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Horizon scanning: new and future therapies in the management of inflammatory bowel disease

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ABSTRACT

The current mainstay treatment modalities for inflammatory bowel disease (IBD) include immunomodulators (methotrexate and thiopurines), biologics (antitumour necrosis factor alpha (TNF-α) being the most commonly used) and other monoclonal antibodies such as the anti-integrins and anti-interleukins (IL-12/23). While ideally treatment should be initiated early in the disease process to avoid relapses and complications, the major recurring issue continues to be primary and secondary loss of response, with often 'diminishing returns' in terms of efficacy for the next line of therapies prescribed for patients with IBD. Additional concerns include the long-term risk factors such as malignancy and susceptibility to infections. Recently, there has been an influx of new and emerging medications entering the market that are showing promising efficacy results in patients with moderate-to-severe disease who have previously failed to respond to multiple drugs. This review will focus on these novel and emerging therapies—in essence, 'horizon scanning'—which includes the antiadhesion agents, cytokine inhibitors, Janus kinase inhibitors, phosphodiesterase inhibitors, sphingosine-1 phosphate receptor modulators and MicroRNA-124 (miR-124) upregulators.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory diseases that affect the gastrointestinal tract. Just a few decades ago, these conditions carried a poor prognosis but there have been significant improvements in both the understanding of the disease processes and the development of novel therapeutic modalities.[1] The International Organisation for the Study of Inflammatory Bowel Diseases developed the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-1 and STRIDE-2) programmes, which recommend specific treatment goals to help direct clinical management strategies in both UC and CD for children and adults.[2 3] The steering committee identified and endorsed the importance of targeting clinical response and remission, endoscopic healing, normalisation of C reactive protein/erythrocyte sedimentation rate and faecal calprotectin, prevention of disability, restoration of quality of life and normal growth in children.

The current mainstay treatment modalities for inflammatory bowel disease (IBD) include immunomodulators (methotrexate and thiopurines), biologics (antitumour necrosis factor alpha (TNF-α) being the most commonly used) and other monoclonal antibodies such as the anti-integrins and anti-interleukins (IL-12/23). While ideally treatment should be initiated early in the disease process to avoid relapses and complications,[4 5] the major recurring issue continues to be primary and secondary loss of response,[6 7] with often 'diminishing returns' in terms of efficacy for the next line of therapies prescribed for patients with IBD. Indeed, most clinical trials demonstrate a response rate of under 60%, which only worsens with each failing drug particularly when the withdrawal reason from the first drug is primary failure.[8] Recently, there has been an influx of new and emerging medications entering the market that are showing promising efficacy results in patients with moderate-to-severe disease who have previously failed to respond to multiple drugs. This review will focus on these novel and emerging therapies—in essence, 'horizon scanning'—which will include therapies that are currently in late phase 2 and phase 3 studies and should become globally available in the next 1–2 years. Subsequently, we will focus our discussion on the subcutaneous and oral anti-TNFα preparations, antiadhesion agents, cytokine inhibitors, Janus kinase (JAK) inhibitors, phosphodiesterase (PDE) inhibitors, sphingosine-1 phosphate (S1P) receptor modulators and Micro-RNA-124 (miR-124) upregulators. Figure 1 provides an overview of the mechanisms of action for new and future therapies in this review.

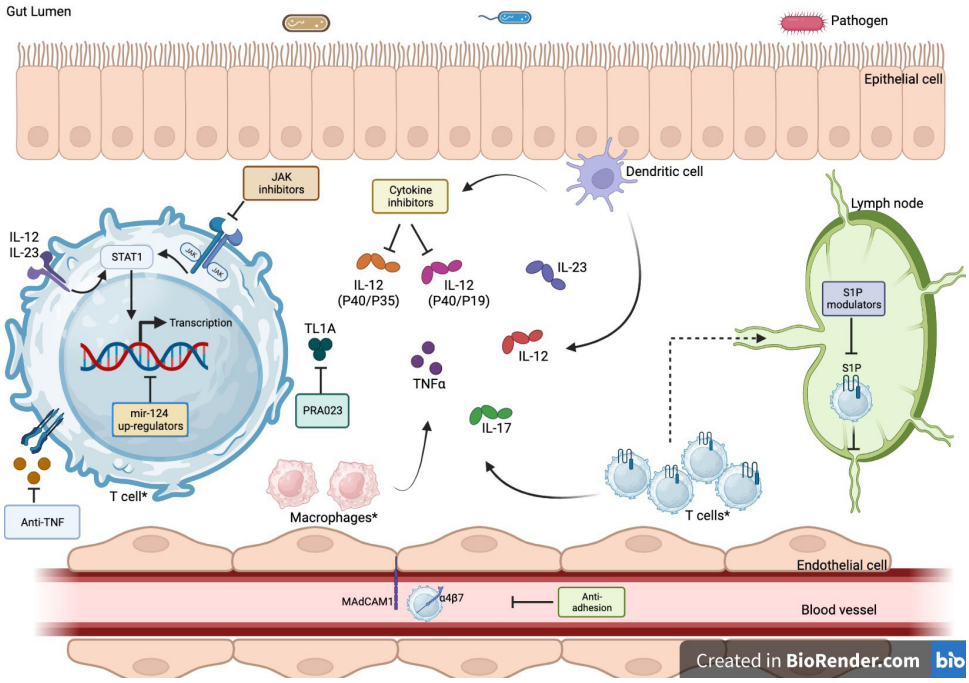

Figure 1 Overview of the mechanisms of action for new and future therapies in the management of inflammatory bowel disease. Antitumour necrosis factor alpha (anti-TNFα) agents include infliximab, adalimumab, golimumab, AVX-470 and OPRX-106. Janus kinase (JAK) inhibitors: tofacitinib, filgotinib and upadacitinib. Cytokine inhibitors: ustekinumab, which targets interleukin (IL) 12, subunit p40/p35; risankizumab, mirikizumab, guselkumab and brazikumab target IL-23, subunit p40/p19. Sphingosine-1-phosphate (S1P) receptor modulators: amiselimod, ozanimod, etrasimod and fingolimod. Antiadhesion agents: vedolizumab, etrolizumab and ontamalimab. The microRNA-124 agent is obefazimod. * indicates the cells which phosphodiesterase (PDE) inhibitors such as apremilast act upon. Image created through the use of www.biorender.com. MAdCAM-1, mucosal addressin cell adhesion molecule 1; STAT, signal transducer and activator of transcription; T cell, T lymphocytes; TL1A, tumour-necrosis factor-like cytokine 1A; α4β7, alpha 4 beta 7.

ANTI-TNFα

The introduction of anti-TNFα therapies in the late 1990s revolutionised the realm of medical therapy and is still considered as the best first-line treatment for both UC and CD.[9] Infliximab has also consistently demonstrated to be the most effective drug in the treatment of perianal fistulating CD.[10 11] The development for subcutaneous and oral routes of administration are underway and show promising preliminary results.

CT-P13

The infliximab biosimilar CT-P13 (Remsima, Inflectra) is identical to the reference infliximab with similar physiochemical characteristics. In 2017, the NOR-SWITCH trial demonstrated that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator.[12] This study, however, combined all disease conditions including UC, CD, rheumatoid, psoriatic and spondylarthritis and was not powered to show non-inferiority in individual diseases. Ye *et al* demonstrated the intravenous formulation (CT-P13 IV) to be non-inferior from the infliximab originator in patients with active CD.[13]

Soon thereafter, the subcutaneous CT-P13 formulation arrived, providing the opportunity for patients to self-administer their medication. Schreiber *et al* initially demonstrated non-inferiority of subcutaneous CT-P13 to intravenous CT-P13.[14] Moreover, the efficacy, safety and immunogenicity outcomes did not differ between patients receiving the subcutaneous or intravenous groups. The REM-SWITCH study published in 2022 confirmed that switching from intravenous to subcutaneous infliximab 120 mg every other week was safe and well-accepted, with a low risk of relapse in patients with IBD. The study further recommended to increase the subcutaneous dose to 240 mg for those patients receiving 10 mg/kg intravenous infliximab.[15] Colombel *et al* recently presented the findings of their LIBERTY-CD phase 3 study.[16] Patients with CD were initially given intravenous 5 mg/kg CT-P13 at weeks 0, 2 and 6 as induction therapy and patients who had a clinical response at week 10 were randomised to receive either the subcutaneous 120 mg CT-P13 or placebo every 2 weeks for 54 weeks. Results demonstrated that at week 54, the subcutaneous CT-P13 was more effective than placebo in maintaining clinical remission (62.3% and 32.1%, respectively, p<0.0001) and response (65.8% and 38.4%, respectively, p<0.0001), endoscopic response rate (51.1% and 17.9% respectively, p<0.0001) and corticosteroid-free remission (39.8% and 22.7% respectively, p=0.04). A real-world study that included 181 patients with IBD demonstrated high treatment persistence rate of 92.3% when switching from intravenous infliximab to subcutaneous CT-P13 with no

difference between weekly versus alternate weekly injections.[17] This study included 25 patients with perianal CD, of which only two patients developed disease worsening and had to be switched back to the intravenous formulation. While median infliximab levels increased from a baseline of 8.9 µg/dL to 16 µg/dL at 3 months, only 7.7% developed antibodies to infliximab. Importantly, patient acceptance and satisfaction rates were high in this study.

It is known that being able to self-administer medication improves ease of convenience for patients, optimises medical resources and reduces hospital-associated costs.[18] There are multiple additional patient benefits including reduced travel, loss of productivity and costs associated with fuel and hospital parking.[19] Unfortunately, the risk of serious side effects remains, including reactivation of tuberculosis, opportunistic infections and long-term risk of malignancy.[14 20] It would be ideal to be able to develop an anti-TNFα antibody therapy that not only delivers antibodies directly to the site of inflammation in the gut but simultaneously avoids systemic exposure and immunosuppression. Of great interest is the ongoing production of two oral anti-TNFα therapies that are exploring the efficacy of treating IBD while hopefully also reducing the systemic side effects.

AVX-470

AVX-470 and AVX-470m are oral polyclonal bovine-derived anti-TNFα therapies produced from the colostrum of cows that have been immunised with recombinant human or murine TNF, respectively. Bhol *et al* demonstrated these oral medications to be functionally comparable with infliximab in in vitro studies with mice.[21] Furthermore, orally administered AVX-470m effectively reduced disease severity in several mouse models of IBD by penetrating the colonic mucosa and delivering anti-TNF to the site of inflammation with minimal systemic exposure. Human trials thus far have showed AVX-470 to be safe and well tolerated in patients with UC at a dose of 3.5 g/day.[22 23] Further studies are ongoing.

OPRX-106

OPRX-106 is an oral plant-cell expressing recombinant TNF fusion protein (rTNFR-Fc). The rTNFR-Fc consists of the soluble form of the human TNF2 receptor fused to the Fc fragment of a human IgG_1 antibody domain, which imparts it a longer serum half-life. The plant cell wall contains cellulose which serves as a natural protective agent against the gastric environment.[24] Preclinical studies with OPRX-106 demonstrated improvement in colitis-induced mice.[25] Safety and exploratory immune modulatory effects of orally administered OPRX-106 has recently been shown in a phase 1 human study.[26] Almon *et al* published their results in 2021 demonstrating clinical response and remission with OPRX-106 in 67% and 28%, respectively, in patients with mild to moderate UC.[24] No immune suppression was noted by the lack of bone marrow suppression or alterations in subsets of lymphocytes. While further data are awaited, these results no doubt provide an exciting avenue to explore for larger controlled studies in patients with IBD.

PRA023

Tumour-necrosis factor-like cytokine 1A (TL1A) is an upstream regulator of pro-inflammatory cytokines and fibrosis signals. PRA023 is an anti-TL1A monoclonal antibody currently in development for multiple inflammatory/fibrotic diseases. A phase 2 induction study (ARTEMIS-UC) assessed the efficacy and safety of intravenous PRA023 (1000 mg on day 1 and 500 mg at weeks 2, 6 and 10) in moderately to severely active UC.[27] The primary endpoint was clinical remission at week 12 with secondary endpoints being endoscopic and histological improvement and patient-reported outcome measures. Forty-eight per cent of patients in the treatment group had been exposed to at least one advanced therapy, which included biologics and/or JAK inhibitors/S1P modulators. A significantly greater proportion of patients who received PRA023 achieved clinical remission at week 12 compared with placebo (26.5% vs 1.5%, respectively; p<0.0001) and endoscopic improvement in 36.8% vs 6%, respectively; p<0.0001. No serious adverse events, opportunistic infections or infusion reactions were reported in the treatment group. The treatment group, however, did report a higher number of COVID-19 infections.

