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Inflammatory Bowel Disease (G Lichtenstein, Section Editor)

Novel Therapies for Inflammatory Bowel Disease

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Abstract

Purpose of review Significant advances in the discovery of novel therapeutic targets for inflammatory bowel disease address a crucial need for patients refractory to available treatment options. We will review the recent literature and data available for novel therapies for adult patients with Crohn's disease (CD) and ulcerative colitis (UC), limited to those currently in phase III trials with a focus on clinical endpoints and safety.
Recent findings Emerging therapeutic agents currently in phase III trials including IL-23 inhibitors (risankizumab, guselkumab, and mirikizumab), JAK inhibitors (filgotinib and upadacitinib), and S1P1 modulators (ozanimod and etrasimod) are effective in the treatment of patients with moderate to severe CD and UC. Therapies with greater selectivity, including IL-23 inhibitors, have favorable safety profiles. Small molecules including JAK inhibitors and S1P receptor modulators are both orally administered and non-immunogenic. Emerging novel agents recently approved or currently in phase III trials appear to be effective and safe for the treatment of CD and UC and will expand options for medically refractory patients. Future comparative effectiveness studies and progress in precision medicine may influence therapy selection.

Abbreviations

AE	Adverse events
CD	Crohn's disease
FDA	Food and Drug Administration
HDL	High-density lipoprotein
IgG	Immunoglobulin G
IBD	Inflammatory bowel disease

IL	Interleukin
IV	Intravenous
JAK/STAT	Janus kinase/signal transducer and activator of transcription
LDL	Low-density lipoprotein
MS	Multiple sclerosis
S1P	Sphingtosine-1-phosphate
SC	Subcutaneous
TNFα	Tumor necrosis factor α
BID	Twice-daily
UC	Ulcerative colitis
UEGW	United European Gastroenterology Week
UNITI	Ustekinumab as induction and maintenance therapy in CD
IM-UNITI	Ustekinumab as maintenance therapy in CD
UNIFI	Ustekinumab as induction and maintenance therapy in UC
LUCENT	Mirikizumab therapy in UC (phase III)
SERENITY	Mirikizumab therapy in CD (phase II)
VIVID-1	Mirikizumab therapy in CD (phase III)
GALAXI	Guselkumab therapy in CD (phase II/III)
QUASAR	Guselkumab therapy in UC
OCTAVE	Tofacitinib as induction and maintenance therapy in UC
FITZROY	Filgotinib therapy in CD (phase II)
DIVERSITY, DIVERGENCE	Filgotonib therapy in CD (phase II/III)
SELECTION	Filgotinib therapy in UC (phase IIb/III)
CELEST	Upadacitinib as induction and maintenance therapy in CD (phase II)
TOUCHSTONE	Ozanimod as induction and maintenance therapy in UC (phase II)
True North	Ozanimod as induction and maintenance therapy in UC (phase III)
STEPSTONE	Ozanimod as induction and maintenance therapy in CD (phase II)

Introduction

The introduction of monoclonal antibodies directed against tumor necrosis factor α (TNFα) transformed the management of inflammatory bowel disease (IBD). However, the remission rate with TNFα antagonists is 50–69%, nearly 40% of patients lose response after 1 year of treatment, and those who lose response have lower rates of response to subsequent TNFα antagonists and similarly other biologic agents [1–4]. Despite advances in biologics with alternative mechanisms of action, the current response ceiling for biologic therapy across various classes is 65% in both Crohn's disease (CD) and ulcerative colitis (UC). This is likely due to treatment-related immunogenicity and multiple upregulated pathways for which there are continued strides towards novel therapeutic targets. We will review the recent literature published and additional data available for novel therapies for adult patients with IBD, limited to those currently in phase III trials with a focus on clinical endpoints and safety.

Interleukin (IL)-12/IL-23 inhibition

The cytokines IL-12 and IL-23 play a critical role in the pathogenesis of IBD, playing a vital role in lymphocyte differentiation of the innate immune response. They are composed of a shared p40 chain which pairs with a p35 chain to form IL-12 and a p19 chain to form IL-23. The gene encoding the IL-23 receptor and the locus for the gene encoding the p40 chain have been identified as risk factors for IBD through genome-wide association studies. [5]

Ustekinumab

Ustekinumab is a human immunoglobulin G1 (IgG_1) monoclonal antibody which targets the shared p40 subunit of IL-12 and IL-23 and is approved for both CD and UC. UNITI-1, UNITI-2, and IM-UNITI substantiated its efficacy in CD over placebo [6]. In the long-term extension study, continued treatment with ustekinumab through 152 weeks resulted in maintained response and remission in a majority of patients, no new safety signals, and a low rate of antibodies to ustekinumab (4.6%) [7]. Those with CD who did not respond to standard maintenance dosing of 90 mg every 8 weeks showed improved activity with a shortened interval of 90 mg every 4 weeks. [8] Data from three phase III trials showed significantly higher week 8 endoscopic response with ustekinumab compared to placebo based on reduction of SES-CD score from baseline (2.8 vs 0.7, $p = 0.012$). [9]

