RESEARCH PAPER

A Review On Targeted Treatment Update On Ulcerative Colitis.

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ABSTRACT

Ulcerative colitis (UC) is a chronic, relapsing-remitting inflammatory bowel disease (IBD) that predominantly affects the colonic mucosa. The disease significantly impacts the quality of life of patients and presents a rising global health concern due to increasing prevalence, particularly in newly industrialized countries. Recent advances in understanding the pathophysiology of UC have led to the development of targeted therapies aimed at modulating specific immune pathways, minimizing systemic immunosuppression, and improving therapeutic outcomes. This review provides an updated overview of the etiology, epidemiology, and immunopathogenesis of UC, with a special focus on the recent developments in targeted treatments including biologics (anti-TNF, anti-integrins, anti-interleukins), small molecules (JAK inhibitors, S1P receptor modulators), and novel investigational therapies. The paper also evaluates their efficacy, safety profiles, mechanisms of action, and place in current clinical practice. Understanding these advances is essential for optimizing treatment strategies and improving patient outcomes in UC.

Keywords: Ulcerative Colitis; Targeted Therapy; Inflammatory Bowel Disease; Biologics; Jak Inhibitors; Immune Modulation; Anti-Tnf Agents; Vedolizumab; Upadacitinib; Gut Microbiota; Immunopathogenesis.

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Introduction

Overview of Ulcerative Colitis (UC)

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory bowel disease that primarily affects the mucosal lining of the colon and rectum, resulting in continuous inflammation and the formation of ulcers along the large intestine(1)(2). The disease typically begins in the rectum and may extend proximally in a continuous fashion to involve part or the entire colon. UC is characterized by a relapsing and remitting course, with periods of symptom flare-ups alternating with intervals of remission(3). The classic symptoms include bloody diarrhea, rectal urgency, tenesmus, and varying degrees of abdominal pain, often relieved by defecation(4). Other manifestations can include weight loss, fatigue, anemia, and, in severe cases, systemic symptoms such as fever(5).

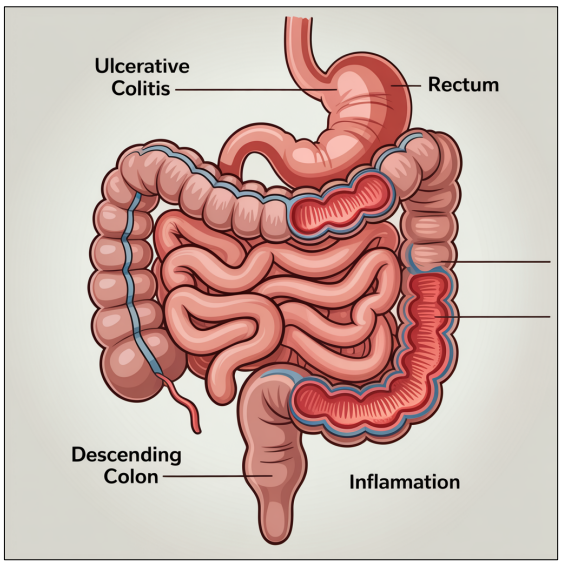

Figure 1. Ulcerative colitis

The exact cause of UC remains unknown, but its pathogenesis is believed to be multifactorial, involving genetic susceptibility, immune system dysregulation, environmental triggers, and alterations in the gut microbiota(6). A family history of UC increases the risk, and several genetic loci have been associated with disease

susceptibility(7). Environmental factors, such as diet, certain medications, and possibly exposure to chemicals, may also contribute, though no single cause has been identified(8).

UC is diagnosed based on a combination of clinical presentation, laboratory tests, endoscopic findings, and histological examination of colonic biopsies, with colonoscopy revealing continuous mucosal inflammation, erythema, friability, and superficial ulcerations(9). The disease can range in extent from ulcerative proctitis (limited to the rectum) to pancolitis (affecting the entire colon)(10).

The global burden of UC is substantial, with an estimated prevalence of up to 5 million cases worldwide and rising incidence, particularly in newly industrialized countries(11). The disease can lead to significant complications, including an increased risk of colorectal cancer, severe bleeding, toxic megacolon, and extra-intestinal manifestations affecting the skin, eyes, joints, or liver. Management focuses on inducing and maintaining remission, improving quality of life, and minimizing long-term complications through a combination of medications, lifestyle modifications, and, in refractory cases, surgery(12).

Epidemiology and global burden

Ulcerative colitis (UC) represents a significant and growing global health burden, with an estimated 5 million cases worldwide as of 2023, and its incidence continues to rise, particularly in newly industrialized countries(13). The highest incidence and prevalence rates are observed in Northern Europe, North America, and Oceania, where prevalence can exceed 500 cases per 100,000 in some countries such as the UK and Norway(14). In North America, prevalence estimates range from 202 to 238 per 100,000, while in Europe, rates vary from about 100 to over 500 per 100,000 depending on the region. In contrast, Asian, African, and South American countries report much lower rates, with incidence often below 5 per 100,000 and prevalence under 70 per 100,000, though these figures are steadily increasing as urbanization and Westernized lifestyles spread.

UC typically has a bimodal age distribution, with the main peak of onset between ages 15 and 30 and a smaller peak between 50 and 70 years. There is no strong sex predilection, and risk is higher in non-smokers and those who have undergone appendectomy after age 20(15). The disease is chronic and relapsing, contributing to substantial morbidity, reduced quality of life, and increased healthcare costs. In the United States, for example, UC affects more than 1.2 million people and contributes significantly to the overall inflammatory bowel disease burden(16).

Globally, the rising prevalence of UC is attributed to factors such as urbanization, dietary changes, environmental exposures, and improved diagnostic awareness. While the incidence in Western countries has stabilized or even declined in some regions, prevalence continues to rise due to improved survival and chronicity of the disease. In contrast, many Asian, African, and South American countries are experiencing a rapid increase in both incidence and prevalence, reflecting ongoing epidemiological transition(17).

