New Non-anti-TNF-α Biological Therapies for the Treatment of Inflammatory Bowel Disease

35

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Introduction

Blockade of the tumor necrosis factor alpha (TNF-α) pathway has been a major advancement for the treatment of inflammatory bowel disease (IBD). A substantial proportion of patients with moderate to severe Crohn's disease (CD) do not have a response to treatment with TNFα antagonists (primary nonresponse), and among patients who do have a response, it is often not sustained (secondary nonresponse) or side effects require discontinuation of medical therapy. As a consequence of this, there is an ongoing need to develop new biologics with different mechanisms of action. This chapter will discuss the major non-anti-TNF-α biological agents in the pipeline that are currently undergoing evaluation in order to effectively and safely treat patients with IBD. Figures 35.1 and 35.2 illustrate the drugs currently in the pipeline and Table 35.1 is a summary of the treatments that will be discussed in this chapter.

Cytokine Targets

IL-12/IL-23

Interleukin (IL)-12 and IL-23 have been shown to have a central role in the inflammatory pathway in Crohn's disease, psoriasis and multiple sclerosis [2]. The IL-12 family of cytokines (which includes IL-23) is involved in stimulating innate immunity and developing adaptive immunity. Interleukin-12 and interleukin-23 are key proinflammatory cytokines involved in type 1 helper T (Th1) cell response, which is characterized by a marked accumulation of macrophages making interleukin-12, the major Th1-inducing factor, in Crohn's disease mucosa [3, 4]. Risk for developing CD and UC has been demonstrated through genome-wide association studies studying variants of the gene encoding the IL-23 receptor and the locus for the gene encoding the p40 chain [5]. It was also suggested that the production of both IL-12 and IL-23 is downregulated in patients with Crohn's disease but not with ulcerative colitis following administration of IL-12p40 monoclonal antibody [6].

IL-12 is a heterodimer of p40 and p35 subunits. IL-12 induces the differentiation of naïve CD4+ T cells into T helper 1 cells that produce interferon (IFN) gamma and mediates cellular immunity [7]. IL-23 is a heterodimer of the same p40 subunit and a p19 subunit which induces naïve CD4+ T cells into T helper 17 cells which then induce the production of proinflammatory cytokines such as IL-17, IL-6, and TNF-α [8].

Ustekinumab

Ustekinumab (originally known as CNTO 1275) is a human monoclonal antibody (IgG1) that targets the IL-12/23 shared p40 subunit. The result is the inhibition of IL-12 and IL-23 binding to their receptor on the surface of T cells, natural killer cells, and antigen-presenting cells (see Fig. 35.3).

Ustekinumab has been shown to be clinically effective in the treatment of moderate to severe CD in phase II studies. There were two groups studied with population 1 being double-blind, placebo-controlled, parallel-group, crossover at week 8 study and population 2 being an open-label study [10]. Both groups were followed up for 28 weeks. Group 1 comprised of 104 patients with moderate to severe Crohn's disease despite treatment with 5-ASA, antibiotics, corticosteroids, infliximab, and/or immunomodulators who were randomly assigned to one of four arms of treatment: subcutaneous placebo at weeks 0–3 followed by subcutaneous ustekinumab 90 mg at weeks 8–11; subcutaneous ustekinumab 90 mg at weeks 0–3 followed by subcutaneous placebo at weeks 8–11; intravenous placebo at week 0 followed by intravenous ustekinumab 4.5 mg/kg at week 8; or intravenous ustekinumab 4.5 mg/kg at week 0 followed by

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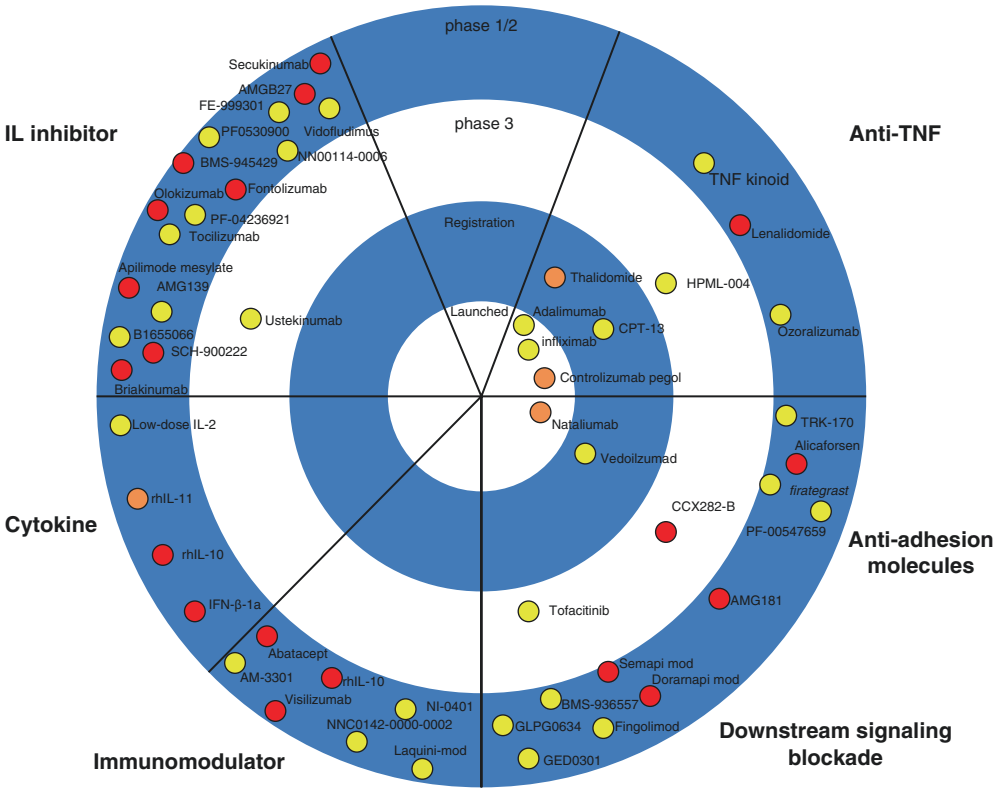

Fig. 35.1 Drugs in pipeline for CD (Amiot and Peyrin-Biroulet [1])

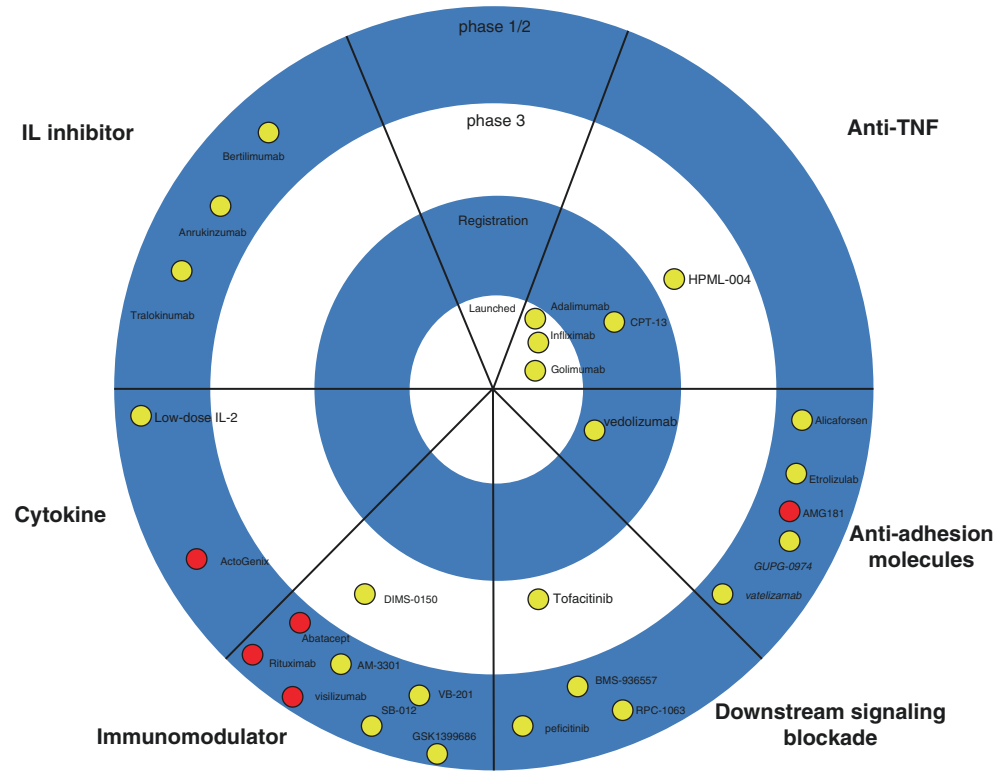

Fig. 35.2 Drugs in pipeline for UC (Amiot and Peyrin-Biroulet [1])

intravenous placebo at week 8. Group 2 consisted of 27 patients who previously failed to respond to a three-dose induction of infliximab 5 mg/kg or lost response to infliximab maintenance every 8 weeks despite dose escalation to 10 mg/kg who were randomly assigned to open-label therapy with either 4 weekly subcutaneous injections ustekinumab

Table 35.1 Treatments discussed in this chapter

Target	Name	Development in IBD	Mechanism of action
Cytokines			
IL-12/IL-23	Ustekinumab MEDI 2070 (AMG 139) BI 655066 (risukizumab)	Phase III (CD, UC) Phase II (CD)	Inhibits p40 subunit Blocks binding of IL-23 to its receptor Inhibits the p19 unit
IL-6	PF-04236921	Phase II (CD)	IL-6 inhibitor
IL-13	Tralokinumab QAX576 Bertilimumab	Phase II (UC) Phase II (CD) Phase II (CD, UC)	IL-13 receptor antagonist Inhibits of IL-13 Blocks the activity of eotaxin-1
IL-17	Vidofludimus	Phase II	Inhibits IL-17 secretion
IL-21	ATR107 NNC0114-0006	Phase I Phase II (CD)	Anti-IL-21 receptor antibody IL-21 inhibitor
Signaling pathways mediated by cytokines			
JAK/STAT	Tofacitinib GLPG0634 (Filgotinib)	Phase III (UC) Phase II (CD)	Inhibits JAK1 and JAK3 JAK1 inhibitor
TGF-b	GED0301 (Mongersen)	Phase III/II (CD/UC)	SMAD7 antisense oligonucleotide
Chemokines			
IL-10 antagonist	BMS936557 (eldelumab)	Phase II (CD, UC)	CXCL-10 inhibitor
Antiadhesion molecules	Natalizumab	Approved (CD)	α4 integrin antaogmist
	Vedolizumab	Approved (CD, UC)	α4β7 integrin antagonist
	Etrolizumab	Phase III (CD, UC)	Blocks β7 subunit of α4β7 and αEβ7 integrins
	PF-00547659	Phase II (CD, UC)	MAdCAM-1 protein inhibitor
	AJM300	Phase III (UC)	α4 integrin antagonist
	Alicaforsen	Phase III (UC)	Targets intercellular adhesion molecule 1 (ICAM-1)
	AMG181 (abrilumab)	D/c'd	α4β7 integrin antagonist
	Firategrast		α4 integrin antagonist
	GLPG0974	Phase II (UC)	Against FFA2
	TRK-170	Phase II (CD)	α4β1/α4β7 integrin antagonist
Anti-inflammatory cytokine	IL-10		IL-10 replacement
T-cell stimulation and induction of apoptosis blockades	Laquinimod DIMS0150	Phase II (CD) Phase III (UC)	Modulation of immune cells Activates TLR9
Spingosine-1-phosphate receptor modulators	Fingolimod APD334 RPC1063 (ozanimod)	Phase II (UC) Phase III/II (UC/CD)	Traps lymphocytes in lymph nodes

90 mg at weeks 0–3 or single intravenous ustekinumab 4.5 mg/kg at week 0. The primary endpoint was clinical response at week 8 (a reduction of at ≥25 % and 70 points in the CDAI score from baseline). In group 1 the primary endpoint was assessed for combined subcutaneous and intravenous ustekinumab administered before crossover to placebo ($n = 51$) versus combined subcutaneous and intravenous placebo administered before crossover to ustekinumab ($n = 53$). There was no significant difference in rates of clinical response between ustekinumab and placebo at week 8 (49 % vs. 40 %, $P = 0.34$). However, superiority of ustekinumab over placebo was observed in achieving clinical response at week 4 and at week 6 (53 % vs. 30 % at both time points, $P = 0.02$). Of note, among patients in group 1 who had prior exposure to infliximab given at submaximal infliximab doses or regimens ustekinumab was significantly superior to placebo with clinical response rates of 59 % and 26 %, respectively ($P = 0.022$). Among group 2, clinical response rates at week 8 were 43 % and 54 % for subcutaneous and intravenous route of administration of ustekinumab, respectively. It was thus concluded that ustekinumab has the potential of inducing clinical response in patients with moderate to severe active Crohn's disease with the most prominent effect at weeks 4 through 6 and in patients with prior exposure to infliximab.

Ustekinumab in CD was further studied in a phase IIb randomized, double-blind, placebo-controlled trial with an 8-week induction and 26-week maintenance evaluation

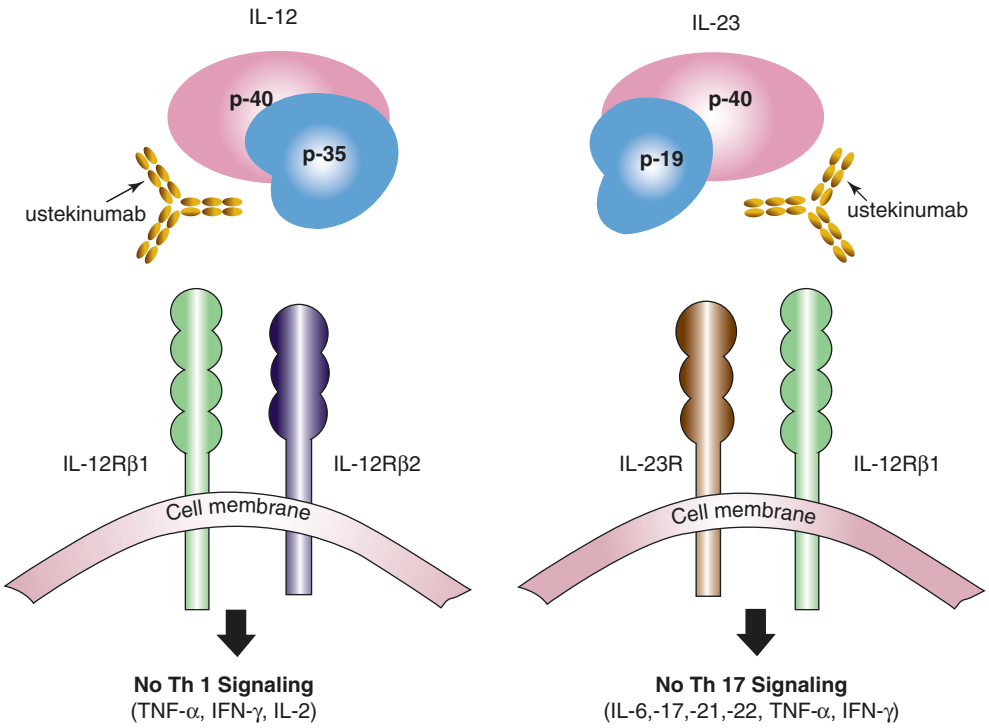

Fig. 35.3 Ustekinumab mechanism of action (Onuora [9])

period for patients previously exposed to anti-TNF therapy who either had primary nonresponse, secondary nonresponse or intolerance to anti-TNF treatment [11]. During the induction phase, 526 patients were randomly assigned to receive a weight-based dose of intravenous (IV) ustekinumab (1, 3, or 6 mg/kg) or placebo. Responders and nonresponders were separately randomized to subcutaneous (SC) ustekinumab 90 mg or placebo at weeks 8 and 16. The primary endpoint was clinical response (≥100-point decrease from baseline CDAI) at week 6. 39.7 % of patients at 6 mg/kg vs. 23.5 % of patients receiving placebo achieved clinical response at week 6 (P = 0.005). Clinical remission rates at week 6, however, were similar between the ustekinumab and placebo groups. Among patients with a response to ustekinumab in the induction phase, 69.4 % vs. 42.5 % and 41.7 % vs. 27.4 % of patients receiving 90 mg of ustekinumab vs. placebo in the maintenance phase continued to have a clinical response and clinical remission at week 22. In addition, 30.6 % vs. 17.8 % of patients in the ustekinumab vs. placebo group were in glucocorticoid-free remission at week 22 (p = 0.048). Of note, for those patients who did not achieve clinical response after induction with ustekinumab, further therapy with the drug was no different than placebo in terms of clinical response at week 22.

