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REVIEW

Emerging Therapies for Ulcerative Colitis: Updates from Recent Clinical Trials

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Abstract: Ulcerative colitis (UC) is a chronic and progressive inflammatory disorder that affects the colon. The advent of advanced therapies such as biologic agents and small molecules has revolutionized the management of UC. Despite the expanding therapeutic armamentarium of advanced therapies to treat UC, the overall net remission rates and durability of currently available agents are relatively low. This highlights the need for further drug development and more innovative clinical trial design. There are currently multiple emerging agents in the pipeline for the management of UC. This includes agents with alternative routes of administration such as oral or subcutaneous tumor necrosis factor inhibitors or novel mechanisms of action such as toll-like receptor 9 (TLR9) agonist cobitolimod and phosphodiesterase 4 inhibitor apremilast. In this review, we will highlight novel and emerging advanced therapies currently in the pipeline for the management of UC.

Keywords: inflammatory bowel disease, ulcerative colitis, small molecules, biologics, novel therapy

Background

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory condition that affects the mucosa of the colon and rectum.[1] The highest incidence of the disease is in Northern Europe and Canada at 24.3 and 19.2/100,000, respectively.[2] Prevalence rates are also the highest in these two regions, at 505/100,000 in Northern Europe and 248/100,000 in Canada.[2] Ulcerative colitis is also considered a progressive disease as it is associated with increased risk of disease extension, dysplasia/neoplasia, fibrosis and rectal dysfunction.[3] Observational studies suggest that one-third of patients with left-sided colitis or disease limited to the rectum will develop pancolitis over a period of 10 years.[4] The changing epidemiology and the progressive nature of the disease require a clear understanding of the available and soon to become available therapeutic agents to treat UC and the different aspects of their pharmacology.

The first class of advanced therapies approved in UC was tumor necrosis factor alpha inhibitor (TNFi) with infliximab in 2005.[5] The use of TNFi in UC, however, is limited by the risk of opportunistic infections, immunogenicity, and high rates of primary and secondary loss of response.[6] Therefore, the armamentarium of biologics expanded by the approval of two more classes of monoclonal antibodies; anti-integrins such as vedolizumab and interleukin (IL) 12/23 inhibitors such as ustekinumab. In addition, several small molecule classes have been approved for the treatment of moderate-to-severe UC. These agents have the advantage of a relatively rapid onset of action, lack of immunogenicity and an oral route of administration. These small molecules include Janus Kinase (JAK) inhibitors such as tofacitinib, upadacitinib and filgotinib; and sphingosine-1-phosphate receptor (S1PR) modulators such as ozanimod.[7–10] Despite the growing options of approved biologics and small molecules to treat moderate-to-severe UC, the net remission rates with these agents remain low at around 20–40%.[11] Net remission refers to the proportion of all patients who entered the induction phase and remained in remission at the end of the maintenance phase of clinical trials.[11] This calls for the need for further future drug development. The aim of this review is to provide an update on the pipeline of therapeutic agents to treat UC (Table 1 and 2, Figure 1).

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Table 1 Summary of Advanced Therapies in Phase II/III for the Management of Ulcerative Colitis

Drug Class	Agent	Target	Mode of Delivery	Stage
Anti-TNF	CT-P13	TNF	SC	Phase III completed
	OPRX-106	TNF	Oral	Phase II completed
JAK inhibitors	Ivarmacitinib	JAK1	Oral	Phase II completed/Phase III recruiting
	Brepocitinib (PF-06700841)	JAK1/TYK2	Oral	Phase IIb completed
	Ritlecitinib (PF-06651600)	JAK3/TEC kinase inhibitor	Oral	Phase IIb completed
	Peficitinib	Pan-JAK (JAK3)	Oral	Phase IIb completed (No dose response relationship)
	Izencitinib (TD-1473)	Pan-JAK (gut selective)	Oral	Phase IIb completed (primary endpoint not met)
	Deucravacitinib (BMS-986165)	TYK2	Oral	Phase II completed (primary endpoint not met)
Anti-Trafficking Agents	Etrolizumab	$\alpha4\beta7$ and $\alpha E\beta7$ integrins	SC	Phase III completed
	Carotegrast methyl (AJM300)	$\alpha4$ integrin	Oral	Phase III completed
	Ontamalimab (PF-00547659)	MAdCAM	SC	Phase II completed
	Abrilumab (AMG181)	$\alpha4\beta7$ integrin	SC	Phase II completed
	PN-943	$\alpha4\beta7$ integrin (gut restricted)	Oral	Phase II completed (primary endpoint not met)
	PTG-100	$\alpha4\beta7$ integrin	Oral	Phase IIa completed (primary endpoint not met)
IL-23 Inhibitors	Mirikizumab	IL23/p19 subunit	IV, SC	Phase III completed
	Risankizumab	IL23/p19 subunit	IV, SC	Phase III completed (results pending)
	Brazikumab	IL23/p19 subunit	IV, SC	Development Halted
	Guselkumab	IL23/p19 subunit	IV, SC	Phase IIb/III active
S1P Receptor Modulators	Etrasimod	S1PR1, S1PR4 and S1PR5	Oral	Phase III completed
	CBP-307	S1PR1	Oral	Phase II completed
	Amiselimod (MT-1303)	S1PR1	Oral	Phase II recruiting
PDE4 Inhibitors	Apremilast	PDE4	Oral	Phase II completed
TLR9 Agonist	Cobitolimod	TLR9	Topical (enema)	Phase IIb completed/Phase III recruiting

Abbreviations: TNF, tumor necrosis factor; JAK, janus kinase; TYK 2, tyrosine kinase 2; S1P, sphingosine 1 phosphate; S1PR, sphingosine 1 phosphate receptor; PDE4, phosphodiesterase 4; TLR9, toll-like receptor 9; $\alpha4\beta7$, alpha4-beta7; $\alpha E\beta7$, alphaE-beta7; $\alpha4$, alpha4; MAdCAM, mucosal addressin cell adhesion molecule-1; IL-23, interleukin 23; IV, intravenous; SC, subcutaneous.

Tumor Necrosis Factor Inhibitors (TNFi)

Subcutaneous CT-P13

The infliximab biosimilar CT-P13 has been shown to be safe and effective in patients with inflammatory bowel disease (IBD) in its intravenous (IV) formulation.[12,13] The development of a subcutaneous (SC) formulation containing 120 mg/mL provides patients with the opportunity for self-administration and elimination of need for frequent IV infusion center visits.[14] Subcutaneous CT-P13 gained approval by the European Medicine Agency (EMA) for the same indications for which IV infliximab has been previously approved.[15]

The efficacy of the SC formulation of CT-P13 as a maintenance treatment in UC was assessed in the LIBERTY-UC Phase 3 trial.[16] Patients with moderate-to-severe UC (modified Mayo score 5–9 with endoscopic sub-score of ≥2 points) received open-label induction with IV CT-P13 (5 mg/kg) at weeks 0, 2 and 6. At week 10, clinical responders were randomized (2:1) to receive either CT-P13 SC 120 mg or placebo every 2 weeks for 54 weeks. Of the 548 patients enrolled, 79.9% responded to open-label CT-P13 IV induction and were randomized at week 10. The primary endpoint of clinical remission at week 54 was achieved in 43.2% of those receiving CT-P13 SC compared to 20.8% in the placebo arm ($p < 0.0001$). CT-P13 met statistical significance in key secondary endpoints including clinical response, endoscopic-histologic mucosal improvement, and corticosteroid free remission. The safety profile of CT-P13 was comparable to placebo.[16]

Oral TNFi

Oral immunotherapy is an attractive clinical approach that has the potential of inducing immune modulation at the level of the digestive tract without resulting in systemic immune suppression.[17]

OPRX-106

OPRX-106 was developed as a potential effective oral TNFi therapy in UC.[18] It consists of plant cells expressing recombinant anti-TNF fusion protein with an amino acid sequencing that is similar to the TNFi etanercept.[18] Twenty-four patients with mild-to-moderate UC were enrolled (18 completed the study) in an open-label Phase IIa, randomized trial evaluating the safety, pharmacokinetics and exploratory efficacy of OPRX-106.[18] Patients received either 2 mg or 8 mg daily of OPRX-106 for 8 weeks. OPRX-106 was well tolerated with no subjects discontinuing the trial medication due to side effects. Clinical response (decrease in the Mayo score of at least 3 points, decrease in the rectal bleeding sub-score of at least 1 point, a rectal bleeding sub-score of 0 or 1) was reported in 2/3rd of patients. Mucosal healing, as assessed by investigators at the site, was reported in 33% of patients.[18] Despite the overall favorable efficacy and safety profile of this agent, it is not clear if its development will go on further to a phase 3 trial.