Pathophysiology of Ulcerative Colitis

The pathophysiology of ulcerative colitis (UC) is multifactorial, involving a combination of epithelial barrier defects, immune system dysregulation, genetic susceptibility, and alterations in the gut microbiota(18). A primary feature is the compromised integrity of the colonic mucosal barrier, where reduced production of mucin and possible defects in tight junctions increase intestinal permeability, allowing luminal antigens to penetrate the mucosa and trigger inflammation(19). This barrier dysfunction is associated with depleted goblet cells and a more permeable mucus layer, which further exposes the underlying tissue to immune activation(20).

The immune response in UC is characterized by an atypical T-helper cell profile, particularly a Th2-dominated response, with increased production of cytokines such as interleukin-5 (IL-5) and interleukin-13 (IL-13), the latter being implicated in direct epithelial cell damage and barrier dysfunction(21). Additionally, Th9 cells producing IL-9 have been identified and are thought to inhibit mucosal repair and exacerbate inflammation. The lamina propria of the colon in UC patients shows increased numbers of activated dendritic cells and macrophages, which express higher levels of toll-like receptors (TLR2 and TLR4) and present antigens that further stimulate the adaptive immune response. There is also an upregulation of chemoattractants like CXCL8 and adhesion molecules such as Mad-CAM1, promoting leukocyte recruitment and infiltration into the mucosa(22).

Genetic factors play a significant role, with several susceptibility loci identified, including genes involved in immune regulation and epithelial barrier

maintenance(23). Environmental factors, such as diet and possibly infections, may act as triggers in genetically predisposed individuals. The gut microbiota is also altered in UC, with decreased microbial diversity and an increase in certain bacteria that may contribute to ongoing mucosal inflammation and immune activation(24).

Histologically, UC is marked by diffuse infiltration of the mucosa with lymphocytes, plasma cells, and granulocytes, goblet cell depletion, crypt distortion, and the formation of mucosal ulcers and pseudo polyps during active disease. Overall, the interplay between a defective epithelial barrier, dysregulated immune responses, genetic predisposition, and microbial factors underlies the chronic, relapsing inflammation seen in ulcerative colitis(25).

Table 1. The main classes of targeted therapies and conventional drugs used in the treatment of ulcerative colitis.

Drug Class	Examples	Mechanism of Action	Notes
5-Aminosalicylates (5-ASA)	Mesalamine, Sulfasalazine	Inhibit prostaglandin and leukotriene synthesis	First-line for mild to moderate UC
Corticosteroids	Prednisone, Budesonide	Suppress broad immune and inflammatory responses	Used for induction, not maintenance
Immunosuppressants	Azathioprine, 6-Mercaptopurine	Inhibit purine synthesis, reduce lymphocyte proliferation	Maintenance therapy, slow onset
Anti-TNF Biologics	Infliximab, Adalimumab	Block tumor necrosis factor-alpha (TNF-α)	For moderate to severe UC
Anti-Integrin Biologics	Vedolizumab	Inhibit lymphocyte trafficking to gut (α4β7 integrin)	Gut-selective, fewer systemic effects
Anti-IL-12/23 Biologics	Ustekinumab	Block IL-12 and IL-23 cytokines	For moderate to severe UC
JAK Inhibitors	Tofacitinib, Upadacitinib	Inhibit Janus kinase enzymes, block cytokine signaling	Oral small molecules, rapid onset
S1P Receptor Modulators	Ozanimod, Etrasimod	Prevent lymphocyte egress from lymph nodes	Oral, for moderate to severe UC

Immune dysregulation and inflammation

Immune dysregulation and inflammation are central to the pathogenesis of ulcerative colitis (UC), involving both the innate and adaptive branches of the immune system. In UC, the immune response is characterized by an excessive reaction to resident gut microbiota and dietary antigens, leading to chronic inflammation of the colonic mucosa. Innate immune cells-such as neutrophils, dendritic cells, and macrophages-play a crucial role in the early stages of disease, with neutrophils constituting the main component of the inflammatory infiltrate and releasing neutrophil extracellular traps (NETs) to combat pathogens. Dendritic cells and macrophages further amplify inflammation by presenting antigens and producing pro-inflammatory cytokines(26).

On the adaptive side, UC is typically associated with a Th2-type immune response, with increased secretion of cytokines like IL-5 and IL-13, which drive B cell activation and contribute to mucosal damage(27). Recent research has also highlighted the involvement of Th9 and Th17 cells, which produce cytokines that exacerbate inflammation and

impair mucosal healing. Regulatory T cells, which normally suppress excessive immune responses, are often reduced in UC, further tipping the balance toward chronic inflammation(28).

Molecular studies have identified key genes and cellular pathways involved in UC immune dysregulation. Notably, the upregulation of tissue inhibitor of metalloproteinase 1 (TIMP1) and downregulation of G protein subunit gamma 5 (GNG5) are linked to disease progression, with TIMP1 associated with T cell exhaustion and persistent inflammation. The pro-inflammatory environment in UC is marked by a predominance of M1 macrophages, activated CD4+ T cells, and neutrophils, while regulatory and resting immune cells are diminished, reflecting a sustained and self-perpetuating inflammatory state. This complex interplay between immune cells, cytokines, and genetic factors underpins the chronic and relapsing nature of UC inflammation(29).

Genetic and environmental influences

Genetic and environmental influences both play significant roles in the development and progression of ulcerative colitis (UC). Genetically, UC tends to cluster in families, with individuals having a first-degree relative affected by UC being up to four times more likely to develop the disease themselves. Research has identified numerous genetic variations associated with UC, including polymorphisms in genes involved in immune regulation (such as CCR7, CXCL10, and MMP9) and genes that affect the integrity of the intestinal barrier. These genetic factors can lead to abnormal immune responses, such as T cells mistakenly attacking the gut's own bacteria or an overly aggressive reaction to intestinal pathogens, both of which contribute to chronic inflammation seen in UC(30).