The UNIFI study proved the efficacy of ustekinumab in the treatment of UC with 961 patients assigned to ustekinumab (130 mg or 6 mg/kg) intravenously (IV) versus placebo during induction followed by a maintenance of ustekinumab 90 mg every 8 or 12 weeks subcutaneously (SC) versus placebo for responders [10•]. At the end of the 8-week induction period, ustekinumab induced clinical remission (total Mayo score ≤ 2 and no sub-score > 1) at a significantly higher rate with both doses of 130 mg (15.6%) and 6 mg/kg (15.5%) than placebo (5.3%) ($p < 0.001$). Among those who responded to induction therapy and underwent a second randomization, clinical remission at week 44 was significantly higher among those assigned to ustekinumab 90 mg every 12 weeks (38.4%) and every 8 weeks (43.8%) compared to placebo (24%) ($p = 0.002$ and $p < 0.001$, respectively). The rate of adverse events (AE) was similar among the ustekinumab 130 mg dose, 6 mg/kg dose, and placebo during induction (41.4%, 50.6%, 48.0%) and maintenance phase with 90 mg every 8 weeks dosing, every 12 weeks dosing, and placebo (77.3%, 69.2%, 78.9%). There were 3 deaths, 7 cancers, and 4 opportunistic infections in patients receiving ustekinumab. 10•.

While the effect of ustekinumab may be secondary to blockade of IL-12, IL-23, or both, sparing the blockade of IL-12 may keep the immune response to pathogens intact with improved safety. [11].

Selective IL-23 inhibition

Brazikumab, risankizumab, mirikizumab, and guselkumab are monoclonal antibodies which selectively target the p19 subunit of IL-23.

Brazikumab

Brazikumab is a human IgG_2 monoclonal antibody. In a phase IIa, double-blind, placebo-controlled study, adults with moderate-to-severe CD and prior anti-TNFα therapy failure received IV brazikumab (700 mg) or placebo at weeks 0 and 4 followed by open-label SC dosing (210 mg) every 4 weeks from weeks 12 through 112 [12]. The primary outcome was clinical response at week 8, defined by a CDAI score < 150 or a 100-point decrease in CDAI from baseline. At week 8, those who received brazikumab had a significantly higher rate of clinical response than placebo (49.2% vs 26.7%, $p = 0.010$) and of reaching the week 8 composite endpoint of clinical response and a 50% reduction of either fecal calprotectin or C-reactive protein (42.4% vs 10%, $p < 0.001$). In the open-label period, clinical response, clinical remission, and the composite outcome occurred in similar proportions among those receiving brazikumab and placebo at week 24; week 24 clinical response occurred in 53.8% of patients who continued to receive brazikumab and in 57.7% of those who had received placebo during the double-blind period. A favorable safety profile was observed with the most common AEs of headache and nasopharyngitis and a greater proportion of AEs occurring in the placebo arm. Higher baseline concentrations of IL-22, whose expression is induced by IL-23, were associated with a higher likelihood of response to brazikumab compared to placebo [12].

Phase IIb/III studies are ongoing for patients with CD including parallel arms for comparison to the TNFα inhibitor, adalimumab [13]. Phase II studies and open-label extension are actively studying the efficacy and safety of brazikumab in 375 patients with moderate-to-severe UC with parallel, randomized assignment of three distinctive doses of brazikumab, standard dosing of vedolizumab, and placebo [14].

Risankizumab

Risankizumab is a humanized IgG_1 monoclonal antibody. Similar to brazikumab, risankizumab is administrated through IV induction followed by SC dosing. Phase II data is available from 121 adult patients with moderate-to-severe CD (79% prior anti-TNFα failure) across 36 international referral sites [15]. Patients were randomized to risankizumab IV infusion doses of 200 mg and 600 mg and placebo, stratified by prior exposure to anti-TNFα therapy, with a primary outcome of clinical remission (CDAI < 150) at week 12. Week 12 clinical remission was achieved in 24% of patients receiving 200 mg of risankizumab versus 37% receiving 600 mg ($p = 0.0252$) and in 15% of placebo patients (pooled risankizumab remission vs placebo- 31% vs 15%, $p = 0.049$). Rates of AEs were comparable across all groups. The

most common AEs were nausea and worsening of underlying CD activity; no deaths occurred, and serious infection occurred in one patient receiving risankizumab and three receiving placebo. [15].

The open-label extension study examined an extended IV induction (600 mg every 4 weeks for 12 weeks) in those who had not achieved deep remission (endoscopic and histologic remission) during the initial 12-week induction period, and those who were in clinical remission at week 26 received open-label SC dosing of 180 mg every 8 weeks for 26 weeks. Remission was maintained in a high percentage of patients at week 52 (71%) with maintenance of clinical response in 81%, endoscopic remission in 35%, and endoscopic response in 55% of patients [16]. The results from the phase II open-label extension revealed no new safety signals with nasopharyngitis (31%), gastroenteritis (23%), and fatigue (20%) reported as the most common AEs; serious infections were reported in 9% and opportunistic infections in 5% of patients. No malignancies or death occurred [17]. The phase III, parallel-arm trial for moderate-to-severe CD has completed recruitment [18]; patients with UC are undergoing active enrollment in phase II/III trials [19].

