

Feature Review

Novel Targeted Therapies for Inflammatory Bowel Disease

Mehmet Coskun,^{1,2} Severine Vermeire,³ and Ole Haagen Nielsen^{1,*}

Our growing understanding of the immunopathogenesis of inflammatory bowel disease (IBD) has opened new avenues for developing targeted therapies. These advances in treatment options targeting different mechanisms of action offer new hope for personalized management. In this review we highlight emerging novel and easily administered therapeutics that may be viable candidates for the management of IBD, such as antibodies against interleukin 6 (IL-6) and IL-12/23, small molecules including Janus kinase inhibitors, antisense oligonucleotide against *SMAD7* mRNA, and inhibitors of leukocyte trafficking to intestinal sites of inflammation (e.g., sphingosine 1-phosphate receptor modulators). We also provide an update on the current status in clinical development of these new classes of therapeutics.

The Need for Improved Therapies for IBD

IBD is a chronic disorder characterized by life-long treatment and incurable idiopathic intestinal inflammation, of which ulcerative colitis (UC) [1] and Crohn's disease (CD) [2] are the two most prevailing entities. Symptoms include abdominal pain, diarrhea, rectal bleeding, weight loss, malnutrition, and fever. Currently the prevalence of IBD in the Western world is estimated to be up to 0.5% of the general population [3], and IBD represents a huge economic burden for the society in direct medical costs and in indirect costs as a result of impaired work performance during flaring disease, including sick leave [4]. Thus, in Europe alone, the direct costs are estimated to exceed €5.6 billion annually [5].

The etiology of IBD is unknown but involves a complex interaction between genetic susceptibility, altered microbiota, and environmental factors that trigger an aberrant immune response causing an impaired mucosal barrier function [6–10]. While CD has been considered to be a type 1 T helper cell (T_H1)- and T_H17-mediated condition, UC has, however, been associated with a non-conventional T_H2 response, and each has a unique **cytokine** (see [Glossary](#)) profile that is essential for the condition. However, the complexity of IBD immunopathogenesis is supported by an imbalance of additional T cell subsets (e.g., regulatory T cells, natural killer T cells, and T_H9 cells) [8,11,12] and their interplay, which could explain the complexity of the immune response in patients with IBD. As a consequence, there is an imbalance in the production of various cytokines in patients with active IBD, including tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , IL-6, IL-8, IL-10, IL-12, IL-17, and IL-23, and transforming growth factor- β (TGF- β) [7]. Thus, understanding the role of such cytokines has been an important advance in IBD therapies.

Both innate and adaptive immune responses are highly dependent upon trafficking of immune cells from their site of origin to target organs. This process is regulated by essential mechanisms that involve recognition and interaction of transmembrane **integrins** on T cells with tissue-specific **adhesion molecules** expressed on the endothelial cells of blood vessels and lymphatics ([Figure 1](#)) [13]. Several integrins participate in this mechanism, including $\alpha_4\beta_1$ expressed

Trends

Conventional therapy for IBD is often ineffective in a subgroup of patients and may have significant side effects.

Small molecules that specifically target proinflammatory pathways in the intestine are likely candidates for IBD treatment owing to their advantages in production, storage, delivery, and pharmacokinetics.

Investigating and integrating multiple aspects of disease pathogenesis will be necessary to develop novel and effective targeted therapies for IBD.

The unmet need for novel drugs is not only a medical challenge but also an important issue for society in the effort to improve work capacity and to reduce sick leave among this patient cohort.

Future efforts in IBD management should aim to develop clinical decision-making algorithms that might help to tailor treatment to the needs of individual patients.

¹Department of Gastroenterology, Medical Section, Herlev Hospital, University of Copenhagen, Denmark

²The Bioinformatics Centre, Department of Biology, and Biotech Research and Innovation Centre (BRIC), University of Copenhagen, Denmark

³Department of Gastroenterology, University Hospital Gasthuisberg, Leuven, Belgium

*Correspondence: ohn@dadlnet.dk (O.H. Nielsen).

on most leukocytes; $\alpha_4\beta_7$, expressed on gut-specific lymphocytes; and $\alpha_E\beta_7$, expressed on intraepithelial lymphocytes [14]. These integrins bind to vascular cell adhesion molecule-1 (VCAM-1), mucosal addressin cell adhesion molecule-1 (MAdCAM-1), or E-cadherin, respectively, and direct leukocyte trafficking to target organs. In particular, IBD is characterized by an increased infiltration of leukocytes into the inflamed intestinal mucosa, which contributes to a persistent inflammation. Hence, leukocyte trafficking has a central role in the immunopathogenesis of IBD, and inhibition of leukocyte trafficking to the gut mucosa has been recognized as another important target for the development of IBD drugs [15].

Since the introduction of biologic agents, the traditional therapeutic dogma has shifted away from nonspecific immunomodulators, including glucocorticoids, thiopurines, and methotrexate [16,17], toward a pathway-based anti-inflammatory approach. Although the introduction of TNF inhibitors (i.e., infliximab, adalimumab, golimumab, and certolizumab pegol) as well as anti-integrins (i.e., natalizumab and vedolizumab) has initiated a new therapeutic era in the treatment of flares and maintenance of clinical remission [18,19], these biologics are, however, only clinically effective in a subgroup of patients with IBD [20]. Indeed, a significant number of patients experience relapse of inflammation after cessation of treatment [21]. The overall risk of relapse 12 months after discontinuation of anti-TNF therapy is 40% in CD and 28% in UC [22]; although the incidence of surgery is decreasing, up to 20% of patients with UC require colectomy for medically refractory disease, and ~50% of patients with CD need surgery within 10 years of diagnosis [23]. Thus, the pathogenesis and treatment of IBD is complex and may vary between patients, emphasizing a persistent need to uncover the underlying pathogenic mechanisms and to facilitate effective drug development.

Therapeutic Agents Targeting Cytokines and Their Pathways

The introduction of TNF inhibitors offered proof of principle that blockade of a single cytokine pathway may be sufficient to induce complete and sustainable remission of chronic intestinal inflammation. However, failure to induce response or remission with anti-TNF therapy in subgroups of patients indicates that other inflammatory (i.e., non-TNF-driven) pathways may be dominant in these patients. Moreover, managing patients who are primary or secondary nonresponders to anti-TNF therapy is a true challenge, especially because 10–30% of patients with IBD do not gain any benefit from anti-TNF therapy (primary nonresponders), and up to 50% of those who do initially respond will lose response over time (secondary nonresponders) [24]. Consequently, the search for alternative therapeutic targets beyond TNF has intensified, and several promising candidates targeting inflammatory cytokines and essential pathways of importance for novel treatment strategies have been identified (Figure 1 and Table 1).