However, genetics alone do not account for all cases of UC, and environmental factors are also crucial. Key environmental triggers include air pollution, smoking, diet (especially Western diets high in processed foods), early-life antibiotic use, infections, and stress(31). For example, exposure to sulfur dioxide and other pollutants has been associated with an increased risk of developing UC, particularly in younger individuals(32). Urbanization and industrialization have paralleled rising UC incidence in developing countries, suggesting a strong environmental component. Additionally, factors such as reduced exposure to greenspace, ingestion of microplastics, and certain medications (like NSAIDs) have been implicated in increasing UC risk(33). The interplay between genetic susceptibility and these environmental exposures likely determines an individual's risk of developing UC and influences disease severity and course(34).

Role of microbiota and mucosal immunity

The gut microbiota and mucosal immunity play a pivotal role in the pathogenesis and progression of ulcerative colitis (UC). In healthy individuals, a diverse and balanced gut microbiota supports intestinal barrier integrity, regulates immune responses, and prevents colonization by pathogenic bacteria. In UC, this equilibrium is disrupted, leading to a state of dysbiosis characterized by reduced microbial diversity and an imbalance between beneficial commensal and potentially harmful bacteria(35). This dysbiosis compromises the intestinal mucosal barrier, increasing permeability and allowing luminal antigens and bacteria to interact more directly with the immune system, which triggers and perpetuates mucosal inflammation(36).

The interaction between the gut microbiota and mucosal immunity is mediated through pattern recognition receptors (such as Toll-like receptors and NOD-like receptors) expressed on intestinal epithelial and immune cells. In UC, abnormal recognition and response to microbial antigens result in the overactivation of innate and adaptive immune pathways, leading to chronic inflammation. Furthermore, the depletion of mucus-producing goblet cells and alterations in mucus barrier proteins (like MUC2) weaken the physical barrier, making the mucosa more susceptible to injury and immune cell infiltration(37).

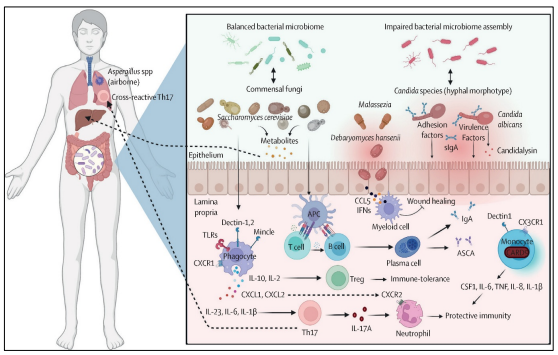

Figure 2. Interplay between gut mycobiome and host immunity in association with the assembly of the bacterial microbiome.

ASCA=anti-Saccharomyces cerevisiae antibody. Treg=regulatory T cell. Th17=T-helper-17 cell.(

Source of images- https://pubmed.ncbi.nlm.nih.gov/36182668/)

Environmental factors, such as diet, antibiotics, and lifestyle, can further influence the composition and function of the gut microbiota, exacerbating dysbiosis and immune dysfunction(38). Emerging evidence also suggests that extraintestinal microbiota, such as those from the oral cavity and respiratory tract, may contribute to systemic and intestinal inflammation in UC(39). Overall, the disruption of the gut microbiota-mucosal immunity axis creates a self-perpetuating cycle of barrier dysfunction, immune activation, and inflammation that underlies the chronic and relapsing course of ulcerative colitis(40).

Biologics in Ulcerative Colitis: Anti-TNF Agents (Infliximab, Adalimumab)

Anti-TNF agents, such as infliximab and adalimumab, have become foundational therapies in the management of moderate-to-severe ulcerative colitis (UC). These biologic drugs work by targeting and neutralizing tumor necrosis factor-alpha (TNF-α), a key pro-inflammatory cytokine involved in the pathogenesis of UC(41). Infliximab is a chimeric monoclonal antibody administered intravenously, while adalimumab is a fully human monoclonal antibody given via subcutaneous injection, offering greater convenience for long-term use. Both agents have demonstrated significant efficacy in inducing and maintaining clinical remission, achieving mucosal healing, and reducing the need for corticosteroids and colectomy in patients with UC who are refractory to conventional therapies(42). Clinical trials have shown that infliximab can induce clinical response in up to 60% of patients by week 8 and maintain remission in approximately 45% at one year, while adalimumab has shown similar benefits with a more favorable immunogenicity profile due to its fully human structure(43). However, both drugs carry risks of serious infections, including tuberculosis reactivation, and rare malignancies, necessitating careful patient selection and monitoring. The introduction of anti-TNF agents has significantly improved outcomes for many UC patients, though loss of response due to antibody formation and cost considerations remain important challenges in clinical practice(44).

Conventional drug therapy

Conventional drug therapy for ulcerative colitis (UC) is structured around the goals of inducing and maintaining remission, minimizing flare-ups, and reducing the need for surgery. The mainstay medications include aminosalicylates (5-ASA), corticosteroids, and immunomodulators, each with specific indications based on disease severity and patient response.

Aminosalicylates (5-ASA) such as mesalamine and sulfasalazine are considered first-line therapy for mild to moderate UC. These agents act locally in the colon to reduce inflammation by inhibiting the synthesis of pro-inflammatory mediators. They are effective for both inducing and maintaining remission, with oral and rectal formulations available depending on the extent of disease. Adherence to 5-ASA therapy is crucial, as nonadherence is a common cause of relapse(45).