A similar phase 2a study for patients with CD (APOLLO-CD) demonstrated clinical remission rates at week 12 of 49% in the treatment group vs 16% in placebo group (p<0.001) and an endoscopic response of 26% vs 12%, respectively (p<0.001).[28] At least 70.9% of patients were previously treated with at least one biological therapy and over 50% had two or more biological therapies. Phase 3 studies for both UC and CD are now ongoing.

ANTIADHESION AGENTS

A key contributor to chronic inflammation is altered leucocyte recruitment and there are multiple molecules that regulate the trafficking of leukocytes out of lymph nodes and into sites of inflammation within the gastrointestinal tract.[29] One of the targets is the α4β7 integrin, which is a glycoprotein that resides on the surface of leukocytes, including T and B cell lymphocytes, natural killer cells and eosinophils.[30] It interacts with the mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) on the intestinal vasculature allowing for the efflux of lymphocytes into the intestine.[31] MAdCAM-1 is predominantly expressed on the endothelium of high endothelial venules in the gut and gut-associated lymphoid tissues, and has been shown to be upregulated in IBD.[32] Table 1 summarises the phase 3 trials of all the antiadhesion agents in both UC and CD.

Subcutaneous vedolizumab

Vedolizumab is a humanised monoclonal IgG_1 antibody specific for the α4β7 integrin, which allows for gut-specific blockage of lymphocyte trafficking. The intravenous route is currently used for the induction

Table 1 The evidence for the use of anti-adhesion agents in phase 3 maintenance studies for both Crohn's disease (CD) and ulcerative colitis (UC)

Name of drug	Route of administration	Dose and frequency	CD Study name	CD Primary endpoint	CD Results (treatment vs placebo)	UC Study name	UC Primary endpoint	UC Results (treatment vs placebo)
Vedolizumab	Subcutaneous	108 mg 2 weekly	VISIBLE 2	Clinical remission at week 52	48% vs 34% p=0.008	VISIBLE 1	Clinical remission at week 52	Subcutaneous: 46.2% Intravenous 42.6% Placebo 14.3%
Etrolizumab	Subcutaneous	105 mg 4 weekly	BERGAMOT	Clinical remission and endoscopic improvement at week 66	Clinical: 35% vs 24% p=0.0088 Endoscopic: 24% vs 12% p=0.0026	HIBISCUS HICKORY LAUREL GARDENIA	Clinical remission at week 10, 66, 62, 54	None of the maintenance trials showed a significant benefit with etrolizumab over placebo in the primary or coprimary endpoints
Ontamalimab	Subcutaneous	75 mg or 225 mg 4 weekly	CARMEN-CD	Study ongoing		FIGARO-UC	Study ongoing	

and maintenance of both UC and CD.[33 34] In 2021, a randomised trial (VISIBLE 1) investigated the efficacy of subcutaneous vedolizumab compared with intravenous vedolizumab or placebo in patients with UC.[35] All patients received 300 mg of intravenous vedolizumab at weeks 0 and 2. Patients who had a clinical response at week 6 were then randomly assigned maintenance treatment with either 2-weekly subcutaneous vedolizumab 108 mg, 8-weekly intravenous vedolizumab 300 mg or placebo. The primary endpoint was clinical remission at week 52, defined as a total Mayo score of ≤2 with no subscore >1. The subcutaneous group demonstrated clinical remission rates of 46.2% compared with 42.6% intravenous and 14.3% placebo (p<0.001). The subcutaneous group also demonstrated greater endoscopic improvement. Subcutaneous and intravenous safety profiles were similar although the incidence of injection-site reactions was more frequent in patients receiving the subcutaneous route. However, majority were mild and none resulted in discontinuation. The VISIBLE-2 study similarly investigated the subcutaneous use in patients with CD, showing clinical remission rates of 48% compared with 34% in the placebo group (p=0.008).[36] Real-world data have since confirmed its efficacy and also demonstrated considerable cost-effectiveness against intravenous treatment of 15%.[37]

Etrolizumab

Etrolizumab is a monoclonal anti-integrin antibody that specifically binds to the β7 subunit of both α4β7 and αEβ7 integrins. This allows etrolizumab to regulate inflammatory cell migration to the intestinal system and modulates its actions on the intestinal epithelium.[38]

Four phase 3 studies have been published investigating the use of 105 mg subcutaneous etrolizumab given 4 weekly in moderately to severely active UC.[39–42] Two of these studies directly compared the efficacy against an anti-TNF agent and placebo.[39 42] Only two trials demonstrated a significant benefit in induction of remission—HIBISCUS trial[39] (19.4% etrolizumab vs 6.9% placebo, p=0.017) and the HICKORY trial[40] (18.5% etrolizumab vs 6.3% placebo, p=0.0033). None of these trials, however, demonstrated a significant benefit in maintenance of remission in the primary or coprimary endpoints. Etrolizumab also did not prove to be superior to anti-TNF (adalimumab[39] or infliximab[42]) with numerically similar results in both primary and secondary endpoints. No unexpected safety signals were reported in any of the trials.

The BERGAMOT study was a phase 3 trial investigating the efficacy of etrolizumab in moderately to severely active CD.[43] Induction dosing was randomised to either 105 mg (every 4 weeks) or 210 mg (at weeks 0, 4, 8 and 12) of subcutaneous etrolizumab compared with placebo. At week 14, all patients who responded were rerandomised to receive either 105 mg etrolizumab or placebo every 4 weeks for 52 weeks. Coprimary endpoints were clinical remission and endoscopic improvement (≥50% reduction

in the Simple Endoscopic Score for CD) at weeks 14 and 66. Interestingly, a significantly higher proportion of patients achieved clinical remission and endoscopic improvement with etrolizumab compared with placebo during the maintenance phase (clinical: 35% vs 24%, respectively p=0.0088; endoscopic: 24% vs 12%, respectively p=0.0026)), but not during induction (clinical: 33% vs 29%, p=0.52, endoscopic: 27% vs 22%, p=0.32). The most common treatment related adverse event were injection site erythema, arthralgia and headache.

Ontamalimab

Ontamalimab is a fully human monoclonal antibody that binds selectively and with high affinity to MAdCAM-1.[44] The TURANDOT II[45] and OPERA II[46] studies are phase 2 trials for exploring the safety and tolerability of 4-weekly subcutaneous ontamalimab in UC and CD, respectively. Dosing was either 75 mg or 225 mg. In both studies, ontamalimab was well tolerated with the most common adverse events being worsening of disease. Clinical benefit was seen in both studies although a large proportion of patients required dose escalation to 225 mg. The results from these studies supports phase 3 clinical testing of ontamalimab in both UC (FIGARO-UC; NCT03290781) and CD (CARMEN-CD; NCT03566823), which is currently ongoing.

CYTOKINE INHIBITORS

Studies have shown that IL-12, 22 and 23 are involved in IBD pathogenesis with IL-12 and 23 playing a crucial role in the maintenance of inflammation.[47] It is suggested that IL-12 is involved in the initiation of intestinal inflammation caused by epithelial barrier disruptions and works together with IL-23 to maintain chronicity.[48] However, there has been more recent research suggesting that IL-12 possesses some anti-inflammatory activity in animal models.[49] Table 2 summarises the phase 3 studies of the current cytokine inhibitors being tested for UC and CD.

Ustekinumab biosimilar

Ustekinumab is a fully human IgG_1 monoclonal antibody that blocks the biological activity of interleukin-12 and interleukin-23 through their common p40 subunit.[50] It was the first anti-IL drug developed and approved for CD and UC, given intravenously for the first dose and then subsequently given subcutaneously.[50 51] The ustekinumab patents are due to expire in September 2023 in USA and in January 2024 in Europe,[52] allowing for biosimilars to be brought into the market. Seven different biosimilars of ustekinumab (BAT2206, CT-P43, FYB202, NeuLara, ABP654, SB17, AVT04) are currently in development and going through phase 1–3 trials, although all publicly available information on these clinical trials thus far involves patients with plaque psoriasis.[53] The European Medicines Agency has approved the application for AVT04 in patients with plaque psoriasis and is expected to be released in the second half of 2023.

Table 2 The phase 3 maintenance trial evidence for the use of cytokine inhibitors specifically targeting IL-23 subunit p19 in both Crohn's disease and ulcerative colitis

			Crohn's disease			Ulcerative colitis		
Name of drug	Route of administration	Dose and frequency	Study name	Primary endpoint	Results (treatment vs placebo)	Study name	Primary endpoint	Results (treatment vs placebo)
Risankizumab	Subcutaneous	360 mg 4 weekly	FORTIFY	Clinical remission and endoscopic response at week 52	Clinical: 52% vs 41% Endoscopic: 47% vs 22%	INSPIRE	Study ongoing	
Mirikizumab	Subcutaneous	200 mg 4 weekly	VIVID	Study ongoing		LUCENT-2	Clinical remission at week 40	63.6% vs 36% p<0.001
Guselkumab	Intravenous	200 mg 4 weekly	–	Study ongoing		QUASAR	Clinical response at week 12	200 mg: 61.4% 400 mg: 60.7% Placebo: 27.6% p<0.001
Brazikumab	Subcutaneous	700 mg 4 weekly	All trials have been discontinued					

Rani therapeutics has partnered with Celltrion to develop an oral drug delivery programme for a ustekinumab biosimilar, RT-111.[54] This is designed to be a capsule, RaniPill, that is, ingested into the stomach and once it reaches the intestine, the capsule injects the drug into the intestinal wall. The RaniPill intends to replace subcutaneous or intravenous injection of biologics and drugs with oral dosing and is designed to administer drugs with bioavailability that is comparable to a subcutaneous injection. While initial phase 1 trials have shown promising results, further work is still needed to determine its future within the IBD armamentarium.

In the meantime, there are other monoclonal antibodies that are being developed to specifically target IL-23 through their subunit p19.

Risankizumab

This is a new humanised monoclonal antibody that has only recently been released in the UK and the USA for use in moderate to severely active CD.[55 56] This was following the release of two induction studies (ADVANCE and MOTIVATE)[57] and one maintenance study (FORTIFY),[58] which demonstrated that subcutaneous risankizumab was a safe and efficacious treatment for both induction and maintenance of CD. At week 52, greater clinical remission and endoscopic response rates were reached with 360 mg risankizumab versus placebo (clinical: 52% vs 41%, respectively; endoscopic: 47% vs 22%, respectively). Adverse event rates were similar among groups with worsening disease, arthralgia and headache the most frequently reported in all treatment groups.

A phase 3 induction study (INSPIRE) for patients with UC is currently ongoing. AbbVie has released an early press statement with preliminary results demonstrating that risankizumab has met the primary endpoint of clinical remission at week 12 compared with placebo (20.3% vs 6.2%, respectively, p<0.00001).[59] The patients enrolled in this study were intolerant or showed inadequate response to conventional and/or advanced therapies. Key secondary endpoints were also met at week 12, including endoscopic improvement (36.5% vs 12.1%, p<0.00001) and histological endoscopic mucosal improvement (24.5% vs 7.7%, p<0.00001).

Mirikizumab

Mirikizumab is a humanised IgG_4 monoclonal antibody that is administered intravenously or subcutaneously every 4 weeks and studies have explored induction doses of 200 mg, 600 mg and 1000 mg. The phase 2 trial for patients with UC demonstrated mirikizumab to be effective in inducing a clinical response after 12 weeks (50 mg: 15.9%, p=0.066; 200 mg: 22.6%, p=0.004; 600 mg: 11.5%, p=0.142 vs placebo 4.8%).[60] The subsequent phase 3 study (LUCENT-2) met its primary endpoint with clinical remission achieved by 63.6% from the treatment arm 200 mg vs 36% from the placebo arm at week 40 (p<0.001).[61] Furthermore, the rates of corticosteroid-free remission, endoscopic remission and histological endoscopic mucosal remission were all superior in the treatment arm compared with the placebo, regardless of patients receiving previous advanced therapy. Similarly, D'Haens *et al* conducted two randomised control phase 3 trials of mirikizumab in UC with an induction dose of 300 mg for 12 weeks followed by maintenance dose of 200 mg. Significantly higher percentages of patients in the mirikizumab group compared with the placebo group had clinical remission at week 12 (24.2% vs 13.3%, p<0.001) and at week 40 (49.9% vs 25.1%, p<0.001).[62]

The phase 2 study for CD (SERENITY) has also shown superiority in its primary endpoint of inducing endoscopic response at week 12 with intravenous mirikizumab (200 mg: 25.8%, p=0.079; 600 mg: 37.5%, p=0.003; 1000 mg: 43.8%, p<0.001 vs placebo 10.9%). Patients who responded were rerandomised to either intravenous or subcutaneous 300 mg. Endoscopic response at week 52 was 58.5% and 58.7% in the intravenous and subcutaneous groups, respectively.[63] The frequency of serious adverse events and discontinuations were higher in the non-randomised maintenance cohort with the most commonly reported adverse events being headache, weight gain and nasopharyngitis. The phase 3 study (VIVID) is ongoing.