Mirikizumab

Mirikizumab is a humanized IgG_4 monoclonal antibody. A phase II trial studying its efficacy and safety was conducted in 249 patients with moderate-to-severe UC over 12 weeks with a primary endpoint of week 12 clinical remission (Mayo sub-score of 0 for rectal bleeding, with 1-point decrease of stool frequency and endoscopic sub-score ≤ 1). Patients were randomized to IV placebo, mirikizumab 50 mg or 200 mg with exposure-based dosing, or mirikizumab 600 mg with fixed dosing at weeks 0, 4, and 8 weeks during induction. Mirikizumab recipients with a clinical response at week 12 (decrease in 9-point Mayo score, including ≥ 2 points and $\geq 35\%$ from baseline with either a decrease of rectal bleeding sub-score of ≥ 1 or a rectal bleeding sub-score ≤ 1) were randomized to receive 200 mg SC every 4 weeks or every 12 weeks during the maintenance period. At week 12, clinical remission rates were 4.8% with placebo versus 15.9% in the mirikizumab 50 mg group ($p = 0.66$), 22.6% in the 200 mg group ($p = 0.004$), and 11.5% in the 600 mg group (0.142); endoscopic improvement rates were 6.3% in placebo patients versus 23.8% in the mirikizumab 50 mg group ($p = 0.012$), 30.6% in the 200 mg group ($p = 0.0007$), and 13.1% in the 600 mg group ($p = 0.215$). Of the 93 patients randomized to maintenance mirikizumab dosing, week 52 clinical remission rates were 53.7% and 39.7% for patients treated every 4 and every 12 weeks respectively. No differences were seen in early endoscopic remission. Biologic-naïve and experienced groups experienced similar patterns of clinical remission and endoscopic response with rates numerically higher among biologic-naïve patients. The most frequent AEs included nasopharyngitis, cough, nausea, headache, and worsening UC disease activity [20].

Patients who had not met the week 12 clinical response criteria were offered participation in an open-label, extended induction for an additional 12 weeks with either 600 mg or 1000 mg IV mirikizumab every 4 weeks followed by 200 mg maintenance dosing. In patients who received the 12-week

extension induction, clinical response was achieved in 50.0% of patients with the 600 mg dose and 43.8% with the 1000 mg dose; 15.0% and 9.4% achieved clinical remission, respectively. At week 24, maintenance of clinical response was observed in 65.8%, clinical remission 26.3%, and endoscopic improvement in 34.2%, with no new safety concerns [21].

Mirikizumab appears safe in the treatment of UC in patients who did not respond to prior biologic therapies. Fifty percent of those who did not respond to an initial 12-week induction showed clinical response with an additional 12-week induction extension. The optimal dose is still being investigated as study sizes were sufficient to evaluate clinical activity. Phase III studies are actively recruiting patients with UC, examining patients with prior biologic failure (LUCENT-1), IV and SC dosing (LUCENT-2), and the open-label extension (LUCENT-3) [22].

Abstracts from the 2019 Digestive Diseases Week and 2020 United European Gastroenterology Week (UEGW) summarized results of the phase II (SERENITY) results examining mirikizumab for the treatment of CD [23]. The phase II, parallel-arm, double-blind study randomized 191 patients with moderate-to-severe CD with 2:1:1:2 allocation to IV 200 mg, 600 mg, and 1000 mg of mirikizumab and placebo at weeks 0, 4, and 8. At week 12, the primary endpoint of endoscopic response (50% reduction from baseline SES-CD) was significantly greater for all mirikizumab groups compared to 10.9% of patients receiving placebo (200 mg- 25.8%, $p = 0.079$), 600 mg- 37.5% $p = 0.003$, 1000 mg- 43.8%, $p < 0.001$). Endoscopic remission occurred in 1.6% of the placebo group compared to 15.6% and 20.3% of patients treated with 600 mg and 1000 mg of mirikizumab ($p = 0.032$, $p = 0.009$, respectively). Rates of clinical remission, defined by patient-reported outcomes (PRO2 remission), were greater in 600 mg (28.1%) and 1000 mg (21.9%) mirikizumab groups compared to placebo (6.3%) ($p = 0.005$ and $p = 0.025$, respectively). CDAI response and remission rates were greater in all mirikizumab groups compared to placebo, and the rates of AEs were similar to placebo and with the prior safety profile established in UC patients [24]. Recipients of mirikizumab during the 12-week induction who achieved ≥ 1 point improvement in SES-CD were re-randomized to double-blind maintenance of IV treatment every 4 weeks ($N = 41$) versus 300 mg SC every 4 weeks ($N = 46$). Due to the sample size, the IV and SC arms were pooled. Endoscopic response between the IV and SC groups was 56.1% vs 52.2% at week 12 and 58.5% vs 58.7% at week 52; endoscopic remission rates were 14.6% vs 30.4% at week 12 and 19.5% vs 32.6% at week 52. Sustained week 52 endoscopic response and endoscopic remission were seen in 69.6% and 50% of the IV group and 66.7% and 64.3% of the SC group. Similar frequencies of treatment-emergent AEs and serious AEs were observed among both groups [23].

Week 12 endoscopic remission appeared to be dose-dependent. During the maintenance period of SERENITY, phase II data showed sustained efficacy in patients with CD. The phase III study (VIVID-1) is actively recruiting, including a parallel ustekinumab reference arm [25].