AVX-470

AVX-470 is another innovative antibody that is generated by purifying immunoglobulin (Ig) from cows' colostrum immunized with recombinant human TNF. These bovine antibodies are large molecules (160–900 kDa) that are poorly absorbed into the systemic circulation.[19] The in-vitro activity of this molecule is comparable to the activity of infliximab.[20] In three mouse models, the oral administration of AVX-470 resulted in inhibition of gut inflammation without significant systemic immunosuppression.[20] The activity of AVX-470 in this in vitro experiment was similar to that of oral prednisolone or parenteral etanercept.[20] The pharmacokinetics, immunogenicity, efficacy and safety of AVX-470 in patients with UC was assessed in a 4-week clinical trial.[19] The double-blinded, placebo controlled study had three increasing dose cohorts, AVX-470 0.1g twice daily, 0.78g twice daily and 1.17g capsules 3 times daily, which were then designated as 0.2, 1.6 and 3.5g/day, respectively. In each cohort, patients were randomized 3:1 to receive AVX-470 or placebo. One-third of the patients enrolled had previous exposure to TNFi. AVX-470 appeared to be well tolerated with no significant difference in adverse events compared to placebo. Assessment of immunogenicity against AVX-470 showed that the levels of anti-bovine Ig prior to and after treatment were similar in the AVX-470 and placebo groups.[19] There appeared to be minimal absorption into the systemic circulation. Clinical response was reported in 25.9% of patients on AVX-470 compared to 11.1% in placebo. The percentage of patients on AVX-470 3.5g/day who achieved clinical remission was 14.3% (n = 1), endoscopic response was 14.3% (n = 1) and endoscopic

remission 14.3% (n = 1) compared 0% to those receiving placebo. Prior TNFi or immunosuppression exposure did not influence response to AVX-470.

Anti-Lymphocyte Trafficking

Integrin proteins are ubiquitous, heterodimeric, transmembrane receptors that act as signaling proteins.[21] They act as adhesion receptors with the ability to signal in both directions across the plasma membrane.[21] Each integrin receptor consists of an α and β subunit, of which there are several variants. Lymphocyte trafficking into the digestive tract is mainly controlled by the α4β7/MAdCAM-1 pathway.[22] Vedolizumab (VDZ) is a humanized IgG1 monoclonal antibody that blocks α4β7 integrin. Gut selective blockade of leukocyte homing mechanisms with vedolizumab has been shown to be safe and effective in managing UC.[23] Subcutaneous (SC) vedolizumab has also been demonstrated to be effective and has received approval for both CD and UC in 2020 by the European Medicines Agency (EMA).[24]

Etrolizumab

Etrolizumab is an SC humanized monoclonal antibody which targets the β7 subunit of the α4β7 and αEβ7 integrins with high affinity.[25] It blocks binding to their ligands MAdCAM-1 and E-cadherin resulting in inhibition of leukocyte trafficking to the gut and inhibition of retention of leukocytes, respectively.[26] Studies on animal models indicate that the medication selectively targets lymphocyte homing on mucosal surfaces with no impact on migration to non-mucosal tissues.[26]

The clinical development program for etrolizumab in UC included five clinical trials, three comparing it to placebo and two with an active TNFi comparator. Investigators enrolled more than 2000 patients worldwide for these trials.[27–30]

Etrolizumab was compared to placebo in the phase 3 HICKORY trial.[28] The induction phase of 14 weeks had two cohorts. In one cohort, patients received open-label induction. The second cohort was randomized to either etrolizumab or placebo. Remission rates were 18.5% and 6.3% in the etrolizumab and placebo groups, respectively (p = 0.0033). Patients with clinical response were re-randomized to the maintenance phase of the trial which spanned an additional 52 weeks. At week 66, there was no difference in remission rates between those who continued etrolizumab and those who received placebo at 24.1% vs 20.2% (p = 0.50).[28] In the maintenance phase 3 trial (LAUREL), after an open-label induction period, responders were re-randomized to etrolizumab versus placebo. The trial failed to meet the primary endpoint of clinical remission at week 62.[29]

HIBISCUS I&II were two identical phase 3 double blinded, randomized, placebo-controlled and adalimumab-controlled trials. The trials randomized patients with moderate-to-severe UC (who failed conventional therapy and were naive to TNFi) to etrolizumab 105 mg SC every 4 weeks, adalimumab standard induction dose or placebo.[27] In HIBISCUS I, week 10 clinical remission rates were 19.4% in the etrolizumab group vs 6.9% in the placebo group (p = 0.017). The results of HIBISCUS II showed no significant difference in clinical remission rates between etrolizumab and placebo groups (18.2% vs 11.1%; p = 0.17). Etrolizumab failed to show superiority over adalimumab in key secondary endpoints at week 10. This includes clinical response, endoscopic improvement, endoscopic remission, and histological remission.[27] The authors speculated that the assumption of 25% absolute difference in remission rates between etrolizumab and placebo, on which sample size calculation was made, was too optimistic. Therefore, a larger sample size may have shown a difference.[27]

The GARDENIA trial compared etrolizumab to infliximab in TNFi naive patients with moderate-to-severe UC. In a treat through design, the trial failed to show a difference in the primary endpoint of clinical response at week 10 and clinical remission at week 54 (18.6% in the etrolizumab group vs 19.75% in the infliximab group (P = 0.81)).[30]

A potential etiology of the negative results of these Phase III trials is the etrolizumab dose chosen. The 105 mg dose was chosen based on the Phase II EUCALYPTUS trial where two doses were compared to placebo, SC etrolizumab 100 mg at weeks 0, 4, and 8, with placebo at week 2; or 420 mg loading dose at week 0 followed by 300 mg at weeks 2, 4, and 8, subjects in the third arm received matching placebo.[25] Both doses were adequate to maintain β7 receptor occupancy (in blood and colonic tissue) during the 10-week study period. There was no difference in exposure–response relationship within around four times the exposure range[25,27] That study had a relatively small sample size of 81

etrolizumab treated patients, two-thirds of whom were exposed to TNFi in the past. This casts a shadow on the generalizability of the results showing efficacy of the 100 mg dose.[27]

AJM300

AJM300 (carotegrast methyl) is an oral small molecule which has anti α4-integrin properties. HCA2969, the active metabolite of AJM300, selectively inhibits binding of α4 integrin (α4β7/α4β1) to the cell adhesion molecules.[31] It shares the same mechanism of action as natalizumab. The association between progressive multifocal leukoencephalopathy (PML) and natalizumab led the investigators to limit the trial of AJM 300 initially to the induction phase only.[32] In a phase IIa study in patients with moderate-to-severe UC who failed conventional therapy, AJM300 showed efficacy in achieving clinical response, clinical remission, endoscopic improvement, and histological improvement, compared with placebo.[33]

In a phase III multicenter, randomized, double-blind clinical trial conducted in Japan, the efficacy of AJM300 was assessed in patients who failed conventional therapy.[34] Unlike many other phase III trials, this protocol allowed for the inclusion of patients with disease limited to the rectum. The trial started with a two-week single blinded run-in period where all patients received placebo therapy to reduce any potential positive effect of placebo. At the end of the run-in period, those with active disease (Mayo scores of 6–10 points, endoscopic sub-score ≥2 points, and rectal bleeding sub-score ≥1) were randomized to oral placebo or AJM300 three times daily after meals for 8 weeks.[34] Clinical response at week 8 (primary endpoint) was achieved by 45% in the AJM300 group versus 21% in the placebo arm ($p = 0.00028$). Those who did not achieve endoscopic remission or cessation of rectal bleeding at week 8 were continued on AJM300 until 24 weeks. At week 24, a significantly higher proportion of patients taking AJM300 achieved clinical response, symptomatic remission, endoscopic response and remission.