Table 2. Comparison of Conventional and Targeted Therapies in Ulcerative Colitis

Drug Class	Examples	Mechanism of Action	Use	Limitations
5-ASA	Mesalamine, Sulfasalazine	Inhibits prostaglandin & leukotriene synthesis	Mild-to-moderate UC	Limited efficacy in moderate/severe disease
Corticosteroids	Prednisone, Budesonide	Broad immune suppression	Acute flares	Not for maintenance; systemic side effects
Immunomodulators	Azathioprine, 6-Mercaptopurine	Inhibits purine synthesis	Maintenance	Slow onset; risk of infections
Anti-TNF agents	Infliximab, Adalimumab	Neutralizes TNF-α cytokine	Moderate-to-severe UC	Immunogenicity, infection risk
Anti-integrin	Vedolizumab	Blocks α4β7 integrin,	Moderate-to-	Gut-specific, slower onset

		reducing lymphocyte trafficking	severe UC	
Anti-IL-12/23	Ustekinumab	Inhibits IL-12 and IL-23 cytokines	Biologic-refractory cases	High cost
JAK Inhibitors	Tofacitinib, Upadacitinib	Inhibits JAK/STAT signaling pathways	Moderate-to-severe UC	Risk of thrombosis, infections
S1P Receptor Modulators	Ozanimod, Etrasimod	Prevents lymphocyte egress from lymph nodes	Emerging oral therapies	Requires monitoring

Corticosteroids are reserved for patients with moderate to severe UC or those who do not respond adequately to 5-ASA therapy. Oral corticosteroids (prednisone, budesonide) are typically used for outpatient management, while intravenous corticosteroids (methylprednisolone, hydrocortisone) are the standard of care for acute severe UC requiring hospitalization(46). Steroids are highly effective for short-term control of inflammation, with most patients experiencing symptomatic improvement within days. However, due to significant adverse effects and lack of efficacy for long-term maintenance, corticosteroids are not recommended for prolonged use. Patients who cannot taper steroids below a certain threshold or relapse quickly after discontinuation are considered steroid-dependent and require escalation of therapy(47).

Immunomodulators such as azathioprine and 6-mercaptopurine are used for maintenance of remission, particularly in patients who are steroid-dependent or have frequent relapses. These agents work by suppressing the immune response but have a slow onset of action and are not suitable for acute flare management(48). In cases of steroid-refractory or steroid-dependent disease, combination therapy with immunomodulators or transition to biologic agents may be necessary.

For patients with severe or refractory UC, additional options include calcineurin inhibitors (e.g., cyclosporine) as rescue therapy and, in some cases, early introduction of biologics(49) The choice and sequence of conventional therapies depend on disease severity, prior treatment response, and individual patient factors. Overall, conventional drug therapy remains foundational in UC management, but its limitations-such as steroid dependence, adverse effects, and incomplete long-term control-highlight the need for newer, targeted treatments(50).

JAK inhibitors and small molecules

Janus kinase (JAK) inhibitors and other small molecule therapies represent a significant advancement in the targeted treatment of moderate to severe ulcerative colitis (UC), particularly for patients who have not responded adequately to conventional therapies or biologics. These therapies are orally administered and work by interfering with specific intracellular signaling pathways involved in inflammation(51).

JAK inhibitors—such as tofacitinib and upadacitinib—block the activity of Janus kinase enzymes, which are crucial for transmitting signals from multiple pro-inflammatory cytokines involved in UC pathogenesis. By inhibiting these pathways, JAK inhibitors can effectively reduce inflammation and induce remission. Tofacitinib, for example, has been shown in real-world studies to achieve steroid-free clinical remission in over half of patients at 78 weeks, with endoscopic remission rates of about 45%(52). These drugs are taken orally, offering convenience over injectable biologics, and are less likely to provoke immune reactions since they are not protein-based(53). However, JAK inhibitors are associated with certain risks, including increased susceptibility to infections (such as shingles), elevated cholesterol, and, in rare cases, blood clots or cardiovascular events, especially in older patients(54).

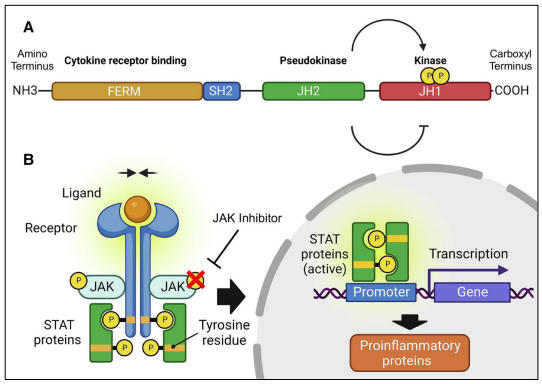

Figure 3.The structure of a JAK protein and the mechanism of action of JAK inhibitors.

Source -https://fg.bmj.com/content/15/1/59

Other small molecule therapies include sphingosine-1-phosphate (S1P) receptor modulators like ozanimod. These agents work by preventing lymphocytes from exiting lymph nodes, thereby reducing the number of inflammatory cells that reach the colon. Ozanimod has demonstrated effectiveness in inducing clinical response and remission in treatment-refractory UC patients, with favorable safety and tolerability profiles, although long-term effectiveness may be modest. Another promising class under investigation is the tyrosine kinase 2 (TYK2) inhibitors, such as TAK-279, which selectively block cytokine signaling pathways involved in UC and have shown efficacy in preclinical models(55).

Emergence of Targeted Drug Delivery Systems

Rationale for targeted delivery in UC

The rationale for targeted drug delivery in ulcerative colitis (UC) centers on the need to maximize therapeutic efficacy at the site of inflammation—the colon—while minimizing systemic exposure and adverse effects. Conventional oral and intravenous therapies often lead to significant systemic side effects, as drugs are absorbed throughout the gastrointestinal tract and the body, not just at the diseased site(56). Targeted delivery systems, such as pH-dependent, time-dependent, and microbially triggered formulations, are designed to release drugs specifically in the colon, thereby increasing local drug concentrations, improving disease control, and reducing the risk of systemic toxicity(57).

Recent advances, including nanoparticle-based and bio-responsive nanosystems, have further enhanced the precision of drug delivery. These systems can exploit the unique microenvironment of the inflamed colon such as altered pH, increased permeability, and specific molecular markers to ensure that drugs are released predominantly at sites of active inflammation(58). This approach not only improves therapeutic outcomes but also decreases dosing frequency, enhances patient adherence, and minimizes adverse effects by sparing healthy tissues(59).

