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REVIEW

Emerging biologics in inflammatory bowel disease

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Abstract Early biologic therapy is recommended in patients with inflammatory bowel disease and poor prognostic factors and in those refractory to conventional medications. Anti-tumor necrosis factor (anti-TNF) agents are the most commonly used biologic agents. However, some patients may not have an initial response to anti-TNF therapy, and one-third will develop loss of response over time. Anti-TNF drugs can also be associated with side effects. In addition, the use of biologics is currently limited by their cost, especially in developing countries. A number of new therapeutic targets, including novel small molecules, and cellular therapy are available or under investigation. These novel molecules include oral Janus kinase (JAK) inhibitor (tofacitinib), interleukin inhibitor (ustekinumab), oral SMAD7 antisense oligonucleotide (mongersen), and anti-integrin inhibitors (vedolizumab). Here, we review the mechanisms of action, the efficacy, and the safety data of these novel agents. Biological products that are highly similar to reference biologic products whose patents have expired—also known as "biosimilars"—can be produced at lower cost with similar efficacy, and are also available for the treatment of IBD. We review the efficacy data for such agents as well.

Keywords Crohn's disease · Ulcerative colitis · Biologics · Biosimilar

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Abbreviations

IBD	Inflammatory bowel disease
CD	Crohn's disease
UC	Ulcerative colitis
TNF	Tumor necrosis factor
JAK	Janus kinase
AVA	Anti-vedolizumab antibody
PML	Progressive multifocal leukoencephalopathy
JC	John Cunningham
FDA	Food and Drug Administration
EMA	European Medicines Agency

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), is an inflammatory disease of the intestinal tract of unknown etiology. The mainstay of treatment for IBD is inducing and maintaining disease remission. New therapeutic goals also involve achieving mucosal healing, which has been shown to lead to improved clinical outcomes, including lower rates of surgical intervention [1–3]. Once an uncommon disease entity in Asia, the incidence of IBD is on the rise [4, 5], and its severity in Asia can be equal to or greater than that in the West. Asian patients with CD frequently progress to complicated disease and have accelerated use of immunosuppressants [6].

CD is often a progressive disease. Patients who initially present with inflammatory disease may eventually develop complications involving strictures or perforation [7]. The extent of UC may also progress over time [8, 9]. Traditionally, a step-up approach, with corticosteroids followed by immunosuppressive agents, has been recommended for the management of IBD [10]. Current evidence, however,

suggests that early combination therapy may result in a better clinical outcome for patients than conventional step-up therapy in both CD [11] and UC [12].

Current biologics and unmet needs

Anti-tumor necrosis factor (anti-TNF) agents are currently the most widely used biologic agents. They are highly effective in the treatment of both CD and UC, and are the mainstay of therapy in patients with fistulizing or perianal CD [13–18]. However, the use of anti-TNF drugs is not without drawbacks. First, up to 30% of patients do not have a response to initial treatment with anti-TNF, also known as primary non-responders [19]. Primary non-responders are unlikely to respond to another anti-TNF agent and require switching to another therapeutic class [20]. Secondary non-responders are patients who have a transient response but ultimately experience a loss of response to anti-TNF therapy [21]. In secondary non-responders, the measurement of trough drug levels and anti-drug antibodies may help guide the subsequent management. In patients with subtherapeutic drug levels, management may involve dose intensification, while patients with detectable antibodies may benefit from switching to another anti-TNF agent [21, 22]. Secondary non-responders with adequate trough levels, however, should switch to a different class of agent [21, 22]. Second, anti-TNF treatment may increase the risk of infection, as was found with the use of infliximab, for example, which was associated with a 1.4- to 1.6-fold increase in serious infections [23, 24]. TNFα is important for granuloma formation [25], and the use of anti-TNF agents has been reportedly associated with a fivefold increased risk of tuberculosis [26, 27]. In addition, anti-TNF therapy has been associated with hepatitis B reactivation [28, 29]. Given that both tuberculosis and hepatitis B are endemic in Asia [30–32], special attention should be paid to these conditions, and vigilant screening and monitoring is necessary in patients treated with anti-TNF agents. Third, the use of anti-TNF drugs has been associated with a small risk of malignancy, and the risk was dose-dependent [33]. The risk of non-melanoma skin cancers and non-Hodgkin lymphoma may be increased with anti-TNF use, and the risk is further increased if anti-TNF agents are combined with thiopurine therapy [34, 35]. In a meta-analysis of CD patients receiving immunosuppressants and anti-TNF agents, the relative risk of lymphoma in patients receiving anti-TNF therapy was 3.23 compared to baseline and 1.7 compared to patients receiving an immunomodulator alone [34].