In terms of safety, seroconversion (from negative to positive) of the anti-JCV occurred in 7% of patients in the placebo arm and 16% in the AJM300 at week 8.[34] There were no cases of PML in subjects enrolled in the study. The most common adverse event was nasopharyngitis (10% in the AJM300 group vs 11% in the placebo group). Overall, AJM300 was well tolerated as there were no significant differences between the groups in terms of adverse events. This was the second phase III trial to assess AJM300 in UC. Data from the first trial was not published. That study was a negative study due to the high placebo effect. Therefore, this trial included a two-week lead-in period. AJM300 (carotegrast methyl) was approved in Japan in 2022 for the treatment of moderate UC in patients who have had an inadequate response to mesalamine.[35]

Abrilumab

Abrilumab (AMG 181 or MEDI 7183) is a human monoclonal IgG2 antibody which targets α4β7 integrin on gut-tropic lymphocytes. This blocks interaction with the α4β7 target ligand MAdCAM-1 and therefore prevents lymphocyte trafficking into mucosal tissue and reduces inflammation.[36] The medication has high bioavailability after SC injection (82–99%) and a relatively long half-life of around 30 days.[36,37]

The phase IIb trial randomized 350 subjects with moderate-to-severe UC to SC abrilumab (7 mg, 21 mg, 70 mg) or matching placebo on days 1, 14, 28 and every 4 weeks thereafter until week 24. Subjects in the fifth arm in this trial received abrilumab 210 mg SC at day one with subsequent placebo injections until week 24. Those who went on to the open-label phase of the study were maintained on abrilumab 210 mg SC every three months.[37] The primary endpoint of remission (defined as Mayo score of 2 or less without individual sub-score >1 point) at week 8 was met in 0%, 2.5%, 13.3%, and 12.7% for the abrilumab 7-mg, 21-mg, 70-mg, and 210-mg groups, respectively, compared to 4.3% in the placebo arm. The two doses of 70-mg and 210-mg had significantly higher odds of achieving remission compared to placebo (70 mg: OR 3.35; 90% CI 1.41–7.95; $p = 0.021$; 210 mg: OR 3.33; 90% CI 1.34–8.26; $p = 0.030$).[37] Similarly, the secondary endpoints of response and mucosal healing were more likely to be achieved with these two doses.[37] Greater clinical remission rates with abrilumab 70-mg and 210-mg were seen in patients with previous TNFi failure. Nominal p-values were not significant for week 8 remission rates in TNFi naïve patients compared to placebo at 0.29 and 0.78 for the 70 mg and 210 mg doses, respectively. The treatment effect of abrilumab over placebo was no longer seen at 24 weeks in this treat-through trial. There were no safety signals with the use of abrilumab compared to placebo. There

were no cases of PML in this cohort of patients. This monoclonal antibody had a low rate of immunogenicity. There were two cases of anti-drug antibodies in the abrilumab group; neither of them were neutralizing antibodies.[37] No phase III trial of abrilumab in UC has been registered.

PN-943

PN-943 is an oral, gut-restricted, anti-α4ß7 integrin that selectively blocks leukocyte activation and trafficking in the gastrointestinal tract.[38] Results of the phase II trial (IDEAL) in patients with UC were presented as an abstract in 2022.[39] The 12-week double-blind, placebo controlled trial randomized patients in 1:1:1 ratio to oral PN-943 450 mg twice daily, 150 mg twice daily or placebo. The primary endpoint of clinical remission at week 12 (3 component Mayo score) in the 450 mg twice daily dose versus placebo was not met at 15.1% vs 14.5% ($p = 0.575$). Nonetheless, treatment effect was noted in the 150 mg group compared to placebo in clinical remission (27.5% vs 14.5%, nominal $p = 0.08$), histologic remission (37.2% vs 14.3%, nominal $p = 0.01$) and endoscopic improvement (43.1% vs 16.4%, nominal $p = 0.002$). In the biologic naive population, a higher proportion of patients in the 150 mg group achieved clinical remission at 30.2% vs 14.0% in the placebo group (nominal $p = 0.035$). Investigators of the study recommended further development of PN-943 in a phase III clinical trial program.[39]

MORF-057

MORF-057 is another oral small molecule that inhibits α4ß7 receptors. Data from the Phase 1 clinical trial were presented as an abstract.[40] The medication was well tolerated when it was given to healthy volunteers and had a favorable safety profile. A phase IIb study (EMERALD-2) was launched in late 2022. The dose ranging trial will enroll patients with moderate-to-severe UC with failure of conventional and/or any advanced therapy. Subjects will be randomized to one of the three different doses of MORF-057 or matching placebo over a 12-week period. The primary end point is clinical remission at week 12 (NCT05611671).

AJM347

AJM347 selectively blocks binding of α4ß7 to MAdCAM-1 in intestinal vascular endothelium. Both AJM347 and its active metabolite CAN2281 are gut selective.[41] The Phase I trial showed the molecule to be well absorbed orally and safe. It maintained selective inhibition of MAdCAM-1 binding to α4β7 integrin on peripheral blood CD4+ T cells without altering the lymphocyte counts in the cerebrospinal fluid (CSF).[41] No phase II/III studies are currently registered for AJM347 in UC.

PTG-100

PTG-100 is an oral α4β7 integrin blocker with limited systemic absorption.[42] The PROPEL phase IIa trial enrolled patients with UC with previous failure of conventional therapy or TNFi. Patients were randomized 1:1:1:1 to PTG −100 150 mg, 300 mg, 900 mg or matching placebo once daily for 12 weeks.[42] The study failed to meet its primary endpoint. It was noted, however, that re-read of the endoscopy videos by a third party demonstrated clinical efficacy of the drug along with histologic remission.[42] Despite failing to meet the primary endpoint in this trial, PTG-100 was well tolerated with no safety signals compared to placebo. There were no cases of *clostridioides difficile* infection, cytomegalovirus reactivation or PML.

Anti-Interleukin 23 (IL-23)

IL-23 is heterodimeric cytokine made up of IL23p19 and IL12p40 subunits that signal through its respective heterodimeric IL23 receptor (comprising IL23R and IL12Rβ1).[43] The process leads to the activation of the Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway which regulates transcription of downstream genes.[43] IL-23 is required for ideal regulation of resident and pathological microbes. The pro-inflammatory properties of the IL-23 cytokine was first reported by Oppmann et al.[44] They described the combination of p19 and p40 to form the composite biologically active cytokine IL-23.[44] Variants of the IL-23R gene have been linked to IBD susceptibility.[45] Patients with IBD have higher intestinal and serum circulating levels of IL-23 and Th17 cytokines.[46] IL-23 receptor loss of function

and inhibition leads to lower risk of IBD and less severe colitis.[47,48] Doses of IL-23 inhibitors used in IBD trials are around double the doses approved in psoriasis and psoriatic arthritis.[49] Mirikizumab, guselkumab, brazikumab, and risankizumab are four anti-IL 23 molecules under development in UC (Table 1 and 2). They are considered second-generation IL-23 inhibitors.

Mirikizumab

Mirikizumab is an IgG4-variant monoclonal antibody that binds to the p19 subunit of IL23. The efficacy and safety of mirikizumab was assessed in a phase II trial in patients with UC.[50] Patients were randomized to IV mirikizumab 50 mg with exposure-based dosing (EBD), 200 mg with EBD or 600 mg fixed dose, or placebo at weeks 0, 4 and 8. In the 50- and 200-mg groups, drug serum concentrations were evaluated at weeks 2 and 6 and the dose was increased (at weeks 4 and 8) based on a prespecified algorithm. Clinical remission rates at week 12 were 15.9% ($p = 0.066$), 22.6% ($p = 0.004$) and 11.5% ($p = 0.142$) in the 50-, 200- and 600-mg groups, respectively, compared to 4.8% in the placebo arm.[50] The primary endpoint of clinical remission at week 12 in the 600 mg dose group compared to placebo was not met at 6.7% (–2.9 to 16.3, $P = 0.142$).[50] Nonetheless, the greater clinical response seen in the mirikizumab group supported proceeding to a phase III trial (LUCENT 1 and 2).

In the LUCENT 1 trial, moderate-to-severe UC patients were randomized in a 3:1 fashion to receive either IV mirikizumab 300 mg or placebo every 4 weeks for 12 weeks. Significantly more patients in the mirikizumab group achieved clinical remission compared to placebo (24.2% vs 13.3%; $p = 0.00006$).[51] Patients who responded to mirikizumab in the induction trial were re-randomized to the LUCENT 2 maintenance trial in which patients received either mirikizumab 200 mg SC every 4 weeks or placebo.[52] The primary endpoint of clinical remission at week 40 was met by 49.9% in the mirikizumab arm vs 25.1% in the placebo arm ($p < 0.001$). Endoscopic remission rates were higher in patients who received mirikizumab compared to those who received placebo. The results were statistically significant in both those who failed conventional therapy and those who failed advanced therapies with biological agents or tofacitinib.[52] In addition to the open-label extension study (LUCENT 3) (NCT03519945), the mirikizumab clinical trial development program includes the novel SHINE 1 phase II trial assessing the safety and efficacy of this agent in pediatric and adolescent populations (NCT04004611) and the LUCENT ACT, a phase 3b trial with an active comparator arm of vedolizumab (NCT04469062).