Guselkumab

The humanised IgG_1 monoclonal antibody, guselkumab, is being investigated for its intravenous use in CD with results from the GALAXI-1 phase 2 study.[64] Of the patients recruited, 50% had refractory disease to prior biological therapy. At week 12, all three dose regimens (200 mg, 600 mg and 1200 mg at weeks 0, 4 and 8) of guselkumab induced greater clinical and endoscopic improvements compared with placebo, with a favourable safety profile. Preliminary results from the phase 3 induction study outcomes for patients with UC (QUASAR) has shown a significantly greater proportion of patients treated with either 200 mg or 400 mg guselkumab achieved the study's primary endpoint of clinical response compared with placebo at week 12 (200mg: 61.4%, p<0.001; 400 mg: 60.7%, p<0.001; placebo: 27.6%).[65] Adverse events were similar in both treatment and placebo groups, with no reports of serious infections, malignancy or death.

The VEGA trial was a proof-of-concept study that explored the combination use of guselkumab with golimumab in UC.[66] In this study, patients were randomly assigned (1:1:1) to either combination therapy (subcutaneous golimumab at weeks 0, 2, 6 and 10 followed by subcutaneous guselkumab at week 0, 4 and 8 and then 8 weekly thereafter), golimumab monotherapy or guselkumab monotherapy. At week 12, 83% in the combination group achieved clinical response compared with 61% in the golimumab monotherapy group and 75% in the guselkumab monotherapy group. At week 50, however, this reduced to 63% in the combination group, 76% in the golimumab group and 65% in the guselkumab monotherapy group.

Brazikumab

Brazikumab is an IgG_2 monoclonal antibody which has gone through phase 2 trials in both CD[67] and UC.[68] To recruit into the CD study, patients had to have failed a TNFα-inhibitor. Clinical response at week 8 demonstrated significant improvement in patients receiving 700 mg brazikumab subcutaneously every 4 weeks compared with placebo (49.2% vs 26.7%, p=0.010), however, this was not sustained at week 24 (53.8% vs 57.7%). EXPEDITION was the long-term phase 2 study exploring the use of brazikumab in UC. The company affiliated with brazikumab, AstraZeneca, released a press statement in June 2023 announcing the discontinuation of the brazikumab IBD programme, which includes the phase IIb/III INTREPID trial for CD and the EXPEDITION trial for UC and their respective open-label extension trials.[69] The cause for the study discontinuation is unknown.

JAK INHIBITORS

Thus far, the drugs described that are in development are administered either intravenously or subcutaneously, resulting in significant costs associated with their delivery and monitoring.[70] This is a burden for both the healthcare system and for patients. The JAK inhibitors are unique and attractive with their route of oral administration.

The JAK family comprises four intracellular tyrosine kinases—JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), and seven transcription factors (STATs). The binding of these factors activates the JAK-STAT pathway via different cytokine receptors and leads to changes in the levels of the immune mediators, such as interferons and interleukins[71] (figure 2). Table 3 summarises the phase 3 studies of the JAK inhibitors in UC and CD.

Tofacitinib

Tofacitinib is a reversible, competitive inhibitor of JAK1 and JAK3 with a lesser degree of interaction with JAK2. While tofacitinib has been approved for use in UC in 2018 by the European Medicines Agency,[72] testing in CD was stopped after phase 2 trials failed to meet its primary endpoints.[73 74] The OCTAVE induction and maintenance UC studies demonstrated greater improvement in patients receiving 10 mg two times per day of oral

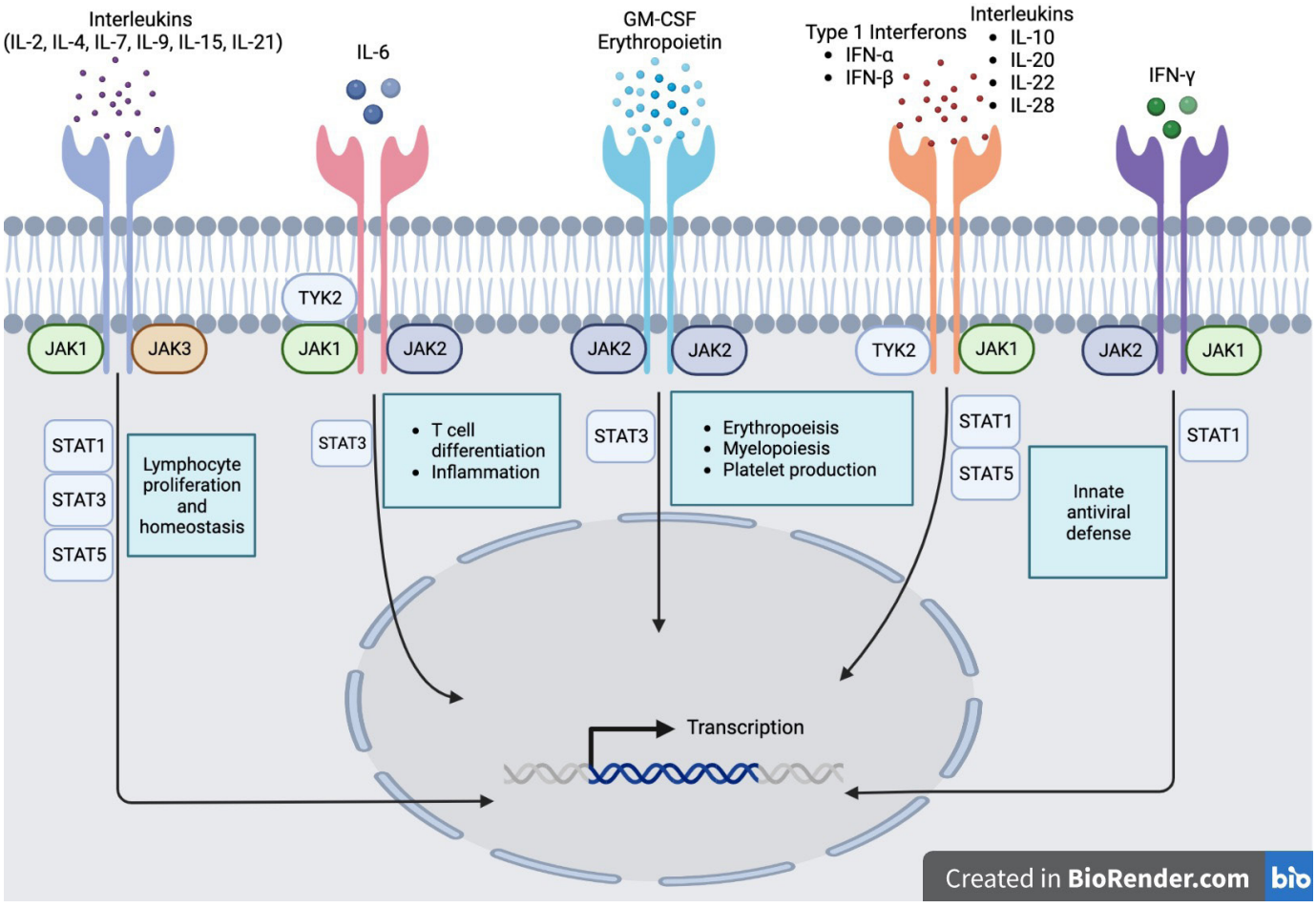

Figure 2 The JAK/STAT pathway. Distinct intracellular signalling pathways are mediated by the JAK family of tyrosine kinases. The JAK-STAT pathways use second messengers to convey extracellular information to the nucleus to affect target gene expression and cellular responses. Image created through the use of www.biorender.com. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin, JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK, tyrosine kinase.

Table 3 The phase 3 maintenance trial evidence for the use of Janus kinase inhibitors in both Crohn's disease and ulcerative colitis

Name of drug	Route of administration	Dose and frequency	Crohn's disease			Ulcerative colitis		
			Study name	Primary endpoint	Results (treatment vs placebo)	Study name	Primary endpoint	Results (treatment vs placebo)
Tofacitinib	Oral	5 or 10 mg Twice daily	–	Study was stopped after phase 2 trials failed to meet primary endpoints		OCTAVE	Clinical remission at week 52	10 mg: 41% 5 mg: 34% Placebo: 11%
Filgotinib	Oral	200 mg Once daily	DIVERSITY	Study ongoing		SELECTION	Clinical remission at week 58	37.2% vs 11.2%
Upadacitinib	Oral	Induction: 45 mg Once daily for 8–12 weeks Maintenance: 30 mg or 15 mg Once daily	U-ENDURE	Clinical remission at week 52	30 mg: 47.6% 15 mg: 37.3% Placebo: 15.1% p<0.001	U-ACCOMPLISH	Clinical remission at week 52	30 mg: 52% 15 mg: 42% Placebo: 12% p<0.0001

tofacitinib compared with 5 mg two times per day tofacitinib and placebo.[75 76] At 52 weeks, clinical remission was achieved in 41% in the 10 mg group compared with 34% in the 5 mg group and 11% in the placebo group. In both trials, however, the rates of overall and severe infection were higher in the tofacitinib group than the placebo group. Further studies demonstrated that tofacitinib was effective and safe in patients previously unresponsive to TNF inhibitors[77 78] and could be used as an effective induction strategy with intravenous corticosteroids in patients hospitalised with acute severe UC.[79] A great concern for the ongoing use of tofacitinib is the risk of deep vein thrombosis and pulmonary embolism, with a pooled analysis demonstrating thrombotic events occurring in patients receiving the higher dose of tofacitinib 10 mg two times per day.[80] Animal studies have also shown tofacitinib to be feticidal and teratogenic.[81] While human data are limited with small sample sizes, the findings thus far do not suggest an adverse safety profile in pregnancy. However, best practice recommendations including the European guidelines state tofacitinib is contraindicated in pregnancy.[82]

Filgotinib

Filgotinib is an oral JAK1 selective inhibitor with a half-life of 6 hours for the parent compound and 23 hours for the active metabolite.[83] This allows for once-daily dosing at either 100 mg or 200 mg. The SELECTION phase 2b/3 study for UC demonstrated greater clinical remission rates with 200 mg compared with placebo at week 58 (37.2% vs 11.2%, respectively).[84] The incidence of adverse events was similar between the treatment and placebo groups.

The comparative FITZROY study for patients with CD also demonstrated greater induced clinical remission rates in the 200 mg group compared with placebo (47% vs 23%, p=0.0077).[85] The phase 3 DIVERSITY study results for CD should be released soon. The phase 2 DIVERGENCE study is exploring the efficacy and safety of filgotinib for the treatment of perianal fistulating CD, with preliminary abstract results at the recent European Crohn's and Colitis Conference demonstrating a greater fistula response at week 24 with the 200 mg filgotinib group (47.1%) compared with placebo (25%).[86 87] Fistula remission had similar results with 47.1% in the 200 mg group compared with 16.7% in the placebo group.

Filgotinib is considered harmful to the fetus according to animal study findings and thus remains contraindicated in pregnancy.[82]

Upadacitinib

Upadacitinib is an oral and highly selective JAK1 inhibitor with a 74-fold selectivity for JAK1 over JAK2. It has a half-life of 4 hours, of which 80% is metabolised in the liver and 20% is renally excreted.[83] Studies in both UC[88] (U-ACHIEVE, U-ACCOMPLISH) and CD[89] (U-EXCEL, U-EXCEED, U-ENDURE) have demonstrated a superior response with upadacitinib compared with placebo in patients where corticosteroids, immunosuppressants

and/or biological therapies resulted in an inappropriate response, a loss of response or intolerance. For patients with UC, statistically significantly more patients achieved clinical remission with upadacitinib 45 mg at 8 weeks. In the maintenance study, clinical remission was achieved by more patients receiving upadacitinib 30 mg (52%) vs 15 mg (42%) and placebo (12%) at week 52, p<0.0001. Adverse events with upadacitinib in the UC studies included worsening of disease, acne, arthralgia, nasopharyngitis and elevation in creatine phosphokinase levels.

