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Emerging Biologic Strategies in Crohn's Disease

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Abstract:

Crohn's disease is an inflammatory bowel disease, which substantially impairs patients' quality of life. Despite ongoing advances, effective long-term management remains challenging in many cases. Conventional therapies are often associated with significant adverse effects and limited suitability for sustained use. This review provides an overview of the current landscape of novel biological therapeutics and their molecular targets. Several biologic therapies are already well established in clinical practice. Among them, IL-23 inhibitors stand out due to their high efficacy in both inducing and maintaining remission. Agents targeting the TL1A pathway, as well as human amniotic epithelial cells have shown promising early results and are currently under further investigation in clinical trials. Nevertheless, discontinuation of some biologics trials proves that not all theoretically attractive targets translate into meaningful clinical outcomes. Importantly, variability in efficacy can be observed even within the same class of drugs. This is exemplified by the success of upadacitinib in contrast to tofacitinib, which did not meet primary endpoints and was not further developed for this indication. Overall, these findings highlight both the progress achieved and the ongoing challenges in optimizing targeted therapies for Crohn's disease.

Key words: Crohn's disease, inflammatory bowel disease, biological therapeutics, innovative therapies

The aim of the work: The aim of this review is to present the current landscape of novel biologic strategies and highlight potential future directions in the treatment of Crohn's disease.

Materials and methods: Our research was based on analysis of PubMed and Google Scholar databases, using key search terms "crohn's disease", "biological therapy", "ustekinumab", "risankizumab", "guselkumab", "mirikizumab", "tofacitinib", "upadacitinib", "duvakitug", "tulisokibart", "haec", "ozanimod","secukinumab", "darvadstrocel", "fontolizumab".

Abbreviations:

ADA - anti-drug antibody

CD - crohn's disease

CDAI - Crohn's Disease Activity Index

DR3 - death receptor 3

EMA - European Medicines Agency

FDA - Food and Drug Administration

hAEC - human amniotic epithelial cells

IBD - inflammatory bowel disease

IFN-γ - interferon-gamma

IL - interleukin

JAK - Janus kinase

JAK–STAT - signal transducer and activator of transcription

MAPKs - mitogen-activated protein kinases

NF-κB - nuclear factor kappa-light-chain-enhancer of activated B cells

PI3K - phosphoinositide 3-kinase

S1P - sphingosine-1-phosphate

TL1A - tumor necrosis factor-like ligand 1A

TNF - tumor necrosis factor

UC - ulcerative colitis

1. Introduction

Crohn's disease is a chronic, progressive and destructive granulomatous inflammatory bowel disorder that can involve any part of the gastrointestinal tract.[1] It belongs to the group of inflammatory bowel diseases. The pathogenesis is multifactorial. It is associated with an abnormal immune response of the intestinal microbiota in genetically predisposed individuals. Presenting symptoms may include diarrhea, abdominal pain, weight loss, nausea, vomiting, fevers or chills, mouth sores, lack of appetite, urgent bowel movements, redness or pain in the eyes from uveitis, iritis or episcleritis, swollen and painful joints, especially knees, hips, and elbows, skin inflammation.[2] Additionally, patients can be expected to have anemia, iron deficiency, low vitamin D levels, B12 deficiency and elevated inflammatory markers including C-reactive protein, erythrocyte sedimentation rate and fecal calprotectin.[2–4] About half of patients develop complications such as fistulas, phlegmons, strictures, or abscesses within 20 years.[5]

2. Traditional therapies

Medical therapies used in the management of Crohn's disease primarily aim to suppress an excessively activated intestinal immune response. Treatment is generally divided into two phases: induction and maintenance. The induction phase involves the administration of a higher dose of a steroid-sparing agent during the initial weeks to months of therapy in order to achieve rapid clinical remission.[2] Corticosteroids inhibit multiple inflammatory pathways by reducing cytokine production and immune cell activation.[6] These agents are highly effective at inducing clinical remission. However, they do not maintain remission over the long term and are unable to promote sustained mucosal healing. Nearly half of the patients who initially respond to corticosteroid therapy subsequently develop steroid dependence or experience disease relapse within one year.[7] Furthermore, the clinical use of corticosteroids is frequently restricted due to the relatively high risk of serious adverse effects, including osteoporosis, diabetes, myopathy, cataracts, hypertension, obesity, skin atrophy and infections.[7,8] To reduce the likelihood of toxicity, current recommendations emphasize that corticosteroids should be used only for short-term therapy and at the lowest effective dose necessary to induce remission in patients with moderately to severely active Crohn's disease.[7]