Mucosal healing was also evaluated in the phase IIb trial. Fifty patients were evaluated and 1 out of 9 vs. 8 out of 41 patients achieved mucosal healing in the placebo vs. ustekinumab group respectively (P = 1.00) [11].

Having had promising results with the phase II trials, two phase III trials are completed and a third is underway. UNITI-1 (NCT01369329) is a multicenter, double-blind, placebo-controlled study of ustekinumab for induction of remission in moderate to severe CD in patients with prior failure or intolerance to TNF antagonist therapy [12]. Patients with moderate-severely active CD (defined as a CDAI 220–450) who previously failed or were intolerant to at least 1 TNF-antagonist were randomized (1:1:1) to receive a single dose of IV placebo (PBO), ustekinumab 130 mg, or weight-based tiered ustekinumab dosing approximating 6 mg/kg (260 mg [weight ≤55 kg], 390 mg [weight >55 kg and ≤85 kg], and 520 mg [weight >85 kg]) at week 0. The primary endpoint was clinical response at week 6, defined as reduction from baseline in the CDAI score of >100 points; patients with baseline CDAI score 220–248 were considered to have had a clinical response if a CDAI score of <150 was present. At week 8, patients either transitioned to the UNITI maintenance study (see below) or were followed to week 20. Seven hundred and forty-one patients had had a history of anti-TNF therapy failure either primary nonresponse, secondary nonresponse or intolerance to at least one anti-TNF agent. Primary and secondary endpoints were met at both intravenous doses of ustekinumab. 33.7 % of the ~6 mg/kg and 34.3 % of the 130 mg ustekinumab groups versus 21.5 % in placebo (P = 0.003 and 0.002, respectively) achieved clinical response at week 6. 20.9 % of the ~6 mg/kg group and 15.9 % of the 130 mg ustekinumab group versus

7.3 % on placebo ($P < 0.001$, $P = 0.003$, respectively) were found to be in clinical remission (CDAI <150) at week 8. 37.8 % of the ~6 mg/kg and 33.5 % of the 130 mg ustekinumab groups, versus 20.2 % on placebo (each $P \leq 0.001$) had a clinical response at week 8. Both intravenous ustekinumab induction doses compared to placebo resulted in significant improvements in CDAI, IBDQ, CRP, fecal lactoferrin, and calprotectin. AEs, SAEs, and infections were similar in the treated and placebo groups. One opportunistic infection (*Listeria* meningitis) was reported in the ~6 mg/kg UST group; otherwise no tuberculosis, malignancies, deaths, or major adverse cardiovascular events occurred in ustekinumab treated patients through the week 20 observation.

UNITI-2 (NCT01369342) is identical in design to UNITI-1 and involves patients who have failed conventional treatment (corticosteroids, immunomodulators) or who are corticosteroid dependent without previous failure or intolerance to TNF antagonist therapy. The data were recently presented at the American College of Gastroenterology (Oct 2015 [13]). Six hundred and twenty-eight patients with moderate to severely active Crohn's disease were randomized to receive a single dose of IV placebo ($n = 210$), 130 mg of ustekinumab ($n = 209$) or weight-based tiered dosing of 6 mg/kg of ustekinumab ($n = 209$). The primary endpoint was clinical response at 6 weeks and at 8 weeks, patients either transitioned to the maintenance study or were followed through to 20 weeks. 51.7 % of patients who received 130 mg of ustekinumab and 55.5 % of patients who received 6 mg/kg of ustekinumab vs. 28 % of patients who received placebo ($P < 0.001$) achieved a clinical response at 6 weeks. 47 % of patients who received 130 mg of ustekinumab and 58 % of patients who received 6 mg/kg of ustekinumab vs. 32 % of patients who received placebo ($P < 0.001$) achieved clinical response at week 8. 31 % who received 130 mg of ustekinumab and 40 % of patients who received 6 mg/kg of ustekinumab achieved clinical remission at 8 weeks. Adverse events and serious adverse events were similar between the groups and no malignancies, deaths, opportunistic infections or tuberculosis occurred in patients treated with ustekinumab.

Patients with a clinical response to IV ustekinumab in UNITI-1 or UNITI-2 as mentioned above were eligible for enrollment in the maintenance trial, IM-UNITI (NCT01369355). This study is still ongoing [14]. Patients will be randomized to 90 mg of ustekinumab every 8 weeks, every 12 weeks, or placebo. Patients who receive placebo or ustekinumab every 12 weeks and who lose response are eligible to cross over to receive ustekinumab 90 mg every 8 weeks. The primary outcome will be clinical remission at week 44. Secondary endpoints clinical remission in patients who have previously failed TNF antagonists, clinical response, and corticosteroid-free remission at week 44. Patients who are continuing to do well at week 44 will be eligible to continue to receive ustekinumab in the long-term extension study with follow-up to 3 additional years.

Pediatric Data

Data regarding efficacy of ustekinumab in pediatric CD are lacking. However, Rinawi and colleagues attempted to induce remission with ustekinumab in a 6-year-old patient with active colonic disease, chronic arthritis, and failure to respond to all approved therapies for pediatric CD. The child received three subcutaneous doses of ustekinumab (1.3 mg/kg) at months 0, 1, and 3 which resulted in complete clinical and biochemical remission with no observed adverse events. Clinical response including resolution of diarrhea and arthritis was achieved within the first 2 months of treatment. Furthermore, 1 year after the induction, a weight gain of 3 kg and growth of 8 cm were noted and inflammatory blood markers (CRP, ESR) had normalized and albumin and hemoglobin increased. Remission was maintained with azathioprine 1 year following induction [15].

Bishop and colleagues recently described the use of ustekinumab in four adolescent patients with pediatric Crohn's disease – ages of initiation were 12, 13, 16, and 17. All patients had previously received corticosteroids, methotrexate, azathioprine/6-mercaptopurine, and both infliximab and adalimumab. Two patients showed clinical response and remained on ustekinumab, but two patients discontinued therapy due to continued symptoms and disease complications and required multiple hospitalizations [16].

Safety

In the phase II trials in Crohn's disease, there were no increase in the number of adverse or serious adverse events in patients given ustekinumab through week 8 compared with placebo [10]. There were no serious or opportunistic infections. 14 % vs. 8 % of patients in the placebo group vs. drug group reported worsening CD. Three patients (6 %) in the placebo group experienced one or more serious adverse events: small intestinal stenosis and nonsteroidal anti-inflammatory drug–induced gastrointestinal ulceration, worsening CD and erythema nodosum, worsening CD disease and small intestinal obstruction. Two patients (4 %) in the ustekinumab group experienced one or more serious adverse events: small intestinal obstruction and coronary artery disease.

In the patients in the open-label trial followed through week 28, six patients (6 %) in the population 1 group experienced one or more serious adverse events: worsening CD ($n = 2$), colonic stenosis and pneumothorax ($n = 1$), small intestinal obstruction ($n = 2$), and prostate cancer ($n = 1$).

Four patients (15 %) in the population 2 group experienced one or more serious adverse events: viral gastroenteritis ($n = 1$), nephrolithiasis ($n = 1$), worsening CD ($n = 1$), worsening CD, syncope, and disseminated histoplasmosis ($n = 1$, in a patient receiving prednisone (80 mg/day), azathioprine during the trial and with approximately 3 years prior infliximab use).

In the phase IIb trial, the overall rates of infection were also similar between the ustekinumab and placebo groups during the induction phase [11]. Serious infections were reported in five patients receiving ustekinumab 6 mg/kg (*Clostridium difficile* infection, viral gastroenteritis, urinary tract infection, anal abscess, and vaginal abscess). In one patient receiving ustekinumab 1 mg/kg, there was central catheter infection with *Staphylococcus*, and in one patient receiving placebo, there was an anal abscess. Infusion reactions were similar between the ustekinumab and the placebo groups.

In the maintenance phase, there were no deaths, major adverse cardiovascular events, tuberculosis, or other serious opportunistic infections. One patient who received 1 mg/kg ustekinumab followed by 90 mg of ustekinumab was reported to have basal-cell carcinoma. The most commonly reported adverse events in the maintenance phase, other than those related to CD, were nonserious infections (39.2 %), abdominal pain (7.2 %), nausea (6.1 %), and nasopharyngitis (6.1 %) in the ustekinumab group and these were all numerically lower than events in the placebo group, except for the rate of nasopharyngitis (3.3 %).

The long-term safety profile of ustekinumab has been evaluated in the treatment of psoriasis. Pooled safety data from four clinical trials of ustekinumab for psoriasis revealed a total of 3117 patients received at least one dose of ustekinumab, with a total of 8998 person-years of follow-up, with at least 4 years of exposure in 1482 patients [17]. At year 5, events per 100 patient years of follow-up for ustekinumab 45 mg and 90 mg were as follows: serious adverse events was 7.0 and 7.2, serious infections 0.98 and 1.19, nonmelanoma skin cancers 0.64 and 0.44, and major adverse cardiovascular events (MACE) including myocardial infarction, cerebrovascular accident or cardiovascular death 0.56 and 0.36. Adverse events or rates of overall mortality and other malignancy did not seem to increase over time compared with an age-matched and sex-matched US population.

There has been one case report of central demyelination in 63-year-old woman with CD. This patient had previous exposure to immunomodulator therapy, infliximab, adalimumab, and certolizumab and received ustekinumab through the clinical trial program and afterwards for compassionate reasons. About 1 year after first receiving ustekinumab, she developed progressive weakness and was diagnosed with primary progressive multiple sclerosis [18].

AMG139 (MEDI2070)

In contrast to IL-12 inhibition, IL-23 inhibition has been previously shown to be associated with a decreased incidence of tumor formation [19]. In addition, there have been concerns regarding the safety of ustekinumab and/or briakinumab regarding the incidence of serious infections and major adverse cardiovascular events [19]. Therefore, it is thought that IL-23-specific antagonism may provide similar or greater efficacy than blocking IL-12/23p40 and without the potential risks associated with blocking IL-12. Accordingly, a human IgG2 monoclonal antibody called AMG139 was developed to specifically bind to the IL-23 p19 unit and block binding of IL-23 specifically to its receptor. A phase I trial was just completed assessing the safety and tolerability of AMG139 following the administration of multiple intravenous (IV) or subcutaneous (SC) doses in healthy subjects and in subjects with mild to severe CD [20].

Phase IIb studies are ongoing at the writing of this chapter.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of AMG139 in children or adolescents with IBD.

BI 655066

BI 655066 is a monoclonal antibody that also targets IL-23p19. It is being investigated as a subcutaneous drug in both psoriasis and Crohn's disease. A proof of concept, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II dose-ranging study of BI 655066 in patients with moderately to severely active Crohn's disease is ongoing. The primary outcome measure is clinical remission at week 12, defined as a CDAI score of <150. Secondary outcome measures include CDEIS remission, CDEIS response, mucosal healing, deep remission, and clinical response at week 12 [21]. There is another ongoing an open-label, single-group, long-term safety extension trial ongoing for subjects who responded to treatment with BI 655066 in a preceding trial [22].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of BI 655066 in children or adolescents with IBD.

Safety

Selectively blocking IL-23 vs. IL-12 has been thought to be more targeted with less side effects as a result [23].

A single-rising dose, multicenter, randomized, double-blind, placebo-controlled, within-dose phase I trial was the first-in-human proof-of-concept study and in this study the

clinical and biological effects of BI 655066 was evaluated in patients with moderate to severe plaque psoriasis. Patients received 0.01, 0.05, 0.25, 1, 3, or 5 mg/kg BI 655066 intravenously, 0.25 or 1 mg/kg BI 655066 subcutaneously, or matched placebo. Thirty-nine patients received single-dose BI 655066 intravenously ($n = 18$) or subcutaneously ($n = 13$) or placebo ($n = 8$). BI 655066 was well tolerated. The number of adverse events were similar between the BI 655066 and placebo groups. Four serious adverse events were reported among BI 655066-treated patients and were thought not to be treatment related [24].

IL-6

Interleukin-6 (IL-6) is a cytokine with central roles in immune regulation, inflammation, hematopoiesis, and oncogenesis. It is a contributor of Th-17 differentiation [1]. Increased levels of IL-6 and soluble IL-6 receptor have been demonstrated in both serum and intestinal tissues of the patients with active Crohn's disease and with a more severe form [25].

PF-04236921

PF-04236921 is a monoclonal antibody against IL-6. A phase II placebo-controlled study has been completed to evaluate the safety and efficacy of this subcutaneously administrated antibody in patients with active CD (the ANDANTE study) [26]. There were limitations of the study including early termination which led to small numbers of participants and technical problems with measurement resulting in unreliable or uninterpretable data.

Phase I/II studies are ongoing at the time of writing of the chapter.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of PF-04236921 in children or adolescents with IBD.

IL-13

Interleukin-13 (IL-13) is a central cytokine in the T helper 2 immune response [27–29]. IL-13 has effects on many cell types including B cells, monocytes, macrophages, epithelial cells, smooth muscle cells and neurons and has been indicated in the pathogenesis of many disease including asthma, scleroderma in addition to IBD [30]. Its upregulation has been proposed to be a key driver of mucosal inflammation – specifically in UC.