Guselkumab

The efficacy and safety of guselkumab as an induction therapy in UC was assessed in the phase IIb QUASAR study.[53] Patients were enrolled if they failed either conventional therapy or advanced treatment with TNFi, vedolizumab or tofacitinib. Patients received IV guselkumab at 200 mg, 400 mg or placebo at weeks 0, 4 and 8. Outcomes were assessed at week 12. Around 50% of patients had prior inadequate response or intolerance to advanced therapies. Clinical response was reported in 60.7% and 61.4% of patients in the two guselkumab groups compared to 27.6% in the placebo arm ($p < 0.001$ for both guselkumab dose groups). The rate of adverse events was similar in the treatment arms compared to placebo.[53] The phase III guselkumab clinical trial program (ASTRO) is currently recruiting (NCT05528510).

Guselkumab was also studied in a phase II proof of concept, three-arm clinical trial (VEGA), where guselkumab monotherapy was compared to golimumab monotherapy and combination therapy with guselkumab and golimumab in moderate-to-severe UC who failed conventional and/or advanced therapies with vedolizumab or tofacitinib.[54] At week 12, clinical response was achieved in 83% of patients in the combination therapy group compared to 61% and 75% in the golimumab and guselkumab monotherapy groups, respectively. The primary efficacy endpoint was not met as the combination therapy outcome was not significantly different from the monotherapy groups.[54] At week 12, the median fecal calprotectin concentration was 117.5 mg/kg in the combination therapy group compared to 505 mg/kg in the golimumab monotherapy group and 397.5 mg/kg in the guselkumab monotherapy group. Clinical remission at week 12 was achieved in a higher proportion of patients in the combination therapy group compared to the monotherapy groups (37% vs 21 and 22%).[54] The composite endpoint of endoscopic normalization (Mayo UC endoscopic sub-score of 0) and histological remission at week 12

was achieved in 15% of patients in the combination therapy group compared to 4–7% in the monotherapy groups.[54] In this relatively small and short study, there were no significant safety signals in the combination therapy group.

Brazikumab

Brazikumab (MEDI2070) is an IgG2 human monoclonal antibody targeting the p19 subunit of IL-23.[55] The original design of the phase II trial (EXPEDITION) had an active comparator arm with subjects receiving vedolizumab. However, the protocol was updated in 2021 to include three arms, two different doses of brazikumab and a placebo arm (NCT03616821). In June 2023, AstraZeneca announced the discontinuation of brazikumab development for both UC and CD.[56]

Risankizumab

Risankizumab is a humanized monoclonal antibody that binds and inhibits the p19 subunit of IL-23. Risankizumab has been approved for the treatment of moderate-to-severe CD as it has demonstrated efficacy in inducing and maintaining remission compared to placebo.[57,58] No safety signals were found in the induction or maintenance parts of the phase III clinical trial program in CD.[58] A phase III trial of risankizumab in UC has completed recruitment, and the results are pending (NCT03398135).

Table 2 Summary of Emerging Therapies That Have Completed Phase III Trials

Agent	Target	Mode of Delivery	Dose	Primary Endpoint	Primary Endpoint (Drug vs Placebo)
CT-P13	TNF	SC	120 mg Q2WK	LIBERTY-UC: Clinical remission at WK 52	43.2% vs 20.8% **(p<0.001)**
Etrolizumab	α4β7 and αEβ7 integrins	SC	105 mg Q4WK	HICKORY: Clinical remission WK14 HICKORY: Clinical remission WK 66 HIBISCUS I: Clinical remission WK10 HIBISCUS II: Clinical remission WK10	18.5% vs 6.3% **(p=0.003)** 24.1% vs 20.2% (p=0.50) 19.4% vs 6.9% (p=0.017) 18.2% vs (11.1%) (p=0.17)
Carotegrast methyl (AJM300)	α4 integrin	Oral	960 mg TID	Clinical response WK8	45% vs 21% **(p<0.001)**
Mirikizumab	IL23/p19 subunit	IV (induction) SC (maintenance)	Induction: 300 mg Q4WK Maintenance: 200 mg Q4WK	LUCENT 1: Clinical remission WK12 LUCENT 2: Clinical remission WK40	24.2% vs 13.3% **(p<0.001)** 49.9% vs 25.1% **(p<0.001)**
Upadacitinib	JAK1	Oral	Induction: 45 mg daily Maintenance: 15–30 mg daily	U-ACHIEVE: Clinical remission WK8 U-ACCOMPLISH: Clinical remission WK 8 U-ACHIEVE (Maintenance): Clinical remission WK52	26% vs 5% **(p<0.001)** 33% vs 4% **(p<0.001)** 52% (30 mg) vs 12% **(p<0.001)** 42% (15 mg) vs 12% **(p>0.001)**
Etrasimod	S1PR1, S1PR4 and S1PR5	Oral	2 mg daily	ELEVATE UC 12: Clinical remission WK12 ELEVATE UC 52: Clinical remission WK12 ELEVATE UC 52: Clinical remission WK52	25% vs 15% **(p=0.026)** 27% vs 7% **(p<0.001)** 32% vs 7% **(p<0.001)**

Note: Bold= primary endpoint met.

Abbreviations: TNF, tumor necrosis factor; α4β7, alpha4-beta7; αEβ7, alphaE-beta7; α4, alpha4; IL-23, interleukin 23; JAK, janus kinase; S1PR, sphingosine 1 phosphate receptor; SC, subcutaneous; IV, intravenous; Q2WK, every 2 weeks; Q4WK, every 4 weeks; TID, three times a day; WK, week; UC, ulcerative colitis.

Other Interleukin Modulators

Proleukin (Low-Dose IL-2)

In mouse models, low-dose IL-2 has been shown to promote the expansion of regulatory T-cells and improve colitis.[59] A phase Ib/IIa trial of 26 patients with moderate-to-severe UC reported on the safety, tolerability, and efficacy of daily SC low dose IL-2 (Proleukin).[60] Three different dosage regimens were administered to determine the maximum tolerated dose: 0.3×10^6 IU/m^2/d (dose A), 1×10^6 IU/m^2/d (dose B), or 1.5×10^6 IU/m^2/d (dose C). The drug was well tolerated without serious adverse events. The most common adverse events were mild and included injection reactions, malaise, and fever. At week 8, clinical response (decrease in total Mayo score of ≥3 or ≥30% at week 8) was achieved in 52.6%, while clinical remission (Mayo score ≤2, with no individual sub-score >1, including Mayo endoscopic sub-score) was achieved in 21.1%.[60] Dose B was considered the maximum effective dose with a week 8 clinical response rate of 69.2% and clinical remission rate of 30.8%. These data support further development of low-dose IL-2 in the treatment of moderate-to-severe UC.

AMT-101 (IL-10)

IL-10 is a cytokine that has important anti-inflammatory properties. SC administration of recombinant human IL-10 has been demonstrated to result in clinical and endoscopic improvement in Crohn's disease, but its utilization is limited due to systemic toxicities including anemia and thrombocytopenia.[61] AMT-101 is a gut-selective, oral IL-10 fusion protein. In a phase Ib study, AMT-101 was well tolerated (no incidence of thrombocytopenia or anemia).[62] No systemic toxicities were noted, and AMT-101 systemic levels were below the limit of quantitation as expected with the gut selective mechanism of action. AMT-101 resulted in reduction of fecal calprotectin by 44% (1 mg dose) and 27% (3 mg dose) among patients with a baseline fecal calprotectin >150 µg/g. Histologic improvement was noted in 60% of patients who received AMT-101 compared to 0% in those who received placebo.[62] AMT-101 is being investigated in three-phase II clinical trials of UC patients: (1) a monotherapy study in biologic-naïve and experienced patients (LOMBARD) which is still active but not recruiting (NCT04583358) (2) a combination study with adalimumab in biologic naïve patients (MARKET) which was completed in July 2022 but results are yet to be published (NCT05372939) (3) A study in patients with pouchitis post-ileal pouch-anal anastomosis (FILLMORE).

Efmarodocokin Alfa (UTTR1147A)

Activation of the IL-22 pathways leads to favorable consequences including promoting mucous production, increasing epithelial tight junctions and secretion of antimicrobial peptides.[63] Efmarodocokin alfa (UTTR1147A) is a fusion protein of human IL-22 and crystallizable fragment (Fc) of human IgG4. In a dose escalation phase Ib study, 32 healthy volunteers and 24 patients with moderate-to-severe UC received IV UTTR1147A at 30–90 µg/kg doses given once every 2 weeks or every 4 weeks for 12 weeks.[64] Dermatologic side effects such as dry skin, erythema, and pruritus were most common. These were dose limiting and seen with the 90 µg/kg every 2 weeks dose. Clinical response (an exploratory outcome) was noted in 38.9%.[64]

Two phase II studies were completed investigating the use of UTTR1147A. The first one was designed to investigate pharmacokinetics, efficacy, and safety of UTTR1147A compared to vedolizumab and placebo in moderate-to-severe UC (NCT03558152). The second phase II study is intended to evaluate the long-term safety and tolerability of UTTR1147A in moderate-to-severe UC or CD (NCT03650413). The results of both phase II studies have not been published yet.

