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The Current Ulcerative Colitis (UC) Treatment Algorithm: From 5-ASA to Biological Therapies

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Abstract:

Background: Ulcerative colitis (UC) is a chronic, relapsing inflammatory condition affecting the colonic mucosa, typically progressing proximally from the rectum. Incidence rates are rising globally. The etiology is multifactorial, involving genetic susceptibility and environmental triggers such as smoking status and diet.

Aim: The aim of this article is to provide a comprehensive review of the current therapeutic landscape for ulcerative colitis, evaluating the efficacy and safety of established and novel pharmacological agents based on a systematic review of clinical trials and meta-analyses.

Materials and Methods: The review included scientific papers sourced from the PubMed and Google Scholar databases.

Results: Treatment strategies vary by disease severity. 5-aminosalicylates (5-ASA) remain the first-line therapy for inducing and maintaining remission in mild-to-moderate UC. For moderate-to-severe disease, corticosteroids are effective for induction but limited by systemic toxicity, leading to the development of second-generation formulations like Budesonide MMX. In steroid-refractory or dependent cases, biological therapies—including anti-TNF agents (infliximab, adalimumab), anti-integrins (vedolizumab), and interleukin inhibitors

(ustekinumab) demonstrate significant efficacy. Recently, oral small molecules such as JAK inhibitors (tofacitinib, upadacitinib) and S1P receptor modulators (ozanimod) have emerged as potent, non-immunogenic alternatives.

Conclusions: The management of UC has evolved from symptom control to achieving deep endoscopic remission and improving health-related quality of life. While conventional therapies remain foundational, the expansion of biologics and small molecules offers critical options for refractory patients, helping to reduce colectomy rates. Optimal treatment requires balancing therapeutic efficacy with long-term safety profiles.

Key words: ulcerative colitis; 5-ASA; monoclonal antibodies; JAK kinases; ulcerative colitis treatment; inflammatory bowel disease

Introduction:

Ulcerative colitis (UC) is a chronic inflammatory condition. The pathological changes are at first located in the rectum, later they may extend to proximal segments of the colon as the disease progresses. The inflammation of the mucosal and submucosal layer is relapsing and remitting. (Peyrin -Biroulet et al., 2015).

The disease affects both men and women alike with peak age of onset being between 30 and 40 years old. The incidence has been increasing in recent years. The highest rates have been reported in northern Europe (24.3 per 100 000), Canada (19.2 per 100 000), and Australia (17.4 per 100 000). (Ungaro et al., 2017).

Studies into the risk factors of ulcerative colitis suggest a role of environmental risk factors as well as a genetic component. Twin studies on inflammatory bowel diseases showed concordance rates of UC in monozygotic twins to be 16% and for dizygotic twins to be 4%. (Ananthakrishnan, 2015). Up to date around 200 loci for inflammatory bowel disease have been identified. Some of them are more strongly associated with the risk of developing UC. Examples of such are genes associated with mucosal barrier function and human leukocyte antigen - CDH1 and HNF4A. (Jostins et al., 2012).

The first environmental factor which has been highly attributed to developing UC is smoking. Studies show that both current and former smokers have a higher risk of developing the condition (Wan et al., 2025). However, it has also been proven that active cigarette smokers and non-smokers are at a lower risk for developing the disease (OR 0.58, 95% CI 0.45–0.75). That is compared to the former smokers which have the odds ratio (OR) 1.79, (95% confidence interval (CI) 1.37–2.34). (Mahid et al., 2006, Odes et al., 2001). Appendectomy demonstrates a divergent effect on inflammatory bowel disease, similar to smoking, by showing a different association with UC. A large cohort study of 212,963 patients who underwent appendectomy before age 50 found that the incidence of ulcerative colitis was markedly lower in those who had the procedure for specific inflammatory conditions, such as perforated or non-perforated appendicitis and mesenteric lymphadenitis, compared to those who had it for non-specific abdominal pain. This observation suggests that the protective association against UC is likely

driven by the inflammation of the appendix itself, and the subsequent removal of that inflamed tissue, rather than the simple, mechanical removal of the organ (Andersson et al., 2001).

Diet is a key environmental risk factor that influences UC, often by altering the gut microbiota. High consumption of saturated fats and a high ratio of omega-6 to omega-3 fatty acids are associated with increased risk. In active UC, a milk-free diet may help reduce the frequency of relapses (Ananthakrishnan, 2015). Studies looking into the effect of drugs on the development of UC showed that oral contraceptives, particularly those containing estrogen increase the risk of the condition by about 30% (OR 1.30, 95% CI: 1.13 – 1.49). This risk increases with longer exposure. Conversely, while antibiotics can cause dysbiosis, meta-analyses suggest that antibiotic exposure increases the risk of Crohn's disease (CD) but has no significant association with the risk of developing UC. (Singh et al., 2002).

