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REVIEW

Ulcerative Colitis: Advances in Pathogenesis, Biomarkers, and Therapeutic Strategies

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Abstract: Ulcerative colitis represents an inflammatory bowel disease with multiple contributing factors, marked by persistent inflammation of the colonic mucosa, which can lead to a reduced life expectancy and an elevated likelihood of requiring colectomy as well as developing colorectal cancer. Despite impacting roughly 5 million individuals worldwide, the intricate mechanisms underlying ulcerative colitis are still inadequately defined, hindering the development of effective treatments. Extra-intestinal complications, including enteropathic arthritis, are also addressed in the context of disease burden and management. This review explores the multifaceted pathogenesis of ulcerative colitis, emphasizing critical factors such as abnormalities in the epithelial barrier, irregular immune responses, the release of inflammatory mediators, and alterations in gut microbiota composition. We also underscore recent advancements in diagnostic biomarkers that improve the accuracy of disease detection and monitoring. Conventional medicinal strategies are reviewed alongside the emergence of biological therapies, notably those that target tumor necrosis factor (TNF), interleukins, and integrins, which have significantly altered management approaches. Established therapies (eg, 5-aminosalicylic acid, corticosteroids) and emerging agents (eg, JAK inhibitors, S1P modulators) are clearly delineated. Combination strategies—such as dual biologic regimens or JAK inhibitors combined with anti-integrin agents—are also discussed in dedicated subsections. We discuss novel therapies that utilize small molecule targeting, particularly those that inhibit Janus kinase (JAK) and modulate sphingosine-1-phosphate (S1P) receptors, presenting promising avenues for treatment. Additionally, fecal microbiota transplantation (FMT) is evaluated as a therapeutic option, as it shows promise in restoring microbial balance. Collectively, these advances underscore the pivotal roles of immune dysregulation, biologic therapies, and microbiota modulation in reshaping precision management of ulcerative colitis. This synthesis of current knowledge underscores the necessity for continued research to refine therapeutic strategies and improve patient outcomes in ulcerative colitis.

Keywords: ulcerative colitis, biomarkers, biologic therapies, pathogenesis, fecal microbiota transplantation, immune dysregulation, microbiota modulation

Introduction

Ulcerative colitis (UC), a form of inflammatory bowel disease (IBD), is characterized by inflammation and ulceration predominantly affecting the rectum and colon, although in extensive disease, backwash ileitis may involve the terminal ileum.[1] The clinical manifestation often includes bloody diarrhea, which may be accompanied by additional gastrointestinal symptoms, signs of systemic inflammation, and extra-intestinal complications like sclerosing cholangitis or arthritis. In the past twenty years, UC has increasingly posed a global health concern worldwide, reflecting dynamic changes in its epidemiological landscape.[2] From 2010 to 2019, Japan experienced a notable rise in the annual prevalence per 100,000 individuals, climbing from 5 to 98. Simultaneously, the prevalence in the US rose from 158 to 233. Although the incidence of UC seems to have plateaued among various age groups in the United States, incidence rates among pediatrics and adolescents are still rising.[3]

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The causes of UC are multifaceted, involving a diverse interplay among environmental, genetic, immune, and microbial contributions.[1] Numerous loci tied to a heightened susceptibility to UC have been pinpointed via genome-wide association research, indicating the involvement of genes related to cytokine signaling, microbial recognition, lymphocyte signaling, and autophagy.[4] The consumption of a diet and specific lifestyle factors are related to a greater risk of developing UC, possibly mediated by affecting the microbiome and triggering immune responses to antigens. Although the specific cause is yet to be determined, critical pathogenic mechanisms encompass abnormalities in the intestinal barrier, abnormal immune activity, the secretion of inflammatory mediators, and imbalances within the gut microbiota.[5] In this review, the term "intestinal barrier" is used to broadly refer to the epithelial lining, mucus layer, and immune-microbiota interface. "Epithelial barrier" or "mucosal barrier" are reserved for specific structural or functional contexts to ensure terminological clarity. Individuals with UC frequently exhibit disruptions in their intestinal barrier, notably with a lack of colonic goblet cells and an augmented permeability of the mucus layer. In UC, the immune system may be overactive, leading to an intensified inflammatory response. Chronic inflammation associated with UC may be attributed to immune dysregulation caused by T-cell-mediated processes, cytokines, and additional inflammatory cell populations.[6] In UC, the inflamed mucosal tissue releases elevated levels of inflammatory mediators, like chemokines and cytokines, further aiding in the recruitment and stimulation of immune cells. These mediators potentiate the inflammatory response, thereby exacerbating mucosal injury and sustaining disease activity. Individuals suffering from UC frequently exhibit changes in their gut microbiome, marked by diminished microbial diversity and an overrepresentation of pro-inflammatory bacterial populations.[7]

The therapeutic options for UC have advanced significantly, providing a variety of treatments customized to the severity of the disease, its location, and the distinct responses.[8] Conventional medications for UC, including corticosteroids, aminosalicylates, and immunosuppressants, are vital for alleviating symptoms and minimizing inflammation.[9] Despite their benefits, these treatments frequently have restricted effectiveness and can lead to adverse effects, especially when used over extended periods. Therapies such as those targeting TNF, interleukins, and integrins represent biologics that have brought precision to UC treatment by selectively targeting immune pathways that drive inflammation.[10] S1P receptor modulators and JAK inhibitors, as small molecule agents, have expanded treatment options, offering innovative solutions for those not responding to conventional approaches. Furthermore, FMT is considered a promising new treatment designed to restore the microbial balance within the gut, representing a forward-looking approach to managing UC that remains under rigorous investigation.[11]

This review endeavors to provide a thorough assessment of UC by synthesizing recent progress in understanding its pathogenesis, diagnostic biomarkers, and therapeutic interventions. By systematically distinguishing conventional and emerging management strategies—including biologics, small molecules, and microbiota-directed therapies—we aim to clarify their mechanistic underpinnings and clinical implications. By analyzing both conventional and cutting-edge methods for managing UC, this review aims to provide insights for clinical practice and inform future research, ultimately enhancing outcomes for affected individuals. Special attention is given to combination approaches and precision strategies, addressing ongoing unmet needs in treatment resistance and disease monitoring. Recent mechanistic advances have highlighted critical issues such as anti-TNF treatment resistance, with emerging insights into immune dysregulation and adaptive immune response mechanisms contributing to therapeutic failure. Additionally, the use of biomarkers for long-term disease monitoring remains limited by challenges in specificity, sensitivity, and their inability to predict treatment outcomes over extended periods. Beyond the gut lumen, UC frequently presents with extra-intestinal manifestations (EIM) that significantly impact patient quality of life. Musculoskeletal involvement is the most common EIM, manifesting as peripheral arthritis, axial spondyloarthropathy, or enthesitis. Enteropathic arthritis affects an estimated 10–25% of IBD patients and often parallels intestinal disease activity. A recent single-center study reported that 20% of IBD cases developed arthritis, underscoring the need to integrate rheumatologic management into comprehensive care strategies.[12] These gaps underscore the need for comprehensive research into more effective strategies for managing UC and tailoring personalized therapies.

In summary, the onset of UC involves the interplay of environmental, genetic, immunological, and microbial factors. Unlike previous reviews that summarize treatment mechanisms, our manuscript offers a translational synthesis with clinical decision tools integrating multi-omics stratification and phenotypic tailoring for UC. The next section will contextualize these factors within a unified conceptual framework, highlighting how barrier dysfunction and immune dysregulation sustain chronic mucosal inflammation.

Pathogenesis of UC: Barrier Disruption, Immune Dysregulation, Cytokine Networks, and Microbiome Imbalance

UC arises from a self-amplifying inflammatory loop comprising epithelial barrier defects, immune cell infiltration, dysregulated cytokine networks, and gut microbiota imbalance. These interconnected processes form the conceptual backbone for understanding disease onset, progression, and therapeutic targeting. UC is characterized by a complex pathogenesis, making it difficult to grasp.[13] Epithelial barrier defects, immune dysfunction, and microbial imbalance are fundamental in the onset and continuation of inflammation.[4]

Intestinal Barriers Defects

The compromise of the intestinal barrier is fundamental to the onset of UC, which results in immune imbalance and prolonged inflammation.[5] Under healthy conditions, epithelial cells in the gut establish a shield against antigens and pathogens, which is upheld by mucin and tight junctions. In UC, the weakened barrier, resulting from epithelial cell damage, allows more antigens and pathogens to breach the lamina propria, where they engage with immune cells, triggering their activation.[14] The activated immune cells subsequently secrete pro-inflammatory cytokines, further aggravating inflammation and inducing damage to epithelial cells. The damaged epithelial barrier allows antigens to infiltrate and further intensifies inflammation, creating a destructive cycle.[6] In individuals with UC, impaired goblet cell function results in lower mucin-2 production, causing a weakened mucus layer with decreased protective function. The diminished mucus layer results in enhanced bacterial translocation, initiating immune responses and aggravating inflammation. In UC, tight junction modifications, particularly involving the claudin-2 upregulation, heighten paracellular permeability, promoting the infiltration of antigens, toxins, and bacteria into the lamina propria.[15] The disrupted expression of claudin and other tight junction proteins result in a compromised barrier function in UC. Heightened permeability, driven by epithelial barrier damage, reduced mucus protection, and disrupted tight junctions, permits pathogens to breach the gut epithelium. This provokes an immune reaction, stimulating the liberation of pro-inflammatory cytokines and the initiation of inflammatory processes.