Guselkumab

Guselkumab is a human IgG_1 monoclonal antibody. It is currently approved in the treatment of plaque psoriasis, and phase II and III studies are ongoing for the treatment of CD and UC. GALAXI1 is the phase II study in which patients with moderate-to-severe CD (nearly 50% prior biologic failure) were randomized to IV guselkumab 200 mg, 600 mg, 1200 mg, or placebo at weeks 0, 4, and 8, or ustekinumab 6 mg/kg IV at week 0 followed by 90 mg SC at week 8 [26]. Data of the week 12 interim analysis of 250 enrolled patients was presented at UEGW 2020 [27]. Compared to placebo, guselkumab at all studied doses resulted in a significantly greater mean reduction in CDAI from baseline (placebo- – 36.0, 200 mg- – 154.1, 600 mg- – 144.3, 1200 mg- – 149.5; $p < 0.001$) and a higher rate of clinical remission (CDAI < 150) (placebo- 15.7%, 200 mg- 54%, 600 mg- 56%, 1200 mg- 50%; $p < 0.001$). In patients with prior biologic failure, clinical remission was achieved in 45.5% of patients treated with guselkumab and 12.5% with placebo. Compared to placebo, all guselkumab groups also resulted in higher rates of clinical biomarker response (≥ 50% reduction in CRP or fecal calprotectin from baseline with clinical response) (placebo- 11.8%, 200 mg- 54%, 600 mg- 48%, 1200 mg- 42%; $p < 0.001$), and endoscopic response (placebo- 11.8%, 200 mg- 36%, 600 mg- 40%, 1200 mg- 36%; $p < 0.001$). Early endoscopic remission (SES-CD ≤ 2) did not reach statistical significance but rates were higher than placebo at all doses (placebo- 3.9%, 200 mg- 16%, 600 mg- 10%, 1200 mg- 16%). Rates of AEs were similar across all groups; there were no reported deaths or malignancies [27].

Guselkumab out-performed placebo in the week 12 interim analysis in clinical response, remission, clinical biomarker response, and endoscopic response in patients with moderate-to-severe CD. Phase II/III trials are ongoing (GALAXI 1, 2, 3) [26]. Phase IIb/III studies for the treatment of moderate-to-severe UC (QUASAR) are actively recruiting [28••].

Janus kinase (JAK) inhibition

The Janus kinase/signal transducers and activator of transcription (JAK/STAT) pathway play a critical role in regulatory immune function through signaling pathways of cytokines, growth factors, and protein tyrosine kinases, which are linked to the pathogenesis of IBD [29]. The JAK family comprises four intracellular tyrosine kinases (JAK1, JAK2, JAK3, and tyrosine kinase 2).

Tofacitinib

Tofacitinib is an oral, small-molecule inhibitor of JAK 1 and 3 approved for the treatment of UC since 2018. The OCTAVE induction and maintenance trials proved the efficacy of tofacitinib in patients with UC with an 8-week induction of 10 mg twice-daily (BID) dosing followed by either 5 mg or 10 mg BID maintenance [30••]. Tofacitinib was noted to have a rapid onset of action

and be efficacious in anti-TNFα experienced patients. The phase II study in patients with moderate-to-severe CD failed to reach the primary endpoint with a notably high placebo clinical remission rate of 46% at week 4 [31]. Two additional phase IIb multicenter, randomized, double-blind studies also did not meet primary endpoints in patients with CD at week 8 or 26 at any dose compared to placebo [32].

Based on OCTAVE safety data, tofacitinib is associated with increased risk of herpes zoster infection (approximately 5.6% of patients based on composite data) and hyperlipidemia [30••, 33]. Overall risks of infection and mortality are similar to that observed from prior biologic agents [34]. However, the Food and Drug Administration issued a 2019 black-box warning of an increased risk of thromboembolism and mortality with a 10 mg BID dosage based on interim analysis from a post-marketing trial for rheumatoid arthritis [35]. In a post hoc analysis of 1157 patients with UC exposed to tofacitinib, one patient developed deep vein thrombosis and four pulmonary embolism, all during the open-label extension study, on 10 mg BID dosing (83% of the overall cohort received a predominant dose of 10 mg BID dosing), and in the presence of thromboembolism risk factors alongside UC [36].

Filgotinib

Filgotinib is an oral, small molecule with selective JAK1 inhibition. A randomized, double-blind, placebo-controlled, European phase II study (FITZROY) examined the efficacy and safety of filgotinib in the treatment of moderate-to-severe CD [37]. One hundred seventy-five patients were randomized (3:1) to filgotinib 200 mg daily or placebo for 10 weeks; based on the response at 10 weeks, patients received either filgotinib 200 mg, 100 mg, or placebo for an additional 10 weeks. The primary endpoint of clinical remission (CDAI < 150) at week 10 was achieved at a significantly higher rate with filgotinib 200 mg compared to placebo (47% vs 23%, $p = 0.007$). In the filgotinib group, week 10 clinical remission occurred in 60% of anti-TNFα naïve patients (vs 13% placebo) and 37% of anti-TNFα exposed (vs 29% placebo). Endpoints of early endoscopic response and remission occurred in a greater proportion of filgotinib-treated patients, but were not significant. Pooled analysis through week 20 showed a 3% rate of serious infection in the filgotinib group and a 3% increase in the LDL to HDL ratio in patients treated with filgotinib at week 20 versus a 10% increase in the placebo group [37]. Phase III (DIVERSITY1), long-term extension studies (DIVERSITYLTE), and phase II trials in the small bowel (DIVERGENCE1) and perianal (DIVERGENCE2) disease are in process in the treatment of CD [38].