Traditional immunosuppressants also include azathioprine, 6-mercaptopurine, and methotrexate. Thiopurines are associated with an elevated risk of several adverse outcomes including infections, bone marrow suppression, hepatotoxicity and the development of malignancies such as lymphoma and non-melanoma skin cancers. They have proven effective in maintaining remission, but their ability to induce remission is comparatively limited. Methotrexate has been linked to significant toxicities including liver injury, pulmonary complications and teratogenic effects. Nevertheless, in contrast to biologic agents, traditional drugs remain widely accessible and relatively inexpensive, which makes them a practical therapeutic option in healthcare settings with limited resources.[9]

3. Biological therapies

Biological therapies represent targeted therapeutic strategy, as they act on specific components of the immune system involved in the inflammatory process. Owing to their selectivity, these agents are theoretically associated with fewer off-target effects and a lower risk of complications related to generalized immunosuppression. Evidence from both

randomized clinical trials and real-world studies indicates that biologic therapies achieve higher rates of sustained remission than conventional immunosuppressive treatments, particularly in patients with moderate to severe disease. Nevertheless, their effectiveness is not universal. Approximately 30–40% of patients exhibit primary non-response, while others gradually lose therapeutic benefit over time. The immunogenic nature of these agents may lead to the formation of anti-drug antibodies, which can progressively reduce therapeutic efficacy. In such situations, therapeutic drug monitoring and modification of treatment, either by switching within the same biologic class or to an alternative class, may be required to restore disease control.[9,10]

In 1998 Remicade® (infliximab), the tumor necrosis factor-α inhibitor, received its initial marketing approval from the US Food and Drug Administration for the treatment of Crohn's disease. It was the first biologic to be approved for inflammatory bowel diseases. This achievement resulted from two independent scientific advances in 1975: the identification of tumor necrosis factor and the development of hybridoma technology, which enabled the production of monoclonal antibodies.[11] Infliximab to these days remains widely used in clinical practice due to its well-established efficacy in inducing and maintaining remission and extensively documented long-term safety profile.[12]

Biologics are generally regarded as safer than traditional immunosuppressants in terms of long-term toxicity. Although they are still associated with certain risks. For instance, inhibitors of tumor necrosis factor have been linked to an increased susceptibility to infections, reactivation of latent tuberculosis and the occurrence of paradoxical autoimmune manifestations such as psoriasis or lupus-like syndromes. Despite these, the overall safety and effectiveness profile of biologics has resulted in their preferential recommendation in many contemporary treatment guidelines, particularly for patients at elevated risk of steroid dependence or adverse effects related to conventional immunosuppressive therapy. However, the widespread implementation of biologic treatment remains constrained by economic factors. These agents are substantially more expensive than traditional therapies and financial barriers continue to limit access in many regions.[9,13,14]

4. Novel biological therapeutics and their targets

4.1 IL-23 inhibitors

Interleukin-23 plays a central role in the regulation of adaptive immune responses by promoting the differentiation and maintenance of Th17 lymphocytes, whereas IL-12 primarily drives Th1 cell differentiation. Microbial components such as peptidoglycan can selectively stimulate antigen-presenting cells to produce IL-23 rather than IL-12. This process shapes the character of the inflammatory response. Beyond its role in host defense against intracellular pathogens, IL-23 contributes to the persistence of specific T-cell subsets, including γδ T cells and other early effector populations involved in mucosal immunity.[15]

In the context of Crohn's disease, dysregulation of the IL-23/Th17 axis is considered a key pathogenic mechanism. Excessive IL-23 signaling promotes Th17-mediated inflammation, increased production of pro-inflammatory cytokines and chronic intestinal immune activation. This sustained inflammatory response contributes to tissue damage and the perpetuation of intestinal inflammation characteristic of Crohn's disease.[15] Based on these mechanistic insights selective inhibition of IL-23 has emerged as a promising therapeutic strategy. This approach aims to modulate key immune pathways while potentially avoiding the broader immunosuppression associated with earlier biologic therapies.