For patients with CD, a significantly higher percentage of patients receiving 45 mg were in clinical remission than placebo at week 12. At week 52, a higher percentage of patients had clinical remission with 15 mg (37.3%) or 30 mg (47.6%) than with placebo (15.1%), p<0.001 with an endoscopic response of 27.6% with 15 mg compared with 40.1% with 30 mg and 7.35 with placebo. Herpes zoster infections occurred more frequently in the 45 mg and 30 mg groups, whereas hepatic disorders and neutropenia were seen more frequently in the 30 mg group. Gastrointestinal perforations developed in four patients in the 45 mg group and one patient each in the 30 mg and 15 mg group. It is unclear, however, whether these perforations were a result of the drug or disease itself.

Although no human studies have assessed the safety of this drug in pregnancy, upadacitinib was found to be teratogenic in animal studies and thus is not currently recommended for use in pregnancy.[90]

PDE INHIBITORS

PDEs are a group of enzymes that catalyse cyclic guanosine monophosphate and cyclic adenosine monophosphate breakdown, which results in the upregulation of proinflammatory cytokines.[91] PDE-4 is of greater interest in IBD as it regulates the inflammatory response by increasing the production of proinflammatory mediators, such as TNF-α, IL-23, and decreases the production of anti-inflammatory mediators, such as IL-10[92 93] (figure 3). Table 4 summarises the current phase 3 trials for the PDE inhibitors being studied in UC and CD.

Apremilast

Apremilast is an oral PDE4 inhibitor that inhibits TNF-α and matrix metalloproteinase-3 production in the lamina propria mononuclear cells of patients with IBD.[94] It is currently approved for the treatment of psoriasis and psoriatic arthritis.[95] The phase 2 trial for UC published in 2020 did not meet the primary endpoint of clinical remission.[96] Doses were set at 30 mg or 40 mg, however, minimal benefit was observed with dose escalation. At week 12, clinical remission was achieved by 31.6% of patients receiving 30 mg of apremilast compared with 21.8% in the 40 mg group and 12.1% in the placebo group. The most common adverse effect reported was headache in 21.1% in treatment group vs 6.9% in control group. In previous studies with psoriatic disease, apremilast has been associated with weight loss and an increased, but rare, risk of depression.[97] There are no

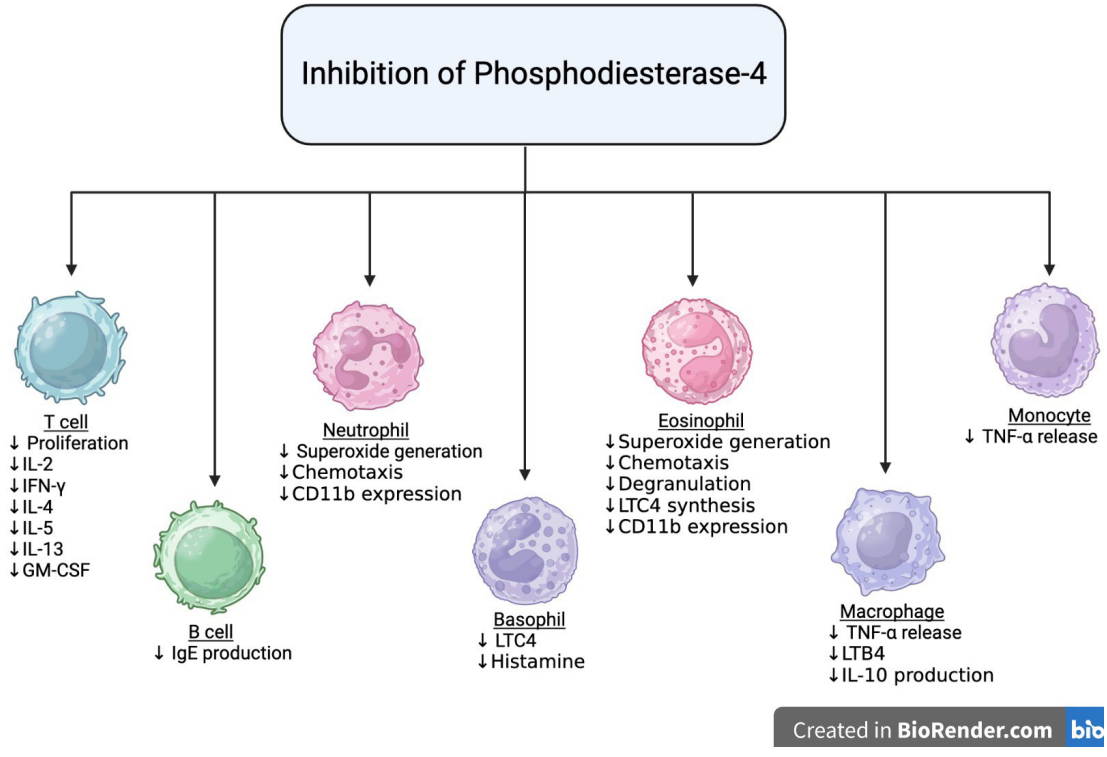

Figure 3 The inflammatory response regulation through the inhibition of the phosphodiesterase-4 enzyme. Image created through the use of www.biorender.com. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; TNF-α, antitumour necrosis factor alpha.

Table 4 The phase 3 maintenance trial evidence for the use of sphingosine-1 phosphate receptor modulators in both Crohn's disease (CD) and ulcerative colitis (UC)

			CD			UC		
Name of drug	Route of administration	Dose and frequency	Study name	Primary endpoint	Results (treatment vs placebo)	Study name	Primary endpoint	Results (treatment vs placebo)
Ozanimod	Oral	0.92 mg Once daily	YELLOWSTONE	Studies ongoing		TRUE NORTH	Clinical remission at week 52	37% vs 18.5% p<0.001
Etrasimod	Oral	2 mg Once daily	CULTIVATE			ELEVATE-UC	Clinical remission at week 52	32% vs 7% p<0.0001

current studies to explore the effects of apremilast in patients with CD.

Other PDE inhibitors are in the very early stages of development currently.

S1P RECEPTOR MODULATORS

S1P is a bioactive lipid mediator that activates the 5 cell surface G protein-coupled receptors $S1P_1$ - $S1P_5$. $S1P_1$ is the most ubiquitous of the S1P receptors and is found in both lymphocytes and endothelial cells.[98 99] The interaction between S1P and $S1P_1$ regulates lymphocyte movement from the spleen and lymph nodes into the systemic circulation. $S1P_1$ receptor modulators bind to S1P receptors, which prevents the cell surface agonist from signalling.[100] This causes the degradation of S1P inside the cells with an overall effect of fewer circulating lymphocytes into the bloodstream, leading to decreased inflammation and tissue damage[101] but also absolute lymphocyte count (figure 4).

Fingolimod

Fingolimod was the first-generation non-selective S1P receptor modulator developed for the treatment of multiple sclerosis in 2010.[102] However, it is not currently being used for IBD due to its numerous serious adverse reactions, including brady-arrhythmias, atrioventricular blocks, basal cell carcinoma and respiratory and lung injuries.[103 104]

Ozanimod

Ozanimod is an oral selective immunomodulatory agonist for $S1P_1$ and $S1P_5$ receptors, which are located on endothelial cells and oligodendrocytes, respectively. Ozanimod has a half-life of up to 11 days, requiring 55 days for complete washout after treatment cessation.[105] It

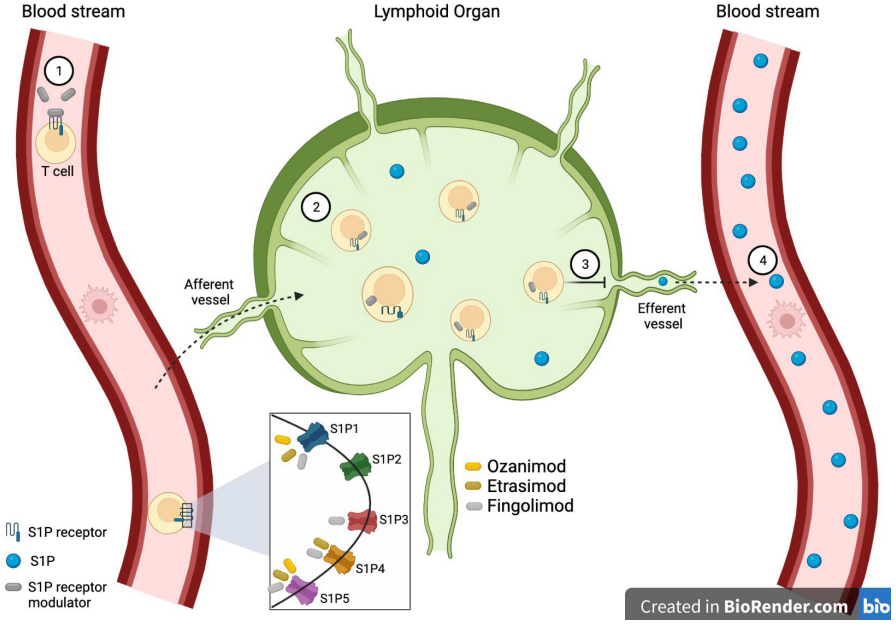

Figure 4 Lymphocyte migration and the effect of sphingosine-1 phosphate (S1P) receptor modulators in the gut. S1P receptor modulators regulate sequestration of T cell lymphocytes. S1P receptor modulators regulate sequestration of T lymphocytes via (1) binding to the S1P receptor, (2) leading to the internalisation of the S1P receptor, (3) altering the S1P gradient and (4) inducing downregulation of T lymphocytes into the bloodstream. This has an overall effect of blocking lymphocyte trafficking to the gut. Image created through the use of www.biorender.com.

was approved for the treatment of multiple sclerosis in 2020.[106]

Ozanimod was granted approval by the Food and Drug Administration for treatment of moderate to severe UC in 2021. This was following positive results from a phase 3 study (TOUCHSTONE and TRUE NORTH), demonstrating a higher proportion of treatment group patients compared with placebo achieving clinical remission during both induction (18.4% vs 6%, respectively; p<0.001) and maintenance at week 10 (37% vs 18.5%, respectively; p<0.001).[107] Recent results further demonstrated that remission was maintained long-term with comparable efficacy at 46 and 94 weeks.[108] Initial phase 2 results for CD (STEPSTONE) have shown endoscopic, histological and clinical improvements within 12 weeks of initiating ozanimod.[109] Phase 3 placebo-controlled trials (YELLOWSTONE) are underway.[110]

Ozanimod avoids interaction with $S1P_2$ and $S1P_3$, thereby reducing the risk of serious adverse effects seen in fingolimod.[107] However, the risk of cardiovascular events is still present and precautions must be taken prior to treatment initiation. Due to the risk of bradycardia, a baseline ECG should be performed in all patients prior to initiating therapy. Cardiology evaluation is recommended in patients with a prolonged QT interval, history of arrhythmias or heart block, ischaemic heart disease or heart failure.[111] A slow uptitration is also advised over 7 days such that the effective dose is first used on day 8, potentially delaying the onset of symptom relief.[107] Contraindications to ozanimod include the use of monoamine oxidase B inhibitors, which increases the risk of drug–drug and drug–food interactions. Other contraindications include severe untreated sleep apnoea, second-degree or third-degree heart block, sick sinus syndrome or sinoatrial block (unless the patient has a pacemaker in situ), and a history of myocardial infarction, stroke, transient ischaemic attacks, unstable angina or class III/IV heart failure in the last 6 months.[111] Due to the lack of human data, ozanimod is contraindicated during pregnancy.[82]

Etrasimod

Etrasimod is an oral selective immunomodulator agonist for the $S1P_1$, $S1P_4$ and $S1P_5$ receptors. It has a half-life of 33 hours, resulting in a relatively fast wash-out period of 1 week,[29 112 113] which is particularly important for family-planning patients. Earlier studies also demonstrated that etrasimod partly reduces circulating levels of specific subsets of adaptive immune cells (T and B cells) with no notable effects on the innate immunity cells such as natural killer cells and monocytes,[114] allowing for the assumption that etrasimod would not result in an increased incidence of infections.