Dysregulated Immune Responses

In UC, immune cell infiltration within the colonic mucosa is a key factor in maintaining inflammation.[6] In the course of UC, neutrophils are drawn to the injured regions of the colonic mucosa by chemotactic signals like chemokines and cytokines.[16] Once recruited, these neutrophils secrete proteolytic enzymes, reactive oxygen species, and cytotoxic molecules that can intensify mucosal damage. In addition, neutrophils also produce neutrophil extracellular traps that assist in entrapping and eliminating pathogens in inflamed tissues, but these neutrophil extracellular traps may worsen tissue damage and trigger further inflammation.[17] In a well-functioning gut, dendritic cells and macrophages can facilitate the production of Tregs, which are crucial for sustaining immune balance and controlling inflammation. The impairment of antigen-presenting cells in UC hampers Treg differentiation, causing a decrease in Treg levels and weaker inflammatory control. In UC, T cell migration to the gut is driven by the interaction between α4β7 integrin on T cells and MAdCAM-1, and targeting this binding can lessen lymphocyte trafficking. In UC, Th2 cells within the gut can facilitate NKT cell activation, boosting inflammation.[18] The disruption of regulatory and effector T cells fuels chronic inflammation, causing sustained epithelial damage.

Release of Inflammatory Mediators

In UC, the chronic inflammation and tissue damage are largely attributed to the discharge of inflammatory molecules like chemokines, cytokines, and proteases. These molecules boost the recruitment of immune cells, sustain the inflammatory process, and weaken the intestinal mucosal structure. In individuals with UC, the intestinal tissues exhibit elevated levels of IL-1β, IL-6, TNF-α, and cytokines linked to Th1, Th2, and Th17 cells.[19] Among these subsets, Th17 cells and the upstream IL-23 signaling axis play a pathogenic role in sustaining mucosal inflammation. IL-23 drives the expansion and activation of Th17 cells, which secrete IL-17A, IL-21, and IL-22, thereby amplifying epithelial barrier disruption and neutrophil recruitment. Targeted biologics such as mirikizumab and risankizumab have demonstrated clinical benefit by interrupting this IL-23/Th17 pathway, reducing

cytokine output and promoting mucosal healing in refractory UC cases. TNF-α can attract immune cells, trigger cytokine activation, and cause epithelial cell apoptosis and tight junction disruption. Its high levels in the colonic mucosa cause mucosal injury and increased permeability. Cytokines like IL-13 and IL-17 impair the repair processes of epithelial cells, leading to persistent mucosal damage.[20] IL-13 promotes epithelial cell apoptosis and disrupts tight junction integrity, thereby weakening the intestinal barrier and intensifying mucosal inflammation. IL-6 and IL-1β are pivotal mediators that drive the stimulation of macrophages and T cells, while also triggering the acute inflammatory response that intensifies inflammatory reactions.[21] IL-8 draws lymphocytes and neutrophils into the inflamed mucosal tissue, where their presence perpetuates the inflammation by producing chemokines and cytokines. The infiltrating leukocytes cause further damage to the intestinal barrier, driving inflammation and heightening the immune reaction. Protease-mediated enzymatic breakdown of tissue weakens the intestinal barrier, enabling further antigen penetration and prolonging inflammation. In addition to injuring the mucosa, protease activity can disrupt the stability of the intestinal barrier.[13] Moreover, the degradation of tight junction proteins and the extracellular matrix raises permeability, allowing additional antigens to infiltrate the intestinal barrier. By triggering signaling cascades like NF-κB and JAK/STAT, pro-inflammatory cytokines induce further release of inflammatory molecules, fueling immune cell activity and intensifying colonic tissue damage. Recent studies have demonstrated that excessive ROS accumulation in inflamed intestinal regions disrupts epithelial tight junctions and compromises barrier integrity, thereby exacerbating mucosal injury in UC. Innovative redox-responsive nanomaterials—such as boronate esters, polydopamine, and metal nanozymes—have shown promise in selectively neutralizing ROS and delivering anti-inflammatory agents to affected sites. Wan et al proposed a layered programmable delivery strategy combining ROS-, pH-, and membrane-targeted nanoparticles, offering enhanced precision and multifunctionality for localized UC therapy.[22]

Imbalance in the Gut Microbiota

Maintaining intestinal homeostasis fundamentally depends on a properly functioning gut microbiota. Its disturbance significantly contributes to the onset of UC by altering immune balance, impairing nutrient digestion, and compromising the intestinal barrier's protective function.[23] UC may advance as a result of shifts in gut microbiota that undermine the gut's defenses and enhance inflammatory processes. The stability of the intestinal barrier is largely influenced by gut microbiota, which assists in mucin formation and tight junction control. Changes in microbial composition compromise this defense, heightening the permeability of the epithelial layer and permitting increased pathogen and antigen penetration, further triggering immune responses and promoting chronic inflammation. Individuals suffering from UC experience a notable decrease in the *Bacteroidetes* and *Firmicutes phyla*, which are crucial for gut health.[24] These phyla not only regulate immune functions but also generate butyrate, vital for upholding the barrier of the intestinal epithelium. Individuals with UC exhibit a substantial reduction in the levels of *Roseburia hominis* and *Faecalibacterium prausnitzii*, which can possess anti-inflammatory characteristics and aid in epithelial health by nourishing colonocytes, reinforcing tight junctions, and decreasing mucosal permeability.[25] A decrease in these bacteria impairs the gut barrier, permitting pathogens and antigens to invade and worsen immune activation. Reduced levels of beneficial bacteria, which encourages Treg differentiation, cause the immune system to lean towards inflammatory Th2 and Th17 cells, leading to heightened production of IL-13 and IL-17, thus contributing to inflammation and mucosal damage. In addition, UC frequently involves an elevation of *Enterobacteriaceae* and *Proteobacteria*, which can stimulate immune responses and drive inflammation through lipopolysaccharide secretion.[26] The released lipopolysaccharide can stimulate Toll-like receptors (TLRs) on immune cells, triggering the production of cytokines and chemokines, boosting immune cell recruitment to the inflamed area, and prolonging inflammation and tissue injury.[27] The resulting dysregulated immune response amplifies the inflammatory dysregulation in the gut, contributing to increased mucosal damage and inflammation.

Overall, barrier impairment, immune cell infiltration, cytokine storms, and microbial imbalance create a self-amplifying inflammatory loop, laying the theoretical groundwork for biomarker-driven and precision-therapy strategies.