4.1.1. Ustekinumab

Ustekinumab (UST) is a fully human IgG1κ monoclonal antibody targeting the p40 subunit shared by the pro-inflammatory cytokines IL-12 and IL-23. By inhibiting these cytokines, ustekinumab attenuates downstream inflammatory signaling and modulates the differentiation of inflammatory T-cell subsets.[16] The drug was approved for the treatment of Crohn's disease in 2016. Its efficacy in patients with moderate-to-severe Crohn's disease was demonstrated in two phase III randomized, double-blind, placebo-controlled 8-week induction trials (UNITI-1 and UNITI-2) and a 44-week maintenance study (IM-UNITI). These multicenter trials were conducted between July 2011 and June 2015 across numerous international sites: 178 centers in 23 countries for UNITI-1, 175 centers in 23 countries for UNITI-2 and 260 centers in 27 countries for IM-UNITI.[16,17] The induction studies showed that intravenous ustekinumab effectively induced clinical response and remission in patients with moderately to severely active Crohn's disease refractory to TNF antagonists or conventional

therapies. Among patients who responded to induction therapy, subcutaneous ustekinumab was significantly more effective than placebo in maintaining remission.[17]

Long-term follow-up studies have demonstrated sustained efficacy and a favorable safety profile with low rates of anti-drug antibodies reported over three years of treatment. Five-year extension data, representing the longest reported experience with IL-12/23 blockade in inflammatory bowel disease, indicate that subcutaneous ustekinumab remains well tolerated and effective in maintaining clinical remission in both TNF-antagonist–naïve patients and those with prior inadequate response or intolerance to such therapies. The safety profile observed over this period remained consistent with that previously established in psoriasis and psoriatic arthritis. Rates of adverse events, serious adverse events, infections, and treatment discontinuations were comparable to those observed with placebo.[18] The most commonly reported adverse effects include nasopharyngitis, headache, fatigue, vomiting after induction therapy, injection-site erythema, bronchitis or upper respiratory tract infection, sinusitis, abdominal pain, fever, influenza-like illness, diarrhea and back pain.[19]

4.1.2. Risankizumab

Risankizumab is a humanized IgG1 monoclonal antibody, an IL-23 p19 inhibitor. It was already approved in 2019 for the treatment of moderate-to-severe plaque psoriasis.[20] Following numerous clinical trials demonstrating its efficacy and safety, risankizumab was approved in 2022 by both the FDA and EMA for the treatment of moderate-to-severe Crohn's disease[21]. Following the official approval of risankizumab for this indication, numerous clinical studies have continued to be conducted, further confirming earlier findings. Alzaabi et al. performed a prospective cohort study including 60 patients with moderate-to-severe Crohn's disease who initiated treatment with risankizumab. The study endpoints comprised clinical remission (CDAI score <150) and biochemical remission (normalised C-reactive protein levels <5 mg/L, faecal calprotectin levels <250 μg/g). Outcomes were assessed after the induction phase (weeks 12–20) and during maintenance therapy (10–14 months). At post-induction follow-up 28 of 60 patients (46.7%) achieved clinical remission, while 52 patients (86.7%) met the criteria for clinical response (reduction in CDAI of at least 100 points). Notably, the therapeutic response to risankizumab was more pronounced among patients for whom it was the first biologic drugs used, compared with those previously treated with other biologics, such as ustekinumab.[22] Available data also indicate that risankizumab therapy is associated with a low incidence of adverse events. The most frequently reported adverse reactions include upper respiratory tract

infections, dermatophytosis, headache, rash, pruritus and fatigue. Interestingly, the first large real-world risankizumab pharmacovigilance study identified several unexpected and novel significant adverse event signals not previously reported in the drug label including cataract, pancreatitis, diabetes mellitus, stress, nephrolithiasis, cholelithiasis, and thrombosis.[23]