Results of the phase IIb/III study (SELECTION) evaluating filgotinib in the induction and maintenance treatment of patients with moderate-to-severe UC have been presented [39]. A cohort of biologic-naïve (659 patients) and biologic-exposed (689 patients) were randomized (2:2:1) to once-daily filgotinib 200 mg, 100 mg, or placebo. In the induction study, the week 10 primary endpoint (clinical remission) and secondary endpoints (endoscopic Mayo sub-score ≤ 1, rectal bleeding sub-score 0), histologic remission, endoscopic improvement). A higher proportion of patients on filgotinib 200 mg per

day achieved clinical remission in both biologic-naïve and exposed patients compared to placebo (26.1% vs 15.3%, $p = 0.0157$; 11.5% vs 4.2%, $p = 0.0103$) as well as key secondary endpoints. The rates of AEs, serious AEs, and discontinuation were similar among filgotinib and placebo groups during induction. In the filgotinib 200 mg group, one case of pulmonary embolus and four cases of herpes zoster occurred [40]. In the maintenance study for 664 patients who achieved clinical remission with filgotinib during the 10-week induction, patients were re-randomized to their induction filgotinib dose or placebo; those who received placebo during induction continued placebo maintenance.

A significantly higher proportion of patients on filgotinib achieved the primary endpoint of endoscopic/rectal bleeding/stool frequency (EBS) remission at week 58 compared to placebo with both the 200 mg (37.2% vs 11.2%, $p < 0.025$) and 100 mg (23.8% vs 13.5%, $p < 0.05$) doses. Patients in the filgotinib 200 mg group also achieved higher proportions of secondary endpoints compared to placebo, including 6-month corticosteroid-free clinical remission (27.2% vs 5.1%), sustained clinical remission (18.1% vs 9.2%), and endoscopic remission (15.6% vs 13.3%). The rate of AEs was similar across groups with one case of thromboembolism in the placebo group and two cases of herpes zoster in the filgotinib arm (one with each dose) [39].

Upadacitinib

Upadacitinib is also an oral, small molecule with selective JAK1 inhibition. A phase II, multicenter, double-blind study (CELEST) randomized 220 patients with moderate-to-severe CD (thiopurine, methotrexate, or biologic-experienced) to upadacitinib 3 mg, 6 mg, 12 mg, or 24 mg BID, 24 mg daily, or placebo for the 16-week induction phase [41]. After induction, patients were re-randomized to upadacitinib 3 mg or 12 mg BID, and 24 mg once daily for a 36-week maintenance period. Clinical remission at week 16 was not significantly higher among all upadacitinib groups compared to placebo (3 mg BID- 13%, 6 mg BID- 27%, 12 mg BID- 11%, 24 mg BID- 22%, 24 mg/day- 14%, placebo- 11%); however, endoscopic remission with upadacitinib was statistically higher than placebo in the 24 mg BID (22% vs 0%, $p < 0.01$) and 24 mg daily (14% vs 0%, $p < 0.05$) groups. At week 52, differences in clinical remission, clinical response, and endoscopic remission were not significant but highest in the upadacitinib 12 mg BID group. During induction, the highest rate of AEs occurred in higher upadacitinib doses > 12 mg BID. Nine patients receiving upadacitinib developed a serious infection during induction and six during maintenance. One patient receiving upadacitinib 24 mg BID developed herpes zoster during induction and two during the maintenance period. Three malignancies (Hodgkin's disease, thymus cancer, and a non-serious non-melanoma skin cancer) were reported in the upadacitinib group; all patients had prior exposure to thiopurines and biologics. Patients in the 12 mg and 24 mg BID upadacitinib groups had significant increases in total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels compared to placebo. During induction, two acute, serious

intestinal perforations occurred in areas of active inflammation of CD in patients receiving upadacitinib; no perforation occurred during maintenance. One patient receiving upadacitinib 3 mg BID developed a mesenteric vein thrombophlebitis; there were no thromboembolic events. No deaths occurred during the study [41].

During the induction phase, endoscopic remission increased with upadacitinib dose in patients with CD. A higher dose of upadacitinib appeared to be associated with a higher rate of AEs including infection during induction; however, a dose-dependent AE rate was not observed during the maintenance phase. Phase III and long-term extension studies are ongoing for patients with CD [42].

The phase IIb study of the U-ACHIEVE program randomized 250 immunosuppressive-experienced patients with moderate-to-severe UC to upadacitinib 7.5 mg, 15 mg, 30 mg, or 45 mg daily or placebo [43]. The primary endpoint of week 8 clinical remission (adapted Mayo score) was significantly higher in the 15 mg, 30 mg, and 45 mg groups compared to 0% receiving placebo (14.3% $p = 0.013$, 13.5% $p = 0.011$, 19.6% $p = 0.002$, respectively). Week 8 endoscopic improvement (Mayo endoscopic sub-score ≤ 1) was significantly higher than placebo (2.2%) with all doses of upadacitinib (14.9% $p = 0.033$, 30.6% $p < 0.001$, 26.9% $p < 0.001$, 35.7% $p < 0.001$, respectively). Rates of AEs were higher in the placebo group and similar across all upadacitinib dose groups. One patient developed moderate cutaneous herpes zoster in the 45 mg upadacitinib group, one patient who received 7.5 mg was diagnosed with melanoma later during the maintenance study, and one patient in the 45 mg group developed thromboembolism 26 days after drug discontinuation in the setting of hospitalization for UC-flare. Significant increase in total, HDL, and LDL cholesterol levels occurred in less than 5% of the upadacitinib group but higher across all treatment doses [43]. Phase III and long-term extension studies are ongoing for patients with UC [44].

