New targets in inflammatory bowel disease therapy: 2021

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Purpose of review
In the rapidly progressing world of inflammatory bowel disease, this review discusses and summarizes new drug targets and results from major clinical trials in order to provide an update to physicians treating patients with inflammatory bowel diseases (IBD).

Recent findings
Multiple new mechanisms in the treatment of IBD are being developed and many are showing promising results in both ulcerative colitis and Crohn's disease patients. In addition to efficacy, some of these treatments may provide safety benefits over existing therapies.

Summary
The IBD physicians' therapeutic armamentarium is rapidly expanding and keeping abreast of these developments is required in order to provide patients with optimized individualized care.

Keywords
biologics, inflammatory bowel disease, new therapeutics, small molecules

INTRODUCTION

The inflammatory bowel diseases (IBD) are a heterogeneous group of conditions divided into two predominant groups, Crohn's disease (CD) and ulcerative colitis (UC). These conditions are characterized by a chronic, progressive, or relapsing and remitting disease course with the gastrointestinal (GI) tract being the major site of inflammatory activity. Unchecked, this inflammation can result in a complicated disease course with undesirable ramifications such as abdominal abscesses, fistulae, strictures, and subsequent bowel obstruction, and increase the risk for GI malignancy. These diseases have a significant impact on patient quality of life, activities of daily living and increase healthcare costs [1,2].

The mainstay of treatment of IBD is immunesuppressive and immune-modulating agents. The biologic treatment era starting with the antitumor necrosis factors (TNF) therapies has heralded significant changes in our ability to obtain and maintain clinical response and remission in a safer manner [3–5]. Further advances have resulted in the development of gut selective biologic agents, the antiintegrins [6,7], targets of different biochemical pathways such as with ustekinumab [8], and the oral small molecule therapy, tofacitinib [9]. Although these treatments have certainly broadened the IBD physician's armamentarium, a significant percentage of patients do not respond to these treatments [10].

As such, new treatment pathways and a greater understanding of mechanisms of treatment failure are required. This will provide more options for patients and greater individualization in treatment decision-making.

This review examines the future of IBD treatments and details current phase I, II, and III clinical trial results. Figure 1 and Table 1 show therapies at their varying stages of clinical development.

ANTI-TRAFFICKING THERAPIES

Antiadhesion molecules

An important part of T-cell-dependent chronic intestinal inflammation in IBD is the homing of T-lymphocytes to the gut. Antiadhesion agents

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KEY POINTS

- There are multiple new biologic and small molecule therapies in advanced stages of development.
- These will provide physicians with a great number of effective and safe options for patients requiring biologic therapy.
- The multitude of mechanisms of action will allow for greater personalization of therapy and allow physicians and patients to balance their choice based on efficacy, safety, and mode of administration.
- These new mechanisms increase the insight into the pathophysiology of IBD and will promote the development of an even greater array of drugs in the future.
- There remains a 'therapeutic ceiling' that will only be exceeded with novel combination approaches or nonimmune-based strategies that change the current paradigms.

target integrins responsible for homing and reduce the inflammatory cell infiltrate [11]. The anti α4β7 integrin antibody vedolizumab is currently approved and widely used in the treatment of both UC and CD [6,7].

The next generation in this treatment class is etrolizumab, a humanized IgG1 monoclonal antibody that selectively binds the β7 subunit and thus blocks both the α4β7 and the αεβ7 intestinal integrins. The etrolizumab phase 3 clinical program is the largest and most comprehensive in IBD and is among the first to include head-to-head trials in UC against an anti-TNF agent. HIBISCUS I and II evaluated the efficacy of etrolizumab for induction head-to-head against adalimumab and placebo in anti-TNF naïve UC patients. This study included 716 patients. In the pooled analysis, clinical remission at week 10 was 18.8% for etrolizumab vs 23.5% for adalimumab ($P = 0.13$). Etrolizumab was well-tolerated with most adverse events being nonserious or grades 1 or 2. The primary outcome was not met and