4.1.3 Guselkumab

Guselkumab is a selective monoclonal antibody targeting the p19 subunit of IL-23, without interfering with IL-12 signaling. Preservation of IL-12–dependent Th1 immunity maintains host defense against intracellular pathogens, potentially improving the safety profile compared with dual IL-12/23 blockade.[21] In randomized Phase III clinical trials, guselkumab demonstrated significant efficacy in achieving both clinical and endoscopic remission among biologic-naïve patients, as well as individuals with prior exposure to advanced therapies. Moreover, no new safety signals were identified. Clinical trials results supported its applicability in routine clinical practice for inflammatory bowel disease.[24,25] Officially approved by EMA and FDA in 2025.

4.1.4. Mirikizumab

Mirikizumab is a humanized monoclonal antibody of the immunoglobulin G4 class that selectively targets the p19 subunit of interleukin-23. It has previously demonstrated therapeutic efficacy in the treatment of psoriasis and ulcerative colitis.[26,27] The drug was approved by the FDA in January 2025 for adults with moderately to severely active Crohn's disease. A positive opinion for this indication had already been issued by the European Medicines Agency (EMA) in December 2024.[28,29] Clinical trials preceded approval in the above-mentioned indication, including the phase 3 VIVID-1 trial, which evaluated the efficacy and safety of mirikizumab in adults with moderately to severely active Crohn's disease.[30] VIVID-1 was a multicenter, randomized, double-blind, placebo-controlled and active-controlled study. It enrolled patients with an inadequate response, intolerance, or loss of response to conventional or prior biologic therapies.[31,32] The trial demonstrated that mirikizumab produced significant therapeutic effects across multiple clinical and endoscopic outcomes when compared with placebo.[31] Analyses of patient-reported outcomes showed that treatment with mirikizumab resulted in marked improvements in health-related quality of life including disease-specific and general health measures, as early as week 12 and these benefits were maintained through week 52 of therapy. In addition to improvements in quality-of-life indicators, patients receiving mirikizumab also

experienced significant gains in work productivity and reductions in activity impairment.[31] Further analyses focusing on symptom burden indicated that mirikizumab therapy led to higher rates of clinically meaningful improvement in fatigue scores at both week 12 and week 52 compared with placebo. Improvements in fatigue were closely associated with enhancements in patient-reported outcomes and overall quality of life. Correlations with objective inflammatory markers were weaker.[32] Collectively, these findings confirm that selective inhibition of IL-23 with mirikizumab provides clinically meaningful benefits in patients with moderately to severely active Crohn's disease, supporting its role as an effective therapeutic option.

4.2. JAK inhibitors

Janus kinases are intracellular tyrosine kinases that include four main isoforms: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). These enzymes are key components of the JAK–STAT signaling pathway, which mediates intracellular transmission of signals from numerous cytokine receptors and regulates immune cell proliferation, differentiation and inflammatory responses.[33] In Crohn's disease excessive production of pro-inflammatory cytokines activates cytokine receptors on immune cells, leading to stimulation of the JAK–STAT pathway and promoting intestinal inflammation.[34] Following cytokine binding, JAK proteins phosphorylate the associated receptors enabling recruitment and activation of STAT transcription factors. Activated STAT proteins subsequently dimerize and translocate to the nucleus. Then they modulate the transcription of genes involved in immune activation and inflammatory processes. Many cytokines implicated in Crohn's disease pathogenesis utilize this signaling mechanism, highlighting the central role of the JAK–STAT pathway in intestinal immune regulation. Because JAK proteins function as critical intermediates in cytokine signaling, pharmacological inhibition of their tyrosine kinase activity can disrupt multiple inflammatory pathways simultaneously, thereby reducing immune-mediated intestinal inflammation and representing a promising therapeutic strategy in inflammatory bowel disease.[33,35] JAK inhibitors have also gained considerable interest because of their lack of immunogenicity, relatively short half-life, and rapid therapeutic onset.[35] In addition to their application in inflammatory bowel disease, these agents are being used in treatment of several other conditions, including rheumatoid arthritis, psoriasis, polycythemia vera, alopecia, thrombocythemia, myelofibrosis, and vitiligo.[36]