Emerging Diagnostic & Prognostic Biomarkers in UC

In UC diagnosis and monitoring, biomarkers ranging from serum CRP and fecal calprotectin to αvβ6 autoantibodies, multi-bacterial panels, and metabolomic signatures are collectively enhancing precision. Investigating biomarkers in UC is highly significant due to their potential to aid diagnosis, enable noninvasive tracking of histological and endoscopic changes, predict disease severity, and forecast treatment outcomes or drug side effects.[28] While serum C-reactive protein

(CRP) and fecal calprotectin are the primary markers available for assessing UC activity, their lack of specificity limits their reliability for mid and long-term prognostic assessments. CRP levels may rise, but their sensitivity is constrained, particularly in mild and moderate UC cases. Faecal calprotectin has higher sensitivity than serum markers but low specificity.[29] For UC individuals in symptomatic remission, a monitoring framework incorporating both biomarkers and symptoms offers significant advantages over strategies based exclusively on symptoms. UC individuals can benefit from the use of serum CRP, fecal calprotectin, and fecal lactoferrin, which contribute significantly to disease surveillance and treatment strategies.[1,29]

In UC, levels of faecal myeloperoxidase were strongly linked to endoscopic activity and were an efficient predictor of disease status. Moreover, a faecal myeloperoxidase concentration exceeding 26 μg/g at baseline was a significant predictor of a 12-month composite endpoint, which comprised intensification of immunomodulator or biologic treatment in response to surgical procedures, hospitalization linked to IBD, steroid administration, and relapse.[30] Despite achieving endoscopic remission, patients suffering from IBD remain susceptible to relapse. In UC individuals undergoing endoscopic remission, epithelial neutrophils were associated with unfavorable outcomes (hazard ratio: 5.198, p=0.01). Furthermore, in UC, Claudin-2 levels were linked to endoscopic and histological activity and were indicative of disease outcomes.[31] UC individuals exhibit a considerable upregulation of integrin αvβ6 in the intestinal epithelium, and serum αvβ6 autoantibodies are being explored as a candidate diagnostic indicator. The sensitivity and specificity of serum αvβ6 autoantibodies were recorded at 0.82 and 0.94, respectively, with an AUC of 0.96. Furthermore, serum αvβ6 autoantibodies exhibited a specificity of 0.96 for distinguishing UC from healthy subjects, 0.88 from non-inflammatory bowel conditions, and 0.80 from Crohn's disease.[32] Anti-integrin αvβ6 antibodies were present in 92.0% of UC individuals, but just 5.2% of the control group exhibited positivity, yielding a diagnostic sensitivity of 92.0% and specificity of 94.8%.[33] Furthermore, anti-αvβ6 autoantibody levels were markedly elevated in those who were diagnosed with UC up to a decade before diagnosis, and these antibodies were linked to poor disease outcomes.[34] Lipid imbalance, with a marked reduction in phosphatidylcholines and triglycerides, was commonly reflected in individuals with UC. Elevated levels of phosphatidylcholine 34:1 (PC34:1) are prevalent in individuals with UC, indicating that disruptions in lipid metabolism contribute to the inflammation associated with the disease.[35] Faecal metabolome signatures are increasingly viewed as a promising avenue for identifying UC biomarkers, offering insights for diagnosis, behavior prediction, and treatment outcome forecasting. The faecal metabolome in IBD individuals reveals shifts in metabolites like tryptophan, sphingolipids, short-chain fatty acids, and vitamins. Notably, the presence of proteolytic fermentation byproducts is significantly heightened in individuals with UC.[36] The elevation of sphingolipid lactosyl-N-palmitoylsphingosine and the reduction of faecal L-urobilin were significant indicators of IBD, and the sphingolipid to L-urobilin ratio was able to distinguish IBD samples from non-IBD ones, achieving an AUC of 0.85.[37] In UC research, genome-wide association studies have made considerable strides, particularly in pinpointing genetic markers and unraveling genetic pathways. Multiple genetic loci linked to UC susceptibility have been pinpointed, especially within the chromosome 6 region involving the major histocompatibility complex. The severity of UC was significantly associated with a locus in the HLA region of chromosome 6, reflected by an odds ratio (OR) of 2.23 ($P=4.22\times10^{-9}$). Moreover, HLA-DRB1*01:03 was identified as a genetic marker linked to severe UC in contrast to milder disease presentations among affected individuals.[38] A total of ten bacterial species were incorporated into diagnostic models to diagnose UC, achieving an AUC of 0.85, which was slightly higher than the AUC of 0.81 for fecal calprotectin. The multibacterial panel exhibited enhanced sensitivity (67%) and specificity (88%) for UC, outperforming fecal calprotectin, which had sensitivities of 57% and specificities of 86%. Moreover, the diagnostic model achieved an AUC of 0.78 in separating UC individuals from those without IBD, confirming the specificity of the multibacterial panel for UC. Furthermore, this panel displayed better performance than fecal calprotectin in distinguishing inactive UC from controls, with an AUC of 0.78 compared to 0.56.[39] The use of metabolic, glycomic, transcriptomic, and proteomic panels may enhance the accuracy of prognostic indicators for UC severity. Recent multi-omic studies, such as Scanu et al (2024), have demonstrated that integrated bacterial, fungal, and metabolic profiles can distinguish UC patients from healthy controls and identify disease-associated biomarkers. Nevertheless, their clinical application is hindered by the complicated framework of the forecasting models.[40] Significant challenges in using biomarkers for UC diagnosis encompass the necessity for standardized testing, the variability of biomarker expression across individuals, and the difficulties in incorporating biomarker data into clinical settings. Ongoing studies strive to improve current biomarkers and unveil new candidates to advance diagnostic approaches. Figure 1 summarizes the biomarker-diagnostic tool linkage and

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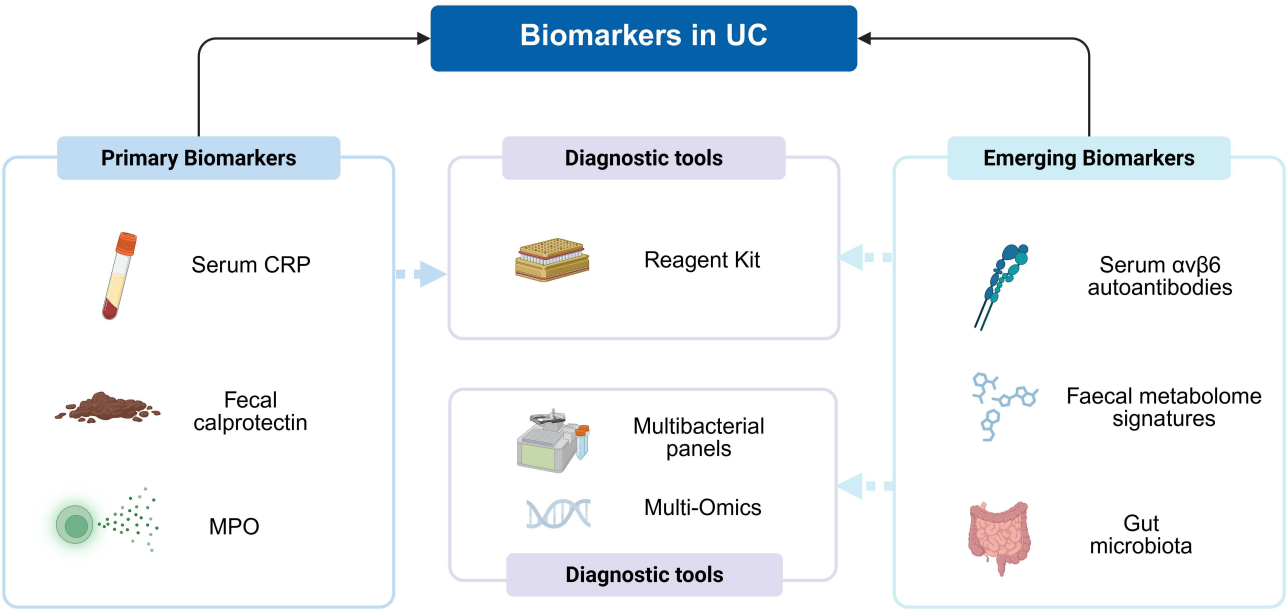

Figure 1 Biomarkers and diagnostic tools in UC.

Table 1 summarizes representative biomarkers categorized by type, target, clinical relevance, and diagnostic accuracy parameters.

While traditional biomarkers remain effective for activity monitoring, multi-omics and microbiome-based models promise greater specificity and long-term prognostic power, providing a stronger foundation for personalized therapy.