With the development of novel approaches to IBD therapy, such as new target molecules for biologic agents and cellular therapy, the treatment paradigm of IBD will change, and these novel biologic agents may provide an alternative for patients who require biologic treatment. These novel targets include, but are not limited to, oral Janus kinase (JAK) inhibitor (tofacitinib), interleukin inhibitor (ustekinumab), oral SMAD7 antisense oligonucleotide (mongersen), and anti-integrin inhibitors (vedolizumab) [36].

The current use of biologics is limited by their cost [37], and public health insurance coverage varies from country to country. In some countries, patients are required to pay for biologic therapy, and this is reflected in lower uptake of biologic therapy in these countries [38]. With the expiration of patents for certain biologics, biological products that are highly similar to the reference product and can be produced at a lower cost with similar efficacy—also known as biosimilars—are already available in some countries, including South Korea and India [39].

Anti-integrin inhibitors

Vedolizumab

Integrins are cellular adhesion transmembrane proteins that are integral to the process of inflammation [40]. The α4β7 integrin mediates selective trafficking of gut-homing CD4+ T lymphocytes to the gut, where they bind to the addressin cell adhesion molecule 1 (MAdCAM-1), expressed on intestinal venules and up-regulated at sites of inflammation [41]. Vedolizumab is a monoclonal antibody that binds specifically to the α4ß7 integrin, resulting in gut-selective anti-inflammatory activity by preventing the infiltration of leucocytes into the gastrointestinal submucosa [42].

The efficacy of vedolizumab in inducing and maintaining remission in patients with UC was investigated in the GEMINI I study [42]. In the induction phase, patients receiving vedolizumab were given intravenous injections at a dose of 300 mg at weeks 0 and 2. In the randomized blinded cohort, 47% of patients receiving vedolizumab achieved the primary endpoint at week 6, significantly higher than that in the placebo group [42]. Patients in either cohort who had a response to vedolizumab at week 6 were enrolled in the maintenance phase, in which they were randomly assigned to one of three groups: vedolizumab every 4 weeks, vedolizumab every 8 weeks, or switching to placebo for up to 52 weeks. Patients in the groups with vedolizumab every 4 weeks and every 8 weeks both achieved significantly higher rates of clinical remission compared to the placebo arm ($p < 0.001$) [42].

A recent Cochrane review including four studies with a low risk of bias showed that vedolizumab was superior to placebo for induction of clinical remission and response

and endoscopic remission in patients with moderate to severe active UC, and for the prevention of relapse in patients with quiescent UC [43].

The GEMINI II trial investigated the efficacy of vedolizumab in patients with moderate to severe active CD. There were two primary endpoints: clinical remission, defined as Crohn's Disease Activity Index (CDAI) score of ≤ 150 at week 6, and CDAI-100 response, defined as ≥ 100-point reduction in CDAI. In the randomized cohort of the induction phase, only the primary endpoint of clinical remission at week 6 reached statistical significance, with patients receiving vedolizumab having a higher rate of clinical remission, while CDAI-100 response did not reach statistical significance [44].

Patients achieving clinical remission at week 6 were enrolled in the maintenance phase. Similar to the GEMINI I study, patients were randomly assigned to one of three groups: vedolizumab every 4 weeks, vedolizumab every 8 weeks, or switching to placebo for up to 52 weeks. At week 52, the rate of clinical remission was higher in both groups receiving vedolizumab than in the placebo group [44].

The GEMINI III trial focused on patients with moderate to severe active CD who had failed anti-TNF therapy. The primary endpoint was clinical remission at week 6 in the anti-TNF failure subgroup. Among patients with CD and anti-TNF intolerance or failure, vedolizumab was not more effective than placebo in achieving clinical remission at week 6 [45]. However, an effect was shown at week 10, with 26.6% of those who received vedolizumab achieving remission, compared with 12.1% in the placebo group ($p = 0.001$) [45]. These data suggest that vedolizumab is effective among patients with CD refractory to conventional therapy, including anti-TNF agents, but that the onset of action is relatively slow, often requiring 10 weeks or more of therapy [45].