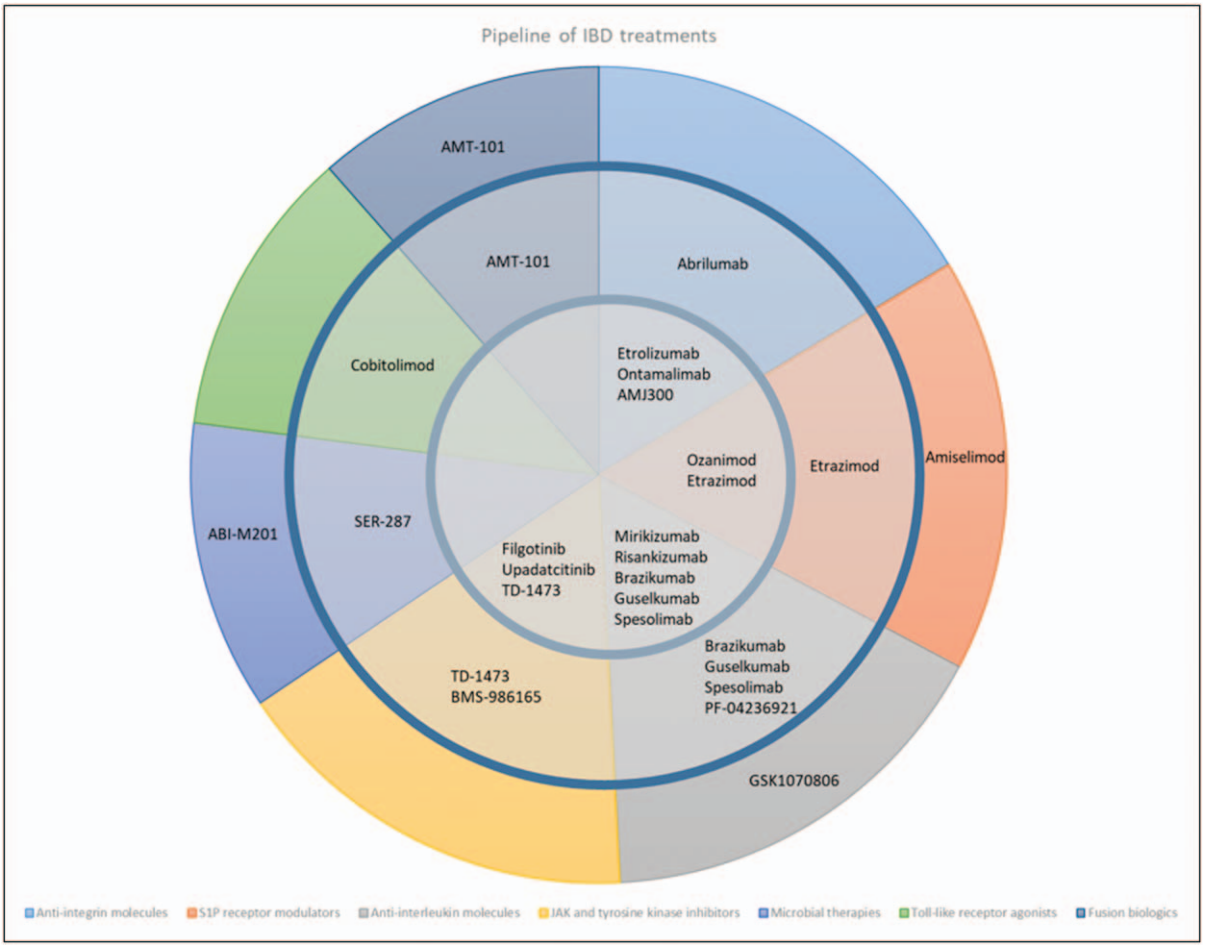

FIGURE 1. Clinical trial pipeline of IBD therapies. Outer ring: Phase 1, Middle ring: Phase 2, Inner circle: Phase 3. IBD, inflammatory bowel diseases.