Conventional Pharmacotherapy: Aminosalicylates, Corticosteroids, and Immunomodulators in UC

This section provides an overview of first- and second-line conventional treatments, detailing their mechanisms of action, clinical efficacy, and major adverse effects. UC represents a persistent, relapsing IBD, distinguished by inflammation and ulcerative lesions in the colon and rectum. Currently, the principal pharmacological options for UC encompass aminosalicylates, corticosteroids, immunosuppressants, and antibiotics.[41] Aminosalicylates, especially 5-aminosalicylic acid (5-ASA), and its analogs, constitute fundamental treatments for individuals suffering from mild to moderate disease, applicable for induction and maintenance treatment.[42] Pharmaceuticals such as sulfasalazine, olsalazine, balsalazide, and mesalamine exert their therapeutic effects by influencing the intestinal mucosa and blocking the synthesis of

Table 1 Diagnostic & Prognostic Biomarkers in UC

Biomarker	Type	Molecular Target	Clinical Relevance	Sensitivity (%)	Specificity (%)
Calprotectin	Protein	Neutrophil cytosol	Differentiates IBD from IBS; tracks mucosal inflammation	80–95	85–90
CRP	Protein	Hepatic acute-phase reactants	Monitors systemic inflammation; less specific for UC	60–70	70–75
ANCA	Autoantibody	Neutrophil antigens	Supports UC diagnosis; non-specific	40–60	80–90
IL-6	Cytokine	Inflammatory signaling	Correlates with disease activity; potential prognostic role	65–75	65–70
MMP-9	Enzyme	ECM degradation	Emerging marker for tissue damage and relapse prediction	70–80	75–85
miR-21	Microrna	Gene regulation	Associated with inflammation and UC severity	~75	~80

inflammatory mediators to mitigate inflammation and its related clinical manifestations. 5-ASA acid exerts its effects by blocking the cyclooxygenase and lipoxygenase pathways, resulting in lower levels of pro-inflammatory mediators. Furthermore, 5-ASA stimulates the activity of PPAR-γ, which subsequently reduces the expression of inflammatory cytokines. Despite the advent of biologics, aminosalicylates continue to be the preferred first-line treatment for mild UC and should be taken into account for moderate cases, given their advantageous risk-benefit ratio.[43] 5-ASA can be utilized in moderate individuals lacking poor prognostic indicators, whereas biologics can be favored in other cases.[44] Corticosteroids are widely utilized as a treatment modality for attaining remission in individuals suffering from moderate to severe disease. Prednisone, budesonide, and hydrocortisone are frequently used corticosteroids that deliver rapid relief of inflammation and symptoms due to their potent anti-inflammatory properties. While corticosteroids can greatly enhance a patient's condition in the short term, prolonged use may result in several side effects, including osteoporosis, weight gain, and an elevated risk of infections. Between 2006 and 2023, prescriptions for prednisolone showed a downward trend, while those for budesonide experienced an uptick. Nonetheless, cumulative corticosteroid exposure among those with IBD persists at a significant level.[45] In a Phase IV trial (NCT01941589), corticosteroids plus mesalamine failed to provide additional advantages for hospitalized individuals suffering from acute severe disease beyond corticosteroids alone.[46] Immunosuppressants represent a crucial treatment alternative for sustaining remission, especially for individuals reliant on corticosteroids or those who have shown insufficient response to 5-ASA treatments. Thiopurines like azathioprine, mercaptopurine, and cyclosporine alleviate inflammation through the suppression of excessive immune system activity.[47] These agents are proficient in controlling symptoms and sustaining remission over a prolonged duration.[48–50] Nonetheless, nearly 40% of individuals are forced to halt thiopurine therapy because of unwanted side effects. Mercaptopurine dosing based on therapeutic drug monitoring is deemed the preferred method for managing UC in individuals who are on thiopurines.[51] The administration of azathioprine is often limited by gastrointestinal intolerance in IBD, with 32.6% of individuals experiencing this adverse effect. Among those who were intolerant to azathioprine, 50% of individuals did not suffer from a resurgence of gastrointestinal intolerance following rechallenge with reduced dosages. Of the 15 individuals who were intolerant to reduced azathioprine doses, 36% showed tolerance after switching to mercaptopurine.[52] Antibiotics can serve as an adjunctive treatment option, particularly in instances where complications arise from infections. While not considered primary therapy for UC, antibiotics like metronidazole and ciprofloxacin can effectively control secondary infections.

Although these agents are effective in mild to moderate cases, their limited efficacy and notable side effects underscore the need for more targeted biologics and small molecules to fill therapeutic gaps.

Biologic Agents Targeting TNF-α, IL-12/23, and Integrin Pathways in UC

Biological therapies are gaining prominence for managing moderate to severe UC, particularly for individuals who fail to achieve satisfactory results with aminosalicylates or corticosteroids.[42] The biologics for treating UC can be categorized into three primary types: anti-TNF therapies, including certolizumab, infliximab, golimumab, and adalimumab; anti-integrin drugs like natalizumab, vedolizumab, and etrolizumab; and anti-interleukin medications including mirikizumab, risankizumab, guselkumab, ustekinumab, and brazikumab.[53] In comparative studies, vedolizumab outperformed adalimumab in the VARSITY trial, achieving higher histologic remission at Week 14 (24% vs 12%) and Week 52 (45% vs 33%), with superior mucosal healing at Week 52. The SERENE-UC exposure-response analysis demonstrated lower serious infection rates with standard-dose versus intensified adalimumab during maintenance. Long-term LTE data show risankizumab and mirikizumab yield similar remission rates (~ 40%), whereas risankizumab has fewer injection-site reactions. Sequencing strategies—such as anti-TNF followed by anti-integrin versus anti-IL-23 agents, or JAK inhibitors post–anti-TNF failure—should be tailored according to patient phenotype and biomarker profile.[54]

Anti-TNF Agents

A monoclonal antibody, infliximab is employed as a biological treatment for UC, targeting TNF-α, a cytokine critical to the immune mechanisms of the disease. Infliximab is prescribed for moderate to severe UC, particularly when standard treatments like corticosteroids or 5-ASA compounds prove ineffective.[55] The shift from intravenous to subcutaneous infliximab supports long-term remission in individuals suffering from UC. To achieve clinical and biochemical remission,

the recommended subcutaneous infliximab concentrations were 12.2 μg/mL by week 12 and 13.2 μg/mL by week 52.[56] Elevated subcutaneous infliximab concentrations are linked to superior treatment results in individuals suffering from IBD, particularly when serum levels exceed 20 μg/mL.[57] In the Phase III LIBERTY-UC study (NCT04205643), individuals with UC who received subcutaneous CT-P13 (an infliximab biosimilar) after intravenous CT-P13 induction had notably higher week 54 clinical remission rates than those given placebo (43.2% versus 20.8%).[58] Infliximab continues to serve as the cornerstone of rescue therapy, with its efficacy being closely tied to its pharmacokinetics.[59,60] Within the framework of rescue interventions for individuals with acute severe disease unresponsive to steroid treatment, both accelerated infliximab (OR: 0.16) and infliximab (OR: 0.2) led to a notable reduction in short-term colectomy rates when compared to placebo.[61] In a phase IV PREDICT-UC trial (NCT02770040), individuals suffering from steroid-refractory acute severe disease exhibited similar clinical response at day 7, irrespective of whether they were given infliximab at 5 mg/kg or 10 mg/kg. Across the accelerated, intensified, and standard induction regimens, clinical responses by day 14, as well as the rates of remission and colectomy by month 3, remained largely unchanged.[62] Infliximab and adalimumab both possess a favorable safety record and contribute to positive outcomes among individuals with moderate to severe disease.[63] The SERENE-UC trial (NCT02065622) conducted an exposure-response evaluation comparing elevated doses of adalimumab with standard dosing in individuals suffering from moderately to severely active disease. Although a temporary increase in the adalimumab failed to yield induction responses, higher dosing concentrations throughout the maintenance phase extending to week 52 resulted in more significant responses.[64] An analysis of the PURSUIT-M (NCT00488631) and PURSUIT-LTE (long-term extension) trials revealed that less than 5% of participants underwent colectomy following prolonged golimumab therapy, extending up to 4 years. Colectomy was primarily performed in individuals who failed to respond to induction therapy and continued with maintenance treatment. These individuals often exhibited more severe disease symptoms at the initial evaluation.[65] Those who encountered TNF therapy failure from either intolerance or delayed loss of response experienced favorable results by transitioning to a non-anti-TNF agent rather than opting for another anti-TNF option.[66]