Olamkicept (SGP130Fc)

IL-6 is a key cytokine that mediates chronic inflammation in IBD through interactions with the soluble IL-6 receptor (sIL-6R) which results in downstream signaling including IL-6 trans-signaling.[65] Olamkicept (sgp130Fc) is an inhibitor of IL-6 trans-signaling by selectively binding and neutralizing the sIL-6R/IL-6 complex. In a phase IIb trial, 91 patients with active UC (defined as full Mayo score ≥5, rectal bleeding score ≥1, endoscopy sub-score ≥2) were randomized to bi-weekly IV olamkicept 600 mg, 300 mg or placebo.[66] The primary endpoint of clinical response at week 12 was noted in 58.6% vs 34.5% in the olamkicept 600 mg vs placebo ($p = 0.03$). The rate of clinical response was not significantly

different between the olamkicept 300 mg group compared to placebo (43.3% vs 34.5%; p = 0.52).[66] Sixteen out of 25 secondary outcomes were met by the olamkicept 600 mg group including mucosal healing (endoscopic sub-score ≤1) at week 12 which was noted in 34.5% vs 3.4% (p < 0.001). The treatment related adverse event rates were similar between the olamkicept and placebo groups. The most common side effects in the olamkicept groups were bilirubinuria, hyperuricemia and elevated aspartate aminotransferase.[66]

Other Biologic Agents

Anti-TNF-Like Ligand 1A (Anti-TL1A)

TNF-like ligand 1A (TL1A) is fibrogenic factor of the TNF superfamily and has been implicated in autoimmune disorders including IBD.[67] TL1A expression is increased in IBD, and the level of expression has been demonstrated to correlate with IBD disease severity.[68,69] Therefore, anti-TL1A agents including PF-06480605 and PRA023 are being developed for the management of moderate-to-severe UC.

PF- 06480605

PF-06480605 is a fully human IgG1 monoclonal antibody against TL1A. In a phase IIa, open-label trial (TUSCANY), 42 patients with moderate-to-severe UC received 500 mg IV of PF-06480605 every 2 weeks (total of 7 doses).[70] The most common adverse events were arthralgia and UC flare. Anti-drug antibodies were noted in 82% (10% were neutralizing). At week 14, endoscopic improvement (Mayo endoscopic sub-score ≤1) was noted in 38.2% (95% CI: 23.82–53.68; p < 0.001).[70] The authors concluded that further study is warranted based on promising results of the phase IIa trial.

PRA023

PRA023 is an IV anti-TL1A monoclonal antibody. In a Phase II, placebo-controlled trial, 135 patients with moderate-to-severe UC were randomized to PRA023 (1000 mg on day 1, 500 mg at week 2, 6 and 10) or placebo.[71] The primary endpoint of clinical remission at week 12 was met in the PRA023 group at 26.5% vs 1.5% in the placebo group (p < 0.0001).[71] The rate of endoscopic improvement was significantly higher in the PRA023 group (36.8% vs 6%; p < 0.0001). The rates of overall and serious adverse events were similar between the two groups. The authors concluded that PRA023 showed a favorable efficacy and safety profile and that phase III studies should be pursued.

Ravagalimab (ABBV-323)

CD40 is expressed on immune, endothelial and epithelial cells and is part of the TNF receptor superfamily.[72] Overexpression of CD40 has been demonstrated in autoimmune disorders including IBD.[72] Therefore, anti-CD40 antagonism is a potential target from the management of UC. Ravagalimab is an anti-CD40 monoclonal antibody that is currently being developed for the management of UC. The phase II multicenter, single arm, open-label study investigating ravagalimab in UC has been completed, but results have not yet been published (NCT03695185).

Spesolimab (BI655130)

Spesolimab is a humanized IgG1 monoclonal antibody against IL-36 receptor signaling. Heightened expression of IL-36 has been documented in IBD.[73] In addition, studies have also demonstrated increased levels of IL-36 receptor agonists in colonic tissue of patients with active UC.[74] Three-phase II/IIa trials were conducted to evaluate the immunogenicity, safety and efficacy of spesolimab in moderate-to-severe UC.[75] Study 1 was a phase II trial that randomized patients to one of the four groups: (1) IV spesolimab single dose followed by placebo on weeks 4 and 8 (2) placebo every 4 weeks (3) IV spesolimab 450 mg every 4 weeks (4) IV spesolimab 1200 mg every 4 weeks for 12 weeks. Study 2 was a phase IIa trial that randomized patients to IV spesolimab 1200 mg every 4 weeks or placebo. Study 3 was an open label, single arm exploratory trial in which patients received IV spesolimab 1200 mg every 4 weeks for 12 weeks. The rates of adverse events were similar between patients who received spesolimab and placebo across studies 1 and 2. Skin rash (5.4%), acne (13.3%), and nasopharyngitis (4.1%) were the most frequently reported adverse events with spesolimab.[75] The overall rate of anti-drug antibodies was 11% (n = 8) in study 1, 14.3% (n = 2) in study 2 and 25% (n = 2) in study 3. The efficacy endpoints were not met with spesolimab across all 3 studies.[75]

Janus Kinase Inhibitors

Janus Kinases (JAK) are a group of tyrosine kinases that are responsible for intracellular signaling of cytokine receptor binding through the Signal Transducer and Activator of Transcription (STAT) pathway.[76] Activation of the JAK-STAT pathway regulates gene transcription of proinflammatory proteins. Cytokines such as IL-9, IL-12, IL-23 and interferon-gamma (IFN-γ) utilize the JAK-STAT pathway and therefore JAK inhibition is appealing for the management of IBD.[77] The JAK family includes JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). JAK3 expression is restricted to lymphoid and myeloid cells (hematopoietic system), while the rest of the JAK family proteins are widely expressed.[77]

Tofacitinib is a non-selective, oral JAK inhibitor approved for the treatment of UC. The pivotal phase III OCTAVE 1–3 trials have demonstrated the efficacy of tofacitinib in inducing and maintaining remission in both biologic naïve and exposed UC patients.[7] Due to safety concerns, tofacitinib has been issued a black box warning and is currently reserved for second line use after anti-TNF treatment in UC.[78] The safety concerns with tofacitinib have sparked interest in the development of more selective JAK inhibitors for the management of UC. Filgotinib is an oral JAK1 selective inhibitor dosed at 200 mg daily. It is currently approved in Great Britain and the European Union for the treatment of adults with moderate-to-severe UC who have failed conventional therapy or biologics. The landmark SELECTION trial was a phase IIb/III trial that demonstrated the effectiveness and safety of filgotinib in UC.[8]

Upadacitinib

Upadacitinib is an oral, JAK 1 selective inhibitor approved in 2022 for the treatment of moderate-to-severe UC. It has higher selectivity for the inhibition of JAK1 compared to other JAKs and TYK2.[79]

Upadacitnib's phase III clinical trial program consisted of two parallel induction studies (U-ACHIEVE [UC1] and U-ACCOMPLISH [UC2]) and a maintenance trial (U-ACHIEVE [UC3]).[9] The primary outcome of clinical remission at week 8 (defined as an adapted Mayo UC score of ≤2 with a rectal bleeding score of 0, stool frequency score ≤1 and endoscopic sub-score ≤1 without friability) was significantly higher in the upadacitinib 45 mg daily group at 26% vs 5% ($p < 0.001$) in UC1 and 33% vs 4% ($p < 0.001$) in UC2. In the subgroup of patients exposed to biologics, clinical remission rates were significantly higher in the upadacitinib groups compared to placebo in both UC1 and UC2.

For the maintenance study (UC3), in an intention-to-treat analysis, the primary outcome of clinical remission (adapted Mayo score) at week 52 was significantly higher in the upadacitinib 30 mg at 52% and upadacitinib 15 mg at 42% vs 12% in the placebo group ($p < 0.001$ for each upadacitinib dose group vs placebo).[9] In the subgroups of patients exposed to biologics, the week 52 clinical remission rates were significantly higher in both upadacitinib dose groups compared to placebo (adjusted treatment difference [95% CI] for the 15 mg group: 33.0 [20.1–45.9]; adjusted treatment difference [95% CI] for the 30 mg group: 41.6 [28.6–54.7]).

Mucosal healing (defined as a Mayo endoscopic sub-score of 0 and a Geboes score <2) was noted in 19% in the upadacitinib 30 mg group ($p = 0.0001$) and 18% in the 15 mg compared to 5% in the placebo group ($p = 0.0003$). All other secondary endpoints were achieved in both upadacitinib dose groups compared to placebo ($p < 0.0001$).