Tralokinumab

Tralokinumab (CAT-354) is an IL-13-specific human immunoglobulin G4 monoclonal antibody that binds to and neutralizes IL-13 [31, 32]. Tralokinumab is being evaluated in phase III clinical studies in patients with asthma and in a phase II study in idiopathic pulmonary fibrosis and may be a treatment for UC.

In a phase IIa, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial, 111 patients with UC (total Mayo score ≥6) were randomized to tralokinumab 300 mg subcutaneous or placebo [33]. The primary endpoint of clinical response at week 8 was 38 % (21/56) for tralokinumab vs. 33 % (18/55) for placebo ($P = 0.406$). Clinical remission rate at week 8 was 18 % (10/56) vs. 6 % (3/55) ($P = 0.033$) and mucosal healing rate was 32 % (18/56) vs. 20 % (11/55) ($P = 0.104$) for tralokinumab vs. placebo.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of tralokinumab in children or adolescents with IBD.

Safety

Tralokinumab had an acceptable safety profile in the only phase IIa study to date [33]. The median duration of exposure was 84 days. The number of patients who experienced adverse events was similar in the tralokinumab and placebo groups. The most frequently reported adverse events were symptoms of UC and headache. The number of patients discontinuing treatment because of adverse events was similar in both groups and the most common adverse event leading to discontinuation was symptoms of UC.

QAX576

QAX576 is a highly potent and specific inhibitor of human IL-13 activity in cell-based in vitro assays. It has been used to treat eosinophilic esophagitis with success [34] and studied in asthma and idiopathic pulmonary fibrosis.

A phase II study to assess the safety and efficacy of intravenously administered QAX576 in patients with fistulizing Crohn's disease has been completed [35]. Another phase II study to test the safety and efficacy of the drug in the treatment of perianal fistulas has also been completed [36]. Results are not available of either of the studies.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of QAX576 in children or adolescents with IBD.

Bertilimumab

Bertilimumab is a fully human, IgG_4-type monoclonal antibody that blocks the activity of a protein called eotaxin-1. Eotaxin-1 plays an important role in inflammation and causes eosinophils to migrate towards sites of inflammation where

they become activated and release substances that result in tissue damage and enhance inflammation.

A randomized, double blind, placebo-controlled, parallel-group, multicenter study in adult patients with active moderate to severe UC is ongoing. Patients are currently being and eligible patients will be randomly assigned in a 2:1 ratio to one of two treatment groups, bertilimumab 10 mg/kg intravenously or matching placebo, respectively [37].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Bertilimumab in children or adolescents with IBD.

IL-17

Vidofludimus

Vidofludimus (4SC-101) is a novel oral immunomodulatory drug that inhibits dihydro-orotate dehydrogenase and lymphocyte proliferation in vitro and inhibits interleukin (IL)-17 secretion in vitro independently of effects on lymphocyte proliferation [38].

A phase IIa open-label, single-arm trial with vidofludimus (ENTRANCE trial) in inflammatory bowel disease was performed. The primary outcome was to assess remission-maintenance potential in steroid dependent IBD patients upon steroid weaning (ECCO 2011). There were 26 CD and UC patients. There was an 88.5 % response rate of both complete and partial responders in patients on vidofludimus vs. 20 % placebo. 53.9 % (14/26) patients were complete responders, 34.6 % (9/26) patients were partial responders and 11.5 % (3/26) patients were nonresponders. There was no difference in response rates between Crohn's disease (85.7 %) and ulcerative colitis (91.7 %). In addition, the average prednisolone consumption dramatically dropped during treatment with the drug. All 26 patients reached a relapse-free prednisolone dose which was significantly ($p < 0.001$) lower than their individual threshold doses at which they experienced relapses prior to entering the study. Mean prednisolone consumption was significantly lowered from 26.5 mg/day (±8.0) at the start of treatment to 1.0 mg/day (±2.7) at week 12.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of vidofludimus in children or adolescents with IBD.

Safety

Vidofludimus was safe and well tolerated by all patients in the ENTRANCE trial. A total of 75 adverse events were reported (53 mild, 18 moderate, 4 severe) of which 19 adverse events were judged as possibly or probably drug related and included nasopharyngitis, abdominal pain, fatigue, insomnia, glucosuria, leucocyturia, microhematuria, musculoskeletal pain, myalgia, tachycardia, and dyspepsia. No drug related serious adverse events were reported.

IL-21

ATR-107

ATR-107 is a fully human anti-IL-21 receptor (IL-21R) monoclonal antibody designed to block IL-21 from binding and activating the receptor as a novel approach to treatment of systemic lupus erythematosus and other autoimmune diseases [39–41]. The ATR-107 target, IL-21R, is expressed on many lymphoid cells, including B cells, activated T cells, natural killer cells, monocytes and dendritic cells and thus ATR-107 is expected to block the effects of IL-21 activation of its receptor (enhanced proliferation of lymphoid cells, B cell differentiation to memory cells and plasma cells, and development of T helper type 17 (Th17) cells) [42, 43]. In addition, anti-inflammatory efficacy resulting from IL-21R blockade has been observed in animal models [44].

Phase I studies are ongoing at the writing of this chapter.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of ATR-107 in children or adolescents with IBD.

NNC0114-0006

NNC0114-0006 is an anti-IL-21-antibody. A randomized, double-blind, placebo-controlled, parallel-group trial phase II study to assess clinical efficacy and safety of NNC0114-0006 in subjects with active Crohn's disease has been completed. Results are not yet known.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of NNC0114-0006 in children or adolescents with IBD.

Blockade of the Downstream Signaling Pathways Mediated by Cytokine

JAK/STAT Pathway

Janus kinases (JAK) 1, 2 and 3 are extremely important in cytokine signaling that is involved in lymphocyte survival, proliferation, differentiation and apoptosis [45]. JAK3 is found only in hematopoietic cells and is part of the signaling

pathway activated by IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 which is crucial in the activation, function and proliferation of lymphocytes [46] (see Fig. 35.4).

Tofacitinib

Tofacitinib (CP-690,550) is an oral small molecule inhibitor of JAK 1 and 3. In vitro studies have shown that it interferes with Th2 and Th17 cell differentiation and blocks the production of IL-17 and IL-22 [48].

In a phase II, double-blind, placebo-controlled trial, the efficacy of tofacitinib in 194 adults with moderately to severely active ulcerative colitis was evaluated [49]. Patients were randomly assigned to receive tofacitinib at a dose of 0.5 mg, 3 mg, 10 mg, or 15 mg or placebo twice daily for 8 weeks. The primary outcome was a clinical response at 8 weeks and occurred in 32 %, 48 %, 61 %, and 78 % of patients receiving tofacitinib at a dose of 0.5 mg ($P = 0.39$), 3 mg ($P = 0.55$), 10 mg ($P = 0.10$), and 15 mg ($P < 0.001$), respectively – compared with 42 % of patients receiving placebo. Clinical remission (Mayo score ≤2 with no subscore >1) at 8 weeks occurred in 13 %, 33 %, 48 %, and 41 % of patients receiving tofacitinib at a dose of 0.5 mg ($P = 0.76$), 3 mg ($P = 0.01$), 10 mg ($P < 0.001$), and 15 mg ($P < 0.001$), respectively, as compared with 10 % of patients receiving placebo. Treatment with the drug resulted in reduced C-reactive protein and fecal calprotectin levels.

Tofacitinib was also evaluated in patients with moderate to severe active CD. Patients were randomized to receive tofacitinib twice daily for 4 weeks at doses of 1 mg, 5 mg, 15 mg, or placebo [50]. The primary endpoint was not met in this phase II trial in CD patients receiving tofacitinib, but the placebo response rate was high. Although no significant clinical differences were observed between actively treated patients and placebo, a reduction in CRP and fecal calprotectin levels among patients given 15 mg tofacitinib twice daily indicated its biologic activity. The primary endpoint was clinical response at week 4 and the rates were as follows: 36 % ($P = 0.467$), 58 % ($P = 0.466$), and 46 % ($P \geq 0.999$) in those patients given 1, 5, or 15 mg tofacitinib twice daily versus 47 % given placebo. A secondary endpoint was clinical remission at week 4 and this was seen in 31 % ($P = 0.417$), 24 % ($P = 0.776$), and 14 % ($P = 0.540$) of patients given 1, 5, and 15 mg tofacitinib, versus 21 % of patients given placebo. As the clinical response was not significant, the trial was negative. However, the placebo response and remission rates were unexpectedly high and in addition, the reduction in fecal calprotectin and C-reactive protein levels among patients receiving 15 mg tofacitinib twice daily suggested biologic activity of the drug. A repeat phase II trial with stricter inclusion criteria defining active Crohn's disease is ongoing [51].

There is currently an ongoing multicenter, randomized, double-blind, placebo-controlled, parallel-group study eval-

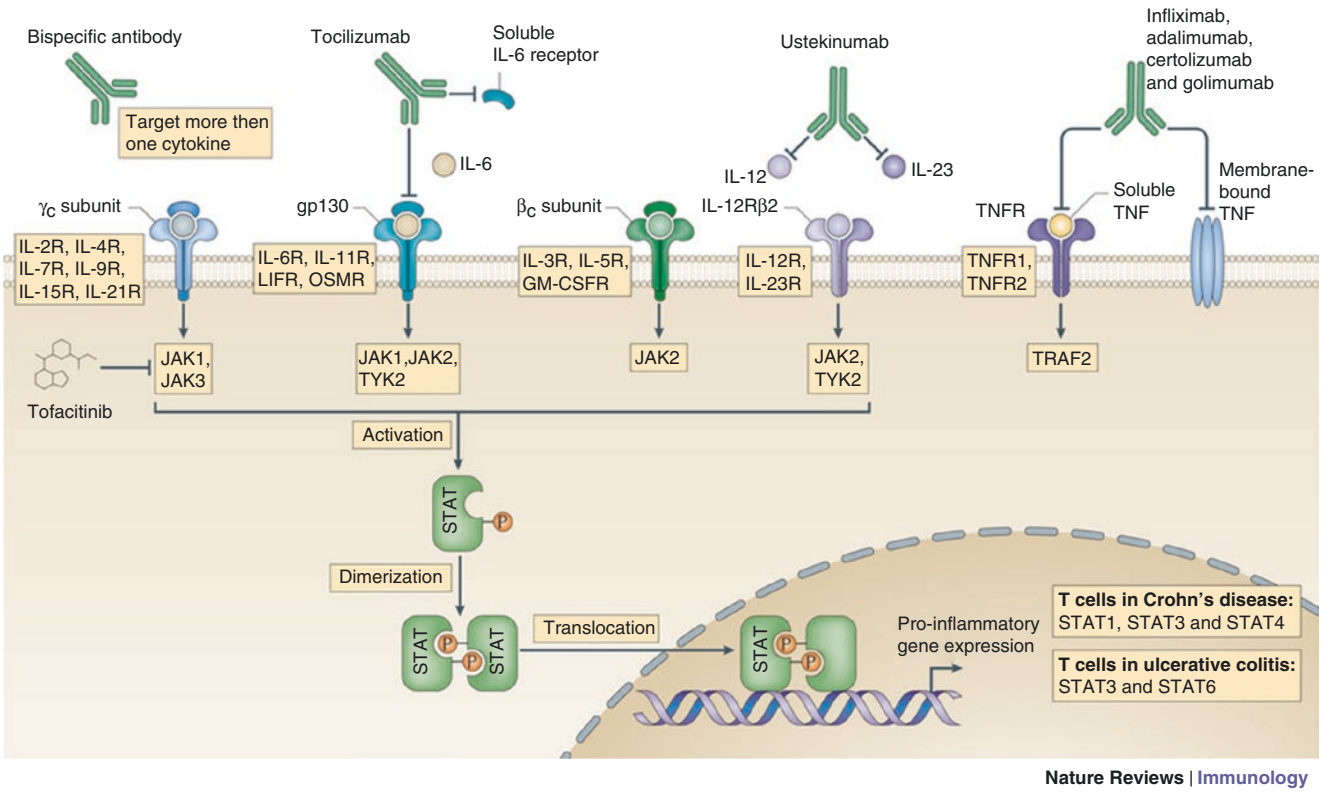

Fig. 35.4 JAK pathway inhibitors (Neurath [47])

uating tofacitinib as a maintenance therapy in patients with ulcerative colitis. Patients will either be given placebo orally twice daily, tofacitinib 5 mg orally twice daily or tofacitinib 10 mg orally twice daily. The primary endpoint is the proportion of subjects in remission at week 52. Secondary outcomes that will be measured is the proportion of patients with mucosal healing at week 52 and number of patients in sustained steroid free remission [52].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of tofacitinib in children or adolescents with IBD.

Safety

Tofacitinib has generally been well tolerated in clinical trials. The most commonly reported adverse events related to infection reported by Sandborn and colleagues were influenza and nasopharyngitis [49, 50]. Two patients receiving the 10 mg dose twice daily had serious adverse events from infection (postoperative abscess, anal abscess). Of significance but uncertain long term consequence, a dose-dependent increase in low-density and high-density lipoprotein cholesterol was seen after 8 weeks of treatment which were reversible after discontinuing the study drugs [49, 50]. It is not clear what the long-term effects of this is. Three patients treated with tofacitinib (one at dose of 10 mg twice daily and two at dose of 15 mg twice daily) had an absolute neutrophil count of less than 1500 (with none being <1000) [53, 54]. Tofacitinib is a true immunosuppressant and there is a concern for increased risk of infections and lymphoma with using this drug compared to other biologics. However, this drug can be used as monotherapy which makes it a very appealing option. Herpes zoster infections have been observed quite frequently and in rheumatoid arthritis, several cases of lymphoma were reported, but the overall risks of infections and mortality with tofacitinib seem to be similar to those observed with other biologic agents [51].

This drug is administered orally and can be used as monotherapy, which makes it a very appealing option.

Other JAK inhibitors are currently under clinical investigation in phase II for both CD and UC [51].

GLPG0634

GLPG0634, has been shown to selectively inhibit JAK1-dependent signaling in cellular and whole blood assays as well as showed remarkable efficacy in collagen induced arthritis disease models for RA in both mouse and rat [55].

There is currently an ongoing phase II clinical trial evaluating the efficacy, safety and tolerability and pharmacokinetics of GLP0634 on Crohn's disease during a 20-week period of time [56].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of GLPG0634 in children or adolescents with IBD.