Following the positive response from the phase 2 and open-label extension trials for etrasimod in UC,[112 115] the phase 3 ELEVATE UC were recently published to evaluate the safety and efficacy of the 2 mg oral daily dose of etrasimod compared with placebo in moderate-to-severe UC.[105] The primary endpoint was clinical remission at weeks 12 and 52 with secondary endpoints of endoscopic improvement, symptomatic remission, histological remission and corticosteroid-free remission. In the study, approximately 30% of recruited patients had previously failed or were intolerant to at least one conventional, biological or JAK therapy. Results demonstrated that a significantly greater proportion of patients in the etrasimod group achieved clinical remission compared with the placebo group at week 52 (32% vs 7%, respectively; p<0.0001). In fact, by week 52, all key secondary endpoints had been met, including sustained clinical remission (18% vs 2%, respectively) and corticosteroid-free remission (32% vs 7%). While adverse events were reported in 71% of patients in the etrasimod group vs 56% in the placebo group, most were considered mild or moderate. The most frequently reported adverse events included anaemia, headache and worsening of UC or UC flare. Overall infections, serious infections and opportunistic infections were similar between the treatment groups. No malignancies were reported but elevated liver enzymes were seen with a higher incidence in the treatment group. Nine events of bradycardia were seen in the treatment group, all discovered by day 2 of treatment initiation, with none reported in the placebo group. Five of these bradycardia events, however, led to study discontinuation.

The phase 2/3 CULTIVATE study reported induction data from the first substudy (substudy A) exploring the doses of 2 mg and 3 mg of oral etrasimod in patients with CD.[116] The primary endpoint of endoscopic response was achieved in 21.4% and 9.8% in the 2 mg and 3 mg groups, respectively. There were a greater number of adverse events reported in the 3 mg vs 2 mg groups although most were mild or moderate and general incidence (4.8% and 2.4%, respectively) and rate of discontinuation (7.3% and 4.8%, respectively) was low in both groups. The extension phase of substudy A and phase 2b substudy 1 are forthcoming.

Amiselimod

Amiselimod is an oral drug that modulates the $S1P_1$ receptor. Trial results for patients with CD were published in 2021 and updated in 2022, which demonstrated that after a 12-week course of 0.4 mg, amiselimod was not superior to placebo for inducing clinical response. Moreover, seven participants had serious adverse events including infections and cardiac disorders, of which four patients had to discontinue the drug.[117] The phase 2 Study for UC is ongoing (NCT04857112).

MICRORNA-124 (MIR-124) UPREGULATOR

MicroRNAs (miRs) are small non-coding RNA oligonucleotides that regulate the expression of a large number of genes and are centrally involved in the pathogenesis of different human inflammatory diseases.[118] Studies have shown that certain miRs are deregulated in IBD,

specifically miR-124, leading to increased levels of STAT3 expression and the transcription activation of its downstream targets.[119] STAT3 is known to be upregulated in UC and has also been implicated in the progression of UC to colon cancer.[120–122]

Obefazimod

Obefazimod is designed to upregulate miR-124, an anti-inflammatory microRNA. It enhances the selective splicing of a single long non-coding RNA to generate miR-124, which downregulates cytokines and chemokines shown to promote inflammation including TNFα, IL-6, IL-17 and Th17+cells. Interestingly, obefazimod was originally developed for the treatment of HIV as ABX464 but has been repurposed for inflammatory conditions due to its anti-inflammatory effect.

A phase 2b double-blind, randomised, placebo-controlled induction trial for obefazimod demonstrated an improvement of 5 points or higher in the modified mayo score in patients with moderate-to-severe UC at week 8 of treatment.[123] Three different doses were explored and all showed a significant least-squares-mean change from baseline in the modified mayo score compared with placebo (−2.9 for the 100 mg group, −3.2 for the 50 mg group, −3.1 for the 25 mg group compared with −1.9 for the placebo group). The most frequently reported adverse event was headache and the only serious adverse event was UC with two patients seen in the treatment group and three in the placebo group. The phase 3 96-week trial results are ongoing and will aim to assess the safety and efficacy of the two doses of obefazimod 25 mg and 50 mg. The global phase 3 programme will include two induction studies (ABTECT-1: NCT05507203 and ABTECT-2: NCT05507216) and the maintenance trial (ABTECT: NCT05535946) with results expected in 2024 and 2025, respectively.

ADVERSE EFFECTS AND CONTRAINDICATIONS FOR THE NEW SMALL MOLECULES

Table 5 summarises the adverse effects and contraindications for the new small molecules that are known to date.

COMBINATION THERAPY

The most successful example of combination therapy was demonstrated in the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease trial, where infliximab and azathioprine together were superior to monotherapy.[124] The use of azathioprine enhanced the bioavailability of infliximab and the prevention of antibodies to infliximab. The data from the UK PANTS study further demonstrated that higher remission rates in patients receiving concomitant immunosuppressive therapy were independent of drug concentration and antibody development.[125] Current research has shifted focus towards the use of advanced combination treatment where two or more advanced treatments (biological agents and/or oral small molecules) are used concomitantly. This approach may be useful in patients with refractory IBD; high-risk phenotypes such as extensive small bowel disease and/or stricturing or fistulising disease; patients with extraintestinal manifestations or concomitant immune-mediated inflammatory diseases. The most common biological combination regimen is with vedolizumab and ustekinumab, vedolizumab and anti-TNF, ustekinumab and anti-TNF. The most frequently evaluated combinations with oral small molecule drugs have been with tofacitinib and either vedolizumab or ustekinumab.[126 127] The body of evidence for the use of advanced combination therapy, however, is largely composed of uncontrolled retrospective case series and cohort studies in highly refractive patients. Thus, it is difficult to extrapolate safety and efficacy of combination therapy. Although the first randomised controlled trial (RCT) evaluating dual biological therapy was in 2007 exploring the use of infliximab with the anti-integrin agent natalizumab, the primary objective was to evaluate safety and tolerability and was not powered to measure efficacy.[128] The VEGA study was a phase 2 induction trial that evaluated the use of the anti-IL-23 agent guselkumab with the anti-TNF agent golimumab in patients with UC.[66] Results showed that patients receiving combination therapy achieved clinical response at week 12 (83%) compared with monotherapy with either guselkumab (74.6%) or golimumab (61.1%). There are now two further phase 2 RCTs investigating combination therapy with guselkumab and golimumab in both UC (DUET-UC; NCT05242484) and CD (DUET-CD; NCT05242471). A triple combination therapy with vedolizumab, adalimumab and methotrexate is being evaluated in the EXPLORER trial (NCT02764762) in patients with CD.

Currently, the practice of advanced combination therapy is 'off-label' (ie, unlicensed) and carries serious risks of infections and unknown longer-term complications. The risks of ongoing active disease should be balanced against the potential risks of combination therapy with full disclosure to the patient. Choosing agents that modulate different pathways and are further apart in the cross-talk maps may increase the chance of improved efficacy. Preference of agent should be given to those with the most favourable safety profile, such as vedolizumab and ustekinumab.[129 130]

FAECAL MICROBIAL TRANSPLANT

The gut microbiome has become of great interest in the management of IBD. FMT, dietary exclusions and modifications, prebiotics and probiotics have had varied success, with the most promising therapy being FMT in patients with UC. The first international Rome consensus conference on gut microbiota and FMT in IBD was published in 2023.[131] This stated that FMT may be effective in the induction of remission in mild to moderate UC, however, there is insufficient evidence to recommend its routine use for UC and should be limited to the research setting.

Table 5 Adverse effects and contraindications for use of the new small molecules (where this information is known)

Name	Adverse effects	Contraindications	Check prior to initiation
Etrolizumab	Injection site erythema Arthralgia Headache	Pregnancy and breast feeding	Hepatitis B, C, HIV status VZV status TB T-spot test Chest X-ray
Risankizumab	Worsening disease Arthralgia Headache Injection site reactions Anaemia Infections	Pregnancy and breast feeding	Hepatitis B, C, HIV status VZV status TB T-spot test Chest X-ray
Mirikizumab	Headache Weight gain nasopharyngitis	Pregnancy and breast feeding	Hepatitis B, C, HIV status VZV status TB T-spot test Chest X-ray
Tofacitinib	VZV Headache Infections VTE	Deep vein thrombosis Pulmonary embolism Pregnancy and breast feeding Active TB Active malignancy Caution in: Current or past long-time smokers VTE risk factors Malignancy risk factors Major adverse cardiovascular risk factors Diabetes	Hepatitis B, C, HIV status VZV status TB T-spot test Chest X-ray
Filgotinib	Nasopharyngitis Headache Nausea		
Upadacitinib	HZV Hepatic dysfunction Neutropoenia		
Ozanimod	Lymphopaenia Increased ALT Headaches Nasopharyngitis Headaches arthralgia	Cardiovascular: MI, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalisation, class III/IV heart failure, Mobitz type II second degree or third-degree atrioventricular block, sick sinus syndrome, sinoatrial block (unless pacemaker), Respiratory: severe untreated sleep apnoea Medication: concurrent use of monoamine oxidase inhibitor Pregnancy and breastfeeding	FBC ECG LFTs VZV Ophthalmic assessment if history of uveitis or macular oedema
Etrasimod	Anaemia Headache Worsening of disease Liver dysfunction Bradycardia	Pregnancy and breast feeding*	FBC ECG LFTs VZV Ophthalmic assessment if history of uveitis or macular oedema*

*Based on current information available.
ALT, alanine aminotransferase; FBC, full blood count; HIV, Human immunodeficiency virus; HZV, herpes zoster virus; LFT, liver function tests; MI, myocardial infarction; TB, tuberculosis; TIA, transient ischaemic attack; VTE, venous thromboembolism; VZV, varicella zoster virus.

This is based on RCTs that have demonstrated patients with UC do not sustain remission beyond 1 year after FMT treatment.[132–134] In CD, there is currently insufficient evidence to recommend FMT in clinical practice and should only be used for research purposes. The data for the use of FMT in CD are very limited with mainly case reports and pilot studies rather than RCTs.[135–137]

BEYOND THE HORIZON

This section provides a brief overview of therapies that are in the early phase 1 or 2 trials and are still distant on the 'horizon' before (and if) they can become widely available as future therapies. Table 6 summarises these drugs and their current phases of development.

