderately active UC. Also, intermittent topical 5-ASA therapy was reported to be superior to oral 5-ASA therapy for preventing relapse of quiescent UC (Ford et al, 2012[a]).

Guidelines

- The Ulcerative Colitis Practice Guidelines in Adults from the American College of Gastroenterology (ACG) (2010) recommend oral mesalamine but do not differentiate between the different oral formulations available; a blanket recommendation for mesalamine is provided. All aminosalicylates are superior to placebo and equivalent to sulfasalazine in acute therapy of UC (Kornbluth et al, 2010). A guideline update is underway (ACG, 2017).
    - For the management of mild to moderate distal colitis, oral aminosalicylates, topical mesalamine, or topical corticosteroids are recommended (Evidence A [defined as High level of evidence; further research is very unlikely to change our confidence in the estimate of effect). Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates (Evidence A). The combination of oral and topical agents is “superior” to each agent used alone (Evidence A). Oral therapies effective for achieving and maintaining remission include balsalazide, mesalamine, olsalazine, and sulfasalazine. For the maintenance of remission in distal disease, mesalamine suppositories are effective for maintenance of remission in patients with proctitis, and mesalamine enemas are effective in patients with distal colitis (Evidence A). Balsalazide, mesalamine, and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone (Evidence A). Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission (Evidence A).
    - For the management of active mild to moderate extensive colitis, oral sulfasalazine or oral aminosalicylates in doses up to 4.8 g per day of the active 5-ASA moiety are considered first line (Evidence A). Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates or patients who require rapid improvement (Evidence B [defined as Moderate level of evidence; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.]). For patients refractory to oral corticosteroids, 6-MP or azathioprine can be used for patients who are acutely ill, requiring intravenous therapy (Evidence A). Infliximab is effective in patients who are steroid refractory or steroid dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. For maintenance of remission for mild to moderate extensive colitis, balsalazide, mesalamine, olsalazine, and sulfasalazine are effective in reducing the number of relapses (Evidence A). Azathioprine or 6-MP can be used for steroid sparing in steroid dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates (Evidence A). Infliximab effectively maintains remission in patient who responded to the infliximab induction regimen (Evidence A).
    - For the management of severe colitis in a patient who is refractory to maximum oral treatment with aminosalicylates, oral prednisone, and topical medications, infliximab is a treatment option if urgent hospitalization is not required (Evidence A). Patients that show signs of toxicity should be hospitalized to receive intravenous steroids. Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown (Evidence A).
- The World Gastroenterology Organization Global Guidelines state that 5-ASA products are useful for treating both colitis flare-ups and maintenance of remission. A combination of oral with topical 5-ASA products is more effective than oral agents alone for induction of remission of mild to moderate UC. Rectal 5-ASA products are more beneficial than rectal corticosteroids in UC. Limited evidence exists for 5-ASA products in CD; these products are mainly used in patients who cannot tolerate corticosteroids. Corticosteroids provide rapid relief of symptoms by suppressing inflammation and should be used to induce remission; they have no role in maintenance of remission and side effects limit duration of use. Budesonide may have less adverse events than other corticosteroid options (Bernstein et al, 2015).
- The ACG recently released a clinical guideline addressing preventive care in IBD. According to published data, patients with IBD do not receive preventive care services at the same rate as general medical patients. Increased coordination between gastroenterology and primary care providers is recommended, as well as proper age-appropriate immunization, cervical and skin cancer screenings, depression and anxiety screening, and smoking cessation counseling for patients with CD (Farraye et al, 2017).