TGF-B

One mechanism by which Crohn's disease develops involves transforming growth factor (TGF)-b which is a suppressive cytokine [57, 58]. SMAD7 is an endogenous inhibitor of the immunosuppressive cytokine transforming growth factor-β1. In Crohn's disease, TGF-b1 activity is inhibited by high Smad7, an intracellular protein that binds to the TGF-b1 receptor and prevents TGF-b1-driven signaling [59, 60]. Studies in mice have consistently shown that the induction of experimental CD-like colitis is associated with enhanced expression of Smad7 and reduced TGF-b1 activity [59]. The inhibition of Smad7 in CD mucosal cells with a specific antisense oligonucleotide has been demonstrated to restore TGF-b1 activity which therefore down-regulates the production of inflammatory cytokines [61].

GED0301 (Mongersen)

GED0301 is an antisense oligonucleotide targeting SMAD7 and is an oral gastro-resistant compound with a pH-dependent, delayed-release of the oligonucleotide in the terminal ileum and right colon.

A phase I clinical trial was performed which showed that GED0301 in active, steroid dependent/resistant CD patients resulted in a clinical benefit in all patients [62, 63].

In a placebo-controlled phase II study in patients with active CD [64], patients were randomized to receive induction treatment with different doses of GED0301 (Mongersen) or placebo for 2 weeks. The primary endpoint was clinical remission and this was seen in 55.0, 65.1, and 9.5 % of patients receiving Mongersen 40 mg/day, 160 mg/day, or placebo ($p < 0.0001$, for both comparisons) at 15 days and maintained for ≥2 weeks. Adverse events were similar across the treatment groups.

This promising molecule is now being investigated in larger trials [51].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of GED0301 in children or adolescents with IBD.

Safety

A phase I clinical trial using GED0301 in active, steroid dependent/resistant CD patients was safe and well tolerated [62]. Adverse events were similar across the treatment groups in a phase II clinical trial [64].

Targeting Chemokines

Chemokines are cytokine proteins expressed in lymphoid and nonlymphoid tissue, thought to be involved in leukocyte trafficking. Their effects are mediated by g-protein coupled transmembrane receptors, which are classified by cysteine residues. Persistent, aberrant leukocyte chemotaxis to inflamed mucosa is thought to play a role in the pathogenesis of inflammatory bowel disease. Increased expression of several chemokines has been reported in patients with ulcerative colitis and Crohn's disease.

IP-10 Antagonists

Interferon-γ-inducible protein-10 (IP-10 or CXCL10) is a chemokine that plays an important role in the migration of cells into sites of inflammation by influencing activation and migration of activated T-cells, monocytes, eosinophils, natural killer, epithelial and endothelial cells [65, 66].

The receptor for CXCL-10 is CXCR3 but IL-10 also seems to modulate cellular function independently of CXCR3 [65]. CXCL10 has been found to be expressed in higher levels in the colonic tissue and plasma of patients with UC [67, 68]. In animal models of UC, blocking CXCL10 has been shown to modify disease progression [53, 66, 69–71].

BMS936557 (MDX-1100, Eldelumab)

BMS-936557 (Eldelumab) is a fully human, monoclonal antibody to CXCL10. A phase I, open-label, dose-escalation study of MDX-1100 was been performed in patients with UC using MDX-1100 [54]. The primary objective of this was to evaluate the safety of single doses of the drug in patients with ulcerative colitis having exacerbation on stable doses of standard therapy. Patients were off anti-TNF therapy for at least 8 weeks prior to the study. Cohorts of patients were given a single infusion of the drug at doses of 0.3, 1.0, 3.0, or 10 mg/kg and were followed for at least 70 days post infusion. A clinical response was defined as UCDAI decrease by ≥3 points at day 29 compared to baseline. Patients who responded were allowed to receive up to three additional infusions at the time of relapse. Peripheral blood mononuclear cells and colon biopsy specimens were studied for expression of CXCL10 and CXCL10-induced proteins. Three patients in the 1.0 mg/kg and two patients in the 3.0 mg/kg cohorts had clinical responses; however, one patient in the 1.0 mg/kg cohort also was started on concomitant immunomodulator therapy 2 months prior to MDX-1100 administration. Two of three responding patients who relapsed after 50, 85, and 93 days, respectively who had then been given additional MDX-1100 doses responded to retreatment. One patient in the 3.0 mg/kg cohort was admitted to the hospital for anemia and worsening UC requiring a colectomy but otherwise the drug was well tolerated.

Mayer, and colleagues in 2014 published data from an 8-week phase II, double-blind, multicenter, randomized study in patients with active ulcerative colitis [65]. Patients with moderately to severely active UC were given either BMS-936557 (10 mg/kg) or placebo intravenously every other week. The primary endpoint was the rate of clinical response at day 57 and secondary endpoints were clinical remission and mucosal healing rates. Fifty-five patients received the drug and 54 patients received placebo. Primary and secondary endpoints were not met. However, what was found was that with higher steady-state trough levels of BMS-936557 (108–235 μg/ml), there was an increased clinical response (87.5 % vs. 37 % $p < 0.001$) and histological improvement (73 % vs. 41 % $P = 0.004$) compared to placebo. Infections occurred in 12.7 % of BMS-936557 treated patients and 5.8 % placebo-treated patients. Two patients (or 3.6 %) discontinued due to adverse events.

In a phase IIb study of patients with ulcerative colitis [65, 72] patients ($n = 121$) with CDAI ≥220 and ≤450 were randomly assigned 1:1:1 to placebo or intravenous eldelumab 10 or 20 mg/kg given on days 1 and 8 and then every other week. Endoscopy videos were collected for all patients at baseline. Patients with a score of 2–3 on the ulcerated surface subscore of the Simplified Endoscopic Score for Crohn's Disease (SES-CD) in at least 1 of 5 segments had a follow up endoscopy at 11 weeks. A central reader read endoscopies in a blinded fashion. Trial endpoints included week 11 clinical response which was defined as a reduction in CDAI 100 points from baseline or an absolute CDAI score <150, clinical remission which was defined as CDAI <150 and endoscopic improvement. There was a trend towards efficacy as remission and response rates at week 11 for the 10 mg/kg dose, 20 mg/kg and placebo groups were 22.5 and 47.5 %, 29.3 and 41.5 %, vs. 20 and 35 % and were higher in anti-TNF-naive patients versus those patients who experienced anti-TNF failures. Both drug groups achieved a greater reduction from baseline in mean endoscopy scores compared to placebo and were similar in the eldelumab-treated groups across the anti-TNF-naive and anti-TNF failure subgroups [73].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of BMS936557 in children or adolescents with IBD.

Safety

Serious adverse events were more common in the eldelumab groups (7.5 and 9.8 %) compared with placebo (5 %) in a phase IIb study of patients with ulcerative colitis [65, 73, 72].

Antiadhesion Molecules

Natalizumab

Natalizumab is a humanized IgG_4 monoclonal antibody against the adhesion molecule α4 integrin, which is involved in migration of leukocytes across the endothelium, and is upregulated in sites of inflamed endothelium. It is administered intravenously every 4 weeks. The efficacy of natalizumab for the treatment of multiple sclerosis has been demonstrated in controlled trials [74, 75, 76]. In November 2004 natalizumab was approved by the Food and Drug Administration (FDA) for the treatment of multiple sclerosis with subsequent withdrawal from the market in February 2005, and then reintroduction with certain restrictions for the treatment of multiple sclerosis in September 2006.

Six randomized, double-blind, placebo-controlled trials assessed the efficacy of in patients with Crohn's disease, whereas only one uncontrolled pilot study has been conducted in patients with ulcerative colitis.

An initial phase IIa trial comprised of 30 patients with active Crohn's disease who received randomly allocated single infusion of either natalizumab 3 mg/kg or placebo and had CDAI evaluated 2 weeks after infusion [77]. There was a significant decrease in baseline CDAI score in patients treated with natalizumab at week 2 (mean drop 45 points, $P = 0.02$), while no significant decrease was observed in placebo arm (mean drop 11 points, $P = 0.2$). It demonstrated a higher rate of clinical remission at week 2 in patients given natalizumab 3 mg/kg compared to placebo (39 % vs. 8 %, $P = 0.1$) [74]. There was no significant difference between natalizumab and placebo in achieving remission at week 2 (39 % vs. 8 %, $P = 0.1$). This pilot trial did not show any significant superiority of natalizumab over placebo in treating patients with Crohn's disease.

The second trial compared natalizumab (single infusion of 3 mg/kg, two infusions of 3 mg/kg or two infusions of 6 mg/kg) versus placebo in 248 patients with moderate to severe Crohn's disease [78]. The primary endpoint (remission, CDAI < 150 points at week 6) rates were 29 % for single infusion of natalizumab ($P = 0.757$), 44 % for two infusions of natalizumab 3 mg/kg ($P = 0.030$) and 31 % for two infusions of natalizumab 6 mg/kg ($P = 0.533$) versus 27 % in placebo arm. Only two doses of natalizumab 3 mg/kg had statistically significant superiority over placebo in achieving clinical remission.

Three Phase III trials have been conducted in Crohn's disease. In Efficacy of Natalizumab as Active Crohn Therapy (ENACT-1), 905 patients with moderate to severe Crohn's disease were randomly assigned to receive induction therapy at weeks 0, 4, and 8 with either natalizumab 300 mg or placebo [79]. The primary endpoint in the induction trial was clinical response defined as at least 70-point decrease in baseline CDAI score at week 10 and it was achieved in 56 % and 49 % of natalizumab and placebo recipients, respectively ($P = 0.05$) [79]. In ENACT-2, 339 patients who had a response to natalizumab in induction ENACT-1 trial at both week 10 and 12 were randomly reassigned to receive 300 mg of natalizumab or placebo every 4 weeks from week 12 through week 56 [79]. The primary endpoint in ENACT-2 trial was a sustained response through week 36. Patients with at least 70-point increase in CDAI score after week 12 with an absolute CDAI score of at least 220 or needed therapeutic intervention after week 12 were considered losing response. Rates of sustained response at week 36 were 61 % in patients receiving maintenance treatment with natalizumab and 28 % in those receiving placebo maintenance ($P < 0.001$). It was demonstrated that maintenance treatment with natalizumab is significantly superior to placebo in patients who responded to induction treatment. Concomitant immunosuppressants did not improve the rates of clinical remission or response [80]. Patients who maintained remission on natalizumab over 12 months in the ENACT-2 trial were enrolled into a subsequent phase III, open-label, 2-year open-label extension trial designed to assess long-term efficacy and safety of natalizumab [81]. This open-label trial comprised of 146 patients who received 12 natalizumab infusions over 12 months. The proportion of patients who maintained remission after 6 (week 24) and 12 (week 48) additional infusions of natalizumab was 89 % and 84 %, respectively. This open-label extension trial supported data from ENACT-2 trial that natalizumab maintains remission over additional 12 months in patients with sustained remission on natalizumab in the preceding 12 months.

In the ENCORE trial, 509 patients with moderate to severe Crohn's disease with elevated C-reactive protein concentrations at baseline were randomized to receive natalizumab 300 mg or placebo at weeks 0, 4, and 8 [82]. Natalizumab was significantly superior over placebo in inducing remission at week 8 that was sustained through week 12 (primary endpoint defined as at least 70-point decrease in CDAI score) with respective proportions of patients of 48 % vs. 32 % ($P < 0.001$). In addition natalizumab was also significantly superior over placebo in achieving additional efficacy endpoint, namely clinical remission at week 8 sustained through week 12 CDAI <150 that was observed in 26 % of natalizumab-treated patients and 16 % of placebo recipients ($P = 0.002$).

Finally, Sands et al. performed a placebo-controlled trial in which 79 patients with active Crohn's disease during ongoing treatment with infliximab 5 mg/kg every 8 weeks for at least 10 weeks before initiation of randomization were randomly assigned to receive three intravenous infusions of either natalizumab 300 mg or placebo every 4 weeks while continuing their initial infliximab regimen during duration of the trial [83]. At week 6 patients treated with natalizumab

plus infliximab experienced mean decrease in their CDAI score of 37.7 points, while those treated with placebo plus infliximab experienced small increase in CDAI score of a mean of 3.5 points ($P = 0.084$). A trend towards greater efficacy of combined treatment with natalizumab and infliximab over infliximab alone was shown in patients with active Crohn's disease not responding to infliximab therapy.

Gordon et al. published results of one small open-label study of 10 patients with active ulcerative colitis who were treated with a single infusion of natalizumab 3 mg/kg [84]. All patients had their disease activity evaluated using Powell-Tuck score 2 weeks after infusion. Treatment with natalizumab resulted in significant decrease in median disease activity score from 10 at baseline to 6 at 2 weeks postinfusion ($P = 0.004$). It was suggested that future randomized, placebo-controlled trials are warranted to further assess the efficacy of natalizumab in ulcerative colitis.

Pediatric Data

There was only one open-label study conducted in 38 pediatric patients (ages 12–17 years) with active Crohn's disease that assessed the efficacy of natalizumab in a pediatric population [84]. Among 38 enrolled patients 31 of them received three intravenous infusions of natalizumab 3 mg/kg at weeks 0, 4, and 8. Disease activity was measured using Pediatric Crohn's disease Activity Index (PCDAI) at baseline and then every 2 weeks through week 12. There was a significant decrease observed in PCDAI score from baseline at every time point ($P < 0.001$) with the greatest decrease observed at week 10 with 55 % of patients achieving clinical response (>15-point decrease from baseline) and 29 % of patients achieving clinical remission (PCDAI <10). These promising findings however need to be validated in large randomized controlled trials.

Safety

In one study in patients with Crohn's disease, 7 % of patients given one or two induction doses of natalizumab (at weeks 0 and 4) had formed anti-natalizumab antibodies at 12 weeks [78]. Patients in the ENACT-2 trial who received concomitant immunosuppressants did not develop persistent anti-natalizumab antibodies, compared to 7.5 % of patients who received natalizumab alone [79]. In patients with multiple sclerosis, the rate of formation of anti-natalizumab antibodies was 9 %, with persistence in 6 % (antibodies detected ≥ 2 more than 42 days apart) [85].

The largest ENACT-1 ($n = 905$) and ENACT-2 ($n = 339$) trials of natalizumab observed that serious adverse events occurred in similar proportion of patients in both trials (7 % in natalizumab and placebo arms in induction ENACT-1 trial and 8 % in natalizumab arm and 10 % in placebo arm in maintenance trial) [81]. However, one patient died (three doses of natalizumab combined with azathioprine during ENACT-1, placebo with azathioprine during ENACT-2 and -5 doses of natalizumab alone after completion of ENACT-2 trial) from progressive multifocal leukoencephalopathy, associated with the JC virus was observed [85]. The other large induction trial ENCORE on 509 patients Adverse events observed similar proportion of adverse events between natalizumab (85 %) and placebo (82 %) arms without any deaths [82]. The most common adverse events that were observed in at least 10 % among either treatment arms were headache, nausea, abdominal pain, nasopharyngitis, dizziness, fatigue, and exacerbation of Crohn's disease. There was a significant greater proportion of patients in natalizumab group versus placebo that experienced nasopharyngitis (11 % vs. 6 %, $p < 0.05$), headache (29 % vs. 21 %, $p < 0.05$) and hypersensitivity reaction (4 % vs. 0.8 %, $p < 0.05$). On the other hand, exacerbation of Crohn's disease was observed in greater proportion of placebo treated patients when compared to natalizumab (13 % vs. 7 %, $P < 0.05$). Antibodies to natalizumab were detected in 9.5 of 241 tested patients treated with natalizumab and in 0.8 % of 236 tested placebo recipients ($P < 0.05$).

