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Review Article

The Role of Mesalamine in the Management of Ulcerative Colitis: A Literature Review

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Abstract

Ulcerative colitis (UC) is a common form of inflammatory bowel disease in adolescents, marked by chronic, relapsing inflammation of the colonic mucosa. Although its pathogenesis involves multiple factors, mesalamine remains the mainstay treatment for mild to moderate cases due to its potent anti-inflammatory effects and favorable safety profile. This literature review aims to summarize evidence-based strategies for using mesalamine to induce and maintain remission across different age groups. Key findings, including its low incidence of adverse effects, suitability for long-term therapy, and potential chemoprotective properties, provide clinicians and patients with greater confidence in optimizing mesalamine therapy for UC.

Keywords: Ulcerative colitis

Introduction

Ulcerative colitis (UC) is a chronic, disabling autoimmune disorder characterized by relapsing inflammation of the colonic mucosa. It typically presents in early adulthood, with peak onset between 15 and 25 years of age, affecting both genders equally. Global incidence and prevalence estimates range from 3–15 per 100,000 and 50–80 per 100,000, respectively, with higher rates reported in technologically advanced countries. As UC predominantly affects the most productive age groups, it carries a significant socioeconomic burden, impacting workforce productivity and quality of life. The disease commonly begins in the rectum, with 40–50% of patients exhibiting disease limited to the rectum or rectosigmoid colon. Approximately 30–40% experience disease extending beyond the sigmoid flexure, and about 20% develop pancolitis involving the entire colon. UC's natural history is marked by frequently relapsing mucosal inflammation, which can lead to debilitating symptoms including frequent bowel movements, rectal bleeding, weight loss, and extraintestinal manifestations such as joint pain. The disease is also associated with an increased long-term risk of colorectal cancer.

Dietary factors are increasingly recognized as contributors to both the development and progression of UC, although the precise mechanisms remain unclear. The Western diet—high in fats, proteins, and processed foods and low in fruits, vegetables, and fiber—has been linked to the rising incidence of inflammatory bowel disease.

5-Aminosalicylic acid (5-ASA) agents, particularly mesalamine, remain the cornerstone of treatment for mild to moderate UC due to their anti-inflammatory properties and favorable safety profile. Mesalamine inhibits pro-inflammatory cytokines, helping to reduce mucosal inflammation while demonstrating minimal adverse effects compared to systemic corticosteroids. Meta-analyses report remission rates of approximately 42% with mesalamine compared to placebo, though some studies note that 58–72% of patients may still fail to achieve full remission. Despite its efficacy, corticosteroids are often used aggressively, even in patients with mild disease, exposing them to potential adverse effects. Optimizing mesalamine use offers a steroid-sparing alternative, supporting safer long-term management.

While generally well-tolerated, rare but serious adverse effects, including renal toxicity, can occur, and high oral pill burden may affect patient adherence. The Mayo Endoscopic Score (MES) is frequently used to assess endoscopic remission, with scores of 0–1 indicating remission. Studies suggest that MES of 1 is associated with higher relapse rates, whereas MES of 0 is the optimal therapeutic target, highlighting the importance of proper 5-ASA dosing to maintain remission.

Beyond its anti-inflammatory effects, mesalamine may provide chemopreventive benefits against colorectal cancer. Considering the complex interplay of cytokines and immune pathways in UC, combination therapies may further enhance treatment efficacy. This literature review aims to examine the clinical role of mesalamine in inducing and maintaining remission, its safety profile, and its potential as a steroid-sparing and chemoprotective therapy, providing evidence-based guidance for physicians and patients in the management of UC.

Review

Search strategy

Inclusion and Exclusion Criteria

In this traditional review, only free, full-text studies published in English within the last ten years—specifically between January 2015 and June 2025—were considered. Eligible publications were required to be based on human research. The literature search was conducted through PubMed and PubMed Advanced Search, using the standard search terms “mesalamine” and “ulcerative colitis.” Studies were included if they involved pediatric or adult participants of any sex who were prescribed, evaluated, or trialed on mesalamine for the treatment of UC.

Exclusion criteria encompassed preprints, articles older than ten years, non-English publications, research evaluating UC managed with other monotherapies, or studies involving participants not receiving mesalamine. These exclusions were applied to reduce bias and ensure the relevance of the data regarding the therapeutic role of mesalamine in UC. Conference abstracts, posters, and presentations without associated full-text articles were also omitted because of insufficient available information.