Anti-Interleukin Drugs

Anti-interleukin therapies in UC are a type of biologic agent that focuses on specific ILs contributing to the inflammatory mechanisms of the condition.[53] Ustekinumab can specifically inhibit IL-12 and IL-23, which are pivotal cytokines in modulating immune reactions and inflammatory processes. In the UNIFI LTE trial (NCT02407236), which assessed ustekinumab in individuals with UC over four years, 55.2% of participants achieved symptomatic remission by week 200. At this time point, 96.4% were free from corticosteroid use among those in remission. Among the 171 participants who received endoscopic assessments, endoscopic improvement was observed in 81.6% of the q12w cohort and 79.8% of the q8w cohort. Throughout the 4-year LTE period, nasopharyngitis, exacerbation of UC, and infections of the upper respiratory tract emerged as the most prevalent adverse reactions.[67] The UNIFI trial (NCT02407236) further revealed that week 2 clinical remission was linked to endoscopic remission and histological remission at week 52, indicating its role as a predictor of favorable results for individuals with UC undergoing ustekinumab treatment. Additionally, the prompt achievement of clinical remission is linked to an increased likelihood of endoscopic and histological remission.[68] Mirikizumab, a monoclonal antibody, selectively interacts with IL-23, a cytokine involved in the inflammatory pathways linked to UC. Mirikizumab has proven effectiveness in inducing (LUCENT-1; NCT03518086) and maintaining (LUCENT-2; NCT03524092) clinical remission in individuals suffering from moderately to severely active disease. In the induction trial, the mirikizumab group had notably greater clinical remission rates at week 12, achieving 24.2% compared to 13.3% in the control group. These results continued at week 40 of the maintenance trial, where remission rates were 49.9% versus 25.1%.[69] The effectiveness of mirikizumab in attaining and sustaining symptom control and overall symptom management was evidenced over 52 weeks.[70] In the Phase II clinical trial (NCT02589665), approximately 50% of participants who received extended mirikizumab doses for another 12 weeks after failing induction therapy achieved a clinical response, with a notable proportion maintaining this response for a duration of up to 52 weeks.[71] Risankizumab specifically targets IL-23, preventing it from binding to its receptor. This mechanism directly disrupts the IL-23/Th17 inflammatory circuit described earlier in the pathogenesis section, mitigating downstream cytokine release and epithelial injury. Risankizumab demonstrated marked enhancements in clinical remission rates

during both the induction study (NCT03398148) and the maintenance study (NCT03398135) among individuals experiencing moderately to severely active disease. In the NCT03398148 trial, the clinical remission rates observed by week 12 were 20.3% for individuals receiving risankizumab, compared to 6.2% in the placebo group. Meanwhile, in the NCT03398135 study, week 52 remission rates reached 40.2% for the 180 mg risankizumab dose, 37.6% for the 360 mg dose, and 25.1% for those given a placebo.[72] The phase IIb QUASAR Induction study (NCT04033445) assessed the efficacy of guselkumab, an IL-23 inhibitor, in treating active disease among those who had insufficient responses or intolerance to prior therapies. At week 12, guselkumab exhibited enhanced clinical response rates of 61.4% for the 200 mg dose and 60.7% for the 400 mg dose, in contrast to the 27.6% rate seen with placebo. Of those who were nonresponders at week 12, 54.3% from the 200 mg cohort and 50.0% from the 400 mg cohort attained clinical response by week 24.[73] In the VEGA study (NCT03662542), guselkumab combined with golimumab showed superior effectiveness for UC compared to each treatment used alone, with week 12 clinical response rates of 83% for golimumab plus guselkumab, 75% for guselkumab, and 61% for golimumab.[74,75] In real-world practice, post-marketing observational data such as Gao et al[76] and non-industry retrospective analyses like Kim et al[77] corroborate the clinical trial findings, reporting drug survival rates exceeding 70% at 12 months and clinical response rates of 60–65% in routine care.

Anti-Integrin Agents

In managing UC, anti-integrin biologics are instrumental in controlling UC symptoms.[53] As a biologic that targets the α4β7 integrin, vedolizumab is utilized for managing moderate to severe disease. The VARSITY trial (NCT02497469) evaluated the effectiveness of intravenous vedolizumab compared to subcutaneous adalimumab in participants suffering from UC. At week 14 and week 52, vedolizumab achieved superior histologic remission rates compared to adalimumab among all participants. At week 52, patients receiving vedolizumab demonstrated superior rates of mucosal healing relative to those treated with adalimumab.[54] In the VEDOIBD (NCT03375424) study, the rate of clinical remission during induction therapy was 23% for individuals receiving vedolizumab, which was lower than the 30.4% observed among those receiving anti-TNF treatment. Following two years of treatment, individuals receiving vedolizumab showed a significant improvement in clinical remission rates, achieving 43.2%, while those on anti-TNF therapies had a rate of 25.8%.[78] Over 5 years, vedolizumab has higher effectiveness than anti-TNF agents as a primary option for UC, even following the failure of infliximab and adalimumab.[66] In the phase IV ENTERPRET study (NCT03029143), it appears that individuals experiencing early nonresponse and elevated drug clearance may not necessitate dose optimization of vedolizumab. By week 30, 18.9% of individuals treated with standard vedolizumab exhibited endoscopic improvement, compared to 14.5% of those on dose-optimized vedolizumab. In the standard cohort, 9.4% of participants reached clinical remission, in contrast to 9.1% among the optimized cohort, with clinical responses noted in 32.1% and 30.9% of participants, respectively.[79] Etrolizumab is an anti-integrin biologic that specifically targets αEβ7 and α4β7 integrins. In the HICKORY trial (NCT02100696), etrolizumab led to higher remission rates at week 14 for individuals with moderately to severely active disease than placebo, with rates of 18.5% compared to 6.3% ($p<0.005$). Nonetheless, individuals showing a clinical response at week 14 displayed no notable distinctions in remission rates at week 66 across both groups (24.1% vs 20.2%, $p=0.50$). During the induction therapy, the predominant severe adverse reaction was a flare of UC, observed in 3% of individuals receiving etrolizumab and in 2% of those receiving placebo. During the maintenance therapy, appendicitis emerged as the predominant severe adverse reaction in individuals receiving etrolizumab, occurring in 2% of patients, while the placebo cohort reported UC flare (2%) and anemia (2%) as the predominant severe adverse reactions.[80] In the LAUREL trial (NCT02165215), maintenance etrolizumab (29.6%) showed no significant advantage over placebo (20.6%) regarding remission rates at week 62 for individuals who responded at week 10 ($p=0.19$).[81] The HICKORY and LAUREL Phase 3 maintenance trials of etrolizumab failed to demonstrate non-inferiority versus placebo, highlighting the challenge of sustaining long-term remission with this agent. The HIBISCUS I (NCT02163759) and HIBISCUS II (NCT02171429) trials examined adalimumab, etrolizumab, and placebo for inducing remission among individuals suffering from moderate to severe disease. In the NCT02163759 trial, 19.4% of individuals treated with etrolizumab attained remission at week 10 compared to 6.9% with placebo (adjusted difference 12.3%, $p=0.017$), while in the NCT02171429 trial, remission rates were 18.2% and 11.1%, respectively (adjusted difference 7.2%, $p=0.17$). Moreover, etrolizumab did not outperform adalimumab for inducing remission,

improving endoscopy results, achieving clinical response, or reaching histological or endoscopic remission. In the NCT02163759 study, 35% of participants receiving etrolizumab, 43% receiving adalimumab, and 36% receiving placebo experienced adverse events. For the NCT02171429 study, the corresponding rates were 44%, 43%, and 46%, respectively. UC flare was the most prevalent adverse reaction among all treatment cohorts.[82] The GARDENIA trial (NCT02136069) assessed etrolizumab in comparison to infliximab in individuals with moderately to severely active disease. At week 54, 18.6% of individuals receiving etrolizumab and 19.7% of those on infliximab attained clinical response by week 10 and clinical remission by week 54.[83] In the NCT03531892 trial, AJM300, an α4-integrin inhibitor, was examined as a potential induction treatment for those suffering from moderately active disease. 45% of participants receiving AJM300 exhibited a clinical response at week 8, in contrast to 21% of those receiving placebo. After the 16-week extension phase, adverse reactions were noted in 39% of participants receiving placebo, compared to 38% in those administered AJM300.[84] Biologics substantially improve remission rates by precisely blocking immune pathways, yet primary nonresponse and loss of response remain challenges that small molecules may help address.

Membrane biomimetic nanocarriers—particularly those coated with macrophage membranes, epithelial-cell mimetics, or hybrid membrane materials—have emerged as promising platforms for targeted UC therapy. These structures exhibit enhanced biocompatibility, immune evasion, and site-specific accumulation in inflamed colonic tissues. Recent developments include multifunctional nanoparticle systems capable of mucosal adhesion, barrier penetration, and inflammation-triggered drug release. The emergence of targeted nanoparticles has revolutionized IBD treatment by enhancing the biological properties of drugs and promoting efficiency and safety. Lei P et al proposed a hierarchically programmed delivery modality that combines CMNs with pH, charge, ROS and ligand-modified responsive nanoparticles. This approach significantly improves delivery efficiency and points the way for future research in this area.[85]

Small Molecule Therapies Modulating JAK/STAT and S1P Signaling in UC

Small molecule therapies in UC operate via distinct immunomodulatory mechanisms. JAK inhibitors, such as tofacitinib and upadacitinib, block intracellular cytokine signal transduction by targeting Janus kinases, thereby dampening multiple cytokine pathways including IL-2, IL-6, and IL-23. In contrast, S1P receptor modulators, exemplified by ozanimod, influence lymphocyte trafficking by sequestering immune cells in lymphoid tissues, reducing mucosal infiltration. Other agents—such as PDE4 inhibitors or calcineurin blockers—act on separate pathways, modulating transcriptional activity or T-cell activation. Table 2 summarizes these mechanistic distinctions along with comparative data on indications, efficacy, and safety profiles. These mechanistic differences underpin divergent clinical applications and risk profiles, which are increasingly informing personalized treatment selection in refractory UC.