A placebo-controlled trial by Sands et al. assessed primarily safety of concurrent therapy with natalizumab in 79 patients with Crohn's disease already receiving infliximab [83]. The observed incidence of adverse events was similar in the treatment groups (natalizumab plus infliximab vs. infliximab plus placebo). The most frequent adverse events in both groups were headache, Crohn's disease exacerbation, nausea, and nasopharyngitis. No one experienced a hypersensitivity-like reaction to natalizumab, whilst 4 patients (5 %) experienced such reactions to infliximab. The development of antibodies to natalizumab was reported in 4%of patients whereas antibodies to infliximab were detected in 14 % of patients.

Data from pediatric open-label study showed that the most common adverse events were headache (26 %), pyrexia (21 %) and exacerbation of Crohn's disease (24 %) [86]. Anti-natalizumab antibodies were detected in 8 % of patients.

Clinical trials and marketing of natalizumab were suspended in February 2005 after two patients with multiple sclerosis treated with natalizumab and interferon beta-1A developed progressive multifocal leukoencephalopathy (PML) from reactivation of the latent human Jacob Creutzfeldt polyoma virus [87, 88]. A third patient treated with natalizumab and prior exposure to azathioprine was reclassified from malignant astrocytoma to PML [89]. An independent adjudication committee performed a safety evaluation in all patients who had recently been treated with natalizumab in clinical trials [90]. Evaluation consisted of a referral to a neurologist, brain magnetic resonance imaging, and polymerase chain reaction analysis of cerebral spinal fluid and serum for JC virus. Of 3826 initial patients enrolled in clinical trials of natalizumab, safety evaluation included 87 % (1275), 91 % (2248), and 92 % (296) of patients with Crohn's disease, multiple sclerosis, and rheumatoid arthritis

patients. No additional cases of PML were identified [90]. The median duration of treatment for all patients was 17.9 months, while that of patients with Crohn's disease was 7 months. The absolute risk of developing PML during treatment with natalizumab was 1:1000 (0.1 %) with 95 % confidence intervals of 1:200–1:2800 [91]. The FDA reapproved natalizumab for multiple sclerosis in September 2006, with the requirement of mandatory participation in a risk management and registry program called the TOUCH program [85].

Vedolizumab (MLN-002, MLN-02, Entyvio®)

Vedolizumab (also known as MLN-002 and MLN-02) is a recombinant IgG1 humanized monoclonal antibody against the adhesion molecule α4β7 integrin and is the first gut-selective humanized monoclonal antibody. In contrast to natalizumab, vedolizumab specifically targets α4β7 integrins that are exclusively present on gut homing T cells and as a result the interaction between α4β7 and antimucosal vascular addressin cell adhesion molecule (MAdCAM)-1 is blocked.

GEMINI I was a double-blind, phase III trial in patients with moderate to severe UC [92]. Patients were randomized to receive vedolizumab (300 mg intravenously) or placebo on day 1 and day 15. The primary endpoint of the induction trial was clinical response at week 6 and this was achieved in 47 % vs. 26 % of patients receiving vedolizumab and placebo, respectively ($P < 0.0001$). Clinical remission at week 6 was seen in 17 % versus 5 % on vedolizumab vs. placebo ($P = 0.0009$) and mucosal healing was seen in 41 and 25 % in the vedolizumab versus placebo groups ($P = 0.0012$). Patients who achieved a clinical response after induction therapy were randomized to receive placebo or further intravenous vedolizumab at 300 mg at 4- or 8-week dosing intervals up to 46 weeks. Clinical remission rates at week 52 were 42 and 45 % in the vedolizumab 8- and 4-weekly groups, respectively, versus 16 % in the placebo arm; $P < 0.0001$. Mucosal healing rates were also significantly higher in the vedolizumab group – 52 and 56 % in the vedolizumab 8- and 4-weekly group versus 20 % in the placebo group; $P < 0.0001$. The overall clinical efficacy was higher with vedolizumab in those patients naive to anti-TNF-naïve compared to those who had a prior failure or intolerance to anti-TNF therapy.

GEMINI II was a clinical trial evaluating vedolizumab in patients with moderate to severe CD [93]. Week 6 clinical remission rates were 13.3 vs. 9.7 % ($P = 0.157$) and 22.7 vs. 10.6 % ($P = 0.005$) in patients who had failed anti-TNF therapy vs. those who were naive to anti-TNF therapy compared to placebo. Week 10 clinical remission rates were 21.7 versus 11 % ($P = 0.0008$) and 24.7 versus 15.4 % ($P = 0.044$) in patients who had failed anti-TNF therapy and anti-TNF naive patients compared to placebo, respectively. Week 52 clinical remission rates were 52 and 27 % in vedolizumab vs. placebo groups naive to anti-TNF but in those patients who had failed anti-TNF therapy, the clinical response rate was lower (28 versus 13 % in the vedolizumab and placebo groups, respectively).

GEMINI III is a placebo-controlled phase III induction trial evaluating the efficacy and safety of vedolizumab in CD patients who had failed anti-TNF therapy [94]. At week 6, clinical remission rates were not found to be superior in vedolizumab vs. placebo groups (15.2 and 12.1 % ($P = 0.433$)). However, at week 10 the therapeutic efficacy of vedolizumab was detected and vedolizumab was statistically superior to placebo for inducing clinical remission at week 10 (26.6 % versus 12.1 % in the vedolizumab vs. placebo groups, respectively ($P = 0.001$).

Overall, the results with vedolizumab seem to be somewhat better in UC compared to CD and the 6-week time point in CD was thought to have been set too early to appreciate optimal efficacy given the mode of action of this agent. In the open-label long-term extension study (GEMINI LTS) there was a suggestion that certain patients benefited from an increase in vedolizumab dosing frequency from every 8 weeks to every 4 weeks.

This drug was approved in 2014 by the FDA and EMA for both UC and CD, refractory to standard therapy and/or anti-TNF agents. It has the potential to become the first line biologic agent in UC given its higher efficacy in TNF-naïve patients.

Pediatric Data

Data on efficacy and safety of vedolizumab are currently not available in literature. However, Zoet and colleagues described an adolescent boy with ulcerative colitis who was started on monotherapy with vedolizumab at the age of 16 after having failed prior treatments including anti-TNF therapy. Before initiation of therapy, endoscopy showed severe ulcerative. After the first two doses of vedolizumab, the patient dramatically improved clinically. At 8 weeks post induction of the drug, endoscopic assessment demonstrated complete mucosal healing and the PUCAI score had improved to 5. At 4 months post induction, no side effects of vedolizumab were seen [95].

Safety

Patients with UC (GEMINI I) and CD (GEMINI II) who completed 52 weeks of vedolizumab treatment were enrolled in GEMINI LTS for an additional 52 weeks. The 2-year efficacy data of vedolizumab in CD and in UC was presented [96] and this showed the safety of vedolizumab in the GEMINI program. To date, there have been no cases of PML. Furthermore, Milch and colleagues conducted a study to determine whether vedolizumab alters T cell subpopulations in cerebrospinal fluid and no significant changes in T cell populations were observed [97]. Also, the incidence of systemic and gastrointestinal infections was similar among patients on vedolizumab or placebo [98].

Only 4 % of patients in the pooled UC and CD patients from GEMINI I and II tested positive for anti-vedolizumab antibodies during maintenance treatment with vedolizumab. Similar rates of antidrug antibodies were observed in the vedolizumab monotherapy and combination (3 % vs. 4 %). Antivedolizumab antibodies might have clinical implications, but further studies are needed to clarify their importance [51].

Furthermore, safety data (May 2009–June 2013) from six trials of vedolizumab were integrated and treatment with vedolizumab for up to 5 years demonstrated a favorable safety profile. In total, 2830 patients had 4811 person-years of vedolizumab. No increased risk of any infection or serious infection was associated with vedolizumab exposure. No cases of progressive multifocal leucoencephalopathy were observed. Infusion-related reactions as defined by the investigator were reported for ≤5 % of patients in each study. Eighteen vedolizumab-exposed patients (<1 %) were diagnosed with a malignancy [99].

Etrolizumab (rhuMAb β7)

Etrolizumab is a humanized monoclonal antibody that selectively targets the β7 subunit of α4β7 and αEβ7 integrins and as a result blocks leucocyte migration.

In a placebo-controlled, randomized phase II trial, patients with moderate to severe UC received subcutaneous etrolizumab (100 mg at weeks 0, 4, and 8, with placebo at week 2 or 420 mg at week 0 and 300 mg etrolizumab at weeks 2, 4, and 8) or placebo [100]. At week 10, etrolizumab was found to be more effective in achieving clinical remission (primary endpoint) as compared to placebo – 21 and 10 % of patients in the 100- or 300 mg etrolizumab group, respectively, and in 0 % of patients receiving placebo; the low placebo rate was thought to be a result of very careful patient selection. This study also revealed the potential role of αE as a biomarker to identify patients that are most likely to benefit from etrolizumab treatment as patients who had a clinical benefit in UC had increased αE expression levels in the inflamed colon.

Phase III studies are now underway in UC and CD.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of etrolizumab in children or adolescents with IBD.

PF-00547659

PF-00547659 is a fully human monoclonal antibody that binds specifically to human MAdCAM-1. Functional assays have shown the drug to block the adhesion of a4b7 integrin expressing cells to MAdCAM-1 [101].

In a randomized, placebo-controlled trial evaluating the safety and efficacy of PF-00547659 in patients with active UC, 80 patients received a single or three doses of PF-00547659 (0.03–10 mg/kg, intravenously or subcutaneously administered) or placebo at 4-week dosing intervals [102]. No statistical differences were found between patients given the drug compared to placebo although some benefits were seen in the actively treated group in terms of clinical and endoscopic improvements. Clinical response at week 4 was seen in 32 and 52 % of patients on placebo or PF-0054659 (all doses) ($P = 0.102$) and clinical response at week 12 was 21 versus 42 % in the placebo and PF-00547659 groups, respectively ($P = 0.156$). Adverse events were similar between the PF-00547659 versus placebo groups with the most common adverse event being abdominal pain [73, 103].

Larger clinical trials evaluating efficacy of PF-00547659 in UC and CD were completed in 2015. The TURANDOT study was a phase II trial evaluating the safety and efficacy of PF-00547659 in patients with UC [104]. Three hundred and fifty-seven adults with UC (with disease extending more than 15 cm beyond the rectum and with a total Mayo Score at least 6 and endoscopic subscore of at least 2) who had failed at least one prior therapy were randomized to receive 7.5, 22.5, 75, or 225 mg of PF-00547659 or placebo every 4 weeks for three doses. Clinical remission at week 12 was the primary endpoint defined as total Mayo score 2 or less with no subscore more than 1. Clinical response (Mayo score decrease 3 and 30 % decrease from baseline) at week 12 and mucosal healing (Mayo endoscopy subscore 1) were secondary endpoints. Clinical remission at week 12 was significantly greater in the 7.5, 22.5, and 75 mg dose groups compared with placebo. Clinical response was greater for the 22.5 and 225 mg groups and mucosal healing was significantly greater in the 22.5 and 75 mg dose groups compared with placebo. Greater differences compared with placebo were observed in anti-TNF naive patients (43 % of patients had not had prior anti-TNF therapy). The 22.5 mg dose was the most effective dose for all endpoints – clinical remission: 16.7 % vs. 2.7 % clinical remission rates, 54.2 % vs. 28.8 % clinical response rates and 27.8 % versus 8.2 % mucosal healing in drug vs. placebo groups (all $P < 0.05$). Overall and serious adverse event rates were similar between all groups.

OPERA is a randomized, multicenter double-blind, placebo-controlled study evaluating the safety and efficacy of PF-00547659 in patients with Crohn's disease [105]. Two hundred and sixty seven adults with moderate to severe Crohn's disease (CDAI 220–450), who had failed or did not tolerate other therapy (anti-TNF and/or immunosuppressant drugs), had C-reactive protein (CRP) more than 3.0 mg/l and ulcers on colonoscopy were randomized to placebo or PF-00547659 at the dose of 22.5 mg, 75 mg, or 225 mg. The primary endpoint was CDAI-70 response at week 8 or 12.

Secondary endpoints included clinical remission and CDAI-100 response. The frequency and level of b7 expression on peripheral CD4þ central memory T cells, CRP and soluble MAdCAM-1 levels were also evaluated. The CDAI-70 response was not significantly different between any of PF-00547659 doses and placebo but in patients who had a baseline CRP level more than 18 remission at week 12 was higher in the drug groups compared to placebo (37 %, 24 and 39 % with increasing doses vs. 14 % placebo). At week 2, soluble MAdCAM-1 decreased significantly in a dose-dependent manner and remained low during the study in patients who received drug. Circulating b7 CD4þ central memory T-lymphocytes had increased in a dose-dependent manner at weeks 8 and 12 in patients treated with PF-00547659. PF-00547659 was well tolerated with the most common adverse events related to the underlying disease.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of PF-00547659 in children or adolescents with IBD.

AJM300

AJM300 is an orally active small molecule with antagonistic properties to α4-integrin. The only trial published in an abstract from a randomized trial involving 71 patients with active Crohn's disease. This study compared oral treatment with either AJM300 (40 mg tid, 120 mg tid, or 240 mg tid) to placebo for 8 weeks [106]. The primary endpoint was the decrease of CDAI score from baseline to final evaluation at week 4 or later, while the secondary efficacy endpoint was clinical response (≥70 point decrease in CDAI). There was no significant difference in clinical response was observed between active treatment and placebo arms. Among patients with high CDAI at baseline a significant decrease from baseline CDAI score (mean decrease 41.5 points, $P = 0.0485$) was observed in those treated with AJM300 at the dose of 120 mg tid and mean 41.6 point decrease from baseline CDAI in those treated with AJM300 at the dose of 240 mg tid (p-value not reported). In addition, patients treated with AJM at the dose of 240 mg tid had significant twofold decrease in C-reactive protein from baseline over 8 weeks ($P = 0.0220$). The investigators suggested that AJM300 at dose 120 mg tid and 240 mg tid showed clinical efficacy in treating patients with active Crohn's disease [106].

Pediatric Data

At the time of writing this chapter there are no published data on the use of AJM300 in children or adolescents with IBD.

Safety

AJM300 was tolerated well with incidence of adverse events that was not dose-dependent (0.0 %, 23.5 %, and 22.2 % for AJM300 40 mg, 120 mg and 240 mg treated patients, respectively, vs. 16.7 % for placebo-treated patients, p-value not reported) [106].