SAFETY SUMMARY

- Contraindications include hypersensitivity to salicylates or any component for the drugs in this class. AZULFIDINE EN-tabs are contraindicated in patients with intestinal or urinary obstruction or in patients with porphyria, as sulfonamides may precipitate an acute attack.
- Warnings include mesalamine acute intolerance syndrome, exacerbations of colitis, and caution using drugs in this class in patients with hepatic or renal impairment. Mesalamine products (LIALDA and PENTASA) and sulfasalazine products (AZULFIDINE and AZULFIDINE EN-tabs) may interfere with laboratory tests for normetanephrine. Rectal mesalamine may cause oligospermia and pancolitis.
- Due to the potential for severe blood dyscrasias, complete blood counts, including differential white cell count, and liver function tests should be performed before starting sulfasalazine therapy (AZULFIDINE and AZULFIDINE EN-tabs) and every second week during the first three months of therapy; tests should be repeated once monthly for three months, then once every three months, and as clinically indicated.
- Rectal budesonide may cause hypercorticism, adrenal axis suppression, and increased risk of infection.
- Concurrent use of nonsteroidal anti-inflammatory drugs (NSAIDs) with mesalamine products may increase the risk of nephrotoxicity; use with caution.
- Oral mesalamine and CANASA should not be used with 6-mercaptopurine and azathioprine due to decreased thiopurine metabolism; an increased risk of myelosuppression may result.
- In general, the inflammatory bowel agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
Balsalazide	Capsule (COLAZAL): 750 mg Tablet (GIAZO): 1.1 g	Treatment of mildly to moderately active UC in patients ≥ 18 years of age: Capsule: 2,250 mg three times daily for up to eight to 12 weeks Treatment of mildly to moderately active UC in patients 5 to 17 years of age: Capsule: 750 or 2,250 mg three times daily for up to eight weeks Treatment of mildly to moderately active UC in males ages ≥ 18 years of age: Tablet: Three 1.1 g tablets twice daily with or without food for up to eight weeks.	Contents of capsules may be sprinkled on applesauce and/or chewed; teeth/tongue discoloration may occur. Tablets may be taken with or without food.
Budesonide	Extended release tablet (UCERIS): 9 mg Rectal foam (UCERIS): 2 mg/actuation	Induction of remission in adults with active, mild to moderate UC: extended release tablet (UCERIS): 9 mg orally once daily in the morning for up to eight weeks. Induction of remission in patients with active mild to moderate distal UC extending up to 40 cm from the anal verge: rectal foam (UCERIS) 1 metered dose administered rectally twice daily (morning and evening) for two weeks followed by 1 metered dose administered rectally once daily (evening) for four weeks.	Swallow tablet whole with water; tablets should not be chewed, crushed, or broken. Tablet may be taken with or without food. Patients should be advised to avoid the consumption of grapefruit juice with UCERIS. Before administering UCERIS rectal foam, patients should empty their