The most common adverse events in the upadacitinib induction groups were nasopharyngitis (4–5%), creatine phosphokinase elevations (5%) and acne (5–7%). Herpes zoster was reported in a total of 3 patients from both induction studies and none in the placebo groups. In the maintenance trial, the overall adverse event rates were similar between the upadacitinib and placebo groups. Herpes zoster infection occurred in 4% ($n = 6$) in both the 15 mg and 30 mg upadacitinib groups compared to none in the placebo group. Two patients in the upadacitinib 30 mg developed venous thromboembolism (1 with underlying obesity and the second had concomitant COVID-19 pneumonia) compared to none in the 15 mg and placebo groups. None of the patients in the upadacitinib maintenance dose groups developed major adverse cardiovascular events (MACE). Non-melanoma skin cancer occurred in 2 patients in the upadacitinib 30 mg group.

Upadacitinib offers the advantage of a once daily oral agent with established efficacy in both biologic naïve and experienced patients with moderate-to-severe UC. One major advantage of upadacitinib is its rapid onset of action. In a post hoc analysis of the U-ACHIEVE and U-ACCOMPLISH induction trials, upadacitinib resulted in improvement in symptoms of stool frequency and rectal bleeding within one day after treatment initiation.[80]

Ivarmacitinib (SHR0302)

Ivarmacitinib is an oral selective JAK1 inhibitor. It has >10 times selectivity for JAK1 compared to JAK2.[81] The AMBER2 study was a phase II, double-blind, placebo-controlled study that randomized 164 patients with moderate-to-severe UC to receive ivarmacitinib 8 mg daily, 4 mg twice daily, 4 mg daily or placebo for 8 weeks.[82] A total of 12 patients (7.3%) were exposed to anti-TNF/biologic agents in the past. The primary endpoint of clinical response at week 8 was higher in all ivarmacitinib dose groups compared to placebo. Clinical remission rates at 8 weeks (stool frequency sub-score ≤1, rectal bleeding sub-score 0, and endoscopic sub-score ≤1) were significantly higher in the ivarmacitinib groups at 22% for 8 mg daily group ($p = 0.020$), 24.4% for both the 4 mg twice daily ($p = 0.013$) and 4 mg daily ($p = 0.011$) groups compared to 4.9% for placebo. Endoscopic improvement (Mayo endoscopic sub-score ≤1) was numerically higher in all ivarmacitinib dose groups compared to placebo but only statistically significant in the 4 mg daily dose group (36.6% vs 14.6%, $p = 0.018$). Treatment-emergent adverse event rates were 43.9% in the 8 mg daily group, 48.8% in the 4 mg daily and twice daily groups, compared to 39.0% in the placebo group. A phase III study of ivarmacitinib in moderate-to-severe UC is ongoing and currently recruiting (NCT05181137).

Peficitinib

Peficitinib is an oral pan-JAK inhibitor with moderate selectivity to JAK3. In a phase IIb study, 219 patients with moderate-to-severe UC were randomized to receive peficitinib 25 mg daily, 75 mg daily, 150 mg daily, 75 mg twice daily or placebo.[83] A dose response relationship was not observed for the primary endpoint of Mayo score change from baseline at week 8. Secondary endpoints including clinical response, clinical remission, and mucosal healing were all numerically higher in patients who received ≥75 mg of peficitinib compared to placebo.[83] Currently, there are no registered phase III studies of peficitinib in UC.

OST-122

OST-122 is a gut selective oral JAK inhibitor with selectivity for JAK3, TYK2 and AMPK-related protein kinase 5 (ARK5). The phase Ib/IIa trial which enrolled 32 patients with moderate-to-severe UC has been recently completed and results are yet to be published (NCT04353791).[84]

Izencitinib (TD-1473)

Izencitinib is an oral, gut-selective pan-JAK inhibitor. The gut-specific design is meant to limit systemic toxicity of pan-JAK inhibition. In a phase I study, 40 patients with moderate-to-severe UC were randomized to receive izencitinib 20 mg, 80 mg, 270 mg or placebo for 28 days.[85] A total of 5 patients in the trial were previously exposed to anti-TNF agents. The rates of clinical response were highest in the 270 mg group at 55%, followed by 20% in the 20 mg and 80 mg groups and 11% in the placebo group. There was a trend in C-reactive protein (CRP) and endoscopic response in the izencitinib groups compared to placebo. Izencitinib was overall well tolerated with similar rates of adverse events to placebo. Further development of izencitinib in UC was halted after the drug failed to meet the primary endpoint in a phase IIb (NCT03758443) dose finding study.[86,87]

Brepocitinib (PF-06700841) and Ritlecitinib (PF-06651600)

Brepocitinib is a selective JAK1/TYK2 inhibitor, and ritlecitinib is a selective JAK3 and TEC kinase inhibitor. Both are oral agents that were recently studied in a phase IIb umbrella study. The VIBRATO study is a double -blind placebo-controlled study that randomized 317 moderate-to-severe UC patients to either ritlecitinib (20 mg, 70 mg or 200 doses), brepocitinib (10 mg, 30 mg or 60 mg doses) or placebo for 8 weeks.[88] Patients then entered a 24-week chronic therapy phase with either ritlecitinib 50 mg, brepocitinib 30 mg or placebo followed by a 4 week follow-up post therapy. The primary endpoint (decrease in total mayo score) was met by all doses of brepocitinib and ritlecitinib with the largest decline noted in the ritlecitinib 200 mg dose. Key secondary endpoints including clinical remission, endoscopic improvement and mucosal healing showed dose-dependent

improvement with both brepocitinib and ritlecitinib.[88] The short-term safety profile of both agents was acceptable. Phase III trials have not been registered yet.

Deucravacitinib (BMS-986165)

Deucravacitinib is an oral TYK2 inhibitor in development for the treatment of moderate-to-severe UC. In a phase II, double-blind trial (LATTICE-UC), 131 patients were randomized to deucravacitinib 6 mg twice daily vs placebo.[89] The trial failed to meet its primary endpoint of clinical remission at 12 weeks defined by the modified Mayo score (stool frequency sub-score ≤1 with a decrease from baseline of at least 1 point, a rectal bleeding sub-score of 0, and an endoscopy sub-score of ≤1). The trial also did not meet key secondary endpoints. Overall, deucravacitinib was well tolerated. A second phase II trial of a higher dose deucravacitinib for induction in moderate-to-severe UC is planned (NCT04613518).[90]

Sphingosine-1-Phosphate Receptor Modulators

Sphingosine-1-phosphate (S1P) is a lysophospholipid molecule involved in a variety of physiological processes.[91,92] S1P acts as a ligand for up to five G protein-coupled receptors, S1P receptors (S1PR1-5), which are expressed in a wide range of cell types.[93] S1P has been implicated in a number of pathological conditions, including cancer, autoimmune diseases, and cardiovascular disease.[93] Modulating S1P signaling has therefore emerged as a potential therapeutic strategy for these diseases. The coupling of S1P with its receptors can lead to internalization of the receptor affecting the S1P gradient and eventual migration/egress of lymphocytes from lymphoid tissue. Fingolimod, an oral non-selective S1PR modulator that binds S1PR1-3-4-5, was the first S1PR modulator investigated and approved in immune-mediated diseases. It is approved for the treatment of multiple sclerosis and although well tolerated, it has not been tested in IBD human trials due to the risk of adverse events such as bradycardia, hypertension, elevated liver tests and infection.[94,95]

Ozanimod

Ozanimod is a potent S1P receptor modulator that binds selectively with high affinity to S1PR1 and S1PR5 and was approved in 2021 by the United States Food and Drug Administration and EMA for the treatment of moderate-to-severe UC.[96,97]

TRUE-NORTH study was a Phase III, randomized, double-blind and placebo controlled clinical trial that was conducted to assess efficacy and safety of induction and maintenance ozanimod in moderate-to-severe UC.[10] The study met its primary endpoint of induction of clinical remission at week 10 (18.4% vs 6.0%, in ozanimod 1 mg group vs placebo, $p < 0.001$). Both endoscopic improvement and mucosal healing during induction were significantly higher in the ozanimod group in comparison to placebo (27.3% vs 11.6%, $p < 0.001$ and 12.6% vs 3.7%, $p < 0.001$, respectively). At week 52 and among responders to induction, the clinical remission rates were significantly higher in the ozanimod group compared to placebo (37.0% vs 18.5%, $p < 0.001$). Both endoscopic improvement and mucosal healing during maintenance were significantly higher in the ozanimod vs the placebo group (45.7% vs 26.4%, $p < 0.001$ and 29.6% vs 14.1%, $p < 0.001$, respectively).[10]

In terms of safety at the end of maintenance, there was no significant difference between the groups in terms of serious adverse events requiring drug discontinuation (1.3% in ozanimod group vs 2.6% in the placebo group). Elevated liver tests, lymphopenia and headaches were the most common adverse events with ozanimod. The rate of herpes zoster infection was 2.2% in the ozanimod group vs 0.4% with placebo.