The most common presenting symptoms are bloody stool and diarrhea. While UC patients can experience symptoms like urgency, frequent bowel movements, fatigue, and abdominal discomfort/cramps, abdominal pain is generally a less prominent feature compared to CD. In severe cases, which affect up to 15% of patients initially, symptoms may also include fevers and weight loss (Ungaro et al., 2017).

According to the Montreal classification UC patients can be divided into 3 groups based on their maximal disease extent. E1 includes patients in which the disease is limited to the rectum, E2, also called left-sided disease, is located distal to splenic flexure. E3, also called extensive colitis can be diagnosed in patients with the most extensive disease located proximal to splenic flexure (Lamb et al., 2019).

Research materials and methods

A comprehensive literature review was conducted using the PubMed and Google Scholar databases. The search focused on systematic reviews, meta-analyses, and key clinical trials published on the topic of treatment of ulcerative colitis. To cover all relevant aspects, the search strategy included keywords such as "ulcerative colitis treatment" "UC" "ulcerative colitis 5-ASA.", "ulcerative colitis glucocorticosteroids" and "ulcerative colitis monoclonal antibodies", "ulcerative colitis small molecules” , “ulcerative colitis thiopurines”.

Aminosalicylates:

Aminosalicylates, specifically compounds containing 5-aminosalicylic acid (5-ASA) or mesalamine, are the cornerstone of therapy for inducing and maintaining remission in mild-to-moderate UC. The therapeutic efficacy of 5-ASA is thought to be mediated through several mechanisms. This includes antioxidant effects - a drug like 5-ASA works by interacting with oxygen-derived species (Dull et al., 1987). They also inhibit the productions of eicosanoids which act as mediators of inflammation in inflammatory bowel disease including UC (Stenson, 1990). In addition sulfasalazine and its metabolites have been shown to reduce the production of antibodies by B-cells (MacDermott et al., 1989).

For patients experiencing mild-to-moderate active UC, oral 5-ASA is highly effective for inducing clinical and endoscopic remission. The initial oral dosage of 5-ASA is typically 2.0-2.4 g per day, if needed it might be increased up to 4.8g per day. It can be administered once a day as such an approach increases adherence and has been shown to have a similar efficacy to administering the drug in divided doses. (Bressler et al., 2015).

The selection of a specific 5-ASA formulation (e.g., delayed-release, sustained-release, or prodrugs like balsalazide) often depends on the extent of the disease and patient tolerance. Different formulations are designed to deliver the 5-ASA molecule to specific segments of the colon. The route of administration significantly impacts efficacy, particularly in active disease. Patients with proctitis or left-sided colitis benefit greatly from topical 5-ASA formulations (suppositories or enemas), as these deliver high concentrations of the drug directly to the

inflamed mucosa while minimizing systemic absorption. For extensive or pan-colitis, a combination of oral and topical 5-ASA is often recommended due to its superior efficacy over monotherapy. A 2013 review evaluating 17 studies with 2925 patients overall compared the efficacy of different oral mesalazine formulations. It was found that there is no significant difference in the proportion of patients with clinical remission (relative risk (RR), 0.94; 95% CI, 0.86–1.02), clinical improvement (RR, 0.89; 95% CI, 0.77–1.01), and relapse at 12 months (RR, 1.01; 95% CI, 0.80–1.28). (Feagan et al., 2013).

A 2002 study by Pruitt et al. compared 173 patients with endoscopically verified UC. They were administered either mesalamine or balsalazide. The results showed a median time to symptomatic remission of 25 days with balsalazide and 37 days with mesalamine. More balsalazide patients showed sigmoidoscopic ($p = 0.002$), stool frequency ($p = 0.006$), rectal bleeding ($p = 0.006$), and physician's global assessment score ($p = 0.013$) improvement by 14 days than mesalamine patients. This led to the conclusion that balsalazide was superior to mesalamine in achieving symptomatic improvement in patients with mild-to-moderate UC (Pruitt et al., 2002).

Consequently, if the first line therapy with amniosalicylates proves effective by inducing remission in a specific patient, they may continue on it, in order to maintain remission. Patients who do not achieve the expected response or exhibit more severe symptoms from the start, should be treated with second-line therapies.