Interleukin 6

IL-6 is a multifunctional cytokine synthesized by a wide variety of cells that influences numerous cell types with multiple biological activities [25,26]. The IL-6 receptor exists as a transmembrane form (IL-6R), expressed mainly on immune cells and hepatocytes, and as a soluble form (sIL-6R) [27]. In the classical signaling (also known as *cis*-signaling) pathway, binding of IL-6 to IL-6R recruits a membrane-bound glycoprotein130 (gp130) coreceptor that initiates downstream signaling, including **Janus kinases** (JAKs) (Figure 1). Alternatively, IL-6 can function through a pathway known as *trans*-signaling by binding to sIL-6R that also interacts with gp130 and activates the same intracellular pathways as *cis*-signaling [28]. *Trans*-signaling enables IL-6 to modulate a broader range of cell types – including those which do not express IL-6R and are unresponsive to IL-6 – because gp130 is ubiquitously expressed. IL-6 has an essential immunoregulatory role and, moreover, it regulates hepatic synthesis of acute-phase reactants, including the inflammatory marker C-reactive protein (CRP) [29]. Despite the crucial physiologic activities of IL-6, excessive production of IL-6 contributes significantly to the pathogenesis of various diseases, including IBD [28], because it is involved in the differentiation of T_H17 cells.

Glossary

Adhesion molecules: proteins located at the cell surface that facilitate cell–cell interactions.

Antisense oligonucleotides: short (13–25 nt), single-stranded synthetic oligonucleotides designed to bind to complementary RNA sequences to downregulate target gene expression.

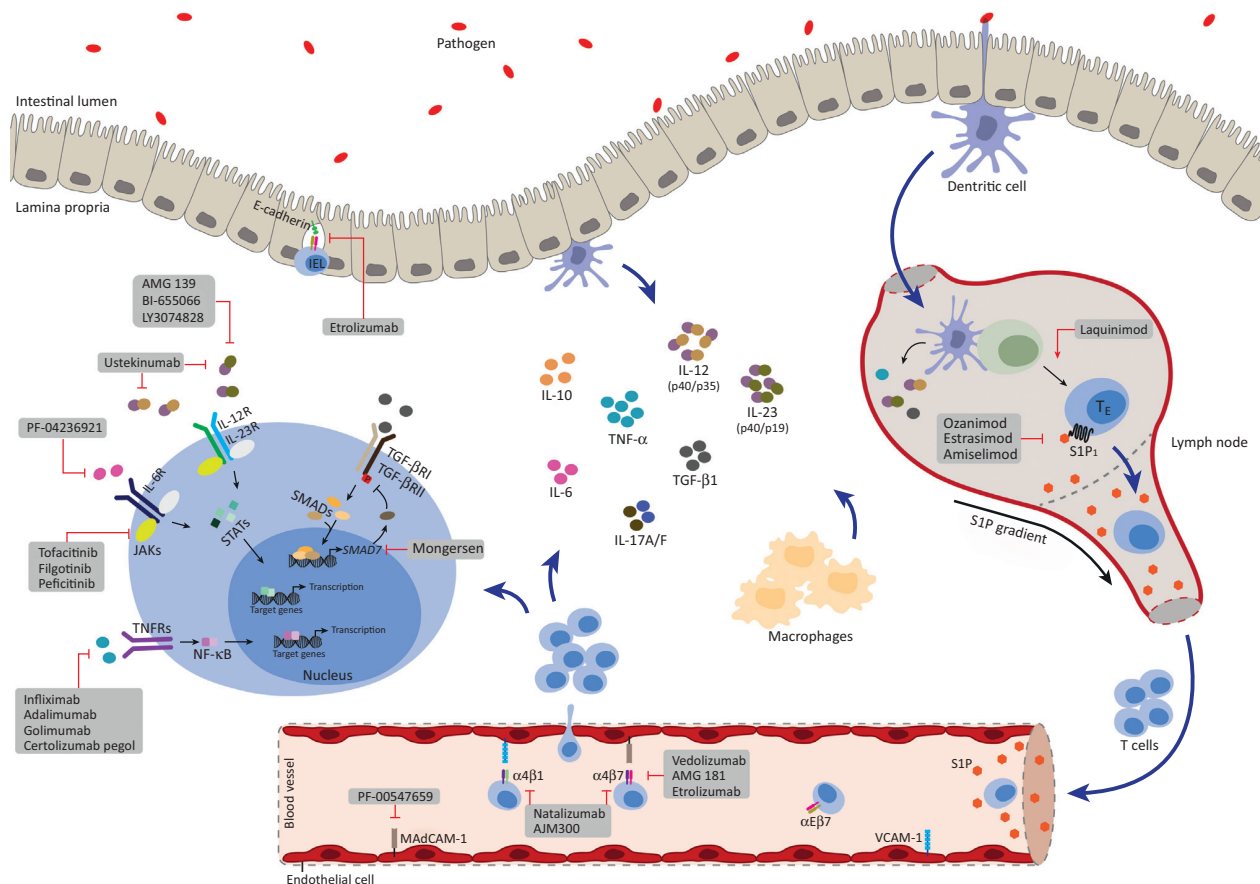
Cytokines: important signaling proteins released by numerous cells to interact and communicate between cells in immune responses.

Integrins: heterodimeric transmembrane receptors composed of α and β subunits that are responsible for cell–cell interactions and adhesion to the extracellular matrix.

Janus kinases (JAKs): intracellular non-receptor tyrosine protein kinases that convert extracellular cytokine-mediated stimuli into a wide range of cellular processes, including cell growth and survival, differentiation, proliferation, and migration.

Lamina propria: a highly vascular thin layer of loose connective tissue located beneath the basement membrane lining a layer of epithelium, and together with the epithelium constitutes the mucosa.

Small molecule: a low molecular weight (<900 Da) synthetic compound that is biologically active. Small molecules are able to cross cellular membranes and are therefore used to design drugs targeting intracellular proteins and their pathways.



Trends in Pharmacological Sciences

Figure 1. Current and Emerging Targeted Therapies for Inflammatory Bowel Disease and their Mechanisms of Action Which Include Blocking Extracellular Signal Molecules and their Underlying Pathways, Interference with Intracellular Signaling Pathways, and Perturbation of Leukocyte Trafficking into the Inflamed Intestinal Mucosa. Abbreviations: IEL, intraepithelial lymphocyte; IL, interleukin; JAK, Janus kinase; MadCAM, mucosal addressin cell adhesion molecule; NF-κB, nuclear factor-κB; P, phosphorylation; S1P, sphingosine-1-phosphate; S1P₁, S1P receptor 1; STAT, signal transducer and activator of transcription; T_E, effector T cell; TGF-β, transforming growth factor-β; TGF-βR, TGF-β receptor; T_N, naïve T cell; TNF-α, tumor necrosis factor-α; TNFR, TNF receptor; VCAM, vascular cell adhesion molecule.