Etrasimod

Etrasimod (APD334) is an oral, once-daily, selective, S1PR modulator (selective for S1PR1, S1PR4, and S1PR5) that has been developed for the treatment of moderate-to-severe UC. In the phase II (OASIS) and open-label extension trials of moderate-to-severe UC, etrasimod demonstrated greater improvement in multiple outcomes including the clinical remission and endoscopic improvement compared to placebo.[98,99]

The phase III trial (ELEVATE) comprised of two independent randomized trials, ELEVATE UC 12 and ELEVATE UC 52, randomly assigned patients with moderate-to-severe UC (2:1) to once-daily oral etrasimod 2 mg or placebo.[100] ELEVATE UC 12 (n = 354) independently assessed induction at week 12. ELEVATE UC 52 (n = 433) consisted of an induction period (12-weeks) followed by a maintenance period (40 weeks) with a treat-through design. The mean duration of UC was between 5.9 and 7.7 years and up to one-third of patients had been exposed to biologics or JAK inhibitors in the past. In ELEVATE UC 12, 25% of patients in the etrasimod group achieved clinical remission compared to 15% in the placebo ($p = 0.026$). At week 12, etrasimod demonstrated significant improvements compared to placebo in secondary endpoints of endoscopic improvement (31% vs 19%), symptomatic remission (47% vs 29%), and endoscopic improvement– histological remission (16% vs 9%).[100]

In ELEVATE UC 52, a significantly higher number of patients in the etrasimod group achieved clinical remission at the end of induction at week 12 (27% vs 7% in the placebo group; $p < 0.0001$) and at week 52 (32% vs 7% in the placebo group; $p < 0.0001$). All key secondary efficacy endpoints were met in the etrasimod group at week 52 which included sustained clinical remission (18% vs 2%) and corticosteroid-free remission (32% vs 7%).[100]

In terms of safety, the rates of serious adverse events were similar between the etrasimod and placebo groups. The rate of elevated liver tests was higher in the etrasimod group compared to placebo (2 patients in the etrasimod group discontinued etrasimod due to elevation of liver tests). Bradycardia was noted in 9 patients receiving etrasimod and none in patients receiving placebo (two were symptomatic and led to drug discontinuation). Macular edema occurred in 2 patients receiving etrasimod and one patient receiving placebo (led to drug discontinuation in 1 patient in the etrasimod group).[100]

Amiselimod

Amiselimod is an S1P receptor modulator with selectivity for S1PR1 and S1PR5 and weaker activity to GIRK (G-protein-coupled inwardly rectifying K+) compared to fingolimod.[101] In a phase IIa trial, 12 weeks of treatment with amiselimod 0.4 mg was not superior to placebo for the induction of clinical response in CD but was overall well tolerated.[102] A phase II trial evaluating the efficacy and safety of amiselimod in mild-to-moderate UC is ongoing (NCT04857112).

CBP-307

CBP-307 is a synthetic, oral S1P receptor modulator with selectivity for S1PR1.[103] A phase II randomized controlled trial evaluating the efficacy and safety of 0.2 mg of CBP-307 in moderate-to-severe UC has been completed. The study did not meet the primary endpoint of least square change of adapted Mayo score from baseline at week 12 at −2.65 vs −2.01 in the placebo group; $p = 0.103$.[104] The study did meet multiple secondary endpoints including clinical remission by adapted (28.3% vs 9.6%; $p = 0.016$) and complete Mayo score (18.9% vs 5.8%; $p = 0.044$). Overall, CBP-307 was well tolerated as there was no significant difference between the groups in rates of serious adverse events and grade 3 or higher adverse events.[104]

KRP-203

KRP-203 is a second generation, oral S1PR1 modulator with only partial agonism to S1PR3 (lower risk of bradycardia). In a phase II trial, 27 patients with moderate-to-severe UC were randomly assigned to KPR-203 1.2 mg or placebo.[105] The primary endpoint of clinical remission (defined as a Mayo score of 0–1) at 8 weeks was met in 14% in the KPR-203 group vs 0% in the placebo group. KPR-203 was well tolerated as there was no difference between the groups in rates of adverse events. No bradycardia events were noted in the study population.[105] Although the study was terminated prematurely due to meeting predefined futility criteria, the authors suggested that larger prospective studies are needed to confirm efficacy and safety of KRP-203.

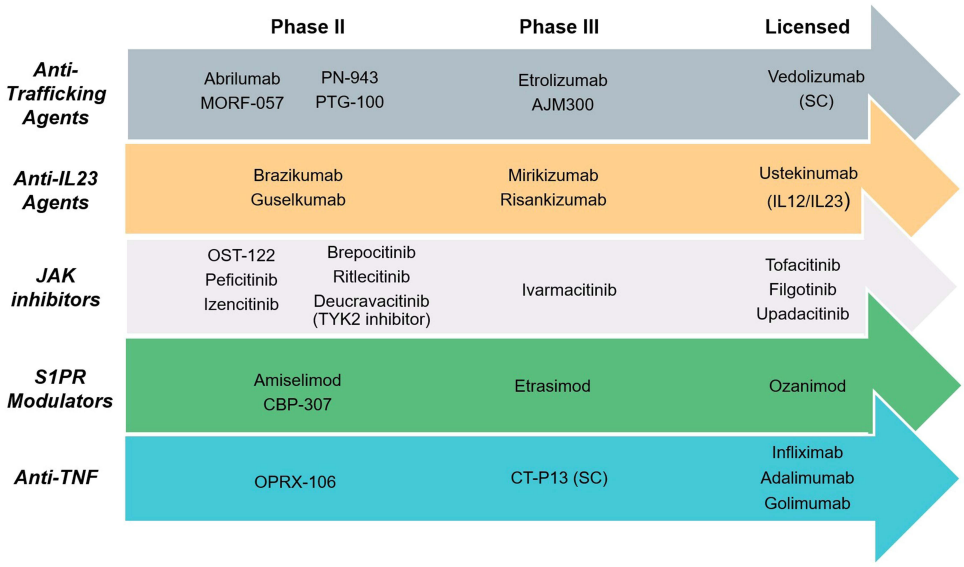

Figure 1 Summary of select advanced therapy classes with current development status of associated agents.
Abbreviations: SC, subcutaneous; IL, interleukin; JAK, janus kinase; TYK2, tyrosine kinase 2; S1PR, sphingosine 1 phosphate receptor; TNF, tumor necrosis factor.

Other Advanced Therapies

ABX464 (Obefazimod)

ABX464 (obefazimod) is a novel, first in class, oral small molecule that upregulates biogenesis of the mRNA inhibitor micro-RNA (miR)-124, which in turn leads to monocyte and macrophage activations. It can stop the production of inflammatory mediators involved in diseases such as rheumatoid arthritis and UC.[106] The safety and efficacy of ABX464 in moderate-to-severe UC was assessed in an 8-week, phase IIa, placebo-controlled, double-blind induction phase followed by an open-label long-term extension.[107] Patients were randomized 2:1 in the induction phase to ABX464 50 mg orally once daily or placebo. Overall, 29 patients completed the study and of those, 22 continued with the long-term extension study. Adverse events at week 8 were reported in 78% of those receiving ABX464 compared to 55% of those receiving placebo. Clinical remission and clinical response at week 8 were achieved in 35% and 70% of those in the ABX464 arm compared to 11.1% and 33.3% in the placebo group.[107]

In a separate phase IIb dose ranging clinical trial, 254 patients with moderate-to-severe UC were randomized 1:1:1:1 to ABX 464 100mg, 50 mg, 25 mg or matching placebo once daily. The delta in the modified Mayo Score from baseline was significantly higher in all three ABX464 groups vs placebo ($p = 0.0039$ for ABX464 100 mg, $p = 0.0003$ for ABX464 50 mg, and $p = 0.0010$ for ABX464 25 mg).[108] The phase 3 clinical program (ABTECT-1 [NCT05507203] and ABTECT-2 [NCT05507216] induction trials – and ABTECT maintenance trial [NCT05535946]) is still recruiting. The study will assess two different doses of ABX464 at 50 mg and 25 mg.