Nanotechnology in IBD treatment

Nanotechnology is rapidly transforming the landscape of inflammatory bowel disease (IBD) treatment, particularly for ulcerative colitis (UC), by enabling highly targeted drug delivery, improving therapeutic efficacy, and minimizing systemic side effects. Nanoparticles—ranging from polymeric and lipid-based carriers to metallic and mesoporous formulations—can be engineered to accumulate selectively in inflamed colonic tissues due to their small size and modifiable surface properties. This selective accumulation is enhanced by the "enhanced permeability and retention" (EPR) effect, where inflamed tissues in UC have leaky vasculature and impaired lymphatic drainage, allowing nanoparticles to concentrate at the disease site and deliver higher local drug doses(60).

Table 3. Nanotechnology-Based Drug Delivery Systems Investigated for UC Treatment

Nanocarrier Type	Drug Encapsulated	Targeting Strategy	Key Benefits	Status
Liposomes	Budesonide, Curcumin	pH-sensitive, colon-targeted	Reduced systemic toxicity, enhanced retention	Preclinical/Clinical
PLGA Nanoparticles	Mesalamine, siRNA	Mucosal adhesion, ligand-modified	Controlled release, mucosal uptake	Preclinical
Chitosan-coated liposomes	Prednisolone	Mucoadhesive, enzymatic trigger	Colon-selective accumulation	Preclinical

Gold nanoparticles	Anti-inflammatory agents	Passive targeting	Anti-oxidative & anti-inflammatory	Early-stage research
Bilirubin NPs	Bilirubin	HA-targeting macrophages	Immune modulation, antioxidant effects	Experimental

Polymeric nanoparticles can encapsulate anti-inflammatory drugs like mesalamine or budesonide, providing controlled and sustained release directly to the inflamed mucosa, which promotes mucosal healing and reduces relapse risk. Lipid-based nanoparticles, such as liposomes, are used to deliver immunosuppressive agents like tacrolimus or corticosteroids, enhancing their efficacy while limiting exposure to healthy tissue. Metallic nanoparticles, including gold nanoparticles, have demonstrated anti-inflammatory and wound-healing properties in preclinical models of UC, further expanding the therapeutic arsenal.

Innovative nanotechnology approaches also include stimuli-responsive nanoparticles that release their drug payload in response to environmental cues—such as the acidic pH or specific enzymes present in inflamed colon tissue—ensuring precise, on-demand drug delivery. Chitosan-based nanoparticles, for example, possess mucoadhesive properties that improve retention at the mucosal surface, allowing for prolonged and efficient drug release.

Nanoparticles are also being explored for the delivery of biologics and RNA-based therapies, such as siRNA, targeting molecular pathways involved in UC pathogenesis. This convergence of biologics and nanotechnology offers the potential for highly specific molecular interventions with optimized drug stability and reduced off-target effects(61).

Liposomal and polymeric drug carriers

Liposomal and polymeric drug carriers are innovative delivery systems increasingly utilized in the treatment of ulcerative colitis (UC) to enhance drug localization, efficacy, and safety.

Liposomal drug carriers are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs. In UC, liposomes have been engineered to provide sustained and controlled release of anti-inflammatory agents such as mesalazine, curcumin, budesonide, and heparin directly at the site of colonic inflammation. For example, curcumin-loaded liposomes have demonstrated the ability to attenuate the clinical symptoms of UC and prevent colon tissue damage by allowing sustained drug release in the gastrointestinal tract(62). Similarly, pH-sensitive liposomes can be designed to release their payload specifically in the colon, improving therapeutic outcomes and minimizing systemic side effects. Liposomal formulations have also been shown to restore mucosal integrity and reduce inflammatory cell infiltration in experimental models, with applications ranging from enema-based therapies to oral and gel-based delivery systems(63).

Polymeric drug carriers such as nanoparticles made from polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and polyethylene glycol (PEG) offer additional advantages for targeted UC therapy. These carriers can be modified with ligands or antibodies to increase adhesion to inflamed colonic tissue, enhancing site-specific drug delivery and retention(64). Polymeric nanoparticles have been used to deliver drugs like resveratrol and folic acid conjugates, showing increased accumulation in inflamed regions and improved anti-inflammatory effects in animal models. Furthermore, polymeric systems can be engineered for controlled or stimuli-responsive drug release, responding to environmental triggers such as pH or enzymes present in the inflamed colon, which further optimizes therapeutic efficacy and reduces off-target effects(65).

Formulation Design for Targeted Delivery

Selection of drugs and excipients

The formulation design for targeted drug delivery in ulcerative colitis (UC) requires careful selection of both the therapeutic agent and the excipients to ensure that the drug is released specifically at the site of inflammation in the colon. The choice of drug is influenced by its physicochemical properties, stability in the gastrointestinal tract, and therapeutic efficacy for UC commonly used drugs include mesalamine, corticosteroids, immunosuppressants, and biologics(66). For targeted delivery, the drug must be protected from premature release or degradation in the stomach and small intestine.

Excipients are selected to facilitate colon-specific release and stability. Common strategies include the use of pH-sensitive polymers (such as Eudragit® L and S), which remain intact in the acidic environment of the stomach but dissolve at the higher pH of the colon, enabling site-specific drug release(57). Biodegradable polymers and polysaccharides that are degraded by colonic bacteria (e.g., pectin, chitosan) are also frequently used, allowing for microbial-triggered drug release. Matrix-based systems, in which the drug is embedded in a polymer that erodes or swells in response to colonic conditions, and timed-release coatings are additional approaches to achieve targeted delivery(58).

The selection of excipients also considers compatibility with the active drug, patient safety, and the ability to manufacture the formulation at scale. Nanoparticle-based systems are increasingly being explored, as they can encapsulate drugs for protection and controlled release, enhance mucosal adhesion, and exploit environmental triggers like pH, enzymes, or reactive oxygen species present in inflamed colonic tissue. Ultimately, the goal is to maximize local drug concentration at the disease site, minimize systemic exposure, and improve therapeutic outcomes for patients with UC(67).