4.2.1. Tofacitinib

Tofacitinib is an example of JAK inhibitor that has shown clear efficacy in ulcerative colitis, but failed to demonstrate sufficient benefit in Crohn's disease is Tofacitinib. Clinical trials conducted in patients with ulcerative colitis demonstrated that treatment with tofacitinib significantly increased rates of clinical remission and mucosal healing. These findings supported its regulatory approval for this indication.[37]

In parallel, the drug was investigated for the treatment of Crohn's disease in randomized phase II clinical trials involving patients with moderate-to-severe disease activity.[26] The study results did not show statistically significant improvements in clinical response or remission rates compared with placebo, despite some evidence of biological activity reflected by reductions in inflammatory biomarkers.[38] Subsequently, two multicenter, randomized, double-blind, placebo-controlled phase IIb trials were conducted to further investigate the efficacy of tofacitinib in Crohn's disease. In these studies, patients received tofacitinib 5 mg or 10 mg twice daily during an 8-week induction phase, followed by a 26-week maintenance period in responders.[39] The phase IIb trials showed that clinical remission rates at week 8 were numerically higher in patients receiving tofacitinib than in those receiving placebo. However, these differences did not reach statistical significance for the primary efficacy endpoints.[39] Because the clinical efficacy was insufficient and primary endpoints were not met, further development of tofacitinib for this indication was not pursued.

4.2.2. Upadacitinib

Upadacitinib is an oral selective Janus kinase inhibitor, that has been approved for the treatment of moderate to severe active CD in adult patients since April 2023 by both EMA and FDA.[40] Clinical development of upadacitinib for Crohn's disease has been evaluated in several clinical trials. An early randomized phase II trial demonstrated that treatment with upadacitinib resulted in dose-dependent improvements in endoscopic remission compared with placebo. Increases in clinical remission were more modest during the induction phase. In this study, endoscopic remission occurred in a higher proportion of patients receiving higher doses of upadacitinib than in those receiving placebo. Several clinical and endoscopic outcomes were maintained during the subsequent maintenance period.[41] Therapeutic potential of upadacitinib was later confirmed in large phase III clinical trials including the U-EXCEL and U-EXCEED induction studies and the U-ENDURE maintenance study. In these trials, induction therapy with

upadacitinib (45 mg once daily) resulted in significantly higher rates of clinical remission and endoscopic response compared with placebo. Among patients who responded to induction therapy, maintenance treatment with upadacitinib (15 mg or 30 mg once daily) led to substantially higher remission and endoscopic response rates than placebo.[42] Overall, these studies demonstrated that upadacitinib can effectively induce and maintain remission in patients with moderate-to-severe CD.

4.3. TL1A inhibitors

Tumor necrosis factor-like ligand 1A is a cytokine belonging to the TNF superfamily that has emerged as an important regulator of intestinal inflammation. It signals through death receptor 3, which is predominantly expressed on activated lymphocytes. Engagement of the TL1A–DR3 pathway activates intracellular signaling cascades involving NF-κB, MAPKs, and PI3K, thereby promoting lymphocyte activation and pro-inflammatory cytokine production. This interaction particularly enhances Th1- and Th17-associated responses in the intestinal mucosa, including increased secretion of mediators such as IFN-γ, IL-6 and IL-17. Elevated expression of TL1A and DR3 has been documented in inflammatory bowel diseases and genetic studies have identified polymorphisms in the TL1A genes.[43–45]

Experimental studies further support a pathogenic role for this signaling axis. In one investigation using single-cell transcriptomic analysis of rectal biopsies from patients with CD and perianal fistulizing disease, activation of TL1A signaling in $CD4^+$ T cells was linked to distinct molecular alterations within the rectal mucosa. The authors identified lymphotoxin-α1β2 and IL-22 as downstream mediators. They influence fibroblast and epithelial cell responses, promoting tissue remodeling and antibacterial defense independently of TNF signaling.[46] Additional experimental evidence comes from murine models examining the role of DR3 in Th9 cells. Functional DR3 signaling enhanced the pro-inflammatory phenotype of Th9 lymphocytes. Its genetic deletion increased anti-inflammatory responses and reduced the severity of intestinal inflammation after adoptive transfer.[47] These findings indicate that TL1A–DR3 signaling amplifies pathogenic immune responses in the intestine, which makes it a novel therapeutic target for patients with CD.