Apremilast

Phosphodiesterases (PDE) catalyze the breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). PDE4 enzymatic activity can eventually result in pro-inflammatory effects as it catalyzes breakdown of 3, 5′ cAMP in T-cells, macrophages and monocytes leading to activation of nuclear transcription factor kappaB (NF-κB).[109,110]

Apremilast is an oral PDE4 inhibitor being developed for the treatment of moderate-to-severe UC. In a phase II, double-blind trial, patients with moderate-to-severe UC were randomized to apremilast 30 mg ($n = 57$), apremilast 40 mg ($n = 55$) or placebo ($n = 58$) twice daily.[111] The primary endpoint of clinical remission at week 12 (total Mayo UC score ≤ 2; no individual score >1) was noted in 31.6% of the 30 mg group vs 12.1% in the placebo group ($p = 0.01$). The clinical remission rate was 21.8% in the 40 mg group ($p = 0.27$ compared to placebo). Endoscopic response (decrease in the Mayo endoscopic sub-score by ≥ 1) was noted 73.7% in the 30 mg group vs 41.4% in the placebo group ($p < 0.0001$).[111] Reduction in CRP and fecal calprotectin was noted in both apremilast groups compared to placebo. The

primary endpoint of the trial was not met based on the above results. On post-hoc analysis, a significantly higher proportion of patients in the apremilast 30 mg (56.1%) and 40 mg (34.5%) groups had a Mayo endoscopic sub-score of ≤1 compared to placebo.

Headache was the most commonly reported side effect at 25.5% in the 40 mg group and 21.1% in the 30 mg group compared to 6.9% in the placebo group. Serious adverse event rates were 2.4% in the placebo group compared to 1.8% in the apremilast 40 mg group. No phase III trial has been registered for apremilast in moderate-to-severe UC yet.

Cobitolimod

Cobitolimod is a topical toll-like receptor 9 (TLR9) agonist. It results in the activation of TLR9 on lymphocytes and antigen presenting cells which lead to induction of regulatory T-cells, eventual production of IL-10 and suppression of TH-17 cells.

A double-blinded study (COLLECT) randomized 131 patients with moderate-to-severe UC to two doses of either topical cobitolimod 30 mg or placebo delivered via colonoscopy.[112] The primary endpoint of clinical remission at week 12 (Clinical Activity Index ≤4) was not met (44.4% in the cobitolimod group vs 46.5% in the placebo group, p = 0.91).[112] Key secondary endpoints including symptomatic remission, mucosal healing and histologic remission were significantly more common in the cobitolimod group. A subsequent phase IIb dose ranging study (CONDUCT) randomized 213 patients with moderate-to-severe UC to one of the five arms: cobitolimod 31 mg, 125 mg, 250 mg at weeks 0 and 3; cobitolimod 125 mg at weeks 0, 1, 2 and 3 or placebo.[113] Study drugs were delivered as rectal enemas. The primary endpoint of clinical remission at week 6 was significantly higher in the cobitolimod 250 mg group at 21% vs 7% in the placebo group (OR 3.8, 80% CI: 1.5–9.5; p = 0.025). The rate of clinical remission at week 6 was not significantly different in the rest of the cobitolimod dose groups compared to placebo. Overall, cobitolimod was well tolerated as rates of treatment emergent adverse events were similar to the placebo group.[113] The phase III trial (CONCLUDE) comparing cobitolimod 250 mg and 500 mg to placebo is actively recruiting patients with left-sided UC (NCT04985968).

Conclusions

The utilization of advanced therapies including biologics and small molecules is indicated in moderate-to-severe UC or in steroid dependent UC. Despite the wide array of currently available pharmacologic agents, the overall net remission rates from pivotal clinical trials remain low across biologics and small molecules in UC.[11] The emerging therapeutic agents in the pipeline offer either new mechanisms of action (ie, TLR9 agonist), more selective mechanisms of action (IL-23 inhibitors) or different routes of administration (Table 1 and 2). This gives hope for both patients and healthcare providers treating UC. This will also pose a challenge for healthcare providers as optimal positioning and sequencing of these therapies will become even more complex. Currently, positioning of advanced therapies relies on clinical factors such as inflammatory burden, route of administration, onset of action, risk of treatment-related adverse events, extra-intestinal manifestations, comorbidities, and cost/availability.

In terms of comparative efficacy between the different agents, there are limited published head-to-head clinical trials such as the VARSITY trial that showed superiority of vedolizumab to adalimumab in moderate-to-severe UC.[114] The HIBISCUS and GARDENIA trials compared etrolizumab to adalimumab and infliximab and demonstrated no difference between the agents in achieving the primary and secondary endpoints. Three network meta-analyses of recently approved agents in UC concluded that upadacitinib ranked highest for induction of clinical remission.[115–117] Upadacitinib also ranked highest in patients previously exposed to biologics. Results of network-meta-analyses should be interpreted in the context of limitations including comparing trials from different decades with different endpoint definitions and a heterogenous patient population.

Small molecules offer multiple advantages compared to biologics in UC. For one, there is ease of administration with the oral route. JAK inhibitors particularly have been demonstrated to have a rapid onset of action with improvement in symptoms noted within 1–7 days on treatment initiation.[80,118] This makes JAK inhibitors an ideal option for the steroid dependent/refractory patient especially if exposed to biologics in the past. In addition, small molecules do not carry the risk of immunogenicity and therefore are not used in combination therapy with immunomodulators. However, a balance must be achieved between efficacy and safety. Since its approval, there have been safety concerns regarding the use of tofacitinib. In comparison to other advanced therapies in IBD, tofacitinib (particularly the 10 mg twice daily dose) is associated with an increased risk of herpes zoster infection with a number needed to harm of 97 (95% CI 19–1022) according to a systematic review and network meta-analysis.[119] More importantly, the ORAL Surveillance study which investigated rheumatoid arthritis patients over the age of 50 years with at least 1

cardiovascular risk factor demonstrated a higher risk of MACE and malignancy in patients taking tofacitinib compared to anti-TNF.[120] In the UC population, results of the integrated analysis of the tofacitinib global program (7.8 years and total 2999.7 patient follow-up years) showed no increased risk of MACE, venous thromboembolism, or malignancy (excluding non-melanoma skin cancer) with tofacitinib.[121] So far, selective JAK inhibitors such as upadacitinib and filgotinib have demonstrated a favorable safety profile but still carry a risk of herpes zoster and long-term studies are needed to confirm their safety profile.

The advent of selective agents such as IL-23 inhibitors (mirikizumab, risankizumab, guselkumab) compared to IL-12/23 inhibitors will raise dilemmas including the role of these agents in patients previously exposed to IL-12/23 inhibitors and whether more selective agents are superior to non-selective ones. In terms of the prior, a real-world study of 100 patients with CD previously exposed to ustekinumab demonstrated almost a 40% steroid-free clinical remission rate to risankizumab at week 12.[122] In addition, risankizumab has been shown to be superior to ustekinumab in a randomized controlled trial of patients with psoriasis.[123] This highlights that selective IL-23 inhibitors should remain a viable option in patients who have been exposed to IL-12/23 inhibitors.

Combining advanced therapies has been proposed as a potential strategy to raise the therapeutic ceiling encountered with current agents to treat moderate-to-severe UC. A systematic review and meta-analysis including 266 patients with 7 different combinations showed a serious adverse event rate of 9.6% and efficacy rates for remission that ranged from 40% to 70%.[124] The VEGA study, although did not meet the primary endpoint, illustrated a signal for therapeutic gain with combination guselkumab plus golimumab compared to monotherapy with each agent.[54] More data is needed on the ideal type of combination, duration of combination therapy, long-term safety, and cost-effectiveness of combination advanced therapies in UC. With the expanding therapeutic pipeline of agents, predictive biomarkers and precision medicine approach will need to be developed for ideal use of advanced therapies in UC.

Abbreviations

cAMP, cyclic adenosine monophosphate: CD, Crohn's disease; CRP, C-reactive protein; EMA, European Medicine Agency; IBD, inflammatory bowel disease; Ig, immunoglobulin; IL, interleukin; IFN, interferon; IV, intravenous; JAK, janus kinase; NF-κB, nuclear transcription factor kappaB; S1P, sphingosine 1-phosphate; SC, subcutaneous; TNFi, tumor necrosis factor inhibitor; TYK, tyrosine kinase; UC, ulcerative colitis.

Disclosure

Dr. Turki AlAmeel: Speaker fees: AbbVie, Takeda, Bristol-Myers Squibb, Janssen Pharmaceuticals, Hikma, Amgen. Advisory board: AbbVie, Takeda, Bristol-Myers Squibb, Janssen Pharmaceuticals, Hikma. Dr. Abdulelah AlMutairdi: Speaker fees: AbbVie, Takeda, Bristol-Myers Squibb. Advisory board: AbbVie, Takeda, Bristol-Myers Squibb, Pfizer. Dr. Badr Al-Bawardy: Speaker fees: AbbVie, Takeda, Bristol-Myers Squibb, Janssen Pharmaceuticals. Advisory board: Bristol-Myers Squibb, Pfizer. The authors report no other conflicts of interest in this work.

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