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
			bowels. After administration before bedtime, patients should not empty bowels again until the next morning. UCERIS rectal foam contains flammable propellants. Patients should avoid fire, flame, and smoking during and immediately following administration.
Mesalamine	Controlled-release capsule (PENTASA): 250 mg 500 mg Delayed-release tablet:* 800 mg (ASACOL HD) 1.2 g (LIALDA) Delayed-release capsule: 400 mg (DELZICOL) Extended-release capsules (APRISO): 0.375 g Rectal suppository (CANASA): 1,000 mg Rectal enema (ROWASA; sfROWASA [sulfite-free formulation]): 4 g/60 mL unit	Induction of remission of mildly to moderately active UC: Controlled-release capsule (PENTASA): 1 g four times daily Induction of remission of active, mild to moderate UC: Delayed-release tablet (LIALDA): 2.4 or 4.8 g once daily with a meal Maintenance of remission of UC in adults: Delayed-release capsule (DELZICOL): 1.6 g daily divided into two to four doses Delayed-release tablet (LIALDA): 2.4 g once daily with a meal Extended-release capsules (APRISO): 1.5 g daily in the morning Treatment of mildly to moderately active UC: Controlled-release capsule (PENTASA): 1 g four times daily Delayed-release capsule (DELZICOL): 800 mg three times daily for six weeks Treatment of mildly to moderately active UC in pediatric patients ages 5 years and older: Delayed-release capsule (DELZICOL): Weight of 17 to 32 kg: daily dose of 36 to 71 mg/kg/day divided into two doses; max dose of 1.2 g per day Weight of 33 to 53 kg: daily dose of 37 to 61 mg/kg/day divided into two	PENTASA: Capsules may be opened and the entire contents sprinkled onto applesauce or yogurt. ASACOL HD: should not be cut, broken, or chewed; take on an empty stomach, at least 1 hour before and 2 hours after a meal DELZICOL: Capsules should not be cut, broken, or chewed; may be taken without regard to food; capsules may be opened for patients who are unable to swallow the capsules whole. Two DELZICOL 400 mg capsules have not been shown to be interchangeable or substitutable with one mesalamine 800 mg delayed release tablet. LIALDA: Take with a meal. CANASA, ROWASA, & sfROWASA: Product may cause staining of surfaces and fabrics; lubricating gel may be used to assist with insertion of suppositories.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		doses; max dose of 2 g per day Weight of 54 to 90 kg: daily dose of 27 to 44 mg/kg/day divided into two doses; max dose of 2.4 g per day Treatment of moderately active UC: Delayed-release tablet (ASACOL HD): 1,600 mg (two 800 mg tablets) three times daily for six weeks Treatment of mildly to moderately active ulcerative proctitis: Rectal suppository (CANASA): 1,000 mg at bedtime, retained for one to three hours (or longer if possible), for a treatment duration of three to six weeks Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis: Rectal enema (ROWASA; sfROWASA): 4 g (one enema) once daily at bedtime, retained for eight hours for three to six weeks based upon symptoms and sigmoidoscopic findings	
Olsalazine	Capsule (DIPENTUM): 250 mg	Maintenance of remission of UC in patients who are intolerant of sulfasalazine: Capsule: 1 g daily in two divided doses	
Sulfasalazine	Tablet (AZULFIDINE): 500 mg Delayed-release tablet (AZULFIDINE EN-tabs): 500 mg	Treatment of mild to moderate UC, and as adjunctive therapy in severe UC, and prolongation of the remission period between acute attacks of UC: Tablet and delayed-release tablet: initial, 3 to 4 g/day in divided doses with dosing intervals not exceeding eight hours; maintenance, 2 g/day Treatment of mild to moderate UC, and as adjunctive therapy in severe UC and prolongation of the remission period between acute attacks of UC age 6 years and older: Tablet and delayed-release tablet: initial, 40 to 60 mg/kg/day divided into three to six doses; maintenance, 30 mg/kg/day divided into four doses If gastric intolerance occurs after the first few doses, reduce dose by half	Sulfasalazine products may cause an orange-yellow discoloration of the urine or skin. AZULFIDINE EN-tabs: swallow tablets whole.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		and slowly titrate over several days. If intolerance continues, stop drug for five to seven days, then re-introduce at a lower dose. Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs (e.g., an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of one or more NSAIDs): Delayed-release tablet: 2 g daily in two evenly divided doses Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs (ages 6 years and older): Delayed-release tablet: 30 to 50 mg/kg of body weight daily in two evenly divided doses; maximum dose, 2 g per day	

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Balsalazide	Capsule: No dosage adjustment required in the elderly; use with caution. Tablet: Monitor blood cell counts during therapy. Studies did not include sufficient numbers of elderly patients to determine if differences between younger and older patients exist.	Capsule: Approved for use in children 5 to 17 years of age. Tablet: Safety and efficacy in pediatric patients have not been established.	Use with caution in patients with a history of renal disease. Evaluate renal function prior to initiation of GIAZO therapy and periodically while on therapy.	Capsule: No dosage adjustment required. Tablet: Use caution and consider liver function testing when administering to patients with liver disease.	No adequate well-controlled studies of balsalazide have been completed in pregnant women. Use during pregnancy only if clearly needed. (COLAZAL) Pregnancy category B (GIAZO) Unknown whether excreted in breast milk; use with caution.
Budesonide (UCERIS tablet and rectal foam)	Insufficient data to determine if differences exist between younger	Safety and efficacy in pediatric patients have	No information	Monitor patients with moderate to severe hepatic	Pregnancy category C Excreted in breast