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Table 1. Clinical development of drugs with novel therapeutic targets in IBD

Category and name	Mechanism of action	Results published	Current phase of development	Indication	Ref
Antitrafficking therapies					
Antiintegrins					
AJM300	Oral, novel, small molecule α4 integrin inhibitor	Phase 2a study, significantly greater clinical and endoscopic remission rates compared with placebo	3	UC	[22,24]
Sphingosine 1 phosphate receptor modulator					
LC51-0255	S1P receptor modulator	Phase 1	2	UC + CD	[57]
OPL-002	S1P receptor modulator	Phase 1	2	UC + CD	[58]
Antiinterleukin antibodies					
Spesolimab	Anti-IL36	Phase 1	2	UC + CD	[59]
PF-04236921	Anti-IL6	Phase 2 study showed significantly greater week 12 clinical remission compared with placebo with durability during the OLE		CD	[60]
JAK and tyrosine kinase inhibitors					
TD-1473	Oral novel, gut selective, pan JAK inhibitor	Phase 1	2	UC + CD	[61]
BMS-986165	TYK-2 inhibitor	Phase 1	2	UC + CD	[62]
Toll-like receptor agonists					
Cobitolimod (DIMS0150)	TLR-9 agonist	Phase 2 study showed significantly higher rates of symptomatic improvement at weeks 4 and 8 with significantly more patients having clinical remission and mucosal healing at week 4, compared with placebo	2	UC	[63]
Interleukin 10 – fusion biologic					
AMT-101	Novel oral human IL-10 fusion protein	Phase 1	2	UC	[64▪]

CD, Crohn's disease; IBD, inflammatory bowel diseases; JAK, Janus kinase; OLE, open label extension; S1P, shingosine-1 phosphate; UC, ulcerative colitis.

etrolizumab was not superior to adalimumab at week 10. However, there was a statistically significant increase in endoscopic remission rates compared with placebo [12▪]. The LAUREL induction and maintenance study evaluated etrolizumab against placebo in anti-TNF naïve UC patients. At week 62, there was no significant difference in clinical remission rates. There was a statistically significant difference in endoscopic improvement, endoscopic remission, and histologic remission in the etrolizumab cohort at week 62 (38% vs 22.5%, $P = 0.024$; 30.6% vs 16.7%, $P = 0.03$ and 42.4% vs 21.8%, $P = 0.008$; respectively). Etrolizumab was well-tolerated throughout the follow-up period [13▪]. The GARDENIA study was a head-to-head induction and maintenance study comparing etrolizumab to infliximab. The primary outcome was not met with clinical remission rates at week 10 and 54 of 18.6% and 19.7% in the etrolizumab and infliximab cohorts respectively. Endoscopic remission was similar between the groups and the safety profile the drugs was comparable [14▪]. Although etrolizumab was not superior to adalimumab or infliximab the rates of clinical and endoscopic outcomes were similar and etrolizumab was well-tolerated. In CD, initial results from the phase III BERGAMOT study investigating etrolizumab in moderately to severely active CD showed that CDAI remission at week 14 was greater in both the 105 mg and 210 mg arms compared with placebo (23% vs 28.9% vs 16.9%, respectively) with comparable side effects between the groups [15].

Another molecule targeting the α4β7 integrin is the monoclonal IgG2 antibody abrilumab (AMG-181). This drug has shown preliminary efficacy in both UC and CD. In UC patients with moderately to severely active disease, a randomized, phase 2b, placebo-controlled, double-blind study including 354 patients showed significantly increased week 8 remission rates at dosages of 70 and 210 mg compared with placebo (13.3%, 12.7% vs 4.3%, $P < 0.05$, respectively). In total, 51% of the study population had

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prior anti-TNF exposure and 44% were on oral corticosteroids at baseline. Overall abrilumab was well-tolerated and authors note a similar side effect profile to both vedolizumab and etrolizumab [16]. In CD, a phase 2b, randomized, multicenter, double-blind, placebo-controlled study did not meet the primary endpoint of clinical remission at week 8 ($P = 0.76$ vs placebo) [17].