Corticosteroids:

Glucocorticosteroids (GCs) play an important role in the management of Inflammatory Bowel Disease. While the therapeutic approach for UC has expanded with the introduction of biological agents, GCs remain the primary therapeutic option for inducing remission in patients with moderate to severe disease activity. However, the clinical utility of these agents is limited by a number of adverse effects. It was a reason for the shift from first-generation systemic steroids to second-generation formulations designed for targeted colonic delivery (Dubois-Camacho et al., 2017).

First-generation corticosteroids, including prednisone, methylprednisolone, and hydrocortisone, act through genomic mechanisms to suppress proinflammatory cytokines such as IL-1β, IL-6, and IL-8, while upregulating anti-inflammatory mediators like IL-10 (Dubois-Camacho et al., 2017).

In clinical practice, these agents demonstrate high efficacy for inducing remission. A systematic review and meta-analysis of randomized controlled trials (RCTs) confirmed that standard glucocorticosteroids are superior to placebo for inducing remission in active UC, with RR of failure to achieve remission of 0.65 (95% CI 0.45–0.93). The Number Needed to Treat (NNT) to achieve remission in one patient with active UC was calculated to be 3, indicating a potent therapeutic effect (Ford et al., 2011).

Despite their efficacy, systemic administration of GCs has a number of concerns regarding side effects. Adverse events are frequent and include effects on metabolism (diabetes, fat redistribution), eyes (glaucoma, cataracts), musculoskeletal system (osteoporosis), and psychological well-being (insomnia, anxiety) (Dubois-Camacho et al., 2017). In trials comparing standard corticosteroids to placebo, adverse events were notably higher in the treatment arm, with a calculated Number Needed to Harm of 4 (Ford et al., 2011). Consequently, current guidelines emphasize that while GCs are effective for induction, they should not be used for maintenance therapy due to these long-term risks.

In order to decrease the systemic toxicity associated with traditional steroids, second-generation corticosteroids with high first-pass metabolism, such as budesonide and beclomethasone dipropionate (BDP), have been developed.

A significant advancement in UC therapy is the development of Budesonide MMX (Multi-Matrix System). It is an extended-release formulation designed to deliver the drug throughout the entire colon. This formulation uses a gastro-resistant outer layer that dissolves at pH 7.0, releasing budesonide directly to the site of inflammation while minimizing systemic absorption (Sandborn et al., 2015).

Pooled analysis from two Phase 3 studies (CORE I and II) evaluated Budesonide MMX in patients with mild-to-moderate active UC. The data demonstrated that a 9 mg daily dose resulted in a combined clinical and colonoscopic remission rate of 17.7%, which was significantly higher than the 6.2% observed in the placebo group ($p=0.0002$). Furthermore, the safety profile of Budesonide MMX was comparable to placebo, with no significant increase in glucocorticoid-related adverse events such as moon face, striae, or fluid retention (Sandborn et al., 2015). This makes Budesonide MMX a viable option for patients who do not respond to 5-ASA therapy but do not yet require systemic corticosteroids (Dubois-Camacho et al., 2017; Sandborn et al., 2015).

In patients with the disease limited to the distal colon or rectum, topical administration allows for high local drug concentrations while reducing systemic exposure. BDP administered as an enema has shown efficacy comparable to standard therapies. In a randomized double-blind trial involving patients with active distal UC, BDP enemas (3 mg) were compared against 5-ASA enemas (2 g) and a combination of both. The study found that while BDP and 5-ASA were equally efficacious as monotherapies, the combination of BDP and 5-ASA was significantly superior, achieving 100% clinical and endoscopic improvement after 4 weeks (Mulder et al., 1996). This suggests a synergistic benefit when combining topical steroids with aminosalicylates for distal disease.

Despite the availability of GC therapies, a number of patients exhibit steroid resistance or steroid dependence. Approximately 19% of Inflammatory Bowel Disease patients are non-responders to GCs, while 20% become dependent, requiring continued therapy to prevent relapse (Dubois-Camacho et al., 2017). The molecular basis for GCs resistance is multifactorial. It has been associated with the overexpression of the glucocorticoid receptor beta isoform. Unlike the active alpha isoform, the beta isoform does not bind GCs and acts as a dominant-negative inhibitor, blocking the transcriptional regulation of inflammatory genes. Studies have shown that mucosal cells in GC-resistant patients express significantly higher levels of the glucocorticoid receptors beta isoform compared to responders. Additionally, polymorphisms in the MDR1 gene, which encodes the P-glycoprotein multidrug transporter, may facilitate the rapid efflux of corticosteroids from target cells, thereby reducing intracellular drug concentration and therapeutic efficacy (Dubois-Camacho et al., 2017). Patients who are found to be steroid resistant or steroid dependent benefit from transition to biological or immunomodulator therapies.