Indeed, IL-6 and sIL-6R are highly expressed in patients with flaring IBD [30–34]. Therefore, it has been anticipated that IL-6 antagonism might constitute a novel therapeutic target in IBD. As a result, antibodies blocking the IL-6 pathway, including tocilizumab, C326, olokizumab (CDP6038), clazakizumab (BMS-945429), and PF-04236921, have been developed. Although these agents have entered Phase I or II clinical trials, only tocilizumab and PF-04236921 completed the trials because the other candidates were either withdrawn, terminated at an earlier point, or showed insufficient efficacy. Indeed, tocilizumab, a humanized anti-IL-6R antibody, has not been studied further in CD since 2004 owing to insufficient benefits in a pilot Phase I trial [35]. In this trial, patients with active CD ($n = 36$) were randomized to receive intravenous (i.v.) placebo or tocilizumab (8 mg/kg every 2 weeks or tocilizumab 8 mg/kg every 4 weeks) for 12 weeks. Clinical response (defined as a decrease in baseline Crohn's Disease Activity Index, CDAI, of ≥ 70 points) was achieved in 80% of patients on the 2 week regimen as compared to 31% in the placebo group ($P = 0.019$). Although tocilizumab was well tolerated, only 20% of patients achieved clinical remission, and no differences in endoscopic or histologic examinations were found [35].

Table 1. Emerging Targeted Therapies for IBD and Their Current Status in Development^a

Drug	Formulation	Target	Admin.	Clinical status ^b	
				CD	UC
PF-04236921	Fully human mAb	IL-6	s.c.	–	–
Ustekinumab	Fully human mAb	IL-12/IL-23 (p40)	i.v./s.c.	Approved ^c	Phase III
AMG-139	Fully human mAb	IL-23 (p19)	i.v./s.c.	Phase II	–
BI-655066	Fully human mAb	IL-23 (p19)	i.v./s.c.	Phase II	–
LY3074828	Humanized mAb	IL-23 (p19)	i.v./s.c.	Phase II	Phase II
Tofacitinib	Small molecule	JAK1/JAK3	Oral	– ^d	Phase III
Filgotinib	Small molecule	JAK1	Oral	Phase III	Phase III
Peficitinib	Small molecule	JAK1/JAK3	Oral	–	–
Mongersen	Antisense oligonucleotide	SMAD7	Oral	Phase III	Phase II
Laquinimod	Small molecule	?	Oral	–	–
Natalizumab	Humanized mAb	α_4 -Integrin	i.v.	Approved ^e	–
AJM300	Small molecule	α_4 -Integrin	Oral	–	–
Vedolizumab	Humanized mAb	$\alpha_4\beta_7$	i.v.	Approved ^f	Approved ^f
AMG 181	Fully human mAb	$\alpha_4\beta_7$	s.c.	Phase II	Phase II
Etrolizumab	Humanized mAb	β_7 -Integrin	i.v./s.c.	Phase III	Phase III
PF-00547659	Fully human mAb	MAdCAM-1	i.v./s.c.	–	Phase II
Ozanimod	Small molecule	S1P ₁ /S1P ₅	Oral	Phase II	Phase III
Etrasimod	Small molecule	S1P ₁	Oral	–	Phase II
Amiselimod	Small molecule	S1P ₁ /S1P ₅	Oral	Phase II	–

^aAbbreviations: Admin., administration; CD, Crohn's disease; IgG, immunoglobulin; i.v., intravenous; JAK, Janus kinase; mAb, monoclonal antibody; MAdCAM, mucosal addressin cell adhesion molecule; S1P₁, sphingosine-1-phosphate receptor 1; s.c., subcutaneous; UC, ulcerative colitis.

^bThe highest level of clinical status was obtained from www.clinicaltrials.gov (accessed October 2016).

^cApproved by the FDA and the EMA.

^dPfizer announced (October 2015) that it would not advance further studies for CD.

^eApproved in the USA.

^fApproved by the FDA and the EMA.

PF-04236921 is a fully human monoclonal IL-6 antibody that has recently completed a Phase II study in patients with CD who failed anti-TNF therapy (ClinicalTrials.gov identifier NCT01345318; ANDANTE II); however, results are still awaited. This study is an extension of a Phase II randomized, multicenter, double-blind, placebo-controlled trial in 247 subjects with refractory CD (NCT01287897; ANDANTE) that investigated placebo versus 10, 50, or 200 mg of PF-04236921 given subcutaneously (s.c.) on days 1 and 28. Only the 50 mg arm achieved a clinical response (primary endpoint CDAI = 70) at both week 8 and week 12 (49% and 47%, respectively) compared to placebo (31% and 29%, respectively; $P < 0.05$ for both). Clinical remission (i.e., CDAI < 150) for 50 mg of PF-04236921 at week 12 was 27% compared to 11% in the placebo group ($P < 0.05$). Dosing in the 200 mg arm was terminated early because of safety concerns related to higher rates of serious adverse events and serious infections [36]. There was one death because of post-operative respiratory failure in the 50 mg group; two cases with gastrointestinal perforations (colon, 50 mg; intestinal, unspecified, 200 mg); and four subjects with serious gastrointestinal abscesses between weeks 0–12, and an additional three subjects during follow-up (>week 12). The overall safety profile appeared acceptable for this refractory patient population, and adverse events were generally balanced across all treatment groups.