Sphingosine-1-phosphate (S1P) receptor modulators

Sphingtosine-1-phosphate (S1P) is a lysophospholipid signaling molecule which regulates lymphocyte migration from lymph nodes and recirculation via extracellular activation of G-protein-coupled S1P1-S1P5 receptors. S1P receptor modulators induce internalization and degradation of S1P receptors on the lymphocyte surface, inhibiting lymphocyte release into circulation. While S1P1, S1P4, and S1P5 regulate the immune system, S1P2 and S1P3 modulation may be associated with systemic risks (cardiovascular, pulmonary, and cancer-related) [45]. The non-selective S1P receptor modulator fingolimod was approved in 2010 for the treatment of multiple sclerosis (MS); due to associated AEs, more selective oral therapies were developed including ozanimod and etrasimod for the novel use in IBD.

Ozanimod

Ozanimod is an oral selective agonist of S1P1 and S1P5 receptors previously approved for the treatment of relapsing MS. Ozanimod was recently approved by the Food and Drug Administration (FDA) for moderate-to-severe UC, and data from phase II studies for moderate-to-severe CD treatment are available.

Approval for ozanimod in the treatment of moderate to severe UC is based on data from phase II (TOUCHSTONE) and phase III (True North) studies in patients with moderate-to-severe UC [46–50]. Contraindications to treatment include patients who in the 6 months prior to treatment-experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated or class III/IV heart failure, heart block or sick sinus syndrome unless the patient has a pacemaker, and history of severe untreated sleep apnea or active monoamine oxidase inhibitor use [46].

The double-blind, placebo-controlled phase II trial (TOUCHSTONE) randomized 197 patients with moderate-to-severe UC to ozanimod 0.5 mg, 1 mg, or placebo daily for up to 32 weeks [47]. The primary outcome of week 8 clinical remission (Mayo score ≤ 2, no sub-score > 1) was 14% in the ozanimod 0.5 mg group, 16% in the 1 mg group, and 6% with placebo ($p = 0.14$ and $p = 0.048$, respectively). The exploratory outcome of week 8 clinical response was also significantly higher in the 1 mg ozanimod group (57%) compared to placebo (37%) ($p = 0.02$), and mucosal healing (Mayo sub-score ≤ 1) occurred at a higher rate with both ozanimod 0.5 mg (28%) and 1 mg (34%) compared to placebo (12%) ($p = 0.03$ and $p = 0.002$, respectively). Patients with clinical improvement ($n = 103$) entered a blind maintenance phase. At week 32, 26% of the 0.5 mg group and 21% of the 1 mg group achieved clinical remission compared to 6% with placebo ($p = 0.002$, $p = 0.01$, respectively). Similarly, week 32 mucosal healing and histologic remission were significantly higher in both ozanimod groups compared to placebo. The trial was of insufficient size and length to assess safety. From baseline to week 8, serum absolute lymphocyte counts decreased by 32% in those receiving 0.5 mg of ozanimod and 49% in the 1 mg group; no patient in either group developed grade 4 lymphopenia. In the ozanimod treatment group, one patient developed asymptomatic first-degree atrioventricular block with sinus bradycardia and four developed an increase in alanine aminotransferase [47].

Results from the phase III double-blind, placebo-controlled induction and maintenance trial (True North) for ozanimod in the treatment of UC were presented at UEGW 2020 [48–50]. During the induction phase, 645 patients were randomized (2:1) to ozanimod 1 mg daily or placebo (stratified by exposure to anti-TNFα therapy and corticosteroid use at screening) [48]. The primary endpoint of week 10 clinical remission (3 component Mayo score: rectal bleeding sub-score 0, stool frequency sub-score ≤ 1, endoscopy sub-score ≤ 1) was achieved in significantly more patients receiving ozanimod 1 mg daily than placebo (18.4% vs 6%, $p < 0.0001$); however, in patients with prior exposure to anti-TNFαs, the rate of clinical remission with ozanimod did not achieve significance over placebo ($p = 0.195$). Secondary endpoints of clinical response (decrease in 9-point Mayo score, including ≥ 2 points and $\geq 35\%$ from baseline with either a decrease of rectal

bleeding sub-score of ≥ 1 or a rectal bleeding sub-score ≤ 1), endoscopic improvement, and mucosal healing rates were significantly higher with ozanimod [48]. Patients with week 10 clinical response ($n = 457$) were randomized to maintenance ozanimod 1 mg daily or placebo [49, 50]. Week 52 clinical remission (3-component Mayo score) was significantly higher with ozanimod compared to placebo overall (37% vs 18.5%, $p < 0.0001$) and in anti-TNFα experienced patients (28.9% vs 10.1%, $p = 0.0053$). Ozanimod treatment produced higher rates of clinical response, endoscopic improvement, and corticosteroid-free remission, and mucosal healing [49].

In terms of safety (ozanimod vs placebo), the most common induction-period AEs were anemia (4.2% vs 5.6%), nasopharyngitis (3.5% vs 1.4%), and headache (3.3% vs 1.9%); bradycardia (0.5% vs 0%) and serious infections (< 1% both groups) were infrequent. No serious AEs occurred during the maintenance study; the most common treatment-emergent AEs were alanine aminotransferase elevation (4.8% vs 0.4%) and headache (3.5% vs 0.4%) [49, 50].