Monoclonal antibodies:

Even though ulcerative colitis can be treated with corticosteroids, the treatment carries plenty of adverse effects of corticosteroid use and patients diagnosed with UC still have a high colectomy rate (Järnerot et al., 2005). This conclusion led to the consideration of other potentially effective therapies for ulcerative colitis, including monoclonal antibodies. There are 3 main groups of biological medication that have been tested for UC and proved to be effective.

The largest group is the tumor necrosis alpha (TNF-alpha) inhibitors, including infliximab, adalimumab and golimumab. The idea to use this group of medication, which is also used to treat for example psoriasis and rheumatoid arthritis, sprung from the fact that increased levels of TNF-alpha had been found in feces from the patients diagnosed with ulcerative colitis. (Järnerot et al., 2005).

Infliximab is a chimeric monoclonal antibody against (TNF-alpha that is one of the most effective medications in inducing and maintaining remission in patients with moderate to severe ulcerative colitis (Reinisch et al., 2011). According to a research conducted in 2005, 69% of patients who received 5mg of infliximab had a clinical response to the medication characterised by a decrease in Mayo score of at least 3, compared to 37% of patients receiving placebo (Rutgeerts et al., 2005). Other research from the same year found that infliximab also decreased colectomy rate; 7 out of 24 patients from the infliximab group had a colectomy in comparison to 14 out of 21 from the placebo group and no serious side effects occurred (Järnerot et al., 2005). The medication was administered intravenously.

Adalimumab is a recombinant human monoclonal antibody targeting TNF-alpha, which, as opposed to infliximab, is administered subcutaneously. Research shows that remission at week 8 was present in 18,5% patients receiving adalimumab in the dose of 160/80 (160mg at week 0, 80 mg at week 2, 40mg at weeks 4 and 6) in comparison to 9,2% in the placebo group. No malignancies in the group receiving adalimumab were observed, compared to 2 in the placebo group, among the 390 patients enrolled in the trial. (Reinisch et al., 2011).

Golimumab is a fully human monoclonal antibody against TNF-alpha, which, just like adalimumab, is administered subcutaneously. In the 2014 clinical trial by Sandborn et al the rate of clinical response at week 6 was 54,9% in patients getting 400/200mg of golimumab, and 30,3% among the placebo group. Both the rates of serious adverse events and serious infection were significantly lower in the group treated with golimumab. (Sandborn et al., 2014).

The second group of monoclonal antibodies used to treat UC are selective integrity antagonists, and a representative of this group is vedolizumab. Vedolizumab is a humanised, gut-selective monoclonal antibody to α4β7 integrin that has been proven effective in treatment of Crohn's disease and ulcerative colitis. It has been considered a safe medication, for the safety profiles between placebo and vedolizumab-treated groups had no major differences. (Colombel et al., 2016).

The last group of medication is interleukin inhibitors. Ustekinumab is an antagonist of the p40 subunit of interleukin 12 (IL-12) and interleukin 23 (IL-23). It has a newer mechanism of action than the previously mentioned medication and is administered intravenously (induction dose) and subcutaneously (maintenance dose). It proved a high effectiveness in inducing remission, for at week 8 over 15% of patients treated with ustekinumab had clinical remission, in opposition to only 5,3% of patients in the placebo group. The trial was conducted in 961 patients and the incidence of serious adverse events was similar in patients treated with ustekinumab and the placebo group. (Sands et al., 2019).

Small molecules:

The treatment options for moderate-to-severe UC have significantly evolved with the introduction of oral small molecules. Unlike monoclonal antibodies, these agents lack immunogenicity and can be administered orally. The two primary groups currently in use are Janus kinase (JAK) inhibitors and sphingosine 1-phosphate (S1P) receptor modulators.

Janus kinases (JAKs) function as intracellular non-receptor tyrosine kinases that transduce signals from cytokine receptors. Upon ligand binding, receptor-associated JAKs undergo auto-activation via transphosphorylation and subsequently phosphorylate specific receptor tyrosine residues. These phosphotyrosines recruit signal transducers and activators of transcription (STAT) proteins, which are then phosphorylated by JAKs. Activated STATs dimerize and translocate to the nucleus to drive gene expression, a process tightly regulated by a suppressor of cytokine signaling (SOCS) proteins. (Agashe et al., 2022).