Compatibility studies (FTIR, DSC)

Compatibility studies using FTIR (Fourier-transform infrared spectroscopy) and DSC (Differential Scanning Calorimetry) are essential steps in the preformulation phase of pharmaceutical development to ensure that the active pharmaceutical ingredient (API) and selected excipients do not interact in a way that could compromise the stability, efficacy, or safety of the final dosage form. FTIR is used to detect chemical interactions by comparing the characteristic absorption peaks of the pure drug and its mixtures with excipients; any disappearance, shift, or appearance of new peaks may indicate an interaction between the API and excipient(68). DSC, on the other hand, assesses physical and thermal compatibility by measuring changes in melting points, endothermic or exothermic transitions, and heat flow in pure drug, excipients, and their mixtures. Significant changes in these thermal events—such as the appearance, disappearance, or shift of peaks—can signal incompatibility(69). Together, FTIR and DSC provide a comprehensive evaluation: FTIR focuses on chemical stability, while DSC highlights physical and thermal interactions, allowing formulation scientists to select excipients that ensure a stable and effective drug product(70).

Optimization of lipid ratios, rotation speed, vacuum pressure.

The optimization of lipid ratios, rotation speed, vacuum pressure, and related parameters is crucial in designing liposomal formulations for targeted drug delivery. The lipid composition—particularly the concentration of phospholipids like DPPC and the DPPC:cholesterol molar ratio—significantly influences the resulting liposome's particle size, polydispersity index (PdI), and encapsulation efficiency. Higher DPPC concentrations generally increase particle size and PdI up to a point, after which further increases can reduce size and improve uniformity. Adjusting the DPPC:cholesterol ratio can decrease particle size but may slightly increase PdI, while also enhancing drug entrapment efficiency. The concentration of the encapsulated drug, such as quercetin, also affects these properties; higher drug concentrations can reduce encapsulation efficiency and slightly decrease particle size due to changes in membrane organization(71).

Process parameters like rotation speed during the thin-film hydration method ensure even distribution of the lipid mixture on the flask wall, promoting homogeneous liposome formation. Vacuum pressure during solvent evaporation is optimized to efficiently remove organic solvents without degrading lipids, which is essential for forming a stable and reproducible lipid film(72). Experimental design methodologies, such as D-optimal or response surface designs, are often used to systematically study the effects of these variables and identify the optimal conditions that yield the desired particle size, PdI, and encapsulation efficiency. Ultimately, careful optimization of these formulation and process parameters is key to producing liposomes with consistent quality and performance for targeted drug delivery in ulcerative colitis and other applications(73).

Techniques: Thin-film hydration, sonication

The thin-film hydration method, also known as the Bangham method, is a foundational technique for preparing liposomes and lipid nanoparticles for drug delivery. In this process, lipids are first dissolved in an organic solvent such as chloroform or a chloroform-methanol mixture, and the solution is placed in a round-bottom flask. The solvent is then evaporated under reduced pressure, typically using a rotary evaporator, to form a uniform thin lipid film

on the inner surface of the flask. This film is further dried under vacuum to ensure complete removal of residual solvent. The next step involves hydrating the lipid film with an aqueous solution such as distilled water or buffer at a temperature above the lipid phase transition point, which triggers the self-assembly of the lipids into multilamellar vesicles (MLVs) or liposomes(74).

After hydration, the resulting liposome suspension often contains vesicles with a heterogeneous size distribution. To achieve more uniform and smaller liposomes, sonication is employed. Sonication uses high-frequency sound waves to break down larger multilamellar vesicles into smaller unilamellar vesicles, improving size homogeneity and encapsulation efficiency. Alternatively, extrusion through polycarbonate membranes can be used for further size control(75).

Table 4. Evaluation Parameters in UC Targeted Drug Delivery Studies

Evaluation Technique	Purpose	Methods
Disease Induction	Mimicking UC in animals	DSS-induced colitis in rats/mice
Drug Entrapment Efficiency	% of drug loaded into nanocarriers	HPLC, UV-spectrophotometry
Zeta Potential and Particle Size	Stability and distribution of vesicles	Dynamic Light Scattering (DLS)
Histopathological Scoring	Assess mucosal healing and inflammation	H&E staining, Geboes score
Fluorescent Imaging	Cellular uptake & localization of nanocarriers	Confocal microscopy, IVIS
In Vitro Release Kinetics	Drug release pattern under physiological conditions	Dialysis method, buffer simulations
Biodistribution Study	Organ/tissue drug accumulation	Fluorescence-tagged tracers, LC-MS/MS

Characterization of Drug Delivery Systems

Vesicle size & morphology (TEM imaging)

Vesicle size and morphology are critical quality attributes in the characterization of liposomal drug delivery systems for ulcerative colitis. Transmission Electron Microscopy (TEM), including its advanced form cryogenic TEM (cryo-TEM), is the gold standard for directly visualizing the size, shape, and internal structure of liposomes at the nanometer scale(76). TEM enables researchers to assess the uniformity, lamellarity (number of bilayers), and overall morphology of vesicles, which are essential for predicting their behavior in biological systems and optimizing drug delivery performance(77).

Cryo-TEM, in particular, preserves liposomes in their native hydrated state by rapid freezing, allowing for accurate measurement of vesicle size, shape, and bilayer organization without the artifacts introduced by staining or dehydration. This technique can distinguish between unilamellar, multilamellar, and multivesicular vesicles, and provides detailed information on particle size distribution—typically ranging from 5 to 500 nm depending on the formulation(78). Negative staining TEM is a faster and simpler alternative that uses electron-dense stains to provide high-contrast images, though it may introduce some structural artifacts(79).

Overall, TEM-based imaging is indispensable for confirming the nanoscale dimensions and morphological integrity of liposomal formulations intended for ulcerative colitis therapy, ensuring reproducibility and supporting regulatory approval(80).