Alicaforsen

Alicaforsen (ISIS 2302) is a 20 base phosphorothioate oligodeoxy-nucleotide that hybridizes to a sequence in the 3′ untranslated region of intercellular adhesion molecule 1 (ICAM-1) mRNA [107]. The translated oligonucleotide-RNA serves as a substrate for the nuclease RNase-H, an ubiquitous intracellular endoribonuclease that recognizes DNA:RNA heteroduplexes as substrate for selective RNA hydrolysis. This results in reduction of ICAM-1 RNA expression and protein levels. Intravenous, subcutaneous, and rectal enema formulations have been studied in patients with Crohn's disease or ulcerative colitis.

There have been three randomized, placebo-controlled trials that assessed the efficacy of alicaforsen administered intravenously [108, 109, 110] and one randomized, placebo-controlled trial that evaluated the efficacy of this agent administered subcutaneously [111] in patients with active Crohn's disease.

A phase IIA, double-blind, randomized, placebo-controlled trial of 20 patients with active Crohn's disease suggested the efficacy of intravenously administered alicaforsen [109]. Patients were randomly assigned to be treated with 13 infusions of either alicaforsen (0.5, 1, or 2 mg/kg, $n = 15$) or placebo ($n = 5$) over the period of 26 days with subsequent 6-month follow-up [111]. The rates of clinical remission (CDAI < 150) at the end of treatment were 47 % and 20 % in active drug and placebo arms, respectively (p-value not reported) [111]. ISIS 2302 showed corticosteroid sparing effect with significantly lower dose of corticosteroids over time when compared to placebo ($p = 0.0001$). Data from subsequent dose ranging pharmacokinetic trial of high-dose alicaforsen administered intravenously at the dose of 300 or 350 mg three times a week for 4 weeks in 22 patients with active Crohn's disease demonstrated that 41 % of patients achieved clinical remission indicating that this agent might be efficacious in treating Crohn's disease. Unfortunately, large randomized, placebo-controlled trials with intravenous alicaforsen did not support these preliminary findings.

In the subsequent large clinical trial that comprised of 299 patients with active steroid dependent (prednisone 10–40 mg) Crohn's disease patients were randomly assigned to intravenous treatment three times a week with either ISIS 2302 (2 mg/kg) or placebo for 2 or 4 weeks and the regimen was

then repeated after 1 month without treatment [108]. The corticosteroid-free remission (CDAI < 150) at week 14 (primary endpoint) was comparable between combined ISIS 2302 and placebo arms (20.2 % vs. 18.8 %, *p*-value not reported). On the other hand, a significantly greater proportion of patients receiving ISIS 2302 than placebo had successful corticosteroids withdrawal at week 14 (78 % vs. 64 %; $P = 0.032$). According to pharmacodynamic analysis statistically significant results for clinical remission, improvement in CDAI and quality of life based on IBD questionnaire were observed in the highest area under the curve subgroup of ISIS 2302 arm when compared to placebo. Finally, data from two double-masked, placebo-controlled trials of patients with Crohn's disease who received intravenous treatment with either alicaforsen ($n = 221$) or placebo ($n = 110$) three times a week for 4 weeks did not show any benefit of alicaforsen over placebo in achieving clinical remission at week 12 with respective remission rates of 33.9 % and 34.5 % ($P = 0.89$) [110]. Subcutaneous administration of alicaforsen also did not demonstrate any superiority over placebo in achieving clinical remission in patients with Crohn's disease. Schreiber et al. randomized 75 patients with corticosteroid-refractory Crohn's disease to subcutaneous treatment with either ISIS 2302 or placebo [111]. The primary endpoint, corticosteroid-free remission at week 14 (CDAI < 150) was observed in 3.3 % of ISIS-2302-treated and 0 % of placebo treated patients. On the other hand, there was a trend towards efficacy of ISIS 2302 in achieving one of the secondary endpoints, namely corticosteroid-free remission at week 26 (13.3 % vs. 6.7 %, *p*-value not reported). Similarly, a greater proportion of patients receiving active drug when compared to placebo achieved a corticosteroid dose <10 mg/day at week 14 (48.3 % vs. 33.3 %) and week 26 (55.0 % vs. 40.0 %) and a prednisone equivalent dose of 0 mg at week 26 [23.3 % vs. 6.7 %, respectively].

There have been three randomized, placebo-controlled trials assessing the efficacy of alicaforsen enemas in patients with active left-side ulcerative colitis [91, 103, 112].

Van Deventer et al. performed a randomized, placebo-controlled trial of alicaforsen enema in 40 patients with mild to moderately active distal ulcerative colitis who received 60 mL of alicaforsen enema (0.1, 0.5, 2, or 4 mg/mL) or placebo once daily for 28 consecutive days. There was observed a significant dose-dependent reduction in disease activity index in patients treated with active drug than placebo at day 29 that was observed for alicaforsen given at the highest dose 4 mg/mL (70 % vs. 28 %, $P = 0.004$). After 3 months alicaforsen 2 mg/mL and 4 mg/mL caused significant reduction in disease activity index when compared to placebo by 72 % and 68 %, respectively (vs. 11.5 % for placebo, $P = 0.016$ and 0.021, respectively). In the subsequent phase II dose ranging, double-blind, placebo-controlled study of alicaforsen enema (120 mg daily for 10 days, then every other day; 240 mg every other day; 240 mg daily for 10 days, then every other day; 240 mg daily) given daily for 6 weeks in 112 patients presenting with acute exacerbation of mild to moderate left-sided ulcerative colitis there was no significant difference observed between active drug and placebo in reduction of disease activity index at week 6 [91]. However, a greater proportion of patients receiving alicaforsen 240 mg daily had prolonged clinical improvement at week 18 (51 % vs. 18 %) and week 30 (50 % vs. 11 %) when compared to placebo. Finally, Miner et al. compared two dose formulations of alicaforsen enema (120 mg or 240 mg) with 4 g mesalamine enema given for 6 weeks in 159 patients with mild to moderate left-sided ulcerative colitis [103]. There was no difference observed between treatment arms in reduction of disease activity index at week 6 with reduction in mean disease activity index when compared to baseline of 50 % for the mesalamine arm and 40 % and 41 % for the 120 and 240 mg alicaforsen groups ($P = 0.27$ and 0.32, respectively). However, higher dose of alicaforsen enema was significantly more efficacious than mesalamine in achieving clinical remission at week 18 (20 % vs. 6 %, $P = 0.03$) [103].

An open-label study of alicaforsen enema given at daily dose of 240 mg for 6 weeks to 15 patients with active ulcerative colitis showed a 46 % reduction in mean disease activity index and 33 % rate of complete mucosal healing at the end of treatment [113]. In addition, alicaforsen concentrations were greater in mucosal colonic tissue biopsies than those observed in plasma suggesting that alicaforsen enemas allow for achieving high local concentrations with little systemic exposure. Another open-label study of 12 patients with chronic pouchitis following an ileal pouch-anal anastomosis for ulcerative colitis showed that alicaforsen enemas given at dose of 240 mg daily for 6 weeks resulted in significant reduction in the mean pouchitis disease activity index from baseline value of 11.42 points to 6.83 points at 6 weeks ($P = 0.001$) [114].

Pediatric Data

At the time of writing this chapter there are no published data on the use of alicaforsen in children or adolescents with IBD.

Safety

Data from large trial of 331 patients treated with intravenous alicaforsen or placebo showed that the only adverse events that occurred in greater proportion of patients treated with alicaforsen were symptoms related to infusion reactions such as fever (22.6 % vs. 14.7 %, *p*-not significant), chills (14 % vs. 1.8 %, $P = 0.0005$), and myalgia (5.4 % vs. 0.92 %) [110]. Data from the second largest trial of 299 patients with Crohn's disease receiving alicaforsen or placebo intravenously showed that the only adverse events that occurred in significantly greater proportion of patients treated with active

drug than placebo were infusion reactions described as transient facial flushing or a feeling of warmth during infusion (11.6 % vs. 4 %, $P = 0.03$) [108]. There was a significantly greater average transient aPTT increase without bleeding sequelae (8.66 s vs. 0.8 s, P +0.0001) after alicaforsen than placebo infusion [108]. Safety analysis of alicaforsen administered subcutaneously in the largest trial of 75 patients determined that injection site reactions, headache, pain, fever, rash, arthritis, asthenia, and flu-like symptoms injection site reactions occurred in greater proportion of patients treated with active drug than placebo with injection site reactions demonstrating the largest difference (23.3 % vs. 0 %, *p*-value not reported) [111].

Gastrointestinal complaints were associated with the alicaforsen enemas in a dose-dependent fashion. Community-acquired pneumonia and sinusitis were also reported and were associated with the study drug [91, 103, 112, 113, 114].

AMG181

AMG181 is a human monoclonal IgG2 antibody that specifically binds to a4b7 heterodimers.

A phase I first inhuman randomized, double-blind, placebo-controlled study conducted in healthy subjects and subjects with UC evaluating the pharmacokinetics and pharmacodynamics, safety, tolerability, and effects of subcutaneous or intravenous AMG181 was performed [115]. Sixty-eight healthy male subjects received a single dose of AMG181 or placebo at 0.7, 2.1, 7, 21, 70 mg SC (or IV), 210 mg SC (or IV), 420 mg IV or placebo. Four patients with UC received 210 mg AMG181 or placebo SC (3:1). Among the findings, AMG181-treated UC subjects were in remission with mucosal healing at weeks 6, 12, and/or 28 and the placebo-treated UC subject experienced a colitis flare at week 6. No treatment-related serious adverse events were observed.

AMG181 is currently being tested in subjects with UC or CD in phase II clinical trials.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of AMG181 in children or adolescents with IBD.

Firategrast (SB 683699)

Firategrast is an orally bioavailable small molecule α4-integrin antagonist [116].

A phase II studies evaluating the effectiveness and safety of the 683,699 in treating subjects with moderately to severely active CD has been completed. Results are not available [117].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Firategrast in children or adolescents with IBD.

GLPG0974

Free fatty acids (FFA) act as inflammatory signaling molecules through receptors such as FFA2, which is activated by short chain fatty acids (SCFA). Through FFA2, SCFAs induce neutrophil activation and migration. In IBD patients, FFA2 expression is up-regulated in the colon.

GLPG0974 is a potent and selective antagonist of FFA2, inhibiting SCFA-induced neutrophil migration and activation in vitro.

In a 4-week, first-in-UC study with GLPG0974 in patients with mild to moderate UC, GLPG0974 was well tolerated and safe. Biomarkers (MPO and FC) indicate that GLPG0974 reduces neutrophil activation and influx, suggesting a role for FFA2 in neutrophil migration in UC. The reduction in neutrophil influx is not sufficient to induce a measurable clinical difference between GLPG0974 treated patients and placebo within 4 weeks [118].

Phase II studies are ongoing.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of GLPG0974 in children or adolescents with IBD.

TRK-170

TRK-170 is a novel orally active alpha4beta1/alpha4beta7 integrin antagonist. A study evaluated the effect of TRK-170, as compared to an anti-alpha4 antibody and prednisolone, on 2, 4, 6-trinitrobenzene sulfonic acid (TNBS)-induced colitis. Oral administration of TRK-170 significantly inhibited the increase of macroscopic damage scores. TRK-170 also reduced the elevation of myeloperoxidase activity in colons, and the increase in colon weight. Efficacy of TRK-170 is almost comparable to the anti-alpha4 antibody and prednisolone at this dosage and dose regimen. Detailed mechanisms of action of TRK-170, such as potential effects on immune cells, are being characterized. These results indicate that TRK-170 is expected to provide an attractive approach for the future therapy of IBD. Because TRK-170 is orally active unlike anti-alpha4 antibody, TRK-170 may be more beneficial than the antibody [119].

Phase II clinical studies are ongoing.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of TRK-170 in children or adolescents with IBD.

Administration of Anti-inflammatory Cytokine

Interleukin-10 (IL-10)

Interleukin-10 is secreted by T helper cells, B cells, monocytes, macrophages, dendritic cells and keratinocytes. It suppresses inflammation by reducing HLA class I expression decreasing secretion of IL-2 and diminishing production of IL-1α, Il-1β, IL-6, IL-8, and TNF-α. The recombinant human rHuIL-10 may be administered subcutaneously, intravenously, or orally via a genetically modified *Lactococcus lactis* (LL-Thy12) in which the thymidylate synthase gene is replaced with a synthetic sequence encoding mature human interleukin-10.

Interleukin-10 has shown efficacy in treatment of chronic hepatitis C [120] , and modest improvement in skin but not arthritic manifestations of psoriasis in a Phase II trial [121]. Open-label and Phase I trials in patients with rheumatoid arthritis failed to show clinical efficacy or decrease in inflammation from synovial biopsies [122, 123].

Several placebo-controlled trials assessed the efficacy of either intravenously or subcutaneously administered rhu-IL-10 in the treatment of patients with active Crohn's disease. A randomized, double-blind, placebo-controlled phase IIa trial by Van Deventer et al. suggested that intravenous bolus of recombinant human IL-10 once daily for 7 consecutive days (rhu-IL-10) might be efficacious for the treatment of active Crohn's disease [124]. Among 46 patients with active steroid-resistant Crohn's disease who were treated with rhu-IL-10 (0.5, 1, 5, 10, or 25 μg/kg) or placebo 50 % treated with active drug and 23 who received placebo achieved a complete remission (decrease in baseline CDAI <150 and >100-point decrease in CDAI when compared to baseline) at any time during 3-week follow-up (*p*-value not reported). The second randomized, placebo-controlled trial of subcutaneous rhuIL-10 (1, 5, 10, or 20 μ/kg) given for 28 consecutive days with subsequent 20-week follow-up in 95 patients with active Crohn's disease observed that only rhu-IL-10 administered at dose 5 μg/kg showed benefit over placebo with 23.5 % (CI, 6.8–49.9 %) and 0 % (CI, 0–14.8 %) rates of complete remission (CDAI <150 and at ≥100 point decrease in CDAI from baseline with improvement or resolution in on endoscopy) measured on day 29 [125].

A double-blind, placebo-controlled phase III trial of 329 patients with chronic, active and refractory to corticosteroids Crohn's disease randomly allocated patients to receive subcutaneous injections with either rhu_IL-10 (1, 4, 8, or 20 μ/kg) or placebo daily for 28 days [126].

There was no significant difference between any of rhu-IL-10 dose and placebo in inducing primary endpoint, clinical remission (CDAI ≤ 150 with concomitant decrease in CDAI ≥ 100 points from baseline) with rates of 18 % for dose 1 μg/kg ($P = 0.79$ vs. placebo), 20 % for dose 4 μg/kg ($P = 0.76$), 20 % for dose 8 μg/kg ($P = 0.76$), 28 % for dose 20 μg/kg ($P = 0.17$) when compared to 18 % for placebo-treated patients [126]. There was a significant superiority in achieving clinical improvement (decrease in CDAI ≥100 points when compared to baseline) in patients who received rhu-IL-10 at the dose 8 μg/kg when compared to placebo (46 % vs. 27 %, $P = 0.034$).