UTTR1147A

This drug is a fusion protein consisting of a linked human IL-22 and crystallisable fragment of the human IgG_4. The primary aim of activating IL-22 is to promote tissue regeneration without causing systemic inflammation, by increasing epithelial tight junctions, promoting mucous production and secreting antimicrobial peptides.[138] A phase 1b study has shown the intravenous UTTR1147A to be safe and well tolerated in both patients with UC and healthy volunteers with the most common adverse

Table 6 New drug therapies currently in the early phases of development

Drug class	Name	Target	Route of administration	Current study phase	
				Ulcerative colitis	Crohn's disease
Human IL-22 Fusion Protein	UTTR1147A	IL-22	Intravenous	Phase 1b	N/A
Toll-like receptor nine agonist	Cobitolimod	TLR-9	Topical (enema)	Phase 2b completed	N/A
Spore-based microbiome	SER-287	*Firmicutes*	Oral	Phase 1b complete	N/A
Anti-interleukin	Spesolimab	IL-36	Intravenous	Phase 2a	N/A
	PF-04236921	IL-6	Subcutaneous	N/A	Phase 2 completed
IL-10 fusion biologic	AMT-101	IL-10	Oral	Phase 1a	N/A
Anti-adhesion molecules	AJM300	α4 integrin	ral	Phase 3 recruiting	N/A

IL, interleukin; N/A, not applicable; TLR-9, toll-like receptor 9.

effects being dermatological, such as dry skin, erythema and pruritis.[139]

Cobitolimod

Cobitolimod binds and activates toll-like receptor 9 (TLR-9) on lymphocytes and antigen presenting cells. Activation of TLR-9 leads to the induction of regulatory T-cells that produce anti-inflammatory molecules such as IL-10 while also suppressing proinflammatory TH-17 cells.[140] The benefit of this drug lies in its topical enema route, which should ideally have low systemic absorption. Although early phase 2 studies for UC are promising (COLLECT and CONDUCT) phase 3 studies have not yet been registered.[141 142]

SER-287

SER-287 is an oral formulation that fractionates spore forming bacteria to specifically target *Firmicutes*. The spore-forming *Firmicutes*, particularly the families *Clostridiaceae, Lachnospiraceae* and *Ruminococcaceae*, produce metabolites, which enhance and maintain the gastrointestinal barrier and mucosal immunity.[143] This bacterium has been shown to be reduced in the intestinal microbiota in patients with UC and has become a target of interest.[144] A phase 1b study demonstrated that patients with mild to moderate UC who were preconditioned with 6 days of oral vancomycin followed by 8 weeks of oral SER-287 had significantly higher rates of clinical remission compared with placebo.[145]

Spesolimab

Spesolimab is a humanised monoclonal antibody that targets the IL-36 signalling pathway, which has been shown to be increased in UC. A phase 2a study demonstrated that while intravenous spesolimab was well tolerated in patients wth UC, efficacy endpoints were not met.[146]

PF-04236921

PF-04236921 is a fully human IgG_2 monoclonal antibody that binds IL-6, suppressing its proinflammatory effects. A phase 2 study was completed for patients with CD which showed the subcutaneous form of PF-04236921 50 mg was more efficacious than placebo in inducing response and remission at week 12. However, significant adverse events of gastrointestinal perforation and abscesses were seen in the treatment group and there are currently no phase 3 trials underway.[147]

AMT-101

IL-10 is a central anti-inflammatory cytokine that is able to modulate pro-inflammatory signals. However, producing a targeted IL-10 drug requires precarious balancing of the benefits of IL-10 without perpetuating its dose-limiting systemic side effects. AMT-101 is a novel oral human IL-10 fusion protein that is genetically fused to a non-toxic and poorly immunogenic fragment of the cholic exotoxin. Phase 1 studies on colitis-induced mice demonstrated a gut-selective response by reaching the intestinal lamina propria before delivering biologically-active IL-10 across the intestinal epithelium, thereby potentially reducing dose-limiting side effects. Phase 1b trials are currently underway in patients with UC.[148]

AJM300

AJM300 is an oral small molecule that targets and inhibits α4 integrin. While it has the advantage of having a very short 1 day duration of action, there is a potential risk for progressive multifocal leukoencephalopathy due to the α4 blockade. Phase 2a and 2b studies showed AJM300 to be more effective than placebo in inducing clinical response, remission and mucosal healing in moderately active patients with UC but the studies were of a small sample size and a short duration of 8 weeks. Phase 3 trials are currently underway for UC.[149]

Stem cell therapy

Achieving sustained remission and mucosal healing continues to remain a challenge with medical drug therapies. Stem cells have the potential to directly improve chronic intestinal inflammation by modulating immune cells and repairing the intestinal mucosal barrier. Although haematopoietic stem cell therapy has been shown to improve disease activity and maintain disease remission in CD, safety is a main concern with risk of severe immunosuppression, lethality and graft rejection.[150–152] Clinical studies with mesenchymal stem cell therapy have primarily focused on patients with refractory perianal fistulous CD with mixed results.[153–155] The main challenge is maintaining homogeneity with uniform standards and control comparisons in the tissue source and culture of stem cells.[156 157] The heterogeneity between individuals in study results ultimately affects the consistency of IBD clinical studies. There also needs to be a standardised protocol regarding infusion mode and dose and time interval of stem cells, with clear indications and contraindications yet to be established. While stem cell therapy in IBD is still very much in its preclinical stages, it has the potential to become a true cure for this debilitating disease.

CONCLUSION

The therapeutic arsenal for the management of IBD is being developed and repurposed at an accelerated rate. What has been discussed in this review is simply the 'tip of the iceberg'. Small molecules have the added advantage of not carrying the risk of immunogenicity that occurs with biological drugs. Therefore, there is potential to use these medications on demand such as during disease flares, to avoid corticosteroid use, or in combination with a biologic to improve clinical remission by targeting multiple immune pathways.[158] However, long-term, real-world and safety data for many of these new medications remain unclear. Furthermore, data in pregnancy and breast feeding are lacking and therefore limits their use in a large subset of the IBD population.[82] The benefits of these new medications include oral administration which is more patient-friendly and eases the extra hospital costs required for the intravenous/subcutaneous agents. However, non-compliance with oral therapies has been well documented in patients with IBD, which may offset the advantages of these oral therapies.[159] Thus, it is now important to understand and develop a precision medicine strategy that targets the right medication for the individual patient, which factors in their medical history, predictors of response, preference of administration, future family planning and disease characteristics.

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REFERENCES

1 Noor NM, Sousa P, Paul S, *et al*. Early diagnosis, early stratification, and early intervention to deliver precision medicine in IBD. *Inflamm Bowel Dis* 2022;28:1254–64.
2 Peyrin-Biroulet L, Sandborn W, Sands BE, *et al*. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol* 2015;110:1324–38.
3 Turner D, Ricciuto A, Lewis A, *et al*. STRIDE-II: an update on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) initiative of the International Organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. *Gastroenterology* 2021;160:1570–83.
4 de Souza HSP, Fiocchi C. Immunopathogenesis of IBD: Current state of the art. *Nat Rev Gastroenterol Hepatol* 2016;13:13–27.
5 Berg DR, Colombel JF, Ungaro R. The role of early biologic therapy in inflammatory bowel disease. *Inflamm Bowel Dis* 2019;25:1896–905.
6 Ben-Horin S, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev* 2014;13:24–30.
7 Lopetuso LR, Gerardi V, Papa V, *et al*. Can we predict the efficacy of anti-TNF-alpha agents *Int J Mol Sci* 2017;18:1973.
8 Gisbert JP, Chaparro M. Primary failure to an anti-TNF agent in inflammatory bowel disease: switch (to a second anti-TNF agent) or swap (for another mechanism of action)? *J Clin Med* 2021;10:5318.
9 Present DH, Rutgeerts P, Targan S, *et al*. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;340:1398–405.
10 Sands BE, Anderson FH, Bernstein CN, *et al*. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;350:876–85.
11 Sun XL, Chen SY, Tao SS, *et al*. Optimized timing of using Infliximab in perianal fistulizing Crohn's disease. *World J Gastroenterol* 2020;26:1554–63.
12 Jørgensen KK, Olsen IC, Goll GL, *et al*. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet* 2017;389:2304–16.
13 Ye BD, Pesegova M, Alexeeva O, *et al*. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study. *Lancet* 2019;393:1699–707.
14 Schreiber S, Ben-Horin S, Leszczyszyn J, *et al*. Randomized controlled trial: subcutaneous vs intravenous Infliximab CT-P13 maintenance in inflammatory bowel disease. *Gastroenterology* 2021;160:2340–53.
15 Buisson A, Nachury M, Reymond M, *et al*. Effectiveness of switching from intravenous to subcutaneous Infliximab in patients with inflammatory bowel diseases: the REMSWITCH study. *Clin Gastroenterol Hepatol* 2023;21:2338–46.
16 Colombel JF, Hanauer SB, Sandborn W. Dop86 subcutaneous Infliximab (CT-P13 SC) as maintenance therapy for Crohn's disease: a phase 3, randomised, placebo-controlled study (LIBERTY-CD). *Journal of Crohn's and Colitis* 2023;17:i161–2.

17 Smith PJ, Critchley L, Storey D, *et al*. Efficacy and safety of elective switching from intravenous to subcutaneous Infliximab [CT-P13]: a multicentre cohort study. *J Crohns Colitis* 2022;16:1436–46.
18 Vavricka SR, Bentele N, Scharl M, *et al*. Systematic assessment of factors influencing preferences of Crohn's disease patients in selecting an anti-tumor necrosis factor agent (CHOOSE TNF TRIAL). *Inflamm Bowel Dis* 2012;18:1523–30.
19 Cronin J, Moore S, Lenihan N, *et al*. The non-drug costs associated with the administration of an intravenous biologic treatment in the hospital setting. *Ir J Med Sci* 2019;188:821–34.
20 Sandborn WJ. State-of-the-art: immunosuppression and biologic therapy. *Dig Dis* 2010;28:536–42.
21 Bhol KC, Tracey DE, Lemos BR, *et al*. AVX-470: A novel oral anti-TNF antibody with therapeutic potential in inflammatory bowel disease. *Inflamm Bowel Dis* 2013;19:2273–81.
22 Harris MS, Hartman D, Lemos BR, *et al*. AVX-470, an orally delivered anti-tumour necrosis factor antibody for treatment of active ulcerative colitis: results of a first-in-human trial. *J Crohns Colitis* 2016;10:631–40.
23 Hartman DS, Tracey DE, Lemos BR, *et al*. Effects of AVX-470, an oral, locally acting anti-tumour necrosis factor antibody, on tissue biomarkers in patients with active ulcerative colitis. *J Crohns Colitis* 2016;10:641–9.
24 Almon E, Shaaltiel Y, Sbeit W, *et al*. Novel orally administered recombinant anti-TNF alpha fusion protein for the treatment of ulcerative colitis: results from a phase 2A clinical trial. *J Clin Gastroenterol* 2021;55:134–40.
25 Ilan Y, Gingis-Velitski S, Ben Ya'aco A, *et al*. A plant cell-expressed recombinant anti-TNF fusion protein is biologically active in the gut and alleviates immune-mediated hepatitis and colitis. *Immunobiology* 2017;222:544–51.
26 Almon E, Khoury T, Drori A, *et al*. An oral administration of a recombinant anti-TNF fusion protein is biologically active in the gut promoting regulatory T cells: results of a phase I clinical trial using a novel oral anti-TNF alpha-based therapy. *J Immunol Methods* 2017;446:21–9.
27 Sands B, Peyrin-Biroulet L, Danese S. OP40 PRA023 demonstrated efficacy and favorable safety as induction therapy for moderately to severely active UC: phase 2 ARTEMIS-UC study results. *Journal of Crohn's and Colitis* 2023;17:i56–9.
28 Feagan BG, Sands B, Siegel CA. Dop87 the anti-TI1A antibody PRA023 demonstrated proof-of-concept in Crohn's disease: phase 2A APOLLO-CD study results. *Journal of Crohn's and Colitis* 2023;17:i162–4.
29 Choden T, Cohen NA, Rubin DT. Sphingosine-1 phosphate receptor Modulators: the next wave of oral therapies in inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2022;18:265–71.
30 Gorfu G, Rivera-Nieves J, Ley K. Role of Beta7 integrins in intestinal lymphocyte homing and retention. *Curr Mol Med* 2009;9:836–50.
31 Bamias G, Clark DJ, Rivera-Nieves J. Leukocyte traffic blockade as a therapeutic strategy in inflammatory bowel disease. *Curr Drug Targets* 2013;14:1490–500.
32 Briskin M, Winsor-Hines D, Shyjan A, *et al*. Human mucosal addressin cell adhesion molecule-1 is preferentially expressed in intestinal tract and associated lymphoid tissue. *Am J Pathol* 1997;151:97–110.
33 Feagan BG, Rutgeerts P, Sands BE, *et al*. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699–710.
34 Sandborn WJ, Feagan BG, Rutgeerts P, *et al*. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369:711–21.
35 Sandborn WJ, Baert F, Danese S, *et al*. Efficacy and safety of vedolizumab subcutaneous formulation in a randomized trial of patients with ulcerative colitis. *Gastroenterology* 2020;158:562–72.
36 Vermeire S, D'Haens G, Baert F, *et al*. Efficacy and safety of subcutaneous vedolizumab in patients with moderately to severely active Crohn's disease: results from the VISIBLE 2 randomised trial. *Journal of Crohn's and Colitis* 2022;16:27–38.
37 Bergqvist V, Holmgren J, Klintman D, *et al*. Real-world data on switching from intravenous to subcutaneous vedolizumab treatment in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2022;55:1389–401.
38 Vermeire S, O'Byrne S, Keir M, *et al*. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. *Lancet* 2014;384:309–18.
39 Rubin DT, Dotan I, DuVall A, *et al*. Etrolizumab versus adalimumab or placebo as induction therapy for moderately to severely active ulcerative colitis (HIBISCUS): two phase 3 randomised, controlled trials. *Lancet Gastroenterol Hepatol* 2022;7:17–27.
40 Peyrin-Biroulet L, Hart A, Bossuyt P, *et al*. Etrolizumab as induction and maintenance therapy for ulcerative colitis in patients previously treated with tumour necrosis factor inhibitors (HICKORY): a phase 3, randomised, controlled trial. *Lancet Gastroenterol Hepatol* 2022;7:128–40.
41 Vermeire S, Lakatos PL, Ritter T, *et al*. Etrolizumab for maintenance therapy in patients with moderately to severely active ulcerative colitis (LAUREL): a randomised, placebo-controlled, double-blind, phase 3 study. *Lancet Gastroenterol Hepatol* 2022;7:28–37.
42 Danese S, Colombel J-F, Lukas M, *et al*. Etrolizumab versus Infliximab for the treatment of moderately to severely active ulcerative colitis (GARDENIA): a randomised, double-blind, double-dummy, phase 3 study. *Lancet Gastroenterol Hepatol* 2022;7:118–27.
43 Sandborn WJ, Panés J, Danese S, *et al*. Etrolizumab as induction and maintenance therapy in patients with moderately to severely active Crohn's disease (BERGAMOT): a randomised, placebo-controlled, double-blind, phase 3 trial. *Lancet Gastroenterol Hepatol* 2023;8:43–55.
44 Pullen N, Molloy E, Carter D, *et al*. Pharmacological characterization of PF-00547659, an anti-human Madcam monoclonal antibody. *Br J Pharmacol* 2009;157:281–93.
45 Reinisch W, Sandborn WJ, Danese S, *et al*. Long-term safety and efficacy of the anti-Madcam-1 monoclonal antibody ontamalimab [SHP647] for the treatment of ulcerative colitis: the open-label study TURANDOT II. *Journal of Crohn's and Colitis* 2021;15:938–49.
46 D'Haens GR, Reinisch W, Lee SD, *et al*. Long-term safety and efficacy of the anti-mucosal addressin cell adhesion molecule-1 monoclonal antibody ontamalimab (SHP647) for the treatment of Crohn's disease: the OPERA II study. *Inflamm Bowel Dis* 2022;28:1034–44.
47 Zurba Y, Gros B, Shehab M. Exploring the pipeline of novel therapies for inflammatory bowel disease. *Biomedicines* 2023;11:747.
48 Eftychi C, Schwarzer R, Vlantis K, *et al*. Temporally distinct functions of the cytokines IL-12 and IL-23 drive chronic colon inflammation in response to intestinal barrier impairment. *Immunity* 2019;51:367–80.
49 Kashani A, Schwartz DA. The expanding role of anti-IL-12 and/or anti-IL-23 antibodies in the treatment of inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2019;15:255–65.
50 Sandborn WJ, Gasink C, Gao L-L, *et al*. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012;367:1519–28.
51 D'Haens G, Dubinsky M, Kobayashi T, *et al*. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2023;388:2444–55.
52 GaBI Journal Editor. Patent expiry dates for BIOLOGICALS: 2018 update. *GaBI J* 2019;8:24–31. 10.5639/gabij.2019.0801.003 Available: http://gabi-journal.net/issues/vol-8-2019-issue-1
53 Mehr S. Ustekinumab Biosimilars update. Biosimilars review and report. 2021.
54 Taylor NP. *Celltrion signs up to support Rani's oral biosimilar copy of J&J's Stelara, lands right of first negotiation*. Fierce Pharma, 2023.
55 Technology Appraisal Guidance (TA888). Risankizumab for previously treated moderately to severely active Crohn's disease. 2023.
56 Abbvie. SKYRIZI® (Risankizumab-Rzaa) receives FDA approval as the first and only specific Interleukin-23 (IL-23) to treat moderately to severely active Crohn's disease in adults. n.d. Available: https://news.abbvie.com/news/press-releases/skyrizi-risankizumab-rzaa-receives-fda-approval-as-first-and-only-specific-interleukin-23-il-23-to-treat-moderately-to-severely-active-crohns-disease-in-adults.htm
57 D'Haens G, Panaccione R, Baert F, *et al*. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. *Lancet* 2022;399:2015–30.
58 Ferrante M, Panaccione R, Baert F, *et al*. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. *Lancet* 2022;399:2031–46.
59 Jenina Nun LS. Risankizumab (SKYRIZI®) achieves primary and all secondary endpoints in phase 3 induction study in patients with ulcerative colitis. Abbvie. Available: https://news.abbvie.com/news/press-releases/risankizumab-skyrizi-achieves-primary-and-all-secondary-endpoints-in-phase-3-induction-study-in-patients-with-ulcerative-colitis.htm#:~:text=%22These%20results%20suggest%20that%20risankizumab,bowel%20urgency%20and%20fecal%20incontinence.%22&text=Primary%20endpoint%20was%