Discussion

This section outlines the use of 5-ASA agents as the first-line pharmacologic therapy for ulcerative colitis (UC). In addition, it reviews the etiology and pathophysiology of UC, its clinical presentation, diagnostic approach, and the current standards of care, with emphasis on where 5-ASA (mesalamine) fits within contemporary treatment algorithms. An evidence-based summary of key studies evaluating the efficacy and role of 5-ASA is provided, along with a discussion of recent advances in UC management.

Etiology and Pathophysiology of Ulcerative colitis

Although ulcerative colitis (UC) is still regarded as an idiopathic disorder, multiple contributory factors have been proposed, including infectious agents, dietary influences, dysregulated immune responses to commensal or self-antigens, and a range of environmental exposures . Increasing evidence highlights the central role of the intestinal microbiota in the initiation and perpetuation of IBD, including UC. Interestingly, the same study noted a protective association between active smoking and UC, with a substantially elevated risk of disease development within two years of smoking cessation.

Diet

In a large prospective multicenter observational study involving 412 patients with ulcerative colitis (UC) in remission on aminosalicylate monotherapy, Barnes et al. found that dietary intake of certain fatty acids was significantly associated with the risk of relapse over 12 months. During the follow-up period, 45 patients (11%) experienced a clinical flare. Among multiple fatty acids analyzed, only myristic acid — a saturated fatty acid abundant in palm oil, coconut oil, and dairy fats — showed a clear dose-response link to relapse, with an odds ratio (OR) of 3.01 (95% CI 1.17–7.74) for the highest versus the lowest intake tertile. By contrast, previously suspected dietary culprits — such as processed meat, alcohol, and sulfur-rich foods — were not independently associated with increased flare risk in multivariable models.

From a pathophysiological perspective, UC involves a dysregulated immune response in the gut mucosa. Impaired immune regulation contributes to persistent inflammation, recruiting leukocytes from the microvasculature into the intestinal mucosa. The infiltrating population is enriched for $CD4^+$ lymphocytes, which help drive a humoral immune response. This chronic immune activation is underpinned by elevated levels of proinflammatory cytokines — including IL-1, IL-6, IL-8, and TNF-α — that perpetuate tissue damage and mucosal dysfunction. Given this immunopathology, pharmacological therapies such as mesalamine (5-aminosalicylic acid) are critical in suppressing inflammation and maintaining remission. In this context, understanding how dietary factors like myristic acid may destabilize remission provides an important rationale for integrating dietary guidance into UC management.

Ulcerative colitis (UC) typically follows a relapsing–remitting course, with the severity of symptoms largely influenced by the extent of colonic involvement. While many patients experience intermittent symptom-free periods, about 10% may present with acute fulminant episodes. The primary clinical features arise from inflammation of the colonic mucosa, most commonly resulting in diarrhea and rectal bleeding. Symptom patterns vary according to disease distribution: patients with left-sided colitis or proctitis frequently report urgency and incomplete evacuation, with constipation occurring in roughly 10%, whereas those with pancolitis more often experience abdominal pain accompanied by bloody, loose stools.

On examination, findings may include signs of anemia, tenderness on abdominal palpation, and blood on digital rectal examination. Chronic diarrhea can also lead to anal fissures and skin tags, though these are more commonly associated with Crohn’s disease. In addition, Clostridioides difficile infection must be considered during evaluation, as it is a known trigger of flares and is linked to

higher surgical rates and mortality. Overall, typical UC symptoms include episodic crampy abdominal pain, rectal bleeding with mucus, straining during defecation, and mild diarrhea, while severe cases may present with fever, anemia, weight loss, and malnutrition.

Extraintestinal manifestations are observed in approximately one-third of UC patients, with up to 25% developing these signs before a formal diagnosis.Peripheral arthritis is the most frequent, followed by dermatologic complications such as pyoderma gangrenosum and hepatobiliary involvement like primary sclerosing cholangitis, all more prevalent in UC than Crohn's disease. Patients with inflammatory bowel disease also face a three- to fourfold increased risk of venous thromboembolism, especially during flares or hospitalization requiring corticosteroid therapy. Therefore, prophylactic measures against thromboembolic events are strongly recommended in these high-risk periods.This wide spectrum of intestinal and systemic manifestations highlights the complexity of UC, emphasizing the need for a comprehensive approach to diagnosis, monitoring, and management, taking into account both mucosal inflammation and systemic complications.