A subsequent randomized, double-blind, placebo-controlled phase III trial (published only in an abstract form) assessed the efficacy of rhu-IL-10 in 373 patients with corticosteroid-dependent Crohn's disease who received once daily subcutaneously for 2 weeks then 3 times per week for 26 weeks either rhu-IL-10 (4 μg/kg or 8 μg/kg) or placebo [127]. Rhu-IL-10 4 μg/kg or 8 μg/kg was not statistically significant more efficacious than placebo in achieving the ability to discontinue corticosteroids by 16 weeks and to maintain clinical remission (CDAI<150) by week 28 with respective rates of 25 %, 32 %, and 29 % (*p*-value not reported). It was suggested that IL-10 at the highest dose 20 μg/kg may increase the production of IFN-γ and neopterin and thus increasing proinflammatory cytokines such as TNF-α, IL-1β and increasing nitric oxide production [128]. Colombel et al. analyzed 65 patients with Crohn's disease after curative ileal or ileocolonic resection and primary anastomosis who were randomized within 2 weeks after surgery to subcutaneous injections of either rhu-IL-10 4 μg/kg once daily, rhu-IL-10 8 μg/kg twice weekly or placebo and were followed-up for 12 weeks [129].

Of 65 patients 58 underwent endoscopy at the end of follow-up that showed that 46 % of patients treated with active drug and 52 % of placebo recipients had recurrent lesions (*p* not significant) [129]. Successful treatment of a murine model of colitis with *L. lactis* secreting interleukin-10 has been reported [130]. Methods for biological containment and formulation for delivery to the human intestine have been developed [131–133]. A pilot Phase Ia study has demonstrated the potential of a genetically modified *L. lactis* (LL-Thy12) given orally at the dose of 10 capsules with 1×10^{10} colony-forming units (CFU) of LLThy12 twice daily for 7 days to 10 patients with active Crohn's disease [134]. In LL-Thy12 the thymidylate synthase gene has been replaced with a synthetic sequence encoding mature human interleukin-10 [133]. Clinical benefit was observed in 8 of 10 patients with 5 patients achieving complete remission (CDAI <150)

and 3 patients experiencing clinical response (decrease in CDAI >70) [134]. Future clinical trials are needed to validate these preliminary findings.

Pediatric Data

At the time of writing this chapter there is no published data on the use of rhu-IL-10 in children or adolescents with IBD.

Safety

The only clinical trial that assessed safety of intravenously administered rhu-IL-10 observed similar proportion of adverse events between active drug and placebo arms. [124] The only exception was the abdominal pain that was reported in 9 % of patients receiving rhu-IL-10 and 31 % of placebo recipients. Data from 329 patients with Crohn's disease who were treated with either rhu-IL-10 (n = 262) or placebo (n = 66) provided the largest population of patients that was assessed for safety of rhu-IL-10 and showed that both active drug and placebo arms had comparable proportion of adverse events (95 % vs. 94 %) [126]. The only events that occurred in greater proportion of patients treated with rhu-IL-10 than placebo were headache (P = 0.02), fever (P = 0.02), back pain (P = 0.01), decrease in hemoglobin concentration (P = 0.0007), dizziness (P = 0.005), and thrombocytopenia (P = 0.0006) [126]. Severe adverse events were observed in 28 % 17 % of patients treated with rhu-IL-10 and placebo, respectively (P = 0.057). A dose-dependent decrease in hemoglobin of unknown mechanism occurred in 33 % of patients treated with rhuIL-10 at the dose of 20 μg/kg when compared to 8 % of placebo patients (P = 0.0003). Thrombocytopenia of unknown mechanism was also observed in greater proportion of patients receiving rhuIL-10 at the dose 8 μg/kg (6, P = 0.04) and rhuIL-10 at the dose 20 μg/kg (27 %, P < 0.0001) when compared to 0 % among placebo recipients. All hematologic abnormalities were reversible upon cessation of study medication.

Reversible anemia and thrombocytopenia are common, as are mild to moderate headaches, fever, back pain, diarrhea, arthralgias, and dizziness. Antibodies to IL-10 have not been detected [129, 126].

Blockade of T Cell Stimulation and Induction of Apoptosis

Laquinimod

Laquinimod is an oral agent that produces anti-inflammatory effects by modulating immune cells with result of reduced synthesis of several cytokines. Laquinimod has been used in multiple sclerosis with success and seems to be a safe medication [135] and is being evaluated in Crohn's disease.

A phase IIa trial was performed using different doses of laquinimod (0.5, 1, 1.5, or 2 mg/day) for 8 weeks in patients with active Crohn's disease [136]. Clinical remission rates at week 8 were as follows: 48.3, 26.7, 13.8, and 17.2 % of patients receiving 0.5, 1, 1.5, and 2 mg laquinimod versus 15.9 % placebo. Overall, induction treatment with laquinimod was tolerated and the most common adverse effects were headache, abdominal pain, nausea, vomiting, and musculoskeletal pain. This may be an effective treatment of Crohn's disease and further studies are needed.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of laquinimod in children or adolescents with IBD.

DIMS0150

DNA based immunomodulatory sequence (DIMS0150) is a single stranded partially modified synthetic oligonucleotide of 19 bases in length and activates the Toll-Like Receptor 9 (TLR9) present in immune cells such as T and B cells, macrophages and plasmacytoid dendritic cells (pDCs) that are found in abundance on mucosal surfaces such as the colonic mucosa. Activation of TLR9 by DIMS0150 results in the local production of potent anti-inflammatory cytokines such as IL-10 and type I interferons from human peripheral blood mononuclear cells (PBMCs) that have also interestingly been shown to increase steroid sensitivity in steroid resistant UC patients and human monocytes [137]. Administration of DIMS0150 in the form of an enema in steroid-refractory subjects with UC allows the drug to come into direct contact with a large number of target cells harboring the TLR9 receptor and has been shown to be beneficial in steroid refractory patients with UC. These cells when activated release steroid sensitizing cytokines which induce a local and peripheral steroid-sensitizing effect [138].

In a study where a single dose of DIMS0150 was given to steroid unresponsive IBD patients on concomitant steroid therapies, single doses of 3 and 30 mg were effective in inducing a clinical response [139]. Five of seven patients (70 %) that received active treatment had a clinical response 1 week after therapy and after more than 8 years, two remained in glucocorticoid free remission.

In a phase II study, 151 patients with mild or moderately active UC were given DIMS0150 as a single rectal dose at one of four dose levels (0.3, 3, 30, and 100 mg) with the hopes of inducing clinical remission. No significant benefit was demonstrated at any dose level.

Another phase IIa proof of concept study was conducted in steroid dependent or steroid resistant UC patients on concomitant steroid therapies evaluating DIMS0150 at a

single dose level of 30 mg [140]. Thirty-four patients were randomized to receive a single rectal administration of placebo or 30 mg of DIMS0150. Blood derived PBMCs were obtained before dosing and assayed to evaluate for a steroid enhancing effect in the presence of DIMS0150 and the established steroid sensitivity marker IL-6 [140] was also used to determine the steroid sensitivity status of the subjects. The study showed that glucocorticoid refractory UC patients most likely to benefit from DIMS0150 treatment.

In an uncontrolled, prospective treatment series, eight patients with chronic active severe UC on concomitant glucocorticoid therapy were given DIMS0150 [138]. Seven patients received a single topical dose of 30 mg and one special case received three doses (given in 4 week intervals). Evaluation of drug efficacy was determined by measuring colitis activity index, endoscopic improvement and histologic disease activity at week 12 with a follow up period of 2 years. In addition, glucocorticoid sensitivity was assayed by measurement of IL-6. All patients showed a rapid reduction in their colitis activity index within 1 week after administration of DIMS0150. At week 4, clinical response was 71 % and clinical remission was in 43 %. By week 12, clinical response was 82 % and clinical remission was 71 %. In the 2-year posttreatment period, all but one of the treated patients avoided colectomy. In addition, treatment with DIMS0150 restored glucocorticoid sensitivity.

DIMS0150 is currently in phase III trials.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of DIMS0150 in children or adolescents with IBD.

Sphingosine-1-Phosphate Receptor Modulators

Sphingolipids are ubiquitous building blocks of eukaryotic cell membranes. S1P (sphingosine-1-phosphate) is a bioactive sphingolipid and its concentration gradient (between tissues and blood) regulates lymphocyte recirculation [141]. In order for lymphocytes to leave lymph nodes, the S1P receptors on the surface of the lymphocyte must bind to S1P and S1P modulators cause the S1P receptors on the surface of lymphocytes to be internalized and degraded preventing lymphocytes from leaving the lymph nodes. As a result lymphocytes are trapped in lymph nodes resulting in a reduction of the peripheral lymphocyte count and circulating effector T cells making fewer immune cells available in the circulating blood to effect tissue damage.

Fingolimod (FTY720, Gilenya™)

FTY720, the prototype drug, is a small-molecule agonist of S1P receptors 1,3,4,5 and is approved by the FDA as the first oral drug for the treatment of MS [142]. Its therapeutic effect is through a poorly understood mechanism independent of leukocyte integrin pathways. It has been found that S1P1 modulation was the driving force behind FTY720's efficacy and that the FTY720-mediated sequestration of circulating lymphocytes or immune modulation correlated with positive therapeutic outcomes [141].

Newer compounds are seemingly more promising for example in the treatment of IBD with a higher selectivity window for S1P1 over S1P3, while still having S1P5 activity as they are structured to have shorter half-lives and a shorter duration of lymphopenia, in contrast to the long-lasting actions of FTY20 [142].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of Fingolimod in children or adolescents with IBD.

APD334

APD334, an orally available $S1P_1$ receptor modulator, discovered by Arena, has therapeutic potential in autoimmune diseases such as ulcerative colitis.

Phase II trial currently underway in UC [143].

Pediatric Data

At the time of writing this chapter, there are no published data on the use of APD334 in children or adolescents with IBD.

RPC1063 (Ozanimod)

RPC1063 is an oral selective agonist for S1P receptors 1 and 5 and has been shown in phase II studies to be effective for the treatment of both multiple sclerosis and ulcerative colitis [144].

The UC TOUCHSTONE phase II study evaluated the safety and efficacy of 0.5 and 1 mg RPC1063 compared to placebo and after the 8 week induction period, there was a continuing maintenance period for responders [145]. One hundred and ninety-seven patients with moderate to severe ulcerative colitis (Mayo score of 6–12 with an endoscopic subscore 2). The primary endpoint of clinical remission (Mayo score 2, no subscore >1) at week 8 was 16.4 % for high dose ($P = 0.048$ versus placebo), 13.8 % for low dose ($P = 0.14$), and 6.2 % for placebo. Secondary endpoints

included the proportion of patients exhibiting clinical response (reduction in Mayo score of 3 and 30 % with a decrease in the rectal bleeding score of 1 or a rectal bleeding score 1), proportion of patients with mucosal improvement (endoscopy score 1), and a change in Mayo score. Ninety five percent of patients completed the induction portion of the study. Clinical response was 56.7 % for high dose ($P = 0.01$), 53.8 % for low dose ($P = 0.06$), and 36.9 % for placebo. Mucosal improvement was 34.3 % for high dose ($P = 0.002$), 27.7 % for low dose ($P = 0.03$), and 12.3 % for placebo. The improvement in Mayo score from baseline was 3.3 points for high dose ($P = 0.003$), 2.6 points for low dose ($P = 0.098$), and 1.9 for placebo. The adverse event profiles were comparable between groups (about 31 % of experiencing a treatment emergent event across all groups) and the most common in the treatment event was worsening of ulcerative colitis and anemia/decreased hemoglobin. Modest effects on heart rate occurred with no notable cardiac, pulmonary, ophthalmologic, or malignancy observed and transient transaminase (ALT 3×) occurred in three patients and decreased with continued treatment.

A phase III trial in ulcerative colitis and a phase II trial in Crohn's disease are being planned.

Pediatric Data

At the time of writing this chapter, there are no published data on the use of RPC1063 in children or adolescents with IBD.

Summary

Blockade of the TNF-a pathway has provided significant strides in the treatment of IBD. However, still a substantial proportion of patients with inflammatory bowel disease specifically moderate to severe Crohn's disease do not have a response to treatment with TNF antagonists and are primary or secondary nonresponders or they develop side effects or intolerances leading to discontinuation of medical therapy. As discussed in this chapter, several new biologic treatments utilizing different mechanisms of action to treat IBD are currently in the pipeline and these therapies are to date are proving to be promising new treatments for IBD.