20clinical%20remission%20(per%20Adapted%20Mayo%20Score) [Accessed 23 Mar 2023].
60 Sandborn WJ, Ferrante M, Bhandari BR, *et al*. Efficacy and safety of mirikizumab in a randomized phase 2 study of patients with ulcerative colitis. *Gastroenterology* 2020;158:537–49.
61 Efficacy and safety of mirikizumab as maintenance therapy in patients with moderately to severely active ulcerative colitis: results from the phase 3 LUCENT-2 study. *Gastroenterol Hepatol (N Y)* 2022;18:3–4.
62 D'Haens G, Dubinsky M, Kobayashi T, *et al*. Mirikizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2023;388:2444–55.
63 Sands BE, Peyrin-Biroulet L, Kierkus J, *et al*. Efficacy and safety of mirikizumab in a randomized phase 2 study of patients with Crohn's disease. *Gastroenterology* 2022;162:495–508.
64 Sandborn WJ, D'Haens GR, Reinisch W, *et al*. Guselkumab for the treatment of Crohn's disease: induction results from the phase 2 GALAXI-1 study. *Gastroenterology* 2022;162:1650–1664.
65 AJe. The efficacy and safety of Guselkumab induction therapy in patients with moderately to severely active ulcerative colitis: results from the phase 3 QUASAR induction study. Presented at: Digestive Disease Week; Chicago, 2023
66 Feagan BG, Sands BE, Sandborn WJ, *et al*. Guselkumab plus golimumab combination therapy versus guselkumab or golimumab monotherapy in patients with ulcerative colitis (VEGA): a randomised, double-blind, controlled, phase 2, proof-of-concept trial. *Lancet Gastroenterol Hepatol* 2023;8:307–20.
67 Sands BE, Chen J, Feagan BG, *et al*. Efficacy and safety of MEDI2070, an antibody against interleukin 23, in patients with moderate to severe Crohn's disease: a phase 2A study. *Gastroenterology* 2017;153:77–86.
68 Yamamoto-Furusho JK, Parra-Holguín NN. Emerging therapeutic options in inflammatory bowel disease. *World J Gastroenterol* 2021;27:8242–61.
69 AztraZeneca. Update on Brazikumab development programme. n.d. Available: https://www.astrazeneca.com/media-centre/press-releases/2023/update-on-brazikumab-development-programme.html
70 Harris C, Cummings JRF. Jak1 inhibition and inflammatory bowel disease. *Rheumatology (Oxford)* 2021;60:ii45–51.
71 Coskun M, Salem M, Pedersen J, *et al*. Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease. *Pharmacol Res* 2013;76:1–8.
72 Fernández-Clotet A, Castro-Poceiro J, Panés J. Tofacitinib for the treatment of ulcerative colitis. *Expert Rev Clin Immunol* 2018;14:881–92.
73 Sandborn WJ, Ghosh S, Panes J, *et al*. A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2014;12:S1542-3565(14)00137-2:1485–93..
74 Panés J, Sandborn WJ, Schreiber S, *et al*. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. *Gut* 2017;66:1049–59.
75 Sandborn WJ, Su C, Sands BE, *et al*. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;376:1723–36.
76 Sands BE, Armuzzi A, Marshall JK, *et al*. Efficacy and safety of tofacitinib dose de-escalation and dose escalation for patients with ulcerative colitis: results from OCTAVE open. *Aliment Pharmacol Ther* 2020;51:271–80.
77 Sandborn WJ, Peyrin-Biroulet L, Sharara AI, *et al*. Efficacy and safety of tofacitinib in ulcerative colitis based on prior tumor necrosis factor inhibitor failure status. *Clinical Gastroenterology and Hepatology* 2022;20:591–601.
78 Weisshof R, Aharoni Golan M, Sossenheimer PH, *et al*. Real-world experience with tofacitinib in IBD at a tertiary center. *Dig Dis Sci* 2019;64:1945–51.
79 Berinstein JA, Sheehan JL, Dias M, *et al*. Tofacitinib for biologic-experienced hospitalized patients with acute severe ulcerative colitis: a retrospective case-control study. *Clin Gastroenterol Hepatol* 2021;19:2112–20.
80 Sandborn WJ, Panés J, Sands BE, *et al*. Venous thromboembolic events in the tofacitinib ulcerative colitis clinical development programme. *Aliment Pharmacol Ther* 2019;50:1068–76.
81 Gisbert JP, Chaparro M. Safety of new biologics (Vedolizumab and Ustekinumab) and small molecules (tofacitinib) during pregnancy: a review. *Drugs* 2020;80:1085–100.
82 Torres J, Chaparro M, Julsgaard M, *et al*. European Crohn's and colitis guidelines on sexuality, fertility, pregnancy, and Lactation. *Journal of Crohn's and Colitis* 2023;17:1–27.
83 Garrido I, Lopes S, Macedo G. The role of new oral treatment in inflammatory bowel disease. *Inflamm Bowel Dis* 2021;27:2010–22.
84 Feagan BG, Danese S, Loftus EV, *et al*. Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2B/3 double-blind, randomised, placebo-controlled trial. *Lancet* 2021;397:2372–84.
85 Vermeire S, Schreiber S, Petryka R, *et al*. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. *Lancet* 2017;389:266–75.
86 Reinisch W, Colombel JF, D'Haens GR. Op18 efficacy and safety of Filgotinib for the treatment of perianal fistulizing Crohn's disease: results from the phase 2 divergence 2 study. *Journal of Crohn's and Colitis* 2022;16:i019–21.
87 Hellstrom WJG, Dolhain RJEM, Ritter TE, *et al*. MANTA and MANTA-ray: rationale and design of trials evaluating effects of filgotinib on semen parameters in patients with inflammatory diseases. *Adv Ther* 2022;39:3403–22.
88 Danese S, Vermeire S, Zhou W, *et al*. Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials. *Lancet* 2022;399:2113–28.
89 Loftus EV Jr, Panés J, Lacerda AP, *et al*. Upadacitinib induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2023;388:1966–80.
90 Akiyama S, Steinberg JM, Kobayashi M, *et al*. Pregnancy and medications for inflammatory bowel disease: an updated narrative review. *World J Clin Cases* 2023;11:1730–40.
91 Liu T, Zhang L, Joo D, *et al*. NF-KB signaling in inflammation. *Signal Transduct Target Ther* 2017;2:17023.
92 Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol* 2012;83:1583–90.
93 Togo S, Liu X, Wang X, *et al*. Pde4 inhibitors roflumilast and rolipram augment PGE2 inhibition of TGF-Beta1-stimulated fibroblasts. *Am J Physiol Lung Cell Mol Physiol* 2009;296:L959–69.
94 Gordon JN, Prothero JD, Thornton CA, *et al*. CC-10004 but not thalidomide or Lenalidomide inhibits lamina propria mononuclear cell TNF-alpha and MMP-3 production in patients with inflammatory bowel disease. *J Crohns Colitis* 2009;3:175–82.
95 Papp K, Reich K, Leonardi CL, *et al*. Apremilast, an oral phosphodiesterase 4 (Pde4) inhibitor, in patients with moderate to severe plaque psoriasis: results of a phase III, randomized, controlled trial (efficacy and safety trial evaluating the effects of Apremilast in psoriasis [ESTEEM] 1). *J Am Acad Dermatol* 2015;73:37–49.
96 Danese S, Neurath MF, Kopoń A, *et al*. Effects of Apremilast, an oral inhibitor of phosphodiesterase 4, in a randomized trial of patients with active ulcerative colitis. *Clin Gastroenterol Hepatol* 2020;18:2526–34.
97 Van Voorhees AS, Stein Gold L, Lebwohl M, *et al*. Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: results of a phase 3B, multicenter, randomized, placebo-controlled, double-blind study. *J Am Acad Dermatol* 2020;83:96–103.
98 Gonzalez-Cabrera PJ, Brown S, Studer SM, *et al*. S1P signaling: new therapies and opportunities. *F1000Prime Rep* 2014;6:109.
99 Peyrin-Biroulet L, Christopher R, Behan D, *et al*. Modulation of sphingosine-1-phosphate in inflammatory bowel disease. *Autoimmun Rev* 2017;16:495–503.
100 Blaho VA, Hla T. An update on the biology of sphingosine 1-phosphate receptors. *J Lipid Res* 2014;55:1596–608.
101 Brinkmann V, Cyster JG, Hla T. FTY720: sphingosine 1-phosphate receptor-1 in the control of lymphocyte egress and endothelial barrier function. *Am J Transplant* 2004;4:1019–25.
102 Ladrón Abia P, Alcalá Vicente C, Martínez Delgado S, *et al*. Fingolimod-induced remission in a patient with ulcerative colitis and multiple sclerosis. *Gastroenterol Hepatol* 2021;44:156–7.
103 Danese S, Furfaro F, Vetrano S. Targeting S1P in inflammatory bowel disease: new avenues for modulating intestinal leukocyte migration. *Journal of Crohn's and Colitis* 2018;12:S678–86.
104 Calabresi PA, Radue E-W, Goodin D, *et al*. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:545–56.
105 Sandborn WJ, Vermeire S, Peyrin-Biroulet L, *et al*. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. *Lancet* 2023;401:1159–71.
106 Lamb YN. Ozanimod: first approval. *Drugs* 2020;80:841–8.