Janus Kinase Inhibitors

The JAK/STAT pathway, vital for mediating inflammatory signaling, is affected by JAK inhibitors.[42] The JAK inhibitor tofacitinib predominantly targets JAK1 and JAK3 and also displays activity against JAK2. The OCTAVE trials established the use of tofacitinib for individuals with moderately to severely active UC. Among individuals in the induction studies, 52.2% who failed to demonstrate a clinical response following 8 weeks of tofacitinib attained a response through extended induction. At the 12-month point in the OCTAVE Open study, 70.3% of those identified as delayed responders continued to show a clinical response, with 44.6% attaining remission and 56.8% experiencing endoscopic improvement, whereas, at month 36, these rates were 56.1%, 52.0%, and 44.6%, respectively.[86] Tofacitinib is a promising option for managing acute severe UC, offering substantial short-term survival without colectomy in individuals who are refractory and deemed candidates for colectomy, with colectomy-free survival rates of 85% at 30 days, 86% at 3 months, and 69% at 6 months.[87] At week 8 of the ORCHID trial (CTRI/2021/10/037641), composite remission rates of 16.28% for tofacitinib and 8.57% for prednisolone in participants suffering from moderately active disease (OR: 2.07, p=0.31).[88] For those experiencing previous anti-TNF exposure, at weeks 12, 24, and 52, tofacitinib had a higher probability of inducing biochemical remission and corticosteroid-free clinical remission than vedolizumab.[89] In the TACOS study (ISRCTN42182437), combining tofacitinib with corticosteroids improved patient response and diminished the reliance on rescue treatment. At day 7, treatment response was noted in 83.01% of individuals receiving tofacitinib, in contrast to 58.82% of those receiving placebo (OR: 3.42, p=0.007), with the tofacitinib cohort showing

Table 2 Comparison of UC Treatment Strategies

Treatment Category	Representative Agents	Indication	Mechanism of Action	Efficacy Highlights	Key Adverse Events
Aminosalicylates	Mesalazine, Sulfasalazine	Mild to moderate UC	Anti-inflammatory via inhibition of prostaglandin & leukotriene synthesis	Induction of remission in >50% of mild cases	Headache, nausea, nephrotoxicity (rare)
Corticosteroids	Prednisolone, Budesonide	Moderate to severe flares	Broad immunosuppression via glucocorticoid receptor activation	Rapid symptom control in acute exacerbation	Weight gain, osteoporosis, hyperglycemia
Immunomodulators	Azathioprine, 6-MP	Steroid-sparing maintenance	Purine analog; inhibits DNA synthesis & lymphocyte proliferation	Remission maintenance in ~40% of cases	Leukopenia, hepatotoxicity, infection risk
Anti-TNF Biologics	Infliximab, Adalimumab	Moderate to severe UC, anti-TNF naïve	Neutralizes TNF-alpha, reducing inflammation	Up to 60% response at induction; ~30% remission	Infusion reactions, infection, malignancy risk
Anti-Integrin Agents	Vedolizumab	Anti-TNF failures or intolerant patients	Blocks α4β7 integrin; gut-selective lymphocyte trafficking	Sustained clinical remission up to 45% at 52 weeks	Nasopharyngitis, headache, rare PML (progressive multifocal leukoencephalopathy)
Anti-Interleukin Agents	Ustekinumab, Mirikizumab	Moderate to severe UC	Inhibits IL-12/23 or IL-23 pathways (Th1/Th17 modulation)	Clinical remission ~20–30%; improving durability	URTI, injection site reactions, rare hypersensitivity
JAK Inhibitors	Tofacitinib, Upadacitinib	Moderate to severe UC, rapid control	Blocks JAK-STAT cytokine signaling	Clinical remission up to 40–50% at 8–12 weeks	Herpes zoster, lipid elevation, thromboembolism risk
S1P Modulators	Ozanimod	Moderate UC	Sequesters lymphocytes via S1P1 receptor	~37% remission at week 10 (True North trial)	Bradycardia, liver enzyme elevation
FMT (Fecal Microbiota Transplant)	Capsule/oral/ donor infusion	Refractory or relapsing mild to moderate UC (investigational)	Microbiota restoration; immune modulation	Remission rates vary (15–57%); durability variable	GI symptoms, donor-dependent serious AEs (rare)
Emerging Therapies	CRISPR, MSCs, RNAi	Investigational	Genetic or cellular modulation of inflammation	Early-phase promising signals	Long-term safety unknown; immunogenicity

a diminished necessity for rescue therapy (OR: 0.27, p=0.01).[90] Upadacitinib specifically targets JAK1, an important JAK/STAT pathway component that mediates inflammatory signals. The clinical effectiveness of upadacitinib as both induction and maintenance treatment for individuals with moderately to severely active disease was demonstrated in the U-ACHIEVE (NCT02819635) and U-ACCOMPLISH (NCT03653026) induction studies, as well as in the U-ACHIEVE maintenance study.[91] Moreover, upadacitinib was evaluated at induction week 16 and maintenance week 52 for individuals participating in the NCT02819635 and NCT03653026 studies. Of the individuals receiving upadacitinib 45 mg, 19.2% failed to attain a clinical response by week 8 and were given an extra 8 weeks. At week 16, 59.1% of individuals attained a clinical response and participated in the NCT03653026 trial. At week 52, 26.5% of individuals taking 15 mg of upadacitinib reached clinical remission, while the rate was 43.6% for those on 30 mg.[92] In the maintenance U-ACHIEVE trial (NCT02819635), 40.4% of individuals on 15 mg of upadacitinib and 53.6% on 30 mg attained clinical remission, whereas only 10.8% of the placebo group reached this outcome.[93] In a real-world experience with upadacitinib for UC, 76.0% of individuals exhibited a clinical response at 4 weeks, rising to 85.2% at 8 weeks, while clinical remission was attained by 69.2% at 4 weeks and 81.5% at 8 weeks. In individuals with prior tofacitinib treatment, 77.8% attained clinical remission by week 8.[94] Moreover, upadacitinib was linked to steroid-free clinical remission after 52 weeks in comparison to tofacitinib, with no notable discrepancies in terms of endoscopic response or remission.[95] In a real-world study, 40% of individuals receiving upadacitinib attained clinical remission following induction therapy, in contrast to 18% of those treated with tofacitinib (p=0.006).[96] Combination approaches—such as JAK inhibitors plus anti-integrin therapy—have yielded mixed results, with some studies showing additive benefits while others report no clear improvement over monotherapy. The effectiveness of filgotinib as an induction and maintenance treatment for individuals suffering from moderately to severely active disease was demonstrated in the SELECTION trial (NCT02914522).[97] The SELECTIONLTE trial (NCT02914535) indicated that filgotinib was effective over an

approximate treatment duration of 4 years. In individuals administered filgotinib at 200 mg and 100 mg, 79.3% and 63.0% attained clinical remission by week 10, respectively, and experienced sustained benefits at week 58.[98] Moreover, clinical remission rates were recorded at 47%, 55.8%, and 64.6% for individuals at weeks 10, 26, and 58, respectively.[99] Another real-world study on filgotinib use for UC revealed clinical remission rates of 71.9% at week 12 and 76.4% at week 24. At week 12, 87.3% of individuals achieved biochemical remission, increasing to 88.9% at week 24. Following a median 42-week follow-up, 82.4% of participants continued on filgotinib. In 2.2% of cases, severe adverse reactions caused drug discontinuation, and moderate adverse effects occurred in 8.8% leading to a temporary interruption of therapy.[100] Ivarmacitinib, a JAK1 inhibitor, was investigated in the AMBER2 study (NCT03675477) involving individuals suffering from moderate to severe active disease. At week 8, those on ivarmacitinib showed significantly better clinical response and remission rates than participants receiving placebo. Treatment-emergent adverse reactions among individuals receiving ivarmacitinib ranged from 43.9% to 48.8%, compared to 39.0% among those on placebo.[101]