In a real-life setting, a retrospective cohort of 212 patients with moderate–severe CD receiving vedolizumab showed a 12-month cumulative rate of clinical remission, mucosal healing, and deep remission of 35, 63 and 26%, respectively [46]. The study revealed that smoking, perianal disease, severe disease, and previous anti-TNF exposure were predictors of poor response to vedolizumab in CD [46]. No head-to-head trials of vedolizumab against active comparators have been reported. Indirect comparisons suggest that vedolizumab is similar to TNF antagonists for inducing remission in UC [15, 47, 48]. Future studies comparing vedolizumab with other biologic agents would provide more concrete evidence of the efficacy of vedolizumab vs. other biologic agents, and the exact position of this drug in the treatment paradigm of UC. Such studies are currently under way.

Vedolizumab has shown a favorable safety profile over an extended treatment period of up to 5 years in a population of over 2800 patients [49]. There was no evidence of increased risk of serious opportunistic infections, and the rate of malignancy was comparable to that observed in IBD [49]. The most common adverse effects reported were generally mild, and included nasopharyngitis, headache, arthralgia, and nausea [49]. There was also no clear sign of increase risk of enteric infection [49]. Less than 5% of patients experienced infusion reactions, which were generally mild (mainly headache and nausea), and infusion was interrupted in less than 1% [49]. Four percent of patients receiving vedolizumab developed anti-vedolizumab antibodies (AVA), and the co-administration of immunosuppressive agents appeared to reduce the AVA positivity rate [49]. Whether AVA translates into poorer efficacy and whether co-administration of immunosuppressive therapy is recommended with the use of vedolizumab must be determined in future clinical studies.

Natalizumab, a monoclonal antibody with efficacy in multiple sclerosis and in CD, inhibits both $\alpha 4\beta 1$ and $\alpha 4\beta 7$ integrins and has been associated with progressive multifocal leukoencephalopathy (PML) [50]. PML is a rare but often untreatable and lethal disorder of the central nervous system, caused by reactivation of the John Cunningham (JC) virus [51], and can be provoked by natalizumab [52]. Based on the experience of a group of multiple sclerosis patients, the estimated incidence of PML was nearly one case per 1000 patients receiving natalizumab [52]. Natalizumab and vedolizumab differ, however, in that natalizumab blocks lymphocyte trafficking to multiple organs, including the brain and gut, while vedolizumab is gut-specific [53]. No significant changes were observed in cerebral spinal fluid T-lymphocyte populations in either humans or primates receiving vedolizumab [53, 54]. In clinical trials involving vedolizumab, patients were screened for neurological symptoms of PML, and shall be referred for further evaluation should they exhibit any symptoms. Despite active efforts to identify cases of PML, it has not been reported thus far in patients receiving vedolizumab [49].

Oral Janus kinase (JAK) inhibitor

Tofacitinib

Janus kinase (JAK) 1 and JAK3 are tyrosine kinases that mediate signal transduction activity involving the common gamma chain of the surface receptors for multiple cytokines, including interleukins 2, 4, 7, 9, 15, and 21 [55, 56]. These cytokines are integral to lymphocyte activation, function, and proliferation. Blockade of this common

gamma chain of multiple cytokines results in suppression of both T and B cells, while maintaining regulatory T-cell function [55–57]. The role of JAKs in inflammatory disorders has made these molecules an attractive potential therapeutic target in IBD [57].

Tofacitinib selectively inhibits JAK1 and JAK3, and has been used for the prevention of organ transplant rejection [58] and the treatment of rheumatoid arthritis [59] and psoriasis [60]. The efficacy of tofacitinib in IBD was recently evaluated in a double-blind placebo-controlled phase 2 trial, in which 194 patients with moderate to severe active UC failing conventional therapy were randomized to receive tofacitinib at a dose of 0.5, 3, 10, or 15 mg or placebo twice daily for 8 weeks. The efficacy of tofacitinib was dose-dependent [61]. Up to 78% of patients receiving 15 mg of tofacitinib achieved the primary endpoint, with clinical response at week 8, while this was achieved by 32, 48 and 61% of those receiving 0.5, 3, and 10 mg, respectively [61]. Only the response in the 15-mg group reached statistical significance compared with the placebo group ($p < 0.001$) [61]. Patients receiving tofacitinib were also more likely to achieve clinical remission (defined as a Mayo score ≤ 2, with no subscore >1) at 8 weeks, endoscopic response, and endoscopic remission [61]. These effects appeared to be dose-dependent as well [61]. There was also a reduction in C-reactive protein (CRP) and fecal calprotectin concentrations in patients receiving tofacitinib [61]. Similar results were shown in the preliminary data from two large phase 3 randomized studies. Analysis of these phase 3 studies found that anti-TNF-naïve patients may respond better than anti-TNF-experienced patients [62]. In addition to clinical improvements, the use of tofacitinib was associated with improvement in health-related quality of life [63]. Patients were also reportedly generally satisfied with the use of tofacitinib, and patient satisfaction was almost completely mediated by improvement in Mayo scale domains [64].