4.3.1 Duvakitug

Duvakitug is a human IgG1 monoclonal antibody, TL1A-inhibitor.[44] The drug is currently not approved for any indication. It is being studied for use in Crohn's disease and ulcerative colitis. Phase 2b has shown promising results. Primary endpoints were met with durable efficacy and good tolerability. The process is now moving into phase 3.[48]

4.3.2.Tulisokibart

Tulisokibart is an anti-TL1A monoclonal antibody. In the phase 2a, multicentre, open-label APOLLO-CD study it was tested as induction treatment in adults with moderately to severely active Crohn's disease with a history of insufficient response, loss of response or intolerance to conventional or approved biological therapies.[49] The results showed encouraging endoscopic and clinical remission rates with well tolerance. The drug has advanced to large-scale, double-blind, placebo-controlled Phase 3 trial investigating induction and maintenance. Its completion is scheduled for 2032. [50]

4.4. Human amniotic epithelial cells

Human amniotic epithelial cells (hAECs) are obtained from the amniotic membrane, the innermost layer of the term placenta located adjacent to the fetus. Their accessibility, low immunogenicity, ability to proliferate, multilineage differentiation potential and high ethical acceptability have contributed to growing interest in their application in regenerative medicine. The therapeutic activity of hAECs appears to be mediated largely through indirect mechanisms rather than through permanent tissue engraftment. Experimental observations indicate that transplanted cells may remain within the intestinal lumen without penetrating the lamina propria. HAECs release a variety of biologically active factors capable of influencing surrounding cells and promoting mucosal repair. Among these secreted factors exosomes (subtype of extracellular vesicles) play a key role. They transport signaling molecules that participate in intercellular communication and tissue regeneration. Exosomes derived from hAECs can be internalized by intestinal epithelial cells, where they stimulate epithelial proliferation and migration, enhance wound closure, and reduce adhesion of inflammatory cells under pro-inflammatory conditions. Through these processes, they contribute to restoration of epithelial barrier integrity. HAECs also exert immunomodulatory activity, reducing inflammatory responses and supporting tissue healing.[51,52] These characteristics make amniotic

epithelial stem cells an attractive candidate for novel therapeutic strategies for inflammatory bowel diseases.

A phase I open-label study evaluated the use of hAECs in ten adult patients with active, complex perianal fistulas associated with CD that were refractory to conventional therapies. A single dose of hAEC was locally administered into the fistula tract following surgical closure of the internal opening. Clinical outcomes were assessed at week 24 and participants were subsequently monitored for a minimum follow-up period of 52 weeks. Results from this first-in-human investigation demonstrated that local injection of allogeneic hAECs was safe, well tolerated and technically feasible over both short- and long-term observation periods. The principal objective of this phase I study was therefore safety assessment rather than efficacy determination and further clinical investigations are currently ongoing.[53] This research area is particularly important given that approximately one third of patients with Crohn's disease develop complex perianal fistulas, a complication that substantially impairs quality of life, negatively affects mental health and increases healthcare utilization. Despite optimal medical management, fistula closure is achieved in only about 30% of cases. Moreover, patients with perianal fistulizing Crohn's disease face an elevated risk of major abdominal surgery as well as rectal and anal malignancies, highlighting the need for more effective therapeutic approaches.[54]