Data for the treatment of moderate-to-severe CD with ozanimod are available from a phase II, uncontrolled, multicenter trial (STEPSTONE) [51]. All patients ($n = 69$) received a 7-day ozanimod dose escalation (4 days of 0.25 mg daily, then 3 days of 0.5 mg daily) followed by 1 mg daily for 11 weeks followed by a 100-week extension period. The primary endpoint was change in SES-CD from baseline to week 12: the mean change from baseline SES-CD was − 2.2 ± 6.0 and 23.2% (95% CI 13.9–34.9) patients experienced an SES-CD decrease in ≥ 50%. The week 12 mean change in CDAI was − 130.4 ± 103.9 and clinical remission (CDAI < 150) was achieved in 39.1% (95% CI 27.6–51.6) and response (CDAI decrease of ≥ 100) in 56.5% (95% CI 44.0–68.4) of patients. AEs were attributed to worsening CD activity (26%); there were no cases of cardiovascular events reported [51]. Phase III induction and maintenance studies are ongoing [52].

Etrasimod

Etrasimod is an oral selective agonist of S1P1, S1P4, and S1P5 receptors. A phase II, proof-of-concept, double-blind study randomized 156 patients with moderate-to-severe UC to once-daily etrasimod 1 mg, 2 mg, or placebo for 12 weeks [53]. The primary endpoint was a week 12 improvement in the modified Mayo score and was achieved with significance over placebo in the etrasimod 2 mg group (mean difference from placebo 0.99 points; 90% CI 0.30–1.68 $p = 0.009$) but not in the 1 mg group. Endoscopic improvement was more significant with etrasimod 2 mg than placebo (41.8% vs 17.8%, $p = 0.003$). Additional week 12 secondary and exploratory endpoints were achieved at higher rates with etrasimod 2 mg compared to placebo including improvement in two-component Mayo score ($p = 0.002$) and total Mayo score ($p = 0.010$), clinical response (50.6% vs 32.5%, $p = 0.03$), clinical remission (33% vs 8.1%, $p < 0.001$), histologic improvement (31.7% vs 10.2%, $p = 0.006$), and histologic remission (19.5% vs 6.1%, $p = 0.03$). 55.1% of patients reported one or more treatment-emergent AEs, with a higher rate of drug discontinuation in the etrasimod group (3 patients receiving etrasimod

1 mg and 4 receiving etrasimod 2 mg vs none in placebo). The most common AEs in all groups included worsening of UC activity, upper respiratory tract infection, nasopharyngitis, and anemia. First-degree atrioventricular block occurred in two patients and second-degree atrioventricular block type I in one patient receiving etrasimod 2 mg; all three patients had evidence of prior atrioventricular block before etrasimod administration [53]. Phase II and III induction and maintenance trials are active for patients with moderate-to-severe UC [54]. A phase II/III study is actively recruiting patients with moderate-to-severe CD for etrasimod induction and maintenance [55].

Combination therapy

Data are scarce examining the combination of therapies, secondary to safety concerns with added immunosuppression and expected barriers of insurance coverage. A 2018 case series of 6 patients with UC and 4 with CD with active disease on anti-TNFα therapy reached clinical remission after the addition of vedolizumab, with an increased risk of upper respiratory infection [56]. More recently, a case series and meta-analysis were published, consisting mainly of patients with CD receiving vedolizumab and anti-TNFα therapy. The case series of 15 patients (14 with CD) included eight patients who received vedolizumab with an anti-TNFα for a median of 24 months; clinical response was observed in five patients and infection in three [57]. The meta-analysis identified 30 cohort studies or case series of 279 patients (nearly 80% with CD) followed for a median of 32 weeks on either dual biologic or small-molecule therapy. The most common combinations were anti-integrin therapy with either anti-TNFα therapy (48%) or ustekinumab (19%). Pooled rates of clinical and endoscopic remission were 59% and 34% and AEs and serious AEs of 31% and 6.5% [58]. There are only a few reports of IBD therapy combining vedolizumab with golimumab, ustekinumab, or tofacitinib [57, 59, 60]. Calcineurin inhibitors have been used in the acute setting of severe, steroid-refractory IBD as induction or salvage therapy with vedolizumab in small prospective and retrospective studies [61, 62] (Table 1).

Conclusion

Significant progress has been made in the discovery of novel therapeutic targets in the treatment of IBD. This review features emerging therapeutic agents currently in phase III trials, of which IL-23 inhibitors (risankizumab, guselkumab, and mirikizumab), JAK inhibitors (filgotinib and upadacitinib), and S1P1 modulators (ozanimod and etrasimod) are effective for the treatment of CD and UC. Selective IL-23 inhibition has produced favorable

Table 1 Target, therapy, mechanism of action, route of administration, phase of development for moderate-to-severe IBD, and key references and ongoing trials