Tofacitinib is an oral formulation, is convenient, and appeared to be effective in patients with moderate or severe active UC failing conventional therapy. However, its efficacy in maintaining remission has yet to be determined in longer-term study. In CD, tofacitinib failed to demonstrate a significant improvement in clinical response and rate of remission at week 8 in a trial involving patients with moderate or severe CD [65]. Whether the failure of tofacitinib to demonstrate efficacy as induction therapy in CD represents a true drug biological difference from UC, or was due to a high placebo response rate, is not clear [65]. To address this, a phase 2b induction trial (NCT01393626) of tofacitinib in CD is under way [66].

Overall, tofacitinib appeared safe. The most commonly reported adverse effects were generally mild, and included nasopharyngitis and influenza [61]. Specifically, there was a dose-dependent increase in both low-density (LDL) and high-density lipoprotein (HDL) cholesterol concentrations at 8 weeks with tofacitinib, which was reversible after discontinuation of the drug [61]. The mechanism for this is unknown. Significant neutropenia and elevation of creatinine kinase were also reported [61, 62]. It is suggested that patients have their lipid profile, creatinine kinase, and neutrophil count monitored after initiating treatment.

Interleukin inhibitor

Ustekinumab

Genome-wide association studies have shown an association between the IL12/IL23 pathway and CD [67]. Ustekinumab is an interleukin inhibitor which blocks the biological activity of IL-12 and IL-23 through their common p40 subunit, and thus inhibits receptors for these two cytokines on T cells, natural killer cells, and antigen-presenting cells [68]. The efficacy of ustekinumab was investigated by the CERTIFI Study Group. Patients with moderate to severe CD refractory to anti-TNF therapy were recruited to the study. In the induction phase, patients were randomly assigned to receive intravenously administered ustekinumab (at a dose of 1, 3, or 6 mg kg^{-1} of body weight) or placebo. Patients receiving ustekinumab achieved a better clinical response at week 8 than those in the placebo group, with the greatest effect appearing with the group receiving 6 mg kg^{-1} [69].

Patients who achieved clinical response at week 6 were enrolled in the maintenance phase. These patients underwent a second randomization to receive subcutaneous injections of ustekinumab (90 mg) or placebo at weeks 8 and 16. At week 22, the ustekinumab group had higher rates of clinical remission and clinical response than did the placebo group [69]. This effect was also shown in a large open-label cohort from Spain, with up to 84% of the patients receiving ustekinumab achieving a clinical response [70]. In addition, the initial response to ustekinumab and the use of two or more immunosuppressants were found to predict a good response, while previous bowel resection predicted long-term failure with ustekinumab [69]. Another observational study demonstrated that almost two-thirds of patients with CD refractory to at least one anti-TNF agent receiving ustekinumab were able to be free from steroids for up to 12 months [71].

The intravenous injection of ustekinumab was used to induce remission, while subcutaneous injection was used for maintenance therapy. In an earlier phase 2a study, intravenous injection reportedly resulted in improved clinical remission and response [72]. However, it has been postulated that a reduced amount of the drug is generally required to maintain efficacy. In addition, subcutaneous

administration offers greater convenience for patients. Hence, subcutaneous injection was chosen for the maintenance phase [69].

Rates of adverse events and serious adverse events were similar between the ustekinumab and placebo groups. No cases of tuberculosis were reported, and infusion reactions were rare and mild. One case of basal cell carcinoma was reported in the ustekinumab group [69]. In a real-life cohort with a median follow-up of 10 months, no patients withdrew from treatment due to adverse events [69]. Based on experience in dermatology, the use of ustekinumab for up to 5 years is safe, with no increased risk of malignancy, major adverse cardiovascular events, serious infection, or mortality [73, 74]. However, additional long-term data are needed to prove its safety in IBD.