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	and older patients; use with caution.	not been established.		impairment for signs and/or symptoms of hypercorticism.	milk; Consider discontinuing nursing or drug.
Mesalamine (oral)	No dosage adjustment required in the elderly population; use with caution. Monitor complete blood counts in elderly periodically.	Safety and effectiveness in pediatric patients have not been established. DELZICOL: approved for use in pediatric patients 5 years of age and older	No dosage adjustment required; use with caution and monitor routinely. Evaluate renal function prior to initiation of APRISO and DELZICOL	No dosage adjustment required; use with caution.	Pregnancy category B (APRISO; DELZICOL; LIALDA; PENTASA) Limited published data on mesalamine use in pregnant women are insufficient to inform a drug-associated risk (ASACOL HD) Mesalamine and its metabolite have been detected in breast milk; use with caution.
Mesalamine (rectal)	No dosage adjustment required in the elderly; use with caution. Monitor complete blood counts in elderly periodically. (CANASA)	Safety and efficacy in pediatric patients have not been established.	No dosage adjustment advised; use with caution. Evaluate renal function prior to initiation and periodically while using CANASA.	No dosage adjustment advised; use with caution.	Pregnancy category B Limited published data on mesalamine use in pregnant women are insufficient to inform a drug-associated risk (CANASA) Mesalamine and its metabolite have been detected in breast milk; use with caution.
Olsalazine	No dosage adjustment required in the elderly; use with caution.	Safety and efficacy in pediatric patients have not been established.	Patients with impaired renal function should be monitored closely.	Patients with impaired hepatic function should be monitored closely.	Pregnancy category C Small amounts of active metabolite may pass into breast milk and cause diarrhea in infants; unless the benefit outweighs the risks, do not use in nursing women.
Sulfasalazine	No dosage adjustment	Safety and efficacy in	No dosage adjustment	No dosage adjustment	Pregnancy category B (AZULFIDINE)

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	required in the elderly; use with caution.	pediatric patients < 2 years with UC have not been established. FDA-approved for juvenile rheumatoid arthritis and UC for ages six years and older.	advised; use with caution.	advised; use with caution.	No adequate well-controlled studies of sulfasalazine have been completed in pregnant women. Excreted in breast milk; use caution. Insignificant amounts of un-cleaved sulfasalazine detected in breast milk; sulfapyridine levels are 30% to 60% of those in the maternal serum. Reports of bloody stools and/or diarrhea in infants fed breast milk from mothers on sulfasalazine. Monitor infant. Consider discontinuation of nursing or drug.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Treatment goals of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations, and maintain remission from acute inflammation.
- For induction of remission of UC, no differences in efficacy or safety among the oral 5-ASA formulations are apparent (Wang et al, 2016[a]). Oral 5-ASA is similarly effective to sulfasalazine for induction of UC remission. For patients with mild to moderate UC, 2.4 g/day of oral 5-ASA is a safe and effective dose for inducing remission. Patients with moderate UC may benefit from 4.8 g/day of oral 5-ASA (Kornbluth et al, 2010).
- No overall differences in efficacy or safety among the oral 5-ASA formulations have been observed for the maintenance of UC remission, with all oral 5-ASA formulations being superior to placebo (Wang et al, 2016[b]). Sulfasalazine was shown to be superior to oral 5-ASA for maintenance of UC remission; however, when trials of 12 months duration or longer were evaluated, there was no longer a difference between sulfasalazine and 5-ASA. Once daily dosing and traditional dosing of oral 5-ASA regimens were similarly effective for maintenance of UC remission (Feagan and MacDonald, 2012; Feagan et al, 2013).
- Topical rectal therapies are the drugs of choice for distal disease and have been shown to be more effective than oral sulfasalazine therapy. In a meta-analysis, rectal 5-ASA therapy has been shown to be superior to placebo and rectal corticosteroids; however, rectal 5-ASA therapy was not superior to oral 5-ASA for symptomatic improvement or remission rates (Marshall et al, 2010). A smaller meta-analysis conducted in 2012 evaluating maintenance of symptomatic and endoscopic remission of UC, demonstrated that rectal 5-ASA was significantly superior to placebo over 12 months (Marshall et al, 2012). For maintenance of symptomatic and endoscopic remission of UC, rectal 5-ASA was not significantly different compared to oral 5-ASA. It has also been shown in clinical trials that topical mesalamine is more effective than placebo for the prevention of relapse of disease activity in quiescent UC (Ford et