S1P Receptor Modulator

S1P receptor modulatory agents have attracted interest for their role in treating UCcolitis.[102] The phase III True North study (NCT02435992) revealed that Ozanimod outperformed placebo in providing both induction and maintenance treatment for individuals suffering from moderately to severely active disease.[103] The TOUCHSTONE OLE study (NCT02531126) provided insights into ozanimod for individuals experiencing moderately to severely active disease over 4 years.[104] At both week 10 and week 52, individuals experiencing moderately to severely active disease and lacking previous exposure to advanced therapies exhibited notable improvements relative to the placebo group. Among participants on continuous ozanimod with clinical response at week 52, 91% sustained this response at week 94, with 74% exhibiting endoscopic improvement and 57% attaining mucosal healing. Of the individuals treated with ozanimod who failed to demonstrate a clinical response by week 10 and participated in the OLE study, 62% experienced a symptomatic response by OLE week 10.[105] At week 52 of the True North study (NCT02435992), 54% of individuals had attained corticosteroid-free remission. Corticosteroid-free remission, clinical remission, and clinical response at week 94 were observed in 91.4%, 69.1%, and 67.9% of individuals, respectively. Additionally, mucosal healing, histological remission, and endoscopic improvement were exhibited in 56.3%, 67.3%, and 73.3% of individuals, respectively.[106] Etrasimod, a selective S1P receptor agent, targets the S1P1, S1P4, and S1P5 receptors. In individuals with moderately to severely active disease participating in the OASIS trial (NCT02447302), etrasimod 2 mg yielded more significant clinical and endoscopic improvements than placebo.[107] Etrasimod significantly outperformed placebo in terms of histologic remission and endoscopic improvement in the NCT02447302 study. Those receiving etrasimod who attained clinical remission displayed significant reductions in fecal calprotectin and CRP levels at week 12.[108] Following the OASIS trial, 82% of participants became eligible for the OASIS OLE (NCT02536404) study, receiving etrasimod for as long as 52 weeks.[109] In the ELEVATE UC 52 trial (NCT03945188), etrasimod led to higher clinical remission rates than placebo at 12 weeks and week 52 in individuals experiencing moderately to severely active disease. Similarly, 25% of participants who were treated with etrasimod reached clinical remission at 12 weeks, in contrast to 15% of those who received a placebo in the ELEVATE UC 12 (NCT03996369) trial.[110] In the ELEVATE UC study, etrasimod-treated individuals who achieved disease clearance at week 12 had a notably elevated clinical remission rate (73.9%) than those who did not (28.3%) at week 52. At week 12, improvements in histology and endoscopy noted were linked to clinical remission at week 52.[111] Among individuals receiving corticosteroid therapy at baseline in the ELEVATE UC study, at week 52, a markedly elevated rate among those treated with etrasimod (31.2%) reached a corticosteroid-free clinical response than the placebo cohort (7.1%).[112] Etrasimod outperformed placebo in effectiveness for both induction and maintenance treatment, irrespective of prior treatment with biologics or JAK inhibitors.[113]

Combination therapy strategies are increasingly explored for treatment-resistant UC. Dual biologic regimens—such as anti-TNF agents combined with anti-IL-23 biologics—have shown promise in overcoming partial responses. Additionally, co-administration of JAK inhibitors (eg, tofacitinib, upadacitinib) with anti-integrin agents has demonstrated clinical benefit in acute severe UC, particularly in patients refractory to infliximab. A recent editorial by Soldera et al (2024) highlights successful use of tofacitinib alongside infliximab, achieving sustained remission in refractory cases. These approaches represent a clinically important frontier and warrant further investigation in controlled trials.[114]

JAK inhibitors and S1P modulators are favored for their convenience and rapid efficacy, but long-term safety and tolerability require further follow-up data.

Fecal Microbiota Transplantation (FMT): Microbiome Restoration Strategies and Safety in UC

FMT is receiving growing attention as a novel therapeutic option for UC, wherein stool from a healthy individual is transferred to the patient's gastrointestinal system.[115] The process may restore the disrupted gut microbiota, which is crucial in chronic inflammation and immune imbalance. Although the detailed mechanism of FMT in UC has not been fully illuminated, the introduction of a diverse microbiome aids in reducing pro-inflammatory bacteria, promoting anti-inflammatory species, and modulating immune functions. Recent mechanistic studies have identified key microbial taxa and metabolites that influence clinical response to FMT. Species such as Roseburia inulivorans, Faecalibacterium prausnitzii, and Odoribacter splanchnicus produce butyrate and indole derivatives—known to enhance regulatory T-cell induction, support epithelial barrier integrity, and suppress pro-inflammatory cytokine production. In contrast, non-responders often exhibit enrichment of pathobionts such as Escherichia coli, Sutterella wadsworthensis, and elevated lipopolysaccharide synthesis, which activate TLRs and perpetuate inflammation. Furthermore, increased levels of beneficial fungal taxa like Lachancea thermotolerans and reduced abundance of Candida species are associated with better mucosal outcomes. These findings underscore the importance of microbial functional profiles in modulating mucosal immunity and determining FMT efficacy. Individuals with UC may experience remission as a result of FMT. The phase II study (NCT01896635) revealed that FMT facilitated an increase in microbial diversity and a shift in composition, as determined by the analysis of colon and fecal samples obtained both before and following the FMT intervention. Individuals undergoing FMT with Bacteroides in donor stool achieved remission, but individuals with *Streptococcus* species showed no response.[116] In a preliminary study (ACTRN12613000236796) involving individuals suffering from mild to moderate disease, at eight weeks, a seven-day treatment involving anaerobically prepared donor FMT demonstrated greater efficacy in attaining remission than autologous FMT. Of those who attained steroid-free remission of UC at week eight following receiving donor FMT, 42% retained remission after a year. Three serious adverse events were recorded among participants receiving donor FMT and two among those receiving autologous FMT.[117] In the trial (ACTRN 12619000611123), oral lyophilized FMT was assessed for its effectiveness in managing active UC. At week eight, 53% of the FMT participants achieved remission without corticosteroids and exhibited endoscopic improvement, compared to 15% in the placebo cohort. 67% of individuals who received FMT and 85% of those receiving placebo encountered adverse events, primarily consisting of mild gastrointestinal symptoms. Adverse events following FMT remain heterogeneous across trials: mild gastrointestinal symptoms are common, and serious events—although rare—have been documented, underscoring the importance of standardized safety monitoring. During the maintenance phase, ten participants receiving FMT demonstrated a response and were allocated to either persist with open-label FMT or discontinue treatment. At week 56, participants who remained on FMT attained histologic, endoscopic, and clinical remission, whereas none of those who discontinued FMT achieved this outcome.[118] The trial (ISRCTN15475780) evaluated the effectiveness of multi-donor FMT combined with an anti-inflammatory diet for achieving remission and sustaining long-term maintenance through the diet. At eight weeks, FMT plus an anti-inflammatory diet proved more efficacy than standard medical therapy, yielding enhanced clinical outcomes. At 48 weeks, the anti-inflammatory diet showed a greater ability to maintain deep remission than standard medical treatment (25% vs 0%, p=0.007).[119] In the NCT03426683 trial, 57.1% of individuals attained clinical remission, and 76.2% obtained a clinical response following 12 weeks of capsulized FMT. Individuals achieving remission post-FMT were enriched with *Odoribacter splanchnicus* and *Alistipes sp*., and had elevated indolelactic acid levels, while those not achieving remission had elevated biosynthesis of lipopolysaccharides and 12,13-dihydroxy-9Z-octadecenoic acid.[120] In a trial (NCT03426683), the most prevalent fungi identified in fecal specimens were *Basidiomycota* and *Ascomycota*, and the use of capsulized FMT enhanced the diversity of microbial fungi and reshaped their composition. In comparison to individuals who failed to reach remission, those who experienced remission following capsulized FMT displayed notable increases in the levels of *Lachancea thermotolerans, Pyricularia grisea, Kazachstania naganishii*, and *Schizosaccharomyces pombe*. Additionally, individuals undergoing capsulized FMT who achieved remission exhibited lower levels of pathobionts, including *Candida* and *Debaryomyces hansenii*.[121] FMT stands out as a promising therapeutic option for UC. Nonetheless, its efficacy varies widely