Interleukin 12/Interleukin 23

IL-12 and IL-23 are heteromeric cytokines each consisting of two protein subunits – namely the p35/p40 and p19/p40 subunits, respectively. Both cytokines share the p40 subunit, and both are expressed by dendritic cells and play a key role in T cell immune response. The main impact of IL-12 and IL-23 is to induce T_H1 and T_H17 differentiation, respectively [37]. IL-12 signals through the IL-12 receptor (IL-12R), comprising IL-12R β 1 and IL-12R β 2 subunits, while IL-23 binds to the IL-23 receptor (IL-23R) complex, composed of IL-23R and IL-12R β 1 [38], and both cytokines initiate downstream activation of JAK signaling (Figure 1) [39]. Their association with IBD is well-accepted because they are upregulated in patients with IBD, and genetic polymorphisms in the genes encoding IL-23R (*IL23R*) and the p40 subunit (*IL12B*) are associated with susceptibility to IBD [40]. Indeed, while *IL23R* variants are associated with a reduced risk of IBD, *IL12B* variants are associated with an increased risk of IBD [37,41,42]. Thus, the inflammatory role of IL-12 and IL-23 provides a rationale for the development of blocking agents for IBD that are currently under clinical evaluation in Phase II or III trials, including ustekinumab, AMG-139/MEDI2070, BI-655066, and LY3074828 (Table 1). Ustekinumab is a fully human anti-p40 IgG₁ antibody that can be given i.v. or s.c. In a Phase IIa multicenter, double-blind, placebo-controlled trial, 104 patients with moderate to severe CD were assigned to receive either s.c. placebo at weeks 0–3 and ustekinumab 90 mg/week at weeks 8–11; s.c. ustekinumab at weeks 0–3, and then placebo at weeks 8–11; i.v. ustekinumab 4.5 mg/kg at week 0 and placebo at week 8; or i.v. placebo at week 0 and i.v. ustekinumab 4.5 mg/kg at week 8. Clinical response rates in the combined groups receiving ustekinumab were significantly higher at weeks 4 and 6 compared to patients in the combined placebo group (53% versus 30%) [43]. However, the study did not reach its primary endpoint (reductions of $\geq 25\%$ and ≥ 70 points in CDAI from baseline) at week 8 (49% versus 40%, $P = 0.34$). Nevertheless, in the same study it was demonstrated that patients ($n = 27$) who had failed anti-TNF therapy had significantly higher response rates (43% with 90 mg/week s.c. dosing at weeks 0–3 and 54% with single 4.5 mg/kg i.v. dosing). A follow-up Phase IIb trial in CD ($n = 526$) resistant to anti-TNF therapy evaluated induction and maintenance treatment of ustekinumab [44]. The clinical response rates at week 6 (primary endpoint defined by a CDAI reduction from baseline of ≥ 100) were 37%, 34%, 40%, and 24% (for 1, 3, and 6 mg/kg of i.v. ustekinumab and placebo, respectively). In addition, maintenance therapy with ustekinumab (90 mg/week) given s.c. at weeks 8 and 16 was associated with a higher rate of clinical remission at week 22 than placebo (42% versus 27%). These results encouraged the commencement of a Phase III UNITI program, including patients with CD who are intolerant to or who have failed anti-TNF therapy (NCT01369329; UNITI-1), and a similar trial among patients naïve to anti-TNF therapy (NCT01369342; UNITI-2). The clinical response rate in the UNITI-1 study comprising 741 patients with CD at week 6 (primary endpoint, defined by a CDA reduction from baseline of ≥ 100) was 34% for both ~ 6 mg/kg and for 130 mg of s.c. ustekinumab compared to 22% for patients receiving placebo ($P < 0.01$ for both). Clinical remission (CDAI < 150) at week 8 was observed in 21 and 16% for 6 mg/kg and 130 mg of ustekinumab, respectively, versus 7% in the placebo group ($P < 0.001$ and $P = 0.003$, respectively). Similarly, major secondary endpoints of clinical response and clinical remission rates at week 8 also were significantly higher among patients receiving 6 mg/kg (38%, $P \leq 0.001$, and 21%, $P < 0.001$, respectively) or 130 mg ustekinumab (34%, $P \leq 0.001$, and 16%, $P = 0.003$, respectively) compared to patients receiving placebo (20% and 7%, respectively) [45,46]. In the UNITI-2 study including 628 CD patients, the proportion of patients meeting the same primary endpoint was 56% and 52% in those receiving 6 mg/kg and 130 mg ustekinumab, respectively, compared to 29% in patients receiving placebo ($p < 0.001$ for both). Moreover, clinical remission rates at week 6 were 35% and 29%, respectively, for 6 mg/kg and 130 mg of ustekinumab versus 18% in the placebo group ($P = 0.007$ and $P < 0.001$, respectively) [47]. In both UNITI-1 and UNITI-2, the proportion of patients with adverse events, severe adverse events, or infections were similar in all groups. One opportunistic infection (*Listeria meningitis*) was reported in the

6 mg/kg ustekinumab group in UNITI-1. No malignancies, deaths, major adverse cardiovascular events, or tuberculosis occurred in ustekinumab-treated patients in both studies.

Ustekinumab has recently (September, 2016) been approved by the US Food and Drug Administration (FDA) for the treatment of patients with CD who are refractory to conventional and/or anti-TNF therapy. The drug was subsequently approved by the European Medicines Agency (EMA) in November 2016.

In addition, a follow-up multicenter, randomized, placebo-controlled Phase III trial investigated maintenance therapy of ustekinumab in patients with moderate to severe CD (NCT01369355; IM-UNITI) [48]. In this study, subcutaneous ustekinumab (90 mg every 8 weeks [q8w] or every 12 weeks [q12w]) or placebo was given to 388 patients who achieved clinical remission at week 8 in one of the two UNITI studies (UNITI-1 or -2). A significant number of patients in the ustekinumab groups were in clinical remission at week 44 (primary endpoint with CDAI <150) compared to placebo (53% and 49% in the q8w and q12w groups versus 36% in the placebo group, $P = 0.005$ and $P = 0.040$, respectively). Significantly greater numbers of patients also maintained clinical response at week 44 in the q8w (59%) and q12w (58%) ustekinumab groups versus placebo (44%, $P < 0.05$ for both) [48]. Similar proportions of patients with adverse events were seen across treatment groups (81–84%), and the proportions of patients with serious adverse events were 10%, 12%, and 15% among the q8w, q12w, and placebo groups, respectively. No deaths or major adverse cardiovascular events were reported; two patients reported malignancies (one in each of the placebo and q8w groups).

A Phase III trial for UC is currently recruiting participants (NCT02407236; UNIFI). In contrast to ustekinumab, IL-23-specific monoclonal antibodies (specific for the p19 subunit) AMG-139/MEDI2070 and BI-655066 are in early stages of development and have entered Phase II trials for CD (NCT01714726/NCT02574637 and NCT02031276/NCT02513459, respectively), while LY3074828 has entered Phase II for both UC (NCT02589665) and CD (NCT02891226). Recently, results from a Phase II induction therapy trial with BI-655066 in patients with moderate to severe CD ($n = 121$) were reported [49]. In this trial, patients were randomly assigned to receive 200 or 600 mg of BI-655066 i.v. or placebo at weeks 0, 4, and 8. At week 12 (primary endpoint), clinical remission (defined as CDAI <150) was achieved by 24% and 37% of patients with 200 and 600 mg of BI-655066, respectively, compared to 15% of patients with placebo ($P = 0.308$ and $P = 0.025$, respectively). Clinical response rates were 37% and 42% in the 200 and 600 mg of BI-655066 arms versus 21% in the placebo group ($P = 0.103$ and $P = 0.037$, respectively). Overall, BI-655066 was more effective than placebo and was well tolerated, with no dose-related increase in adverse events, and no severe adverse events were reported [49].

Janus Kinase Inhibitors

An alternative approach that has emerged as a potential therapeutic target in IBD is the use of intracellular **small molecule** JAK inhibitors that target and inhibit several proinflammatory signaling pathways simultaneously. JAKs are members of intracellular non-receptor tyrosine protein kinases that transduce extracellular stimuli to modulate a wide range of cellular processes, including cell growth and survival, differentiation, proliferation, and migration. The mammalian JAK family consist of four members – JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2) – as well as seven STAT (signal transducer and activator of transcription) family members – STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 [50]. Binding of cytokines to their receptors mediates receptor dimerization and JAK recruitment. This results in phosphorylation and nuclear translocation of STAT dimers and transcriptional regulation of numerous genes of interest. Given the essential role of JAKs in inflammatory signaling, several inhibitors have been developed. Tofacitinib is an oral JAK inhibitor that mainly inhibits JAK1 and JAK3, thereby blocking the downstream effects of a large subset of proinflammatory cytokines,