Diagnosis

The overall analysis of clinical presentation, laboratory results, endoscopic, histologic, and radiological findings is the hallmark of diagnosing UC, rather than by any single study. Disease severity classification and disease progression are predicted with more invasive procedures, such as Endoscopic findings.Patients with a clinical presentation listed above, endoscopic findings of friable, ulcerated, and edematous mucosa, along with biopsy showing inflammatory infiltration, crypt abscesses, and widespread superficial ulceration, suggest UC.

Generally, anyone with a suspected possibility of UC must have stool examinations, specifically stool

cultures and Clostridium difficile studies, to rule out any colonic infections.Patients can present with

low hemoglobin levels, elevated white cells and thrombocytosis, but low albumin levels are indicative of severe disease and a strong predictor of treatment failure with biologic medications and need for surgical intervention such as colectomy.

Other inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate (ESR), may be elevated. Also, non-specific perinuclear antineutrophil cytoplasmic antibodies may be raised in UC .

Ultimately, endoscopic examination with multiple biopsies is the best way to establish and confirm the diagnosis of UC.

Biomarkers in UC

It is understood that evaluating the colonic wall histological activity may help guide treatment options and indicate the prognosis of UC.

Moreover, patients in histological remission are presumably symptom-free and demonstrate decreased risk of relapses and can avoid hospital visits, surgery, and reduced chances of

developing colon cancer.Nonetheless, biopsy and invasive procedures like endoscopy are not patient-

friendly. Fecal calprotectin is a non-invasive biomarker that relates well to the colonic inflammatory histological activity, hence a great tool for colonic histological assessment in UC.

Calprotectin is identified as a key teeming protein in the neutrophils that is released into the colon during inflammation. It is a dimer formed by the association of S100A8 and S100A9 proteins, which chelate iron and Zinc, conferring antibacterial action. Due to its greater stability, in feces, it is easily a good choice for a non-invasive biomarker and is considered superior to the FIT (fecal immunochemical) test in terms of its diagnostic value. Additionally, studies have shown that patients in clinical remission had fecal calprotectin levels of less than 50mg/l with normal colonoscopy findings. Thus, this highlighted the use of fecal calprotectin in assessing mucosal healing in IBD patients. Several recent studies have compared

the C-reactive protein levels in both CD and UC, respectively, and have demonstrated that the concentration levels of CRP decreased in those treated with infliximab; this result makes CRP an effective tool in both treatment efficacy and monitoring flare-ups. Hence, both fecal calprotectin and CRP levels guide treatment by indicating the severity of the inflammation or active vs clinical remission status of UC.

Genetic Testing

IBD is a polygenic disorder with around 100 risk loci identified, some shared between ulcerative colitis and Crohn's disease, reflecting overlapping immunopathogenesis and treatment responses. These include genes involved in autophagy and innate immunity (e.g., NOD2, ATG16L1, IRGM, JAK2, STAT3), ER and metabolic stress responses (e.g., XBP1, ORMDL3, OCTN), adaptive immunity regulation (e.g., IL23R, IL12B, IL10, PTPN2), and inflammation resolution (e.g., MST1, CCR6, TNFAIP3, PTGER4). Some variants, such as NOD2, are associated with specific subtypes like fibrostenosing Crohn's disease. While most polygenic risks are not yet clinically actionable, testing for monogenic forms—particularly in early-onset pediatric cases—can guide diagnosis, treatment, and prevention.

Source: *Adapted from Kaser et al, Ann Rev Immunol 2010*

Treatment and Management of UC with Mesalamine

Sulfasalazine, an oral 5-ASA prodrug, was first developed for UC. In the colon, gut microbiota split it into its active component, mesalamine, and the inactive sulfapyridine, which is largely responsible for side effects. Other 5-ASA prodrugs, including balsalazide and olsalazine, are similarly converted to mesalamine by bacterial azoreductases. Mesalamine, either orally or as olsalazine, is now preferred for inducing and maintaining remission due to its improved tolerability. For mild to moderate distal UC, topical formulations (enemas or suppositories) are recommended, while a combination of oral and topical mesalamine is advised for left-sided colitis.Table 1 illustrates the stepwise treatment escalation for UC management.

Step 4	**Biologics**
Step 3	**Immuno-therapy**
Step 2	**Steroids**
Step-1	**5-ASA: 5-Aminosalicylic acid**

Stepwise Treatment Escalation Approach for Ulcerative Colitis.