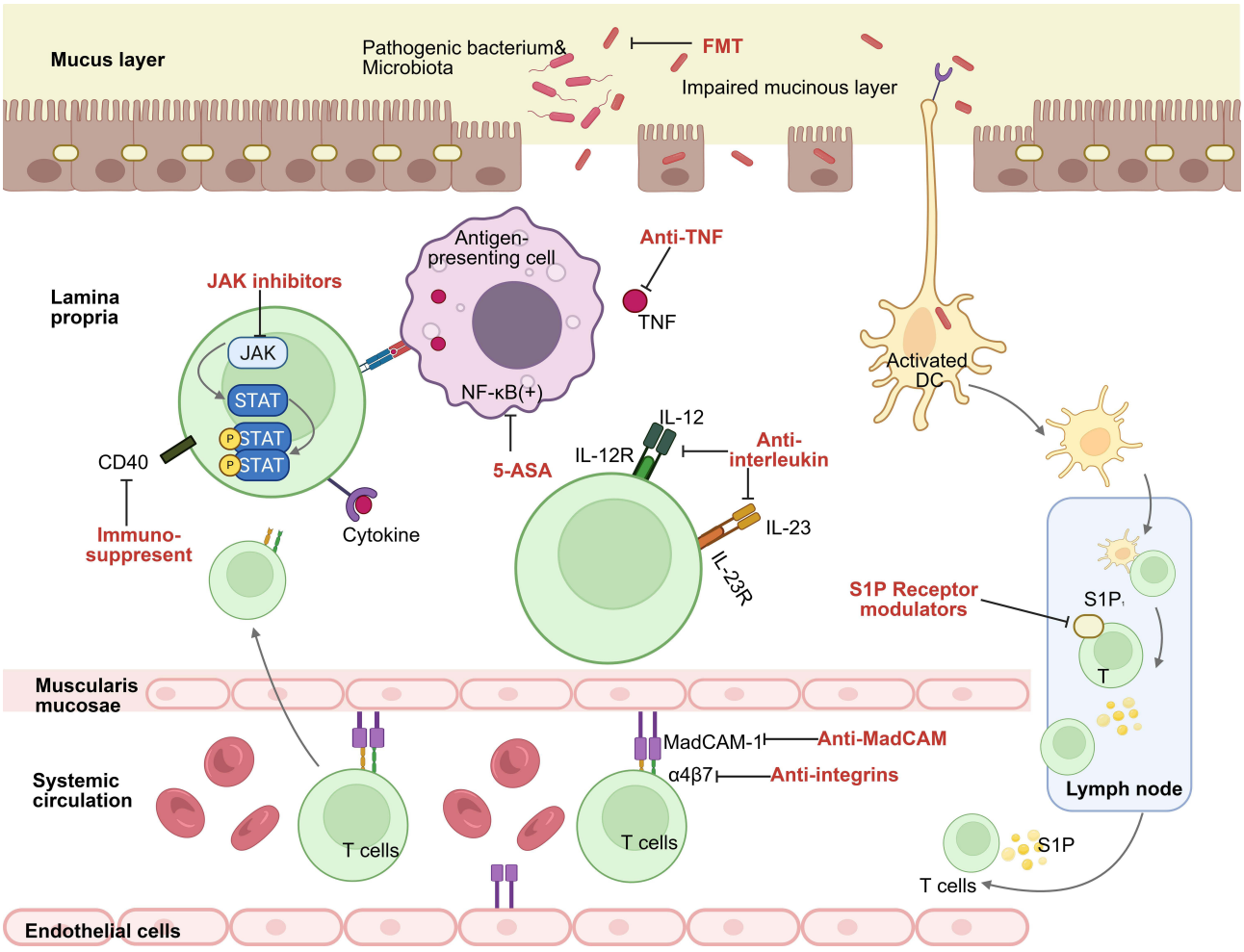

Figure 2 The interplay of key mechanisms and therapeutic targets in UC.

among individuals. While some individuals achieve symptom relief and mucosal healing, others show minimal improvement in disease activity or long-term remission. The findings of a randomized controlled trial (NCT03561532) indicated that FMT does not effectively sustain remission in individuals suffering from UC. During the 12-month follow-up, remission was sustained by 54% of participants receiving FMT, while 41% of participants receiving a placebo achieved the same outcome.[122] In a pilot study, administering budesonide before FMT showed no significant impact on engraftment or clinical results following FMT. Nonetheless, the clinical response was likely dependent on the donor. This implies that FMT effectiveness may be more dependent on the transfer of specific strains than on the total engraftment.[123] Although individual responses vary widely and donor effects are significant, FMT underscores the potential of microbiome interventions in UC management, highlighting the need for standardized protocols and rigorous safety monitoring. Importantly, FMT is not currently an approved therapy for IBD in clinical practice. It remains investigational and should be performed only within the scope of approved clinical trials adhering to standardized protocols and safety oversight. Figure 2 maps the interplay of key mechanisms and therapeutic targets explicitly. A comparative overview of current treatment modalities is presented as Table 2.

Conclusions and Future Directions

UC is a multifaceted condition driven by a combination of epithelial barrier impairment, immune system irregularities, and modifications to the gut microbiome, leading to chronic inflammation of the colonic mucosa. Key mechanistic drivers include epithelial barrier defects, dysregulated immune pathways such as the IL-23/Th17 axis, and aberrant host-microbiome interactions. This review has highlighted the disease's underlying pathophysiology, shedding light on key mechanisms such

as epithelial barrier defects and the release of inflammatory mediators that sustain disease activity. Advances in diagnostics, particularly through the development of emerging biomarkers, offer great potential for improving early detection and enabling personalized management. The therapeutic landscape for UC has evolved substantially, extending beyond conventional therapies like corticosteroids and immunosuppressants. Biological treatments like anti-TNF agents, anti-interleukin drugs, and anti-integrin agents offer more targeted and effective treatment options, significantly reducing disease severity and improving the quality of life. Additionally, the introduction of small molecule inhibitors, such as JAK inhibitors and S1P receptor agents, has broadened the treatment choices, particularly for individuals who have failed to respond to biological treatments. Translational insights such as biomarker-guided drug selection and stratification based on JAK pathway activity offer opportunities to personalize treatment. This approach may improve outcomes in difficult-to-treat populations. Moreover, FMT represents a promising new approach, though further clinical validation is necessary before it becomes a standard treatment. These advances reflect the shift toward more individualized treatment approaches, aligning therapeutic interventions with the specific needs of each patient, ultimately leading to improved clinical outcomes. These findings support a biomarker- and phenotype-driven framework for tailoring therapy, which is essential for achieving durable remission and minimizing adverse events in clinical practice.

Despite considerable advancements, numerous challenges persist in the treatment of UC. Current therapeutic strategies often fail to achieve lasting remission in all patients, highlighting the need for more tailored approaches. The heterogeneity of UC, characterized by diverse disease phenotypes and varying responses to treatments, emphasizes the importance of developing more sophisticated biomarkers to guide personalized treatment plans. Future research must address critical gaps in biomarker validation—such as prospective multi-center cohort studies, standardized omics–clinical phenotype correlations, and clinical qualification of predictive markers. A particular area of focus should be on uncovering the molecular and genetic contributors to therapeutic resistance, as this will be crucial in addressing the limitations of current treatment options. Translational efforts must overcome technical and regulatory hurdles in applying microbiome insights to practice, including standardized donor selection, reproducible sampling, and durability assessment of microbiota-targeted interventions.

Research efforts must also be directed toward exploring new therapeutic targets. Of particular interest are strategies aimed at restoring epithelial barrier integrity and re-establishing microbial balance, which may offer more sustained control of UC. Microbiome-targeted therapies, such as FMT, require rigorous testing in clinical trials to determine their role in long-term disease management. Furthermore, advances in gene editing and cell-based therapies hold significant potential for transformative, disease-modifying treatments. Emerging technologies such as gene editing (eg, CRISPR/Cas9-mediated modulation of inflammatory genes), RNA interference for silencing aberrant cytokine signals, and mesenchymal stem cell–based therapies have demonstrated preclinical and early-phase promise in attenuating inflammation and promoting mucosal healing. Although these approaches remain investigational, they represent frontier areas for disease-modifying interventions. Innovative strategies, including AI-driven predictive modeling, systematic evaluation of sequential and combination regimens (eg, small molecules with biologics), offer promise for revolutionizing UC management. Collectively, these recommendations provide a clear, actionable roadmap for next-generation research, focusing on biomarker standardization, microbiome translation, long-term safety surveillance, and innovative combination strategies to advance precision medicine in UC.

Future research should prioritize: (1) validation of multi-omics biomarkers; (2) comparative long-term safety data across therapeutic classes; and (3) development of microbiome and stem-cell-based interventions. Such efforts will enhance precision medicine in UC. This review has synthesized recent mechanistic advances and clinical trial findings to support these future directions and optimize UC management strategies.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; S.Y. Bu and X.Z. Cheng took part in

drafting and revising the article; M. Chen critically reviewed the article and gave final approval of the version to be published; Y.D. Yu have agreed on the journal to which the article has been submitted; Y.D. Yu and S.Y. Bu agree to be accountable for all aspects of the work.

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