5. Discontinued or unsuccessful biologics

5.1. S1P receptor modulators

Sphingosine-1-phosphate is a biologically active sphingolipid metabolite derived from ceramide that participates in numerous immune and vascular processes. It is produced mainly by erythrocytes and endothelial cells. One of the key physiological roles of S1P is the regulation of lymphocyte trafficking, which is guided by gradients of S1P concentration between lymphoid tissues and the circulation. The biological effects of S1P are primarily mediated through a family of five G-protein-coupled receptors (S1PR1–S1PR5). Among them, S1PR1 plays a particularly important role in immune regulation and inflammatory responses. Activation of the S1P–S1PR1 signaling axis controls the egress of both T and B lymphocytes from lymphoid organs and facilitates their migration toward peripheral inflammatory sites. This signaling pathway also promotes the development of a pro-inflammatory immune profile. Specifically, it favors differentiation of naïve T cells into T helper 1 cells, while simultaneously suppressing the generation of FoxP3-positive regulatory T cells, thereby shifting the immune

balance toward inflammation. In addition, S1PR1 signaling enhances the differentiation and peripheral migration of Th17 cells. S1P signaling also influences B-cell biology. Interaction of S1P with S1PR1 supports B-cell chemotaxis and survival and facilitates the mobilization of immature B cells from the bone marrow into the circulation. Experimental studies have shown that S1P modulates the intestinal epithelial barrier by influencing the expression and localization of E-cadherin at tight junctions. Intracellular S1P can also interact with TNF receptor-associated factor-2, leading to activation of the NF-κB signaling pathway and subsequent production of pro-inflammatory cytokines. Additional intracellular interactions may influence cell-cycle regulation, apoptosis and cellular survival by altering gene transcription.[55] These mechanisms constituted S1P receptor modulators as a promising strategy for the treatment of IBD.

5.1.1 Ozanimod

Ozanimod is an oral S1P receptor modulator that is already approved for the treatment of moderately to severely active ulcerative colitis. Its potential role in Crohn's disease has been investigated in the YELLOWSTONE program. This program comprises phase 3 randomized, double-blind, placebo-controlled induction and maintenance trials, as well as an open-label extension study. During the induction phase, patients with an inadequate response or intolerance to at least one prior Crohn's disease therapy were randomized to receive either ozanimod once daily or placebo for 12 weeks. Participants who achieved a response to ozanimod were subsequently rerandomized to continue active treatment or switch to placebo for a 52-week maintenance period. Individuals who did not qualify for maintenance therapy, experience relapse during maintenance or complete the maintenance phase or at least one year of the STEPSTONE trial could enter an open-label extension and receive ozanimod for up to 234 weeks. Earlier evaluation of ozanimod in CD was conducted in the phase 2 STEPSTONE study, which assessed the efficacy and demonstrated clinical, endoscopic,and histological improvement. However, subsequent results from a phase 3 failed to meet the primary endpoint. No statistically significant difference in clinical remission was observed between the ozanimod and placebo groups.[56,57] At present, further investigations of ozanimod in CD are not being continued. These findings highlight that novel therapeutic strategies may not demonstrate uniform efficacy across all forms of inflammatory bowel diseases, as illustrated by the effectiveness of ozanimod in UC, but not in CD.

5.2. Secukinumab

Secukinumab is a fully human monoclonal antibody targeting interleukin-17A. FDA-approved indications include moderate to severe plaque psoriasis, palmoplantar psoriasis, generalized pustular psoriasis, psoriatic arthritis, and ankylosing spondylitis.[58] In a double-blind, randomized, placebo-controlled proof-of-concept study involving 59 patients with moderate to severe Crohn's disease Hueber et al. evaluated the safety and efficacy of secukinumab for the treatment of active Crohn's disease. The results were unfavorable, as IL-17A blockade was ineffective and associated with higher rates of adverse events compared with placebo.[59] Notably, cases of Crohn's disease developing during secukinumab therapy administered for other autoimmune conditions have also been reported.[60–62] These observations suggest that inhibition of IL-17A may disrupt its protective role in intestinal immune homeostasis. Currently, no clinical studies are being conducted to investigate secukinumab as a therapeutic option for Crohn's disease.