including IL-2, IL-3, IL-4, IL-5, IL-6, IL-12, IL-15, IL-21, and interferon- γ [50,51]. Tofacitinib was shown to be effective in a randomized, placebo-controlled Phase II trial among 194 patients with active UC. Clinical responses to tofacitinib at week 8 (primary endpoint) were dose-dependent (0.5, 3, 10, and 15 mg tofacitinib twice daily) and were reported in 32% ($P = 0.39$), 48% ($P = 0.55$), 61% ($P = 0.10$), and 78% ($P < 0.001$), respectively, compared to 42% of patients in the placebo group [52]. Although tofacitinib was well tolerated and no major safety concerns were reported, two serious infection-related adverse events were observed in the 10 mg group. Moreover, there was a dose-dependent increase in both low- and high-density lipoprotein cholesterol and three patients treated with tofacitinib had an absolute neutrophil count of less than 1500 cells/mm³. Nevertheless, these results led to the initiation of two Phase III induction trials (OCTAVE Induction 1 and 2) conducted in patients with moderate to severe UC (NCT01465763 and NCT01458951, respectively). Patients were randomized to receive tofacitinib 10 mg twice daily or placebo for 8 weeks (primary endpoint, defined as a total Mayo score of ≤ 2 , no subscore > 1 , and a rectal bleeding subscore of 0). At week 8, significantly more patients receiving tofacitinib 10 mg twice daily achieved remission ($P < 0.01$ and $P < 0.001$, respectively), mucosal healing ($P < 0.001$ for both), and clinical response ($P < 0.001$ for both) in both studies versus placebo [53]. Of note, tofacitinib 10 mg twice daily seems to be superior to placebo regardless of prior TNF therapy, however, greater effects were observed in secondary nonresponders to TNF therapy compared to primary TNF failures [54]. The rates of adverse events in OCTAVE Induction 1 and 2 were similar across groups. One patient died (tofacitinib 10 mg; dissecting aortic aneurysm), and increased serum lipid (total cholesterol, low- and high-density lipoprotein) and creatine kinase levels were seen with tofacitinib treatment [53].

In addition, two other Phase III trials evaluating the maintenance (OCTAVE Sustain) and long-term effects (OCTAVE Open) of tofacitinib in patients with UC are ongoing and still recruiting (NCT01458574 and NCT01470612, respectively). By contrast, administration of tofacitinib (1, 5, or 15 mg twice daily) or placebo in a Phase II trial comprising 139 patients with moderate to severe CD failed to induce a significant clinical response in a 4 week induction study [55]. However, whether the failure of tofacitinib was the result of the short duration of the study, the small sample size, or the high placebo response rates (47%), or was a true negative result remains unclear. Thus a larger Phase IIb induction trial of tofacitinib in moderate to severe CD has been conducted. Of 280 patients, 44% and 43% achieved clinical remission at week 8 with 5 and 10 mg of tofacitinib twice daily, respectively, versus 37% for the placebo group [56]. Moreover, 180 patients, of whom 128 had completed the induction study with a clinical response (a decrease of CDAI ≥ 100 points from baseline) or clinical remission (CDAI < 150), were included in a 26-week maintenance study. The proportions of patients with clinical response or remission at week 26 were not significant because rates were 40% and 56% for 5 or 10 mg of tofacitinib twice daily versus 38% for placebo [57]. Although an open-label Phase II maintenance study of tofacitinib in CD has recently been completed (NCT01470599), and the results are awaited, further studies will not be advanced for CD (as announced by Pfizer in October 2015).

In addition to tofacitinib, filgotinib (GLPG0634) [58], a novel oral JAK1-selective small-molecule inhibitor, potentially resulting in better safety profile, has been evaluated in a Phase II trial in patients with CD. In this study, 174 patients (either anti-TNF naïve or failures) were randomly assigned to receive 200 mg/day of filgotinib or placebo for 10 weeks [59]. After 10 weeks, patients continued to receive filgotinib 100 or 200 mg/day or placebo for another 10 weeks. At week 10, clinical remission (primary endpoint defined as CDAI < 150) rates were 48% in the filgotinib group versus 23% in the placebo group ($P = 0.007$). Clinical responses were 60% in the filgotinib group versus 41% in the placebo group ($P = 0.037$). Similar incidences of early discontinuations, adverse events, and serious adverse events including infections were observed in both groups over the 10 weeks, with the majority of the severe adverse events related to worsening of CD [59]. Filgotinib is proceeding to two Phase III studies for CD

(NCT02914561 and NCT02914600) and two Phase III studies for UC (NCT02914522 and NCT02914535).

Another clinical Phase II trial of an oral JAK1/JAK3 inhibitor (peficitinib/ASP015K) has recently been conducted in UC (NCT01959282), and the results are awaited.

SMAD7 Antisense Oligonucleotide

TGF- β 1 is a pleiotropic cytokine that is important for cell homeostasis in virtue of its anti-inflammatory properties. Briefly, TGF- β 1 signals through a heteromeric transmembrane protein kinase receptor complex consisting of receptor types I and II, which in turn phosphorylates the downstream canonical SMAD2/3 complex. In this pathway, SMAD7 is an intracellular negative regulator of TGF- β 1 signaling by blocking the activation of the SMAD2/3 complex (Figure 1). In fact, although TGF- β 1 is highly produced in IBD it is unable to signal owing to the high SMAD7 activity in patients with IBD [60]. Therefore, restoring the TGF- β 1 signaling pathway has been a focus in the search for novel therapeutic compounds for management of IBD [61]. This search led to the development of an intracellular **antisense oligonucleotide** [62], mongersen (GED-0301), an oral formulation containing an anti-SMAD7 oligonucleotide that specifically targets SMAD7 mRNA (Figure 1). Mongersen facilitates RNase H-mediated degradation of SMAD7 mRNA, and inhibits the production and activity of SMAD7 [63]. Thus mongersen restores the production of TGF- β 1, which, in turn, induces anti-inflammatory signaling. In a multicenter, double-blind, placebo-controlled Phase II trial, 166 patients with moderate to severe CD were randomized to receive one of three doses of mongersen (10, 40, or 160 mg/day) or placebo for 2 weeks only [64]. The proportions of patients meeting the primary endpoint (i.e., CDAI <150 on day 15 and maintenance of this score up to day 28) were 12%, 55%, and 65% in the 10, 40, and 160 mg/day groups, respectively, versus 10% in the placebo group. A total of nine serious adverse events were reported in six patients, and most were related to CD symptoms and complications (e.g., abdominal pain, seton placement for perianal fistula, pyrexia, and surgery for hemorrhoid thrombosis). The rate of adverse events did not differ among groups [64,65]. However, a drawback was the length of this study and the fact that it solely relied on evaluation of clinical parameters; future trials therefore will be necessary to determine the impact of mongersen on mucosal healing. Currently, two randomized multicenter Phase III studies for induction and maintenance therapy of patients with active CD (NCT02596893 and NCT02641392) as well as an open-label Phase III trial in CD (NCT02685683) are in progress. In addition, mongersen has lately entered a multicenter open-label Phase II study to explore its efficacy and safety in subjects with active UC (NCT02601300).