Zeta potential & stability studies

Zeta potential is a key parameter in the characterization of liposomal and nanoparticle drug delivery systems for ulcerative colitis, as it reflects the surface charge of the vesicles and strongly influences their colloidal stability, aggregation behavior, and interactions with biological membranes(81). Liposomes with a high absolute zeta potential value (greater than +30 mV or less than −30 mV) are generally considered stable, as the strong electrostatic repulsion between particles prevents aggregation and flocculation during storage and administration. The zeta potential can be

tailored by adjusting the lipid composition and incorporating charge-imparting agents such as stearylamine (for positive charge) or dicetyl phosphate (for negative charge), with optimized formulations showing values like +30.1 mV or −36.7 mV and vesicle sizes in the 80–110 nm range(82).

Stability studies involve monitoring changes in zeta potential, particle size, and polydispersity index over time under various storage conditions. A significant drop in the absolute value of zeta potential or an increase in particle size and polydispersity may indicate vesicle aggregation, fusion, or degradation, signaling compromised formulation stability. Additionally, the zeta potential affects biological performance, including circulation time, cellular uptake, and potential toxicity, making its assessment crucial for developing effective and safe drug delivery systems for ulcerative colitis(83).

Drug loading & encapsulation efficiency

Drug loading and encapsulation efficiency are critical parameters in the development of liposomal and nanoparticle drug delivery systems for ulcerative colitis, as they directly influence therapeutic efficacy, dosing, and safety profiles. Drug loading refers to the amount of drug incorporated into the carrier system relative to the total weight of the formulation, while encapsulation efficiency is the percentage of the initial drug input that is successfully entrapped within the vesicles during formulation(65).

Several studies have demonstrated that optimizing lipid composition, drug-to-lipid ratio, and preparation techniques can significantly enhance encapsulation efficiency and drug loading. For example, mesalazine liposomal gel formulations prepared by thin-film hydration and varying lecithin/cholesterol ratios have shown good entrapment efficiencies, making them effective for UC treatment(84). Similarly, pH-sensitive and layer-by-layer coated liposomes have been used to improve the loading and sustained release of anti-inflammatory drugs, ensuring that a higher proportion of the drug reaches the inflamed colon. The inclusion of excipients like cholesterol can stabilize the lipid bilayer, further increasing drug retention within the vesicles(85).

Efficient drug loading and high encapsulation efficiency are essential for maximizing local drug concentration at the site of inflammation, reducing systemic exposure, and improving patient outcomes in ulcerative colitis therapy(86). These parameters are routinely measured during formulation development and are optimized through careful selection of lipids, drug ratios, and processing conditions.

In vitro drug release & kinetics

In vitro drug release and kinetics studies are essential for evaluating the performance of liposomal and nanoparticle drug delivery systems designed for ulcerative colitis. These studies simulate gastrointestinal conditions to assess how effectively and specifically the drug is released from its carrier at the target site. For example, a recent study on an oral liposomal formulation of budesonide (a corticosteroid used in IBD) demonstrated that the liposomal prodrug exhibited high stability in acidic gastric conditions, with only about 5% of the drug released over six hours in simulated gastric fluid (SGF, pH 1.5). In contrast, drug release accelerated significantly in simulated intestinal fluid (SIF, pH 6.8), aligning with the desired colon-targeted delivery profile(87).

The release mechanism in this system was further shown to be enzyme-responsive: the prodrug was stable in the absence of esterase but underwent rapid hydrolysis and conversion to active budesonide in the presence of esterase, mimicking the enzymatic environment of inflamed colonic tissue(88). Nearly complete conversion to the active drug was observed within 48 hours under esterase-rich conditions(89). This dual pH- and enzyme-responsive release ensures minimal premature drug loss in the stomach and efficient activation at the site of inflammation.

Kinetic modeling of these systems often reveals non-Fickian (anomalous) diffusion or first-order release profiles, reflecting the complex interplay of diffusion, carrier degradation, and environmental triggers. Such tailored release kinetics are crucial for maximizing local drug concentrations at the inflamed colon while reducing systemic exposure and side effects, as demonstrated by improved therapeutic outcomes in preclinical models(90).

Ex Vivo and In Vivo Evaluation Techniques

In preclinical models of ulcerative colitis (UC), evaluation of targeted drug carriers combines in vivo disease induction with ex vivo tissue analyses. A common approach is to induce experimental colitis in rodents (typically mice or rats) by administering dextran sulfate sodium (DSS) in drinking water. DSS (usually 3–5%) given for several days provokes colonic epithelial injury and inflammation resembling UC. Disease progression is monitored by

body-weight loss, stool consistency and bleeding (the Disease Activity Index or DAI) For example, 4% DSS for 5 days caused a steadily rising DAI in mice as epithelial injury developed. Additional outcome measures include colon shortening, weight, and myeloperoxidase (MPO) activity – all of which correlate with inflammation(91).

In vivo colitis induction (DSS model): Rodents receive DSS (e.g. 4% in drinking water for 5–7 days) to induce acute colitis. Animals are weighed daily and fecal blood or consistency is scored. The composite DAI combines weight loss, stool score, and bleeding. Typical DSS treatment leads to significant weight loss, loose or bloody stools, and shortened colon length. Effective therapy (e.g. a targeted nanoparticle) will attenuate these changes relative to untreated controls. For instance, DSS-induced mice display high DAI by day 6, whereas animals treated with colon-targeted carriers show slower weight loss and reduced bleeding.

Tissue Drug Entrapment and Biodistribution

To quantify drug localization in the colon, excised tissues are typically homogenized and assayed (e.g. by HPLC or mass spectrometry). In one approach, colonic segments are rinsed, weighed, and homogenized; drug is then extracted and measured. Alternatively, an *ex vivo* entrapment assay uses everted gut sacs: intestinal loops are everted in physiological buffer and incubated with the formulation to measure uptake. These methods reveal the fraction of administered drug that "trapped" in inflamed tissue.