Oral SMAD7 antisense oligonucleotide

Mongersen

A diminished ability to mount an efficient counter-regulatory TGF-β1 response to inflammatory stimuli is believed to be instrumental in the pathogenesis of CD [75]. This is caused by increased levels of SMAD7, an intracellular protein that binds to the TGF-β receptor and prevents TGF-β1-associated and SMAD-associated signaling [75]. Hence, SMAD7 is a potential target for treatment of IBD. Mongersen (GED0301) is an oral formulation containing the SMAD7 antisense oligonucleotide that hybridizes to the human SMAD7 messenger RNA and facilitates ribonuclease (RNase) H-mediated RNA degradation through a classic antisense mechanism [76]. It was developed as an oral preparation with a pH-dependent coating designed to deliver the active substance primarily to the lumen of the terminal ileum and right colon [76]. In vivo data involving a mouse model have shown that oral administration of SMAD7 antisense oligonucleotide can down-regulate SMAD7 and alleviate CD-like colitis [77].

A double-blind placebo-controlled phase 2 trial involving 166 patients with moderate to severe CD, with disease at the terminal ileum or right-sided colon, were randomized to receive placebo or mongersen in doses of 10, 40, and 160 mg daily. Up to 65% of patients receiving mongersen achieved clinical remission at day 15, which was maintained for at least 2 weeks [76]. The rate of clinical response reached as high as 72% in the mongersen group, and was significantly higher than that in the placebo group [76]. Both clinical remission and clinical response were observed most frequently in the group receiving 160 mg daily [76].

A post hoc analysis of the above phase 2 study revealed that patients with higher CDAI scores required higher doses of mongersen to achieve clinical remission, while baseline CRP levels and disease duration did not appear to affect the dosage required to induce clinical remission [78]. This shed light on the dosing requirement for mongersen, and should be further confirmed in a larger-scale phase 3 study. It should be noted that the study excluded patients with known lesions in the stomach, proximal small intestine, transverse colon, or left colon. Patients were also excluded if they had strictures, fistulae, or perianal disease. Therefore, current data support the use of mongersen only in patients with terminal ileum or colonic involvement, without strictures or fistula formation.

There was no increased risk of infection observed in the study group in the induction phase compared to the placebo group [76]. Most serious adverse events in the study group were related to hospitalization due to underlying CD. Most adverse events were mild and were comparable between the placebo and mongersen groups [76]. Overall, mongersen appeared to be safe, but the current data involved only a small number of patients with a short (approximately 8-week) follow-up. Hence, longer-term data are needed to confirm the safety of mongersen.

Thalidomide

Thalidomide is an "old" medication, having been used as a sedative and antiemetic in the 1960s. However, its teratogenic effects led to discontinued use of the drug [79]. Until recently, thalidomide was again used again in various autoimmune conditions [80] and for treatment of multiple myeloma [81]. Thalidomide has been shown to inhibit TNF-α production by monocytes and other cells [82–84], and its use in CD has been investigated.

Thalidomide is useful for patients with steroid-dependent luminal CD, and even in patients with fistulizing disease. Studies have reported that clinical response at month 3 was 60–75%, with 20–40% patients able to maintain remission [85–89], and about 40% of patients able to stop steroids [85]. In a randomized controlled trial studying the effect of thalidomide on clinical remission in pediatric refractory CD, the mean duration of remission in the thalidomide group was 181.1 weeks, compared to 6.3 weeks in the placebo group ($p < 0.001$) [90].

Thalidomide has potent teratogenicity (e.g., amelia and phocomelia) [91]. It is labeled as a pregnancy category X drug by the US Food and Drug Administration (FDA), which signifies that it is contraindicated in pregnancy [92]. All women of childbearing age should be informed of the potential teratogenicity and advised to use two complementary contraceptive methods if taking thalidomide [93].

Sedation is a common side effect of thalidomide [85]. Use of the drug, and long-term use in particular, has been associated with peripheral neuropathy [94]. Up to 38% of

patients were reported to experience neuropathy [86], and thalidomide-induced neuropathy was typically a sensory axonal disturbance [87]. Up to 46% of patients withdrew from therapy due to adverse events at 24 months, with neuropathy the main reason for thalidomide withdrawal [86], thus limiting the long-term use of the drug for maintaining remission.