107 Sandborn WJ, Feagan BG, D'Haens G, *et al*. Ozanimod as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2021;385:1280–91.
108 Danese S, Colombel JF, Ponich T, *et al*. Dop44 long-term use of ozanimod in patients with moderately to severely active ulcerative colitis. European Crohns and Colitis Organisation; Copenhagen, Denmark, 2023
109 Feagan BG, Sandborn WJ, Danese S, *et al*. Ozanimod induction therapy for patients with moderate to severe Crohn's disease: a single-arm, phase 2, prospective observer-blinded Endpoint study. *Lancet Gastroenterol Hepatol* 2020;5:819–28.
110 Feagan BG, Schreiber S, Afzali A, *et al*. Ozanimod as a novel oral small molecule therapy for the treatment of Crohn's disease: the YELLOWSTONE clinical trial program. *Contemp Clin Trials* 2022;122:106958.
111 Becher N, Swaminath A, Sultan K. A literature review of ozanimod therapy in inflammatory bowel disease: from concept to practical application. *Ther Clin Risk Manag* 2022;18:913–27.
112 Sandborn WJ, Peyrin-Biroulet L, Zhang J, *et al*. Efficacy and safety of etrasimod in a phase 2 randomized trial of patients with ulcerative colitis. *Gastroenterology* 2020;158:550–61.
113 Peyrin-Biroulet L, Morgan M, Christopher R, *et al*. P-179 safety, pharmacokinetics and pharmacodynamics of Etrasimod (Apd334), an oral selective S1P receptor modulator, after dose-escalation, in healthy volunteers. *Inflamm Bowel Dis* 2017;23:S60–1.
114 Komori K, Lee C, Acevedo L, *et al*. SU100 Effect of etrasimod on circulating lymphocyte subsets: data from a randomized phase 1 study in healthy Japanese and caucasian men. *Gastroenterology* 2021;160:S–617.
115 Vermeire S, Chiorean M, Panés J, *et al*. Long-term safety and efficacy of etrasimod for ulcerative colitis: results from the open-label extension of the OASIS study. *Journal of Crohn's and Colitis* 2021;15:950–9.
116 D'Haens G, Dubinsky MC, Peyrin-Biroulet L. P632 Etrasimod induction therapy in moderately to severely active Crohn's disease: results from a phase 2, randomised, double-blind Substudy. *Journal of Crohn's and Colitis* 2023;17:i764–5.
117 D'Haens G, Danese S, Davies M, *et al*. Placebo-controlled study to evaluate safety, tolerability, and efficacy of amiselimod in patients with moderate to severe active Crohn's disease. *Journal of Crohn's and Colitis* 2022;16:746–56.
118 Koukos G, Polytarchou C, Kaplan JL, *et al*. Microrna-124 regulates Stat3 expression and is down-regulated in colon tissues of pediatric patients with ulcerative colitis. *Gastroenterology* 2013;145:842–52.
119 Dalal SR, Kwon JH. The role of MicroRNA in inflammatory bowel disease. *Gastroenterol Hepatol (N Y)* 2010;6:714–22.
120 Sugimoto K. Role of Stat3 in inflammatory bowel disease. *World J Gastroenterol* 2008;14:5110–4.
121 Musso A, Dentelli P, Carlino A, *et al*. Signal transducers and activators of transcription 3 signaling pathway: an essential mediator of inflammatory bowel disease and other forms of intestinal inflammation. *Inflamm Bowel Dis* 2005;11:91–8.
122 Atreya R, Neurath MF. Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer. *Clin Rev Allergy Immunol* 2005;28:187–96.
123 Vermeire S, Sands BE, Tilg H, *et al*. Abx464 (Obefazimod) for moderate-to-severe, active ulcerative colitis: a phase 2B, double-blind, randomised, placebo-controlled induction trial and 48 week, open-label extension. *Lancet Gastroenterol Hepatol* 2022;7:1024–35.
124 Colombel JF, Sandborn WJ, Reinisch W, *et al*. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;362:1383–95.
125 Kennedy NA, Heap GA, Green HD, *et al*. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, Multicentre, cohort study. *Lancet Gastroenterol Hepatol* 2019;4:341–53.
126 Ahmed W, Galati J, Kumar A, *et al*. Dual biologic or small molecule therapy for treatment of inflammatory bowel disease: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2022;20:e361–79.
127 Mas EB, Calvo XC. Selecting the best combined biological therapy for refractory inflammatory bowel disease patients. *J Clin Med* 2022;11:1076.
128 Sands BE, Kozarek R, Spainhour J, *et al*. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving Infliximab. *Inflamm Bowel Dis* 2007;13:2–11.
129 Schreiber S, Dignass A, Peyrin-Biroulet L, *et al*. Systematic review with meta-analysis: real-world effectiveness and safety of vedolizumab in patients with inflammatory bowel disease. *J Gastroenterol* 2018;53:1048–64.
130 Sandborn WJ, Rebuck R, Wang Y, *et al*. Five-year efficacy and safety of ustekinumab treatment in Crohn's disease: the IM-UNITI trial. *Clin Gastroenterol Hepatol* 2022;20:578–90.
131 Lopetuso LR, Deleu S, Godny L, *et al*. The first International Rome consensus conference on gut microbiota and faecal microbiota transplantation in inflammatory bowel disease. *Gut* 2023;72:1642–50.
132 Moayyedi P, Surette MG, Kim PT, *et al*. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology* 2015;149:102–9.
133 Costello SP, Hughes PA, Waters O, *et al*. Effect of fecal microbiota transplantation on 8-week remission in patients with ulcerative colitis: a randomized clinical trial. *JAMA* 2019;321:156–64.
134 Paramsothy S, Kamm MA, Kaakoush NO, *et al*. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. *Lancet* 2017;389:1218–28.
135 Cheng F, Huang Z, Wei W, *et al*. Fecal microbiota transplantation for Crohn's disease: a systematic review and meta-analysis. *Tech Coloproctol* 2021;25:495–504.
136 Vermeire S, Joossens M, Verbeke K, *et al*. Donor species richness determines faecal microbiota transplantation success in inflammatory bowel disease. *ECCOJC* 2016;10:387–94.
137 Sokol H, Landman C, Seksik P, *et al*. Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. *Microbiome* 2020;8:12.
138 Rothenberg ME, Wang Y, Lekkerkerker A, *et al*. Randomized phase I healthy volunteer study of UTTR1147A (IL-22Fc): a potential therapy for epithelial injury. *Clin Pharmacol Ther* 2019;105:177–89.
139 Wagner F, Mansfield J, Geier C, *et al*. P420 A randomised, observer-blinded phase IB multiple, ascending dose study of UTTR1147A, an IL-22Fc fusion protein, in healthy volunteers and ulcerative colitis patients. *Journal of Crohn's and Colitis* 2020;14:S382–3.
140 Al-Bawardy B, Shivashankar R, Proctor DD. Novel and emerging therapies for inflammatory bowel disease. *Front Pharmacol* 2021;12:651415.
141 Atreya R, Bloom S, Scaldaferri F, *et al*. Clinical effects of a topically applied toll-like receptor 9 agonist in active moderate-to-severe ulcerative colitis. *ECCOJC* 2016;10:1294–302.
142 Atreya R, Peyrin-Biroulet L, Klymenko A, *et al*. Cobitolimod for moderate-to-severe, left-sided ulcerative colitis (CONDUCT): a phase 2B randomised, double-blind, placebo-controlled, dose-ranging induction trial. *Lancet Gastroenterol Hepatol* 2020;5:1063–75.
143 Kostic AD, Xavier RJ, Gevers D. The Microbiome in inflammatory bowel disease: current status and the future ahead. *Gastroenterology* 2014;146:1489–99.
144 Paramsothy S, Nielsen S, Kamm MA, *et al*. Specific bacteria and metabolites associated with response to fecal microbiota transplantation in patients with ulcerative colitis. *Gastroenterology* 2019;156:1440–54.
145 Henn MR, O'Brien EJ, Diao L, *et al*. A phase 1B safety study of SER-287, a spore-based microbiome therapeutic, for active mild to moderate ulcerative colitis. *Gastroenterology* 2021;160:115–127.
146 Ferrante M, Irving PM, Selinger CP, *et al*. Safety and tolerability of spesolimab in patients with ulcerative colitis. *Expert Opin Drug Saf* 2023;22:141–52.
147 Danese S, Vermeire S, Hellstern P, *et al*. Randomised trial and open-label extension study of an anti-Interleukin-6 antibody in Crohn's disease (ANDANTE I and II). *Gut* 2019;68:40–8.
148 Mrsny R, Kanwar B, Mahmood T. *Treatment of ulcerative colitis with AMT-101, a novel oral interleukin-10 immunomodulatory fusion biologic that traffics across the intestinal epithelium*. GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND: OXFORD UNIV PRESS, 2020: S039–40.
149 Yoshimura N, Watanabe M, Motoya S, *et al*. Safety and efficacy of AJM300, an oral antagonist of A4 integrin, in induction therapy for patients with active ulcerative colitis. *Gastroenterology* 2015;149:1775–83.
150 Ruiz MA, Junior RLK, Piron-Ruiz L, *et al*. Medical, ethical, and legal aspects of hematopoietic stem cell transplantation for Crohn's disease in Brazil. *World J Stem Cells* 2020;12:1113–23.
151 Burt RK, Craig RM, Milanetti F, *et al*. Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. *Blood* 2010;116:6123–32.
152 Hawkey CJ, Allez M, Clark MM, *et al*. Autologous hematopoetic stem cell transplantation for refractory Crohn disease: a randomized clinical trial. *JAMA* 2015;314:2524–34.

153 Garcia-Olmo D, Herreros D, Pascual I, *et al*. Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. *Dis Colon Rectum* 2009;52:79–86.
154 Herreros MD, Garcia-Arranz M, Guadalajara H, *et al*. Autologous expanded adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistulas: a phase III randomized clinical trial (FATT 1: Fistula advanced therapy trial 1) and long-term evaluation. *Dis Colon Rectum* 2012;55:762–72.
155 Wang R, Yao Q, Chen W, *et al*. Stem cell therapy for Crohn's disease: systematic review and meta-analysis of preclinical and clinical studies. *Stem Cell Res Ther* 2021;12:463.
156 Tian C-M, Zhang Y, Yang M-F, *et al*. Stem cell therapy in inflammatory bowel disease: a review of achievements and challenges. *J Inflamm Res* 2023;16:2089–119.
157 Zhang H-M, Yuan S, Meng H, *et al*. Stem cell-based therapies for inflammatory bowel disease. *Int J Mol Sci* 2022;23:8494.
158 Khanna R, Chande N, Marshall JK. Ozanimod for the treatment of ulcerative colitis. *Gastroenterology* 2022;162:2104–6.
159 Shale MJ, Riley SA. Studies of compliance with delayed-release mesalazine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;18:191–8.