Laquinimod

Laquinimod is an oral small-molecule immunomodulator with anti-inflammatory properties as a result of suppressing the production of several proinflammatory cytokines. In particular, it suppresses T_H1 and T_H17 cells, and induces a T_H2 shift of the immune response [66,67] by an as yet unknown mechanism. A multicenter double-blind Phase II study in patients with active CD has recently revealed significant clinical improvement and favorable safety for laquinimod [68]. In this study, laquinimod or placebo were administered once or twice daily at different doses to patients with active CD ($n = 180$) for 8 weeks. Clinical remission (CDAI <150) rates achieved were 48%, 27%, 14%, and 17% for patients receiving 0.5, 1, 1.5, or 2 mg/day ($n = 117$) versus 16% in the placebo group ($n = 63$). Laquinimod was well tolerated, and the overall incidence of serious adverse events was similar to that of the pooled placebo group; all doses reduced fecal calprotectin levels.

Therapeutic Agents Targeting Leukocyte Trafficking

As mentioned above, migration and infiltration of leukocytes from the blood to the site of inflammation in the intestinal mucosa is an important aspect of IBD pathogenesis. Thus, agents

targeting leukocyte trafficking have been developed (Figure 1) and, while some agents have been approved for IBD, other promising agents are currently under evaluation for this disorder (Table 1).

α_4 -Integrin Inhibitors

Natalizumab is a recombinant humanized IgG₄ monoclonal antibody directed against the α_4 -integrin subunit on leukocytes, and was the first anti-integrin molecule introduced and proven effective in the induction and maintenance of remission in patients with CD [69,70]. By targeting the shared α_4 subunit, natalizumab blocks the interaction of $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins with VCAM-1 and MAdCAM-1, respectively, which are highly expressed on endothelial cells of the intestinal **lamina propria** during inflammation (Figure 1). Unfortunately, because VCAM-1 is also expressed in the central nervous system, targeting β_1 integrin $\alpha_4\beta_1$ also limits immune surveillance of the central nervous system. Consequently, it was revealed in clinical trials (ENCORE and ENACT) that natalizumab, although clinical results were encouraging for patients with CD, augmented the risk of John Cunningham (JC) virus activation in the brain, leading to progressive multifocal leukoencephalopathy (PML) [69,70], a serious and often lethal infection [71]. Thus, in the devastating neurologic condition of multiple sclerosis where natalizumab is frequently used, the risk of PML is 1.6 per 1000 patients during the first 2 years of natalizumab monotherapy in patients with prior immunomodulator exposure and with positive anti-JC virus antibodies [72]. Whether the risk of PML is similar in patients with CD has not been determined. Nevertheless, the use of natalizumab for the treatment of patients with CD has been approved only in the USA and some other countries, but not by the EMA.

Despite the safety issues of natalizumab, AJM300, an orally administered small-molecule α_4 -integrin antagonist, has been developed and evaluated in UC. The efficacy of AJM300 was evaluated in 102 Japanese patients with moderately-active UC in a double-blind, placebo-controlled Phase IIa study in which patients were randomized to receive 960 mg of AJM300 or placebo thrice daily for 8 weeks [73]. Clinical response (i.e., a decrease in the Mayo score of ≥ 3 points and a decrease of $\geq 30\%$ from baseline, with a decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding subscore of 0 or 1) and remission (i.e., Mayo score ≤ 2 and no subscore >1) rates at week 8 were 63% and 24%, respectively, in the AJM300 group versus 26% and 4%, respectively, in the placebo group ($P < 0.001$ and $P = 0.001$, respectively). Even though no serious adverse events have been reported, the fact that AJM300 might share mechanisms of action with natalizumab raises concerns about its therapeutic potential.

Integrin $\alpha_4\beta_7$ -Specific Inhibitors

Following the increased safety concerns of α_4 -integrin inhibitors, gut-selective $\alpha_4\beta_7$ inhibitors with a more acceptable safety profile have been developed. Vedolizumab is an IgG₁ humanized monoclonal antibody that specifically inhibits integrin $\alpha_4\beta_7$ on T cells and blocks the interaction between $\alpha_4\beta_7$ and MAdCAM-1 (Figure 1). Vedolizumab has been evaluated in the GEMINI studies and is the first anti-integrin antibody approved for treatment of patients with UC and CD who are refractory to conventional and/or anti-TNF therapy. Two similar multicenter, randomized, placebo-controlled trials demonstrated that i.v. administration of vedolizumab (at a dose of 300 mg) was effective as either induction or maintenance therapy for UC as well as CD (GEMINI I and GEMINI II trials, respectively) [74,75]. In the GEMINI I trial ($n = 895$ patients with active UC), i. v. administration of vedolizumab (300 mg at weeks 0 and 2) in the induction phase resulted in an impressive response rate of 47% by week 6 (primary endpoint defined as a reduction in the Mayo Score of ≥ 3 points and a decrease of $\geq 30\%$ from baseline, with a decrease in the rectal bleeding subscore of ≥ 1 point or an absolute rectal bleeding score of 0 or 1), compared to 26% in the placebo group ($P < 0.001$). In the study of maintenance, 42% of patients who continued to receive vedolizumab every 8 weeks, and 45% of patients who continued to receive vedolizumab every 4 weeks were in clinical remission (i.e., Mayo score ≤ 2 and no subscore >1), compared to

16% of patients who switched to placebo ($P < 0.001$ for both) at week 52 [74]. In the GEMINI II trial ($n = 1115$ patients with active CD), a clinical remission rate of 15% was achieved at week 6 (primary endpoint defined as CDAI ≤ 150) in the vedolizumab group (300 mg at weeks 0 and 2), compared to 7% in the placebo group ($P = 0.02$). Among responders to induction therapy, 39% and 36% of patients receiving vedolizumab every 8 or every 4 weeks, respectively, were in clinical remission (i.e., CDAI ≤ 150) compared to 22% for the placebo group ($P < 0.001$ and $P = 0.004$, respectively) at week 52 [75]. In addition, a second randomized, double-blind, placebo-controlled multicenter Phase III trial (GEMINI III) has assessed the safety and efficacy of vedolizumab for induction of clinical response and remission in patients with CD ($n = 416$). Primary endpoint (i.e., clinical remission defined as CDAI ≤ 150) at week 6 in patients ($n = 315$) who had failed previous anti-TNF therapy was not achieved because only 15% of those given 300 mg vedolizumab at weeks 0, 2, and 6 were in remission compared to 12% of those given placebo ($P = 0.433$). Thus, exploratory analyses showed that, at week 10, a higher proportion of patients on vedolizumab achieved clinical remission than those given placebo (27% versus 12%, nominal $P = 0.001$) [76]. In addition, 31% of patients with CD naïve to TNF inhibitors ($n = 101$) given vedolizumab achieved remission at week 6, versus 12% for placebo ($P = 0.012$). At week 10, the remission rates were 35% for vedolizumab versus 16% for placebo ($P = 0.025$) [76].

Taken together, the three GEMINI studies indicate that vedolizumab is effective to induce and maintain remission in patients with UC, as well as in the maintenance of clinical remission in CD, because of a slower onset of action, often requiring 10 weeks or more of therapy in CD. In addition, a *post hoc* analysis of the data from the GEMINI I study confirmed that vedolizumab could induce and maintain clinical response and remission in patients with UC, both in patients naïve to TNF and in TNF failures [77].