Biosimilars

IBD imposes a huge economic burden on healthcare systems in many countries. The major utilization and cost of healthcare related to IBD has shifted from hospitalization and surgery to medication, and biologic therapy in particular [95]. Biologic medicines comprise proteins or other substances derived from a biological source [96]. A biosimilar product is a biological product that is highly similar to a reference product, with no clinically meaningful differences in terms of safety or efficacy [97]. Due to their highly complex nature, biosimilar agents may not be identical to the reference product, but the active ingredients are essentially the same as those of the reference product [98]. The FDA allows only minor differences in clinically inactive components in biosimilar products [97]. These drugs are intended to be designed as a less expensive version of the reference product [99]. In some countries, biosimilars can offer savings of up to 72% compared to the original biological product [100]. A multi-country budget impact analysis of biosimilars for the treatment of rheumatoid arthritis has shown that the use of biosimilars resulted in significant cost savings [101]. Another budget impact model for a biosimilar of infliximab in CD also predicted budget savings, resulting in cost savings that would offset the cost of treating additional CD patients [102].

Biosimilars in IBD

CT-P13 is a biosimilar version of infliximab and is the first monoclonal antibody biosimilar being used in clinical practice [103]. It has been approved by the European Medicines Agency (EMA) for use in all indications for which infliximab is approved, including the treatment of IBD [104].

Multiple studies have shown that CT-P13 appears to have comparable efficacy and safety for patients requiring induction therapy and maintenance of remission in IBD [105, 106]. Switching from the infliximab originator to its biosimilar was also shown to be safe in pediatric CD patients, and appeared to be as effective as the originator [107, 108].

A post-marketing study of CT-P13 in patients with IBD showed no unexpected treatment-emergent adverse events [109]. However, patients with previous infliximab exposure exhibited lower response rates and were more likely to develop allergic reactions [106].

Both the FDA and EMA require biosimilar products to show safety and efficacy similar to the reference product before registration [97, 98]. With additional data forthcoming, it is expected that biosimilars will be the next generation of drugs for the treatment of IBD [110].

Position of new biologics in the treatment paradigm of IBD

Given the favorable safety profile of vedolizumab, it may be used as a first-line biologic agent, especially in patients at high risk of infection. It is more efficacious in UC than in CD, and in anti-TNF-naïve patients than in patients who are anti-TNF-experienced. Ustekinumab can be considered in patients with moderate to severe CD refractory to anti-TNF treatment. Tofacitinib may be considered in patients with moderate or severe UC who failed first-line therapy, and may be used in both anti-TNF-naïve and anti-TNF-experienced patients. Mongersen is suitable in a highly selected group of patients with inflammatory-type CD who have steroid-dependent or refractory disease at the terminal ileum or right-sided colon. It is suitable for both anti-TNF-naïve and experienced patients. In view of the lack of long-term safety data for ustekinumab, tofacitinib, and mongersen, the use of these medications in patients at high risk of infection is not recommended. Thalidomide is an alternative agent for patients with steroid-refractory CD who have limited access to biologic therapy. Given the comparable efficacy and safety, with the additional advantage in cost savings, biosimilars represent a new generation of drugs for the treatment of IBD, especially in countries where cost is a concern.

Conclusions

Several novel agents targeting different inflammatory pathways in IBD are available or under investigation. Many of these have demonstrated good efficacy and safety profiles, and can serve as a treatment alternative for patients who have failed first-line therapy (Table 1). The anti-$\alpha 4\beta 7$ integrin in particular has an excellent safety profile due to its gut-selective properties, and may be used as first-line therapy, especially in patients at high risk of infection. Biosimilars have lower costs but comparable efficacy and safety profiles, rendering them particularly useful in countries where cost is a concern.

Table 1 Summary of emerging biologics in inflammatory bowel disease and their potential position in the treatment paradigm

	Mechanism of action	Proposed position in the treatment paradigm of IBD	Side effects
Vedolizumab	α4β7 integrin inhibitor	May be used as first-line treatment Efficacy stronger in UC than in CD	Generally mild (e.g. nasopharyngitis, headache, arthralgia, and nausea)
Tofacitinib	JAK1 and JAK3 inhibitors	Moderate to severe UC who failed conventional line therapy	Dose-dependent increase in both LDL and HDL Neutropenia Raised CK
Ustekinumab	IL12/IL23 inhibitor	Moderate to severe CD that is refractory to anti-TNF therapy	Generally mild (e.g. mild infusion reaction)
Mongersen	SMAD7 antisense oligonucleotide	Steroid-dependent or steroid-refractory CD	Generally mild (e.g. arthralgia and urinary tract infections)
Thalidomide	TNF-α inhibitor	Steroid-dependent luminal or fistulizing CD	Teratogenicity Neuropathy Sedation

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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