The anti-MAdCAM-1, ontamalimab (SHP647, PF-00547659), is a monoclonal IgG2 humanized antibody targeting the intestinal adhesion molecule, MAdCAM-1. A phase 2, randomized, double-blind, placebo-controlled clinical (TURANDOT) trial in patients with active UC showed significantly greater week 12 remission rates compared with placebo [18]. In CD, the phase 2 OPERA study did not reach statistical significance in terms of clinical endpoints [19]. The OPERA II study, an open-label extension study showed that remission rates were sustained over a period of 72 weeks and the drug was generally well-tolerated [20,21]. There are currently five phase 3 studies underway to investigate the use of ontamalimab in both UC and CD.

Sphingosine-1 phosphate receptor modulator

Shingosine-1 phosphate (S1P) signaling on central memory T-cells facilitates their exit from lymph nodes. Internalization of the S1P receptor prevents lymphocytes from responding to S1P and are retained in the lymph node, thus inhibiting their recruitment to inflamed tissue [22]. Protective immunity is generally preserved as effector memory T-cells do not circulate through the lymph nodes. Ozanimod is an S1P modulator that downregulates S1P receptor subtypes 1 and 5 [23]. In a phase 2 randomized controlled trial (RCT) in patients with moderately to severely active UC, 1 mg of ozanimod showed significantly greater clinical response and remission rates compared with placebo (16% vs 6%, $P = 0.048$). In this study, endoscopic remission rates at week 8 were also significantly greater in the treatment groups. The adverse event profile was similar to placebo [24]. The 4-year open-label extension study showed durable efficacy with no new safety markers in UC patients [25]. The phase 3 TRUE NORTH study in patients with moderately to severely active UC showed that ozanimod results in significant benefits in clinical, endoscopic, histologic, and mucosal healing endpoints at week 52 compared with placebo [26▪]. Currently, phase 3 trials in CD and UC patients are underway.

An oral S1P receptor modulator targeting receptor subtypes 1,4 and 5, etrasimod, has been assessed in a phase 2, proof-of-concept, double-blind, parallel-group study in UC patients. At week 12, etrasimod resulted in a significant improvement in modified Mayo clinical scores and significantly greater clinical remission and endoscopic improvement rates compared with placebo (33% vs 8.1% and 41.8% vs 17.8%, $P = 0.003$, respectively). In addition, most adverse events were mild [27]. In the subsequent open-label extension study, of 31 patients who continued 2 mg etrasimod, 70%, 35%, and 45% had clinical response, clinical remission, and endoscopic improvement, respectively [28]. There are currently a phase 2 trials in CD and multiple phase 3 trials in UC underway (Fig. 1).

ANTI-INTERLEUKIN ANTIBODIES

Interleukin-23, which is a member of the IL-12 family of cytokines has 2 components: the p40 subunit found also on IL-12 and the p19 subunit found exclusively on IL-23. IL-23 plays an important role in the maintenance and amplification of T helper 17 (Th17) and the stimulation of many innate immune cells important in the pathogenesis of IBD [29–31]. The monoclonal antibody, ustekinumab, which is directed against the p40 subunit of IL-12 and IL-23 has shown success in the treatment of CD and UC [8,32,33]. However, studies in psoriasis have revealed that more specific targeting of the p19 subunit and thus only the IL-23 molecule may be more effective [34,35].