Concerning the safety profiles of vedolizumab, an integrated summary of the safety data of vedolizumab has recently been reported [78]. This study included safety data from six clinical trials (both UC and CD) of patients receiving ≥ 1 dose of vedolizumab or placebo. In the overall safety population, 248 and 20 vedolizumab-exposed patients experienced an adverse or severe adverse event, respectively, per 100 person-years (PYs) of follow-up, compared to 419 and 28 patients receiving placebo. No increased risk of any infection or serious infection was associated with vedolizumab exposure. Serious clostridial infections, sepsis, and tuberculosis were reported infrequently ($\leq 0.6\%$ of patients). Importantly, no cases of PML were observed. Eighteen vedolizumab-exposed patients ($<1\%$) were diagnosed with malignancy [78]. Overall, a favorable benefit–risk profile makes vedolizumab a useful option for the long-term treatment of IBD, and this has also been supported by two recent interim reports from the ongoing, open-label GEMINI long-term safety (LTS) Phase III extension trial (NCT00790933) of vedolizumab for UC and CD [79,80].

Another similar agent, the fully human IgG₂ monoclonal antibody AMG 181 that binds to the integrin $\alpha_4\beta_7$ heterodimer, has been developed and evaluated in a Phase I study in UC ($n = 68$). The pharmacokinetics/pharmacodynamics, safety, and efficacy profiles for patients receiving s. c. AMG 181 were acceptable and suitable for further testing in IBD [81]. Hence, AMG 181 is currently being evaluated in Phase II trials in patients with UC (NCT01694485) and CD (NCT01696396).

β_7 -Integrin Inhibitor

Etrolizumab is a humanized IgG₁ monoclonal anti- β_7 antibody that prevents the interaction of integrins $\alpha_4\beta_7$ and $\alpha E\beta_7$ with their ligands, MAdCAM-1 and E-cadherin, respectively. Because $\alpha E\beta_7$ is expressed on mucosal intraepithelial lymphocytes, and because the cell-adhesion molecule E-cadherin is expressed on epithelial cells, it is presumed that etrolizumab, by targeting and blocking both $\alpha_4\beta_7$:MAdCAM-1 and $\alpha E\beta_7$:E-cadherin interactions, can reduce lymphocyte

trafficking to the gut as well as retention of lymphocytes in the intraepithelial compartment (Figure 1) [82]. Subsequent to a Phase I study showing suitable pharmacokinetics of etrolizumab in patients with moderate to severe UC [83], this agent was further evaluated in a placebo-controlled, randomized Phase II study examining its ability to induce remission in 124 patients with active UC [84]. Patients were randomly assigned to receive 100 mg of s.c. etrolizumab at weeks 0, 4, and 8, or a 420 mg loading dose at week 0, followed by 300 mg at weeks 2, 4, and 8, or placebo. Clinical remission rates at week 10 (primary endpoint defined as a Mayo score ≤ 2 , no subscores > 1) were 21% in the 100 mg etrolizumab group and 10% in the 300 mg groups versus a matching placebo group (0%) ($P = 0.004$ and $P = 0.048$, respectively). Treatment with etrolizumab was well tolerated, with a similar frequency of mild and moderate adverse events in all study groups. Notably, an important aspect of this study was that molecular markers of drug efficacy were studied. This trial revealed that patients with high αE -integrin (*ITGAE*) gene expression or αE -positive cells at baseline in the intestinal epithelium were associated with enhanced clinical remission at week 10 of etrolizumab treatment in UC, with a higher enrichment in anti-TNF-naïve patients [84]. Subsequent retrospective analysis of these data reported, that high levels of *ITGAE* and granzyme A (*GZMA*) gene expression at baseline can identify patients with UC who are most likely to benefit from etrolizumab [85]. However, future prospective trials will be necessary to support and validate these findings.

Etrolizumab is currently being evaluated in a Phase II open-label extension study in patients with UC (NCT01461317), and is proceeding to a large Phase III program that will examine the safety and efficacy of etrolizumab in patients with CD (NCT02403323) and UC (NCT02118584) as well as the efficacy of the drug in patients with UC (NCT02163759, NCT02171429, NCT02136069, NCT02165215, and NCT02100696) and CD (NCT02394028) who are naïve or refractory to, or intolerant of, TNF inhibitors. Some of the studies also include an active comparator arm against TNF inhibitors (NCT02163759, NCT02136069, and NCT02171429). Hence the outcome from this comprehensive Phase III program will discern the potential rationale for UC and/or CD indication(s) of etrolizumab and whether it will become a viable agent in either first- or second-line therapy.

MAdCAM-1 Inhibitor

PF-00547659 is a fully-human IgG₂ monoclonal antibody that selectively targets gut-specific MAdCAM-1 and blocks its ability to act as a ligand for integrin $\alpha_4\beta_7$ (Figure 1). In an initial randomized, placebo-controlled, Phase I study among 80 patients with flaring UC, patients were randomized to receive single or multiple doses (three doses, 4 week intervals) of 0.03–10 mg/kg of PF-00547659 or placebo given i.v. or s.c. [86]. Although clinical response and remission rates were insignificant in the pooled PF-00547659 group compared to placebo, a trend toward an effect and an acceptable safety profile brought PF-00547659 into Phase II clinical trials in both CD and UC. Results in CD (NCT01276509) showed that s.c. PF-00547659 or placebo given in one of three doses (22.5, 75, or 225 mg) did not meet the primary endpoint because of high placebo response [87]. By contrast, among 357 patients with active UC (NCT01620255) receiving PF-00547659 every 4 weeks, clinical remission rates at week 12 (primary endpoint, defined as a Mayo score ≤ 2 with no subscores > 1) were 11%, 17%, 16%, and 6% for 7.5, 22.5, 75, and 225 mg, respectively, versus 3% in the placebo group ($P = < 0.05$, respectively, except for the 225 mg group) [88]. Adverse and serious adverse event rates were similar between the placebo and all drug doses. No obvious dose–response relationship for any of the events monitored was reported. Further, no increases in infections and no cases of PML were observed. Nevertheless, further studies are required, and results from a recently completed Phase II trial in patients with CD are awaited (NCT01298492), while another Phase II maintenance trial in UC (NCT01771809) is progress. Phase III studies are scheduled.