5.3. Darvadstrocel

Darvadstrocel is an allogeneic advanced therapy medicinal product composed of expanded adipose-derived mesenchymal stem cells. It is intended for local administration into complex perianal fistulas associated with CD, particularly in cases where fistulas have shown an inadequate response to at least one conventional or biologic therapy in adult patients with non-active or mildly active luminal disease.[63,64] The proposed mechanism of action is related to the immunomodulatory and anti-inflammatory properties of mesenchymal stem cells. These cells are thought to attenuate local immune responses, impair lymphocyte proliferation, and modify cytokine release at the site of inflammation. As a result, they may facilitate tissue repair and promote fistula healing.[65] Efficacy and safety evidence from the pivotal ADMIRE-CD phase III randomized controlled trial demonstrated that a single local injection of darvadstrocel significantly increased combined remission rates. Remission rates were defined by clinical closure of draining fistulas and absence of collections on imaging and were compared with placebo at 24 weeks, with sustained effects observed through longer follow-up.[66] Observational studies and systematic analyses have further supported the potential for high rates of fistula healing and favorable safety outcomes in real-world clinical practice, although results vary across cohorts.[63] In March 2018 darvadstrocel received centralised marketing authorisation from the European Commission for the treatment of complex perianal fistulas in adult CD

patients fitting these criteria.[64] However, follow-up confirmatory data from the larger phase III ADMIRE-CD II trial failed to meet its primary efficacy endpoint. The available evidence was deemed insufficient to confirm a clinically meaningful benefit relative to risks. Marketing authorisation holder voluntarily withdraw product from the European Union market effective December 2024.[67]

5.4. Fontolizumab

Fontolizumab is a humanized IgG1 monoclonal antibody against interferon-gamma. IFN-γ is a key pro-inflammatory cytokine and a major driver of Crohn's disease pathogenesis. It is produced by Th1 and NK cells in the inflamed mucosa. It drives intestinal damage by promoting inflammation, suppressing epithelial barrier function and inducing PANoptosis (programmed cell death) in intestinal epithelial cells.[68]

Early studies of fontolizumab in patients with active CD produced encouraging findings. Treatment was associated with a reduction in endoscopic severity scores and C-reactive protein levels and the therapy appeared to be generally well tolerated.[69] However, these promising observations were not confirmed in later trials. In a larger phase II study including 133 patients with active Crohn's disease primary efficacy endpoints were not met. Although some reduction in C-reactive protein suggested a potential biological effect, a clear clinical benefit was not demonstrated.[70] As a result, research on the use of fontolizumab for the treatment of Crohn's disease is currently not being continued.

6. Conclusions

Rapid development of novel biologic and targeted therapies is progressively expanding the therapeutic possibilities for Crohn's disease, thanks to advances in immunology and molecular biology. Several biologic agents have already been approved for clinical use and are increasingly incorporated into contemporary treatment algorithms. Among them, inhibitors of the IL-23 pathway such as ustekinumab, risankizumab, guselkumab and mirikizumab have demonstrated substantial efficacy in inducing and maintaining remission. Other therapeutic strategies remain under investigation. Agents targeting the TL1A signaling pathway have demonstrated encouraging results in early clinical studies and are currently being evaluated in larger trials. Moreover, regenerative approaches based on human amniotic epithelial cells represent a novel and promising direction. At the same time, the experience with unsuccessful

or discontinued biologics highlights the complexity of intestinal immune regulation and emphasizes that not all theoretically promising targets translate into clinical benefit. Interestingly, not all agents within the same therapeutic class have demonstrated comparable efficacy. While the selective JAK1 inhibitor upadacitinib has been approved for the treatment of Crohn's disease, tofacitinib failed to meet primary endpoints in clinical trials and its development for this indication was abandoned. It is worth noting, that although Crohn's disease and ulcerative colitis are both classified as inflammatory bowel diseases, the direct transferability of therapeutic strategies between these conditions is limited. Tofacitinib and ozanimod have demonstrated efficacy and received approval in ulcerative colitis, but failed to show satisfactory results in Crohn's disease.

Taken together, these observations reflect both the significant progress achieved in recent years and the remaining unmet clinical needs. Future advances will likely depend not only on the development of new agents, but also on a better understanding of disease mechanisms and treatment response variability. In this context, continued research and careful long-term evaluation of emerging therapies remain crucial.

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