Mirikizumab is a monoclonal antibody targeting the p19 subunit. In a phase 2 RCT investigating mirikizumab in patients with moderately to severely active UC, patients receiving 200 mg mirikizumab had significantly greater clinical remission and endoscopic improvement at week 12, particularly in biologic naïve patients (36.4% vs 8.7%, $P = 0.004$ and 50% vs 8.7%, $P = 0.033$, respectively). Adverse events were similar between the treatment groups [36]. In a sub-analysis of this study, mirikizumab was shown to achieve and sustain greater rates of histologic remission and mucosal healing when compared with placebo through to week 52 of maintenance therapy [37]. In CD, a recently published abstract described the results of a phase 2 RCT conducted in patients with moderately to severely active CD. All three drug dose groups were superior to placebo in terms of clinical response rates. In addition, there was a dose-related increase in response rates (200 mg – 25.8%, 600 mg – 37.5% and 1000 mg – 43.8%). Further, patients in the 600 and 1000 mg groups achieved significantly better endoscopic remission rates ($P = 0.032$ and $P = 0.009$, respectively). There was no difference in adverse events when compared with placebo [38]. The phase 2 SERENITY maintenance study followed patients treated with either mirikizumab intravenously or subcutaneously for

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52 weeks. Of those achieving endoscopic response at week 12, 69.6 and 66.7% in the intravenous and subcutaneous treatment groups, respectively, maintained response at week 52 [39]. The drug also showed no new safety signals.

Rizankizumab also binds the p19 subunit. A phase 2 RCT in patients with moderately to severely active CD who received rizankizumab showed superior clinical remission compared with placebo at week 12 (31% vs 15%, $P = 0.049$) [40]. In the open-label extension study, at weeks 52, clinical remission was maintained in 71% of patients and was well-tolerated [41]. Of note, 93% of patients in these studies were previously exposed to at least one anti-TNF biologic [40]. There are currently phase 2 and phase 3 studies underway investigating rizankizumab in UC patients.

Another monoclonal antibody targeting IL-23 in development is brazikumab (MEDI2070). In a phase 2 RCT in patients with moderately to severely active CD who had previously failed anti-TNF therapy, at week 8 49.2% of patients receiving brazikumab achieved clinical remission compared with 26.7% in the placebo group ($P = 0.01$). At week 12, a significantly greater proportion of patients receiving brazikumab had a clinical response and a reduction of over 50% in term of biomarkers (c-reactive protein and fecal calprotectin) (37.3% vs 8.3%, $P < 0.001$) [42]. In this study, higher baseline serum concentrations of IL-22, a cytokine induced by IL-23, were associated with a greater likelihood of response to brazikumab. This may provide a biomarker to predict response and thus personalize the use of this treatment in CD patients. Currently, there are multiple phase 2 and phase 3 trials underway for both UC and CD patients.

At present, other treatments targeting the IL23 pathway are under investigation. Recently, interim results from the phase 2 study (GALAXY-1) investigating the IL-23 antagonist, guselkumab, in patients with moderately to severely active CD showed that at all treatment doses (200, 600, or 1200 mg) patients treated with guselkumab had significantly greater clinical response and remission rates compared with placebo (remission: 54%, 56%, 50% vs 15.7%, respectively) and apparent similar efficacy to ustekinumab. Safety at these point appears consistent with that established from other clinical trials [43].

JANUS KINASE AND TYROSINE KINASE INHIBITORS

The Janus kinase (JAK) family comprises of four intracellular tyrosine kinases – JAK1, JAK2, JAK3 and nonreceptor tyrosine-protein kinase 2 – these activate signal transducers and activators of transcription (STATs). This JAK-STAT pathway regulates the expression of multiple mediators involved in inflammatory pathways implicated in the pathogenesis of IBD [44]. Tofacitinib, an oral small molecule pan-JAK inhibitor, has shown success in three UC phase 3 (both induction and maintenance trials [9].

Filgotinib, an oral, once daily administered JAK 1 selective inhibitor, has been studied in moderately to severely active CD. In the phase 2 FITZROY study, significantly more patients achieved clinical remission on filgotinib compared with the placebo after 10 weeks of treatment (47% vs 23%, $P = 0.0077$). There was no significant difference in terms of severe adverse events between the groups at 20 weeks [45]. Currently, phase 3 trials are underway investigating long-term efficacy and safety in CD patients (Fig. 1). The SELECTION phase 2B/3 study investigating filgotinib in patients with moderately to severely active UC showed that a significantly higher rate of patients in the treatment arm achieved a combined endpoint of endoscopic, rectal bleeding and stool frequency remission compared with placebo (37.2% vs 2%, respectively). The 200 mg filgotinib dosage met all key endpoints including endoscopic, histologic and 6-month corticosteroid free remission. There was no increase in adverse event compared with placebo [46].