Sphingosine-1-Phosphate (S1P) Receptor Modulators

Ozanimod (RPC1063) is a novel oral selective small-molecule immunomodulatory agonist mainly for G protein-coupled S1P receptor 1 (S1P₁), which is expressed on the surfaces of lymphocytes, and this drug blocks lymphocyte egress from lymph nodes into the systemic circulation (Figure 1) [89]. However, ozanimod also binds to S1P₅, albeit with less efficacy. Binding of ozanimod to S1P₁ results in internalization and degradation of the receptor, and consequently it prevents lymphocyte trafficking to the sites of inflammation [90]. Results from the first Phase II trial (TOUCHSTONE study) showed encouraging results in patients with UC [91]. A total of 197 patients with moderate to severe UC were randomly assigned to receive ozanimod once daily in two different doses (0.5 or 1 mg) or placebo for 8 weeks (primary endpoint defined as a Mayo score ≤ 2 with no subscore >1). The proportions of patients achieving clinical remission were 16% for 1 mg, 14% for 0.5 mg, and 6% for placebo ($P = 0.048$ and $P = 0.14$, respectively), and clinical response rates were 57%, 54%, and 37%, respectively [91]. Patients who achieved a clinical response at week 8 ($n = 103$) continued with their original treatment through week 32 in a maintenance phase. Clinical remission and response rates were 21% and 51% ($P = 0.011$ and $P < 0.001$), respectively, for 1 mg; 26% and 35% ($P = 0.002$ and $P = 0.057$), respectively, for 0.5 mg; and 6% and 20%, respectively, for the placebo group [91]. Moreover, mucosal healing (defined as endoscopy subscore ≤ 1) was significant (nominal p values) for 0.5 and 1 mg of ozanimod versus placebo at week 8 ($P = 0.03$ and $P = 0.002$, respectively) and week 32 ($P = 0.006$ and $P = 0.005$, respectively). In addition, histologic remission (defined by a Geboes score <2) was significant for 1 and 0.5 mg ($P = <0.001$ and $P = 0.02$, respectively) of ozanimod versus placebo at week 32 but not at the end of the induction period of 8 weeks. Overall ozanimod showed a good safety profile, even though four patients (one treated with 0.5 mg and three treated with 1 mg) had increased hepatic aminotransferase levels [91].

Ozanimod has recently entered Phase III trials on induction and/or maintenance in UC (NCT02435992 and NCT02531126), as well as a Phase II multicenter study examining induction therapy of ozanimod in CD (NCT02531113). The two Phase II trials in UC are still recruiting, while the trial in CD is currently in progress. Moreover, similar agents, such as etrasimod (APD334, a S1P₁ agonist), have entered Phase II trials for UC (NCT02447302 and NCT02536404) and are currently recruiting participants, while two Phase II trials of amiselimod (MT-1303, a S1P₁/S1P₅ agonist) for CD are either ongoing (NCT02389790) or have recently been completed (NCT02378688); however, results are still awaited (Table 1).

Personalized IBD Therapy

Given that IBD is a heterogeneous disorder, devising more innovative drugs not only will strengthen the existing therapeutic armamentarium but also will complicate physician decisions about which medication to prescribe. In IBD, further complexity comes with duration of disease and the history of response to a given therapy. Heterogeneity between patients is in fact one of the major features of IBD, also reflected in differences in disease behavior and a wide range of response/nonresponse to therapeutics [92,93]. Despite huge progress in understanding the pathogenesis of IBD and in the development of novel agents, there are no individualized treatment guidelines and, accordingly, the treatment is predominantly based on symptoms, combined with clinical and endoscopic examinations. In fact, as mentioned earlier, many drugs are only effective in subgroups of patients, and therefore the indiscriminate use of these drugs is costly, ineffective, and may put patients at risk. Thus the only successful application of personalized therapy in IBD at present is therapeutic drug monitoring in patients treated with thiopurines or TNF inhibitors [94,95]. In particular, thiopurine dosing can be adjusted on an individual basis to secure optimal efficacy at minimal risk of side effects by analytical tests including genotyping and phenotyping of thiopurine S-methyltransferase (TPMT), measurement of the thiopurine metabolites [6-thioguanine nucleotide (6-TGN) and

6-methylmercaptopurine (6-MMP)] (reviewed in detail in [16]). With regard to biologics, measurement of serum drug levels and anti-drug antibodies has been shown to be both clinically useful and economically advantageous [96–99]. A better understanding of the pathophysiology and identification of prognostic biomarkers might significantly advance and optimize patient outcomes. However, the successful outcome of personalized therapy of a heterogeneous disorder depends greatly on several factors, including the specific biologic, genetic, and clinical characteristics of each individual, as well as differences in lifestyle, ethnicity, environmental factors, and other underlying diseases. Hence, a multi-parameter approach seems to be most appropriate to develop clinical decision-making algorithms that may help to tailor treatment to the needs of each individual patient. Such prognostic biomarkers could potentially identify relevant subgroups that respond to specific therapies. However, it is crucial to select the right set of patients for such clinical trials. Although personalized therapy may be related to several diagnostic and therapeutic measures that are very expensive, such actionable efforts ultimately may help to reduce costs in the management of patients in clinical settings [100].

Concluding Remarks

An unmet medical need exists for novel easily (preferably orally) administered, efficacious, safe, and more cost-effective therapeutics with distinct mechanisms of action which could lead to more rational treatment of patients with IBD in the future. Although targeting cytokines beyond TNF, and gut homing of disease-exacerbating inflammatory cells, are currently at the forefront of IBD treatment, new cutting-edge approaches and therapeutic strategies for improving IBD care will emerge and are clearly warranted (see Outstanding Questions). Nonetheless, even though a number of potential drugs will probably never reach the stage of clinical application, some may be introduced for management of IBD, in other words induction, maintenance, or as an alternative for patients who are refractory to TNF inhibitors. It is nevertheless plausible that some of those drugs that have failed to prove efficacy as monotherapy could provide improved therapeutic outputs in a multi-targeted approach through a combination of agents targeted to several distinct molecules. In particular, small molecules remain attractive as therapeutics, especially for oral bioavailability, because they are likely to be more acceptable to patients given that they avoid inconvenient i.v. or s.c. injections. Certainly, oral formulations with great promise are tofacitinib and ozanimod for the treatment of UC, and filgotinib and mongersen for the treatment of CD. However, their long-term safety profiles need careful evaluation. Further, in contrast to what is practiced for TNF inhibitors where biomarkers (e.g., circulating anti-TNF drug trough levels as well as antidrug antibodies) might be applied for individual optimal use of these agents [101], biomarkers for guidance of the novel therapies described here is still lacking for their personalized use, and an urgent need for such patient stratification exist. In particular, there is concern whether the JAK inhibitors may lead to unwanted side effects by targeting several cytokines simultaneously, or if long-term use of mongersen might increase TGF- β 1 expression and the development of fibrosis, which might increase the risk of surgery [102]. The pathogenesis of IBD is complex and may vary among patients, which challenges its management. By uncovering the underlying pathogenic triggers, the trend has now moved in the direction of developing novel and easily administered stable drugs targeting specific pathways of the inflammatory cascade in IBD, which brings hope for a more rational treatment strategy in the near future.

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Outstanding Questions

What are the advantages of small molecules over biological drugs for anti-inflammatory therapeutics in the management of IBD?

Would combination therapy with novel drugs aimed at targeting multiple pathways in concurrence or sequentially exert any therapeutic benefit – perhaps even with agents that have failed to prove efficacy when administered alone?

Will it be possible to develop and apply prognostic biomarkers to predict responsiveness and to provide the right drug to the right patients at the right time?

Do novel drugs have any so far unidentified long-term side effects?

Will any of the emerging novel therapeutics become a first-line therapy in IBD?

What will be the main reasons for the choice of first- or second-line therapy when more novel therapeutics obtain approval for treatment of IBD? Will it be their cost-effectiveness, efficacy, or safety – or will we reach a point where the choice of drugs will depend on the individual needs of each patient?

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