Tofacitinib is an oral small-molecule inhibitor of JAK1, JAK3, and essentially JAK2. It was evaluated in the OCTAVE Phase 3 trials. In the induction trials, remission rates at 8 weeks were significantly higher with tofacitinib 10 mg twice daily (18.5% and 16.6%) compared to

placebo (8.2% and 3.6%, respectively). In the OCTAVE Sustain maintenance trial, remission at 52 weeks occurred in 34.3% (5 mg) and 40.6% (10 mg) of patients versus 11.1% in the placebo group (Sandborn et al., 2017).

Another JAK-1 inhibitor - upadacitinib has demonstrated high efficacy, even in refractory populations. In a prospective real-world cohort of 105 patients, 81.5% achieved clinical remission by week 8. Notably, upadacitinib remained effective in patients with prior JAK inhibitor failure; among tofacitinib-exposed patients, 77.8% achieved clinical remission by week 8. Safety data indicated acne was the most common adverse event (22.9%). (Friedberg et al., 2023).

S1P Receptor Modulators function by sequestering lymphocytes in lymph nodes, preventing their migration to sites of inflammation. An example of such - ozanimod was evaluated in the True North Phase 3 trial. During the induction phase of the treatment which lasted 10 weeks, clinical remission was achieved in 18.4% of ozanimod-treated patients compared to 6.0% receiving placebo ($p<0.001$). In the maintenance phase, 37.0% of patients achieved remission at week 52 compared to 18.5% in the placebo group ($p<0.001$) (Sandborn et al., 2021).

Etrasimod, a selective S1P receptor modulator, was assessed in the ELEVATE UC trials using a treat-through design. Patients included in the trials were reported to have inadequate response, intolerance or loss of response to at least one previously used method of therapy. In ELEVATE UC 52, clinical remission rates were significantly higher for etrasimod compared to placebo at both week 12 (27% vs 7%) and week 52 (32% vs 7%). Similarly, in the ELEVATE UC 12 induction trial, 25% of etrasimod patients achieved remission compared to 15% of the placebo group. The safety profile was favorable, however researchers concluded that events such as bradycardia and macular edema require monitoring. (Sandborn et al., 2023).

Restoring health-related quality of life (HRQoL) is a primary goal in the management of moderate-to-severe ulcerative colitis. Research proves that the use of effective therapies, specifically biological agents and JAK inhibitors, consistently provides substantial HRQoL improvements during both induction and long-term maintenance treatment. (Armuzzi et al., 2021).

In cases where pharmacological treatments fail to induce remission a surgical intervention may be required. This is especially true in acute severe UC where hemorrhage or perforation may occur, granting surgical intervention necessary. In ulcerative colitis the general rule is to perform as colon-sparing surgery as possible.

Conclusions:

Ulcerative colitis is a complex, chronic, and progressive condition characterized by a relapsing-remitting course. It significantly burdens the healthcare system and impacts patient quality of life. The disease is driven by a multifaceted etiology involving genetic susceptibility and environmental triggers, such as smoking status and dietary patterns. Understanding these risk factors is crucial. The primary focus of clinical management remains the effective suppression of mucosal inflammation.

The therapeutic options for UC underwent a significant expansion in recent decades. 5-aminosalicylates continue to serve as the cornerstone of first-line therapy for mild-to-moderate disease, proving effective in both induction and maintenance. The management of moderate-to-severe and refractory cases has seen the most profound evolution. While corticosteroids are potent induction agents, their long-term systemic toxicity limits their use, necessitating the shift toward steroid-sparing strategies. The development of second-generation corticosteroids, such as Budesonide MMX, and the introduction of biological agents have greatly altered the natural history of the disease.

Monoclonal antibodies targeting TNF-alpha, integrins, and interleukins have provided viable options for patients who previously faced colectomy. Furthermore, the recent development of small molecules, including JAK inhibitors and S1P receptor modulators, has introduced the convenience of oral administration combined with potent efficacy. This offers an alternative for patients resistant to corticosteroids. Despite these advancements a significant number of patients still experience non-response or loss of response to treatment.

Consequently, the goal for UC management has shifted from simple symptom control to achieving deep endoscopic remission and restoring health-related quality of life (HRQoL). The current challenge for clinicians is choosing the best suited therapy for their patients.. This includes balancing efficacy against safety risks like infection or malignancy. By optimizing therapeutic selection early in the disease course, it is possible to minimize long-term complications and reduce the necessity for surgical intervention, which remains the final salvage option for acute severe or medically refractory disease.

Disclosure

Author's contributions

Conceptualization:ES;
Methodology:VP, ES;
Software:ES;Check:VP;
Formal analysis:ES
Investigation:ES,VP
Resources:ES,VP
Data curation:ES,VP;
Writing-rough preparation:ES
Writing-review and editing:ES,VP
Supervision:ES

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