Another JAK1 selective oral small molecule is upadacitinib. The phase 2 CELESTE study investigating upadacitinib in CD patients with moderately to severely active disease, reported clinical remission in 27% of patients receiving 6 mg compared with 11% in patients receiving placebo ($P < 0.1$). Endoscopic remission was significantly greater in all upadacitinib treatment arms compared with placebo and efficacy was maintained in most treatment arms over 52 weeks of therapy. Of note, during the induction phase of the study, more patients in the treatment arm had infections and serious infections when compared with placebo and patients in the 12 and 24 mg treatment arms had significant increases in total, high-density lipoprotein and low-density lipoprotein levels when compared with placebo [47]. The open-label extension study showed a good safety profile with no new safety signals and good maintenance of response over a 12-month period [48]. In a phase 2 RCT investigating upadacitinib as induction therapy in patients with active UC, at week 8 clinical remission was achieved in 8.5%, 14.3%, 13.5%, and 19.6% of patients receiving 7.5 mg, 15 mg, 30 mg, or 45 mg upadacitinib, respectively compared with none in the placebo group ($P = 0.052$, $P = .013$, $P = 0.011$, and $P = 0.002$ compared with placebo, respectively). Endoscopic remission was also achieved in a significantly greater number of patients in all treatment groups compared with placebo with the greatest

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effect seen in the 45 mg treatment group (35.7% vs 2.2%, $P < 0.001$). In this study there was one case of herpes zoster and one patient developed a deep vein thrombosis and pulmonary embolism (26 days following discontinuation of the therapy and in the 45 mg group). Once again, as with the phase 2 CD study, increases in serum lipid levels were noted [49]. Multiple phase 3 studies investigating upadacitinib in both CD and UC are underway.

MICROBIOTA-BASED INNOVATIONS

Therapies targeting the gut microbiome including fecal microbiota transplantation, dietary exclusions and modifications, prebiotics, and probiotics are under extensive investigation in IBD with varying success [50–54]. These therapies face a number of challenges, including a lack specificity, which may explain their limited success. A potential new therapy is SER-287, which fractionates spore forming bacteria to specifically target Firmicutes thought to be important to gut homeostasis [55]. A recent phase 1B, double blind, RCT investigated the efficacy of SER-287 compared with placebo in 58 patients with UC. At week 8 patients in the vancomycin/SER-287 daily group had significantly higher proportions of clinical remission compared with placebo (40% vs 0%, $P = 0.02$ for vancomycin/SER-287 daily vs placebo/placebo) [56]. Ongoing studies are required to determine the true value of this and other similar treatments.

CONCLUSION

The world of IBD is rapidly evolving as both understanding of the pathogenesis of the diseases is increasing and the ability to target various pathways are being developed. The next few years hold much promise to both the IBD physician and patients alike with a plethora of new therapeutic options expected to be introduced into the market. Nonetheless, there remains a 'therapeutic ceiling' through which these newer therapies have been unable to break. Although an increasing armamentarium of drugs will allow for more decision-making maneuverability with numerous options of mode of delivery, differing mechanisms and greater safety, we have a great deal of work to do. What is still lacking and what requires greater focus is the development of reliable biomarkers to predict response allowing for greater personalization, decreased expenditure on already very expensive medications and hopefully translate to improved patients' quality of life and decreased complications. Combination approaches, sequential or pulse and phased treatment strategies, bacterial derived proteins and additional nonimmune-based strategies must be actively pursued.

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Early trial of a drug with a new treatment pathway and interesting mechanism of action with potential use in many other current therapies

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