Target	Therapy	Mechanism of action	Route of administration	Phase of development for moderate-to-severe IBD	Key references and ongoing trials
Cytokines IL-12/IL-23	Ustekinumab	IL-12/23 p40 subunit inhibitor	IV, SC	CD- approved	UNITI-1, UNITI-2, IM-UNITI (Feagan et al. *NEJM* 2016, Hanauer et al. *J Crohns Colitis* 2020) [6, 7]
				UC- approved	UNIFI (Sands et al. *N Engl J Med* 2019) [10•]
Cytokine IL-23	Brazikumab	IL-23 p19 subunit inhibitor	IV, SC	CD- phase IIa; phase IIb/III ongoing	Sands et al. *Gastroenterology* 2017 [12]
					ClinicalTrials.gov NCT03759288 [13]
				UC- phase II/extension ongoing	ClinicalTrials.gov NCT03616821 [14]
	Risankizumab	IL-23 p19 subunit inhibitor	IV, SC	CD- phase II/extension; phase III ongoing	Feagan et al. *Lancet* 2017 [15]
					Feagan et al. *Lancet Gastroenterol Hepatol* 2018 [16]
					Ferrante et al. *J Crohns Colitis* 2020 [17]
					ClinicalTrials.gov NCT03105128 [18]
				UC- phase II/III ongoing	ClinicalTrials.gov NCT03398148 [19]
	Mirikizumab	IL-23 p19 subunit inhibitor	IV, SC	CD- phase II; phase III ongoing	Sands et al. DDW 2020 [24]
					Sands et al. UEGW 2020 [23]
					ClinicalTrials.gov NCT03926130 [25]
				UC- phase II/extension; phase III ongoing	Sandborn et al. *Gastroenterology* 2020 [20]
					Sandborn et al. *Clin Gastroenterol Hepatol* 2020 [21]
					ClinicalTrials.gov NCT03518086 [22], NCT03524092 [63], NCT 03519945 [64]
	Guselkumab	IL-23 p19 subunit inhibitor	IV, SC	CD- phase II/III ongoing	Sandborn et al. UEGW 2020 [27]
					ClinicalTrials.gov NCT03466411 [26]
				UC- phase IIb/III ongoing	ClinicalTrials.gov NCT04033445 [28••]
JAK/STAT	Tofacitinib	JAK1, JAK3 inhibitor	Oral	CD- phase II primary endpoint not met	Sandborn et al. *Clin Gastroenterol Hepatol* 2014 [31]
					Panés J et al. *Gut* 2017 [32]
				UC- approved	OCTAVE 1, OCTAVE 2, OCTAVE Sustain (Sandborn et al. *N Engl J Med* 2017) [30••]
	Filgotinib	JAK1 inhibitor	Oral	CD- phase II; phase II/III ongoing	FITZROY (Vermeire et al. *Lancet* 2017) [37]
					ClinicalTrials.gov NCT02914561 [38], NCT02914699 [65], NCT03046056 [66], NCT03077412 [67]
				UC- phase IIb/III	SELECTION (Feagan et al. 2021, Peyrin-Biroulet et al. UEGW 2020) [39]
	Upadacitinib	JAK1 inhibitor	Oral	CD- phase II; phase III/extension ongoing	CELEST (Sandborn et al. *Gastroenterology* 2020) [41]
					ClinicalTrials.gov NCT03345836 [42], NCT03345823 [68], NCT03345849 [69]
				UC- phase IIb; phase III/extension ongoing	U-ACHIEVE (Sandborn et al. *Gastroenterology* 2020) [43]
					ClinicalTrials.gov NCT03653026 [44], NCT02819635 [70], NCT03006068 [71]

Table 1 (continued)

Target	Therapy	Mechanism of action	Route of administration	Phase of development for moderate-to-severe IBD	Key references and ongoing trials
S1P receptor	Ozanimod	S1P1, S1P5 agonist	Oral	CD- phase II; phase III ongoing	STEPSTONE (Feagan et al. *Lancet Gastroenterol Hepatol* 2020) [51]
					ClinicalTrials.gov NCT03440372 [52], NCT03440385 [72], NCT03467958 [73], NCT03464097 [74]
				UC- approved	TOUCHSTONE (Sandborn et al. *N Engl J Med* 2016) [47]
					True North (Sandborn et al. UEGW 2020, Danese et al. UEGW 2020, Sandborn et al. UEGW 2020) [48–50]
	Etrasimod	S1P1, S1P4, S1P5 agonist	Oral	CD- phase II/III ongoing	ClinicalTrials.gov NCT04173273 [55]
				UC- phase II; phase II/III ongoing	Sandborn et al. *Gastroenterology* 2020 [53]
					ClinicalTrials.gov NCT04607837 [54], NCT03996369 [75], NCT03945188 [76], NCT03950232 [77], NCT04176588 [78]

safety profiles. Small molecules including JAK inhibitors and S1P receptor modulators have advantages in being orally administered and non-immunogenic, resulting in ease of delivery and absence of immune-mediated loss of response. A few highlighted agents also exhibited efficacy in biologic-exposed patients, for whom the long-term success of novel therapies is crucial and promising. Future algorithms, comparative studies, and advances in precision medicine may help guide the selection of novel therapies.

Declarations

Conflict of Interest

Shivali Berera declares that she has no conflict of interest. Gary R. Lichtenstein has served as a consultant for Abbie, American Regent, Bristol Meyers Squibb, Celgene, Eli Lilly (Data Safety Monitoring Board), Endo Pharmaceuticals, Ferring, Gilead, Janssen Orthobiotech, MedEd Consultants, Merck, Morphic Therapeutics, Pfizer Pharmaceuticals, Prometheus Laboratories, Inc., Romark, Salix Pharmaceuticals, Valeant (Bausch Health) Pharmaceuticals, Shire Pharmaceuticals, Takeda Pharmaceuticals, UCB, Virgo (stock options); CME participant for Allergan, American Gastroenterological Association, American Regent, Chemed, IMEDEX, Ironwood, Merck, Romark, University of Kentucky, Vindico; Author/Editor with honorarium/royalty for Up-To-Date, Springer Science and Business Media, SLACK, Inc., Professional Communications, Inc., Gastroenterology and Hepatology Communications, American College of Gastroenterology; and has obtained funding for Inflammatory Bowel Disease Fellow Education from Janssen Orthobiotech and Pfizer Pharmaceuticals.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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