After sacrifice, the colon (and often small intestine, stomach) is collected and weighed. Tissue is homogenized in solvent, centrifuged, and drug concentration in the supernatant is determined (e.g. by HPLC). This gives a quantitative measure of tissue drug content. In studies of targeted carriers, a markedly higher percentage of drug is found in inflamed colon versus healthy colon. For example, *Shanon Ben et al.* reported that coated liposomal prednisolone achieved ~22.6% entrapment in inflamed rat colon tissue, versus ~9–10% in healthy control tissue. (By contrast, free drug gave much lower colon levels.) Such data directly support targeted delivery: a larger drug reservoir in the diseased colon indicates preferential accumulation of the nanoformulation.

These biodistribution studies are often complemented by measurements of plasma and other organs to confirm selectivity. In advanced models, labeled carriers can be tracked in vivo (e.g. by fluorescent or radioactive labels) to assess whole-body distribution. In all cases, higher drug levels in the inflamed colon relative to non-target tissues validate that the carrier is delivering its payload to the intended site(92).

Histopathological Analysis of Colon Tissue

Histology remains the gold standard for assessing colitis and therapeutic response. After euthanasia, colon samples are fixed (typically in formalin), paraffin-embedded, sectioned, and stained (e.g. with hematoxylin and eosin, or special stains for goblet cells). A pathologist or blinded scorer evaluates key features of mucosal injury: crypt architecture, ulceration, inflammatory infiltrate, goblet cell depletion, edema, and epithelial regeneration. Standard scoring systems (such as the Geboes score) quantify these changes on a defined scale.

Histological staining reveals whether targeted therapy has ameliorated colonic damage. In UC models, inflamed tissue shows extensive ulceration and neutrophil infiltration. Successful treatment restores normal mucosal structure. For example, in rats with chemically-induced colitis, eudragit-coated liposomes delivering prednisolone produced a "marked reduction in inflammation" with clear epithelial re-mucosalization and reduced ulceration, as seen on H&E slides. Similarly, treatment with targeted nanoparticles often yields "remarkable improvements in the histopathological features" of the colon, including fewer infiltrating immune cells and intact crypts. In practice, investigators compare histology scores of treated vs. untreated colitic animals: significantly lower scores (closer to healthy tissue) in the treatment group indicate effective targeting and anti-inflammatory action.

These histological findings corroborate functional outcomes: reduction in neutrophils (e.g. MPO activity), fewer ulcers, and restored goblet cell counts all testify to healing. Thus, colon tissue histopathology not only confirms that the drug reached the site (by showing its effect) but also provides insight into the quality of mucosal repair. Comprehensive reviews note that "histopathological healing" is a key endpoint in IBD models, reflecting long-term remission and mucosal regeneration(93).

Fluorescence Microscopy of Nanocarrier Uptake

Fluorescent labeling of carriers enables direct visualization of cellular uptake and tissue distribution. In vitro, liposomal or polymeric nanoparticles can be labeled with fluorescent dyes (e.g. DiI, DiD, rhodamine) and incubated with target cells such as macrophages or epithelial cells. Uptake

is then imaged by confocal laser scanning microscopy. This reveals whether the carriers are internalized by the relevant cell types and whether targeting ligands (e.g. hyaluronic acid, antibodies) enhance uptake.

Confocal fluorescence microscopy confirms cellular uptake of carriers. For instance, hyaluronic-acid-coated PLGA nanoparticles showed much higher uptake (red fluorescence signal) in LPS-activated macrophages than uncoated particles. In tissue, colon sections from DSS-treated animals can be examined ex vivo. In one study, DSS-colitis mice were orally given Rhodamine-labeled HA-PLGA nanoparticles; subsequent confocal microscopy of colon sections showed strong fluorescence in the inflamed mucosa, with the signal co-localizing to F4/80-positive macrophages. This confirms that the nanocarriers reach and enter target cells in situ.

Whole-body or ex vivo organ imaging (e.g. IVIS) provides a complementary assessment. Fluorescent (or luminescent) reporters on the nanoparticles enable quantification of biodistribution. In a UC mouse model, HA-functionalized bilirubin-loaded PLGA nanoparticles exhibited ~6-fold higher fluorescence in inflamed colon than non-targeted particles. Regions of interest in excised colon segments also revealed intense signal at the disease site, confirming targeted delivery. When combined with immunostaining (e.g. for macrophage markers), fluorescence microscopy can further show colocalization of the carrier with specific cell populations in the inflamed colon(94).

Challenges

Bridging preclinical findings to human trials

Bridging preclinical findings to human trials in ulcerative colitis (UC) remains a critical yet challenging endeavor, with only 5%–10% of promising preclinical studies successfully translating to clinical applications. Key challenges and strategies include:

1. Improving Preclinical Model Relevance

Genetic integration: Models incorporating human IBD risk alleles (e.g., TNFSF15 variants linked to TL1A dysregulation) better replicate disease heterogeneity and inform targeted therapies like tulisokibart, a monoclonal antibody against TL1A(95).

2. Biomarker Development for Precision Medicine

Companion diagnostics: Genetic testing (e.g., TNFSF15 variants) and fecal calprotectin levels help stratify patients likely to respond to therapies like tulisokibart, improving clinical trial success rates.

Dynamic monitoring: Early assessment of mucosal healing via intestinal ultrasound or fecal biomarkers at 6–12 weeks predicts long-term remission, enabling timely therapy adjustments(96).

Conclusion

Ulcerative colitis remains a complex and burdensome disease requiring lifelong management. While conventional therapies like 5-ASA, corticosteroids, and immunomodulators are still relevant, the emergence of targeted biologics and small-molecule therapies has transformed the therapeutic landscape. These agents, designed to interfere with specific immune pathways, offer improved efficacy and safety profiles for many patients. Despite these advances, challenges such as non-response, loss of response, and adverse effects persist. Further research into biomarkers, personalized medicine, and novel treatment targets is crucial to achieving sustained remission and improving the quality of life in patients with UC. Collaborative, multidisciplinary approaches and ongoing clinical trials will continue to shape the future of UC treatment.

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