Mesalamine Optimization and Adjunct Therapies in UC

Mesalamine, the active component of 5-ASA therapies, is preferred over sulfasalazine due to improved tolerability, and can be administered orally, as a prodrug such as olsalazine, or topically

via enemas or suppositories for distal UC. The American Gastroenterological Association emphasizes optimizing mesalamine dosing for mild to moderate UC before considering immunosuppressive therapy. Combining oral and topical mesalamine may improve symptom control, accelerate relief, and enhance anti-inflammatory effects, particularly in extensive UC, although adherence to suppositories is often low and typically limited to flare-ups. Dose escalation of oral 5-ASA in patients with low Mayo endoscopic subscores reduces relapse risk, especially in those on immunomodulators, whereas steroid use may increase relapse risk. Probiotics appear to have limited benefit in UC management.

Beyond symptomatic control, mesalamine may have chemoprotective effects. In patients with concurrent primary sclerosing cholangitis (PSC) and UC, who are at higher colorectal cancer risk, inflammation-induced miR-155 upregulation reduces MMR protein levels, promoting carcinogenesis. Mesalamine was shown to repress miR-155 and restore MMR expression, indicating potential cancer-preventive properties in this high-risk group.

Future Modalities in UC Management

Ulcerative colitis significantly impairs quality of life due to its recurrent and incurable nature. Anti-TNF therapies, such as infliximab and adalimumab, have shifted treatment goals from symptomatic relief to sustained remission. The alternating active and inactive phases of UC are linked to high expression of hub genes, intestinal epithelial cell pyroptosis, and elevated pro-inflammatory factors, which may drive disease recurrence. Future research targeting pyroptosis could help prevent relapse. Additionally, pathway analyses, including NOD-like receptor, NF-κB, TNF, and IL-17 signaling, highlight potential targets for new drug development.

Fecal microbiota transplantation (FMT) is an emerging therapeutic approach. UC patients often have altered gut microbiota, with reduced beneficial bacteria and increased opportunistic pathogens. FMT involves transplanting processed feces from healthy donors to restore microbial diversity and eliminate pathogenic bacteria. Studies have shown eradication of Clostridioides difficile and its virulence factors following FMT, with sustained effects at three- and six-month follow-ups. Targeting gut microbiota and inflammatory pathways represents a promising area for future research and clinical advances in UC management.

Mesalamine Review

Mesalamine is generally available as oral delayed-release formulations with a half-life of approximately 25 hours. It is well tolerated across age groups, with mostly mild, dose-related side effects such as headache, rash with pruritus, nausea, dyspepsia, and vomiting. Taking mesalamine with meals and plenty of fluids may improve adherence and reduce these minor effects. Rare but severe adverse events include pancreatitis, pericarditis, pneumonitis, and hepatotoxicity. Table 1 summarizes various clinical trials evaluating mesalamine use in UC, including different combination therapies and key findings.

Limitations

This review has several limitations. Restricting the search to free full-text and English-language articles may have introduced access and language bias, potentially omitting relevant studies from other regions. Additionally, many articles did not examine clinical severity, diagnostic delays, or symptom onset in detail, limiting the generalizability of mesalamine use in UC. Finally, the studies reviewed often lacked specification of patient populations, which may differ in risk profiles or treatment responses.

Conclusions

The relapsing and chronic nature of UC, driven by colonic mucosal inflammation, underscores the importance of 5-ASA compounds like mesalamine for inducing and maintaining remission in mild to moderate cases. Delayed-release oral mesalamine has proven efficacy, a favorable safety profile, and minimal rare adverse effects, such as renal toxicity, for which periodic monitoring is recommended. In addition to reducing inflammatory cytokines, mesalamine exhibits chemoprotective activity and can serve as a steroid-sparing therapy. This review aims to increase awareness among physicians and patients about mesalamine's role in UC management. Further research, including case-control studies, is needed to better understand its chemoprotective potential and optimize its use in clinical practice.

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

- Concept and design: Dr. Gaurav Sisodia
- Critical review of the manuscript for important intellectual content: Conf. Univ. Dr. Brata Roxana, Dr. Ioana-Larisa Paul
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- Academic support and assistance with literature organization: Dr. Ioana-Larisa Paul
- Drafting of the manuscript: Dr. Gaurav Sisodia

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