al, 2012[b]). Similarly, trials showed budesonide rectal foam was more effective than placebo in inducing remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis (Sandborn et al, 2015).

- According to the 2010 ACG guidelines, oral therapies effective for achieving and maintaining remission in distal disease include aminosalicylates, balsalazide, mesalamine, olsalazine, and sulfasalazine (Kornbluth et al, 2010). Topical mesalamine agents are "superior" to topical steroids or oral aminosalicylates and the combination of oral and topical agents is "superior" to each agent used alone. In maintaining remission of disease, balsalazide, mesalamine, and sulfasalazine are effective, and combination oral and topical therapy is better than oral mesalamine alone.
- The 2010 ACG guidelines recognize sulfasalazine as a first-line agent in the management of mild to moderately active colitis, and note balsalazide, mesalamine, olsalazine, and sulfasalazine as effective therapies for reducing the number of relapses and the maintenance of mild to moderate disease remission (Kornbluth et al, 2010).
- The differences in drug therapies (i.e., pH-dependent parameters) allow for the tailoring of treatment based upon an individual's disease location and severity.
- Overall, oral therapies are generally well tolerated; however, adverse events often limit the use of sulfasalazine in favor of the newer 5-ASA therapy options given their local mechanism of action compared to the systemic absorption of sulfasalazine.

REFERENCES

- American College of Gastroenterology. Clinical Guidelines – Ulcerative Colitis in Adults. Available at: http://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/. Accessed March 8, 2017.
- APRISO prescribing information. Salix Pharmaceuticals, Inc.; Raleigh, NC. June 2016.
- ASACOL HD prescribing information. Warner Chilcott, LLC; Rockaway, NJ. May 2016.
- AZULFIDINE EN-tabs prescribing information. Pfizer; New York, NY. June 2016.
- AZULFIDINE prescribing information. Pfizer; New York, NY. February 2014.
- Bernstein C, Eliakim A, Fedail S, et al. World Gastroenterology Organisation global guidelines on inflammatory bowel disease. Updated August 2015. Available at: http://www.worldgastroenterology.org/UserFiles/file/guidelines/inflammatory-bowel-disease-english-2015.pdf. Accessed March 8, 2017.
- CANASA prescribing information. Allergan USA, Inc. Irvine, CA. September 2016.
- Centers for Disease Control and Prevention (CDC). Epidemiology of the IBD. March 31, 2015. Available at: http://www.cdc.gov/ibd/ibd-epidemiology.htm. Accessed March 8, 2017.
- COLAZAL prescribing information. Salix Pharmaceuticals, Inc.; Bridgewater, NJ. June 2016.
- DELZICOL prescribing information. Warner Chilcott, Rockaway, NJ. March 2016.
- DIPENTUM prescribing information. Meda Pharmaceuticals, Inc. Somerset, NJ. January 2014.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 8, 2017.
- Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG clinical guideline: preventive care in inflammatory bowel disease. Am J Gastroenterol. 2017;112:241-58.
- Feagan BG, Chande N, MacDonald JK. Are there differences in the efficacy and safety of different formulations of oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? Evidence from Cochrane Reviews. Inflamm Bowel Dis. 2013;19(9):2031-40.
- Feagan BG, MacDonald JK. Once daily oral mesalamine compared to conventional dosing for induction and maintenance of remission in ulcerative colitis: A systematic review and meta-analysis. Inflamm Bowel Dis. 2012;18:1785-1794.
- Ford AC, Khan KJ, Achkar JP, et al. Efficacy of oral vs topical, or combined oral and topical 5-aminosalicylates, in UC: Systematic review and meta-analysis. Am J Gastroenterol. 2012[a];107:167-76.
- Ford AC, Khan KJ, Sandborn WJ, et al. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent UC: a meta-analysis. Clinical Gastroenterology and Hepatology. 2012[b];10:513-9.
- Geremia A, Biancheri P, Allan P, et al. Innate and adaptive immunity in inflammatory bowel disease. Autoimmun Rev. 2014 Jan;13(1):3-10.
- GIAZO prescribing information. Salix Pharmaceuticals, Inc., Morrisville, NC. June 2016.
- Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. UC practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol. 2010 Mar;105(3):501-23.
- LIALDA prescribing information. Shire US, Inc.; Wayne, PA. November 2015.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2012, Issue 11. Art No.: CD004118. DOI: 10.1002/14651858.CD004118.pub2.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2010, Issue 1. Art. No.: CD004115. DOI: 10.1002/14651858.CD004115.pub2.
- Micromedex Healthcare Series Web site. http://www.micromedexsolutions.com/home/dispatch. Accessed March 8, 2017.
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH). NIH Publication No. 14–1597. Ulcerative Colitis. September 2014. Available at: http://digestive.niddk.nih.gov/ddiseases/pubs/colitis/. Accessed March 8, 2017.
- PENTASA prescribing information. Shire US, Inc.; Wayne, PA. October 2015.
- Peppercorn MA, Cheifetz AS. Definition, epidemiology, and risk factors in inflammatory bowel disease. UpToDate Web site[a]. www.uptodate.com. Accessed March 8, 2017.
- Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. UpToDate Web site[b]. www.uptodate.com. Accessed March 8, 2017.
- ROWASA prescribing information. Meda Pharmaceuticals, Inc. Somerset, NJ. June 2013.
- Sandborn WJ, Bosworth B, Zakko S, et al. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. Gastroenterology. 2015;148(4):740-750.
- sfROWASA prescribing information. Meda Pharmaceuticals, Inc. Somerset, NJ. June 2013.

- Sherlock ME, MacDonald JK, Griffiths AM, et al. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2015, Issue 10. Art. No.: CD007698. DOI: 10.1002/14651858.CD007698.pub3.
- Tong JL, Huang ML, Xu XT, et al. Once-daily vs multiple-daily mesalamine for patients with ulcerative colitis: a meta-analysis. J Dig Dis. 2012;13:200-7.
- UCERIS extended-release tablet prescribing information. Salix Pharmaceuticals, Inc. Bridgewater, NJ. November 2016.
- UCERIS rectal foam prescribing information. Salix pharmaceuticals, Inc. Bridgewater, NJ. September 2016.
- Wang Y, Parker CE, Bhanji T, et al. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016[a], Issue 4. Art. No.: CD000543. DOI: 10.1002/14651858.CD000543.pub4.
- Wang Y, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2016[b], Issue 5. Art. No.: CD000544. DOI: 10.1002/14651858.CD000544.pub4.
- Zhu Y, Ren-kuan T, Zhao P, et al. Can oral 5-aminosalicyclic acid be administered once daily in the treatment of mild-to-moderate ulcerative colitis? A meta-analysis of randomized-controlled trials. Eur J Gastroenterol Hepatol. 2012;24:487-494.

Publication Date: March 20, 2017