References

1. Amiot A, Peyrin-Biroulet L. Current, new and future biological agents on the horizon for the treatment of inflammatory bowel diseases. Ther Adv Gastroenterol. 2015;8(2):66–82.
2. Toussirot E. The IL23/Th17 pathway as a therapeutic target in chronic inflammatory diseases. Inflamm Allergy Drug Targets. 2012;11:159–68.
3. Peluso I, Pallone F, Monteleone G. Interleukin-12 and Th1 immune response in Crohn's disease: pathogenetic relevance and therapeutic implication. World J Gastroenterol. 2006;12:5606–10.
4. Neurath MF. IL-23: a master regulator in Crohn's disease. Nat Med. 2007;13:26–8.
5. Niederreiter L, Adolph TE, Kaser A. Anti-IL-12/23 in Crohn's disease: bench and bedside. Curr Drug Targets. 2013;14(12):1379–84.
6. Fuss IJ, Becker C, Yang Z, Groden C, Hornung RL, Heller F, Neurath MF, Strober W, Mannon PJ. Both IL-12p70 and IL-23 are synthesized during active Crohn's disease and are down-regulated by treatment with anti-IL-12 p40 monoclonal antibody. Inflamm Bowel Dis. 2006;12:9–15.
7. Parrello T, Monteleone G, Cucchiara S, et al. Up-regulation of the IL-12 receptor beta 2 chain in Crohn's disease. J Immunol. 2000;165:7234–9.
8. Iwakura Y, Ishigame H. The IL-23/IL-17 axis in inflammation. J Clin Invest. 2006;116:1218–22.
9. Onuora S. Ustekinumab after anti-TNF failure: a step closer to the PSUMMIT of psoriatic arthritis therapy? Nat Rev Rheumatol. 2014;10:125.
10. Sandborn WJ, Feagan BG, Fedorak RN, Scherl E, Fleisher MR, Katz S, Johanns J, Blank M, Rutgeerts P. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology. 2008;135:1130–41.
11. Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med. 2012;367:1519–28.
12. Sandborn W, et al. A multicenter, double-blind, placebo-controlled phase3 study of ustekinumab, a human IL-12/23P40 mAB, in moderate-service Crohn's disease refractory to anti-TFNα: UNITI-1. Inflamm Bowel Dis. 2016;22 Suppl 1:S1.
13. ACG October 2015. http://www.healio.com/gastroenterology/inflammatory-bowel-disease/news/online/%7B3319d496-e8ac-41db-8729-1e14070f0af8%7D/uniti-2-trial-stelara-effective-for-treating-crohns-disease.
14. A study to evaluate the safety and efficacy of ustekinumab maintenance therapy in patients with moderately to severely active Crohn's disease (IM-UNITI). Available at: http://clinicaltrials.gov/show/NCT01369355. http://clinicaltrials.gov/show/NCT01369355. Accessed Jan 2016.
15. Rinawi F, et al. Ustekinumab for resistant pediatric Crohn's disease. J Pediatr Gastroenterol Nutr. 2014. [Epub ahead of print].
16. Bishop C, et al. Ustekinumab in pediatric Crohn's disease patients: case review. J Pediatr Gastroenterol Nutr. 2016;63(3):348–51.
17. Papp KA, Griffiths CE, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol. 2013;168:844–54. Leung, Y, Panaccione R. Update on Ustekinumab for the treatment of Crohn's disease. Gastroenterol Clin N Am. 43(2014):619–30.
18. Badat Y, Meissner WG, Laharie D. Demyelination in a patient receiving ustekinumab for refractory Crohn's disease. J Crohns Colitis. 2014;8:1138–9.
19. Kock K, et al. Preclinical development of AMG 139, a human antibody specifically targeting IL-23. Br J Pharmacol. 2015;172:159–72.
20. Multiple ascending doses of AMG 139 in healthy and Crohn's disease subjects, www.clinicaltrials.gov/ct2/show/NCT01258205?term=AMG139&rank=1.
21. A phase II, multicenter, randomized, double-blind, multiple dose, placebo-controlled, parallel-group study to evaluate the efficacy, pharmacokinetics, and safety of BI 655066, an IL-23 p19 antagonist monoclonal antibody, in patients with moderately to severely active Crohn's disease, who are naïve to, or were previously treated with anti-TNF therapy. https://clinicaltrials.gov/ct2/show/NCT02031276. Accessed Jan 2016.

22. A long term extension trial of BI 655066 in patients with moderately to severely active Crohn's disease. https://clinicaltrials.gov/ct2/show/NCT02513459. Accessed Jan 2016.
23. BI 655066 dose ranging in psoriasis, active comparator ustekinumab. https://www.clinicaltrials.gov/ct2/show/NCT02054481?term=BI+655066&rank=3.
24. Krueger JG, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2015;136(1):116–24.e7
25. Ito H. IL-6 and Crohns disease. Curr Drug Targets Inflamm Allergy. 2003;2(2):125–30.
26. A study to assess the efficacy and safety of PF-04236921 in subjects with Crohn's disease who failed anti-TNF therapy (ANDANTE). https://www.clinicaltrials.gov/ct2/show/NCT01287897?term=PF-04236921&rank=3.
27. Fuss IJ, Strober W. The role of IL-13 and NK T cells in experimental and human ulcerative colitis. Mucosal Immunol. 2008;1(Suppl 1):S31–3.
28. Heller F, Florian P, Bojarski C, et al. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. Gastroenterology. 2005;129:550–64.
29. Fuss IJ, Heller F, Boirivant M, et al. Nonclassical CD1d-restricted NK T cells that produce IL-13 characterize an atypical Th2 response in ulcerative colitis. J Clin Invest. 2004;113:1490–7.
30. Hua F, et al. A pharmacokinetic comparison of anrukinzumaban anti- IL-13 monoclonal antibody, among healthy volunteers, asthma and ulcerative colitis patients. Br J Clin Pharmacol. 2015;80(1):101–9.
31. May RD, Monk PD, Cohen ES, et al. Preclinical development of CAT-354, an IL-13 neutralizing antibody, for the treatment of severe uncontrolled asthma. Br J Pharmacol. 2012;166:177–93.
32. Oh CK, Faggioni R, Jin F, et al. An open-label, single-dose bioavailability study of the pharmacokinetics of CAT-354 after subcutaneous and intravenous administration in healthy males. Br J Clin Pharmacol. 2010;69:645–55.
33. Danese S, et al. Tralokinumab for moderate-to-severe UC: a randomised, double-blind, placebo-controlled, phase IIa study. Gut. 2015;64:243–9.
34. Rothenberg ME, et al. Intravenous anti–IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. J Allergy Clin Immunol. 2015;135(2):500–7.
35. A multi-center, randomized, double-blind, active controlled study to assess efficacy, safety and tolerability of the anti-IL13 monoclonal antibody QAX576 in the treatment of perianal fistulas in patients suffering from Crohn's disease. https://clinicaltrials.gov/ct2/show/NCT01355614?term=QAX576&rank=9.
36. A study to assess efficacy, safety and tolerability of the Anti-IL-13 monoclonal antibody QAX576 in the treatment of perinanal fistulas in patients suffering from Crohn's disease. https://clinicaltrials.gov/ct2/show/NCT01316601?term=QAX576&rank=15.
37. A randomized, double-blind, placebo-controlled, parallel group, multi-center study designed to evaluate the safety, efficacy, pharmacokinetic and pharmacodynamic profile of bertilimumab in patients with active moderate to severe ulcerative colitis. clinicaltrials.gov/ct2/show/NCT01671956?term=Bertilimumab&rank=1. Accessed Jan 2016.
38. Fitzpatrick LR. Vidofludimus inhibits colonic interleukin-17 and improves hapten-induced colitis in rats by a unique dual mode of action. J Pharmacol Exp Ther. 2012;342(3):850–60.
39. Xue L, et al. Contribution of enhanced engagement of antigen presentation machinery to the clinical immunogenicity of a human interleukin (IL)-21 receptor-blocking therapeutic antibody. Clin Exp Immunol. 2016;183:102–13.
40. Hua F, et al. Anti-IL21 receptor monoclonal antibody (ATR-107): safety, pharmacokinetics, and pharmacodynamic evaluation in healthy volunteers: a phase I, first-in-human study. J Clin Pharmacol. 2014;54(1):14–22.
41. Vugmeyster Y, Guay H, Szklut P, et al. In vitro potency, pharmacokinetic profiles, and pharmacological activity of optimized anti-IL-21R antibodies in a mouse model of lupus. MAbs. 2010;2:335–46.
42. Vallieres F, Girard D. IL-21 enhances phagocytosis in mononuclear phagocyte cells: identification of spleen tyrosine kinase as a novel molecular target of IL-21. J Immunol. 2013;190:2904–12.
43. Spolski R, Leonard WJ. Interleukin-21: a double-edged sword with therapeutic potential. Nat Rev Drug Discov. 2014;13:379–95.
44. Young DA, Hegen M, Ma HL, et al. Blockade of the interleukin-21/interleukin-21 receptor pathway ameliorates disease in animal models of rheumatoid arthritis. Arthritis Rheum. 2007;56:1152–63.
45. Rietdijk ST, D'Haens GR. Recent developments in the treatment of inflammatory bowel disease. J Dig Dis. 2013;14(6):282–7.
46. Ghoreschi K, Laurence A, O'Shea J. Janus kinases in immune cell signaling. Immunol Rev. 2009;228:273–87.
47. Neurath M. Cytokines in inflammatory bowel disease. Nat Rev Immunol. 2014;14:329–34.
48. Ghoreschi K, Jesson MI, Lee JL, et al. Modulation of innate and adaptive immune responses by tofacitinib (CP-690,550). J Immunol. 2011;186:4234–43.
49. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, Niezychowski W, Study A3921063 Investigators. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med. 2012;367(7):616–24.
50. Sandborn WJ, Ghosh S, Panes J, Vranic I, Wang W, Niezychowski W. A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2014;12:1485–93.
51. Lowenberg M, D'Haens G. Next-generation therapeutics for IBD. Curr Gastroenterol Rep. 2015;17:21.
52. A study of oral CP-690,550 as a maintenance therapy for ulcerative colitis (OCTAVE). ClinicalTrials.gov Identifier: NCT01458574. Last accessed Jan 2016.
53. Hyun JG, Lee G, Brown JB, et al. Anti-interferon-inducible chemokine, CXCL10, reduces colitis by impairing T helper-1 induction and recruitment in mice. Inflamm Bowel Dis. 2005;11:799–805.
54. Hardi R, Mayer L, Targan SR, et al. A phase 1 open-label, single-dose, dose-escalation study of MDX-1100, a high-affinity, neutralizing, fully human Igg1 (kappa) anti-CXCL10 (Ip10) monoclonal antibody, in ulcerative colitis. Gastroenterology. 2008;134:A-99–100.
55. Van Rompaey L, et al. Preclinical characterization of GLPG0634, a selective inhibitor of JAK1, for the treatment of inflammatory diseases. J Immunol. 2013;191:3568–77.
56. Efficacy and safety of GLPG0634 in subjects with active Crohn's disease. https://clinicaltrials.gov/ct2/show/NCT02048618?term=GLPG0634&rank=2.
57. Wahl SM. Transforming growth factor beta: the good, the bad, and the ugly. J Exp Med. 1994;180:1587–90.
58. Letterio JJ, Roberts AB. Regulation of immune responses by TGF-beta. Annu Rev Immunol. 1998;16:137–61.
59. Monteleone G, Kumberova A, Croft NM, Mc Kenzie C, Steer HW, Mac Donald TT. Blocking Smad7 restores TGF-beta1 signaling in chronic inflammatory bowel disease. J Clin Invest. 2001;108:601–9.
60. Monteleone G, Boirivant M, Pallone F, Mac Donald TT. TGF-beta1 and Smad7 in the regulation of IBD. Mucosal Immunol. 2008;1(Suppl 1):S50–3.
61. Boirivant M, Pallone F, Di Giacinto C, et al. Inhibition of Smad7 with a specific antisense oligonucleotide facilitates TGF-beta1-mediated suppression of colitis. Gastroenterology. 2006;131:1786–98.

62. Monteleone G, Fantini MC, Onali S, et al. Phase I clinical trial of Smad7 knockdown using antisense oligonucleotide in patients with active Crohn's disease. Mol Ther. 2012;20:870–6.
63. Zorzi F, et al. A phase 1 open-label trial shows that smad7 antisense oligonucleotide (GED0301) does not increase the risk of small bowel strictures in Crohn's disease. Aliment Pharmacol Ther. 2012;36:850–7.
64. Monteleone G et al. Abstract presentation UEGW 2014, OP203. Vienna.
65. Mayer L, Sandborn WJ, Stepanov Y, Geboes K, Hardi R, Yellin M, Tao X, Xu LA, Salter-Cid L, Gujrathi S, Aranda R, Luo AY. Anti-IP-10 antibody (BMS-936557) for ulcerative colitis: a phase II randomised study. Gut. 2014;63(3):442–50.
66. Kuhne M, Preston B, Wallace S, Chen S, Vasudevan G, Witte A, Cardarelli P. MDX-1100, a fully human anti-CXCL10 (IP-10) antibody, is a high affinity, neutralizing antibody that has entered phase I clinical trials for the treatment of Ulcerative Colitis (UC). J Immunol. 2007;178:S241.
67. Uguccioni M, Gionchetti P, Robbiani DF, et al. Increased expression of IP-10, IL-8,MCP-1, and MCP-3 in ulcerative colitis. Am J Pathol. 1999;155:331–6.
68. Witte A, Kuhne MR, Preston BT, et al. W1170 CXCL10 expression and biological activities in inflammatory bowel disease. Gastroenterology. 2008;134:A-648.
69. Soejima K, BJ R. A functional IFN – inducible protein-10/CXCL10-specific receptor expressed by epithelial and endothelial cells that is neither CXCR3 nor glycosaminoglycan. J Immunol. 2001;167:6576–82.
70. Sasaki S, Yoneyama H, Suzuki K, et al. Blockade of CXCL10 protects mice from acute colitis and enhances crypt cell survival. Eur J Immunol. 2002;32:3197–205.
71. Singh UP, Singh S, Taub DD, et al. Inhibition of IFN-gamma-inducible protein-10 abrogates colitis in IL-10−/− mice. J Immunol. 2003;171:1401–6.
72. Sandborn WJ, Rutgeerts PJ, Colombel J-F, et al. 827 phase IIA, randomized, placebo-controlled evaluation of the efficacy and safety of induction therapy with eldelumab (anti-IP-10 antibody; BMS-936557) in patients with active Crohn's disease. Gastroenterology. 2015;148:S-162–3.
73. Rivera-Nieves J. Strategies that target leukocyte traffic in inflammatory bowel diseases: recent developments. Curr Opin Gastroenterol. 2015;31:441–8.
74. Rudick RA, Stuart WH, Calabresi PA, Confavreux C, Galetta SL, Radue EW, Lublin FD, Weinstock-Guttman B, Wynn DR, Lynn F, Panzara MA, Sandrock AW, Investigators S. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. N Engl J Med. 2006;354:911–23.
75. Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, Willmer-Hulme AJ, Dalton CM, Miszkiel KA, O'Connor PW, International Natalizumab Multiple Sclerosis Trial Group. A controlled trial of natalizumab for relapsing multiple sclerosis [see comment]. N Engl J Med. 2003;348:15–23.
76. Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA, Sandrock AW, Investigators A. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006;354:899–910.
77. Gordon FH, Lai CW, Hamilton MI, Allison MC, Srivastava ED, Fouweather MG, Donoghue S, Greenlees C, Subhani J, AmLot PL, Pounder RE. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. Gastroenterology. 2001;121:268–74.
78. Ghosh S, Goldin E, Gordon FH, Malchow HA, Rask-Madsen J, Rutgeerts P, Vyhnalek P, Zadorova Z, Palmer T, Donoghue S. Natalizumab for active Crohn's disease. N Engl J Med. 2003;348:24–32.
79. Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, Sanders M, Schreiber S, Targan S, van Deventer S, Goldblum R, Despain D, Hogge GS, Rutgeerts P. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med. 2005;353:1912–25.
80. Sandborn W, Colombel J, Enns R, Feagan B, Hanauer S, Lawrance I, Panaccione R, Rutgeerts P, Schreiber S, Targan S, van Deventer S. Maintenance therapy with natalizumab does not require use of concomitant iImmunosuppressants for sustained efficacy in patients with active Crohn's disease: results from the ENACT-2 study. Gastroenterology. 2006;130:A-482 Abstract 1137.
81. Panaccione R, Colombel J, Enns R, Feagan B, Hanauer S, Lawrance I, Rutgeerts P, Sandborn W, Schreiber S, Targan S, van Deventer S. Natalizumab maintains remission in patients with moderately to severely active Crohn's disease for up to 2-years: results from an open-label extension study. Gastroenterology. 2006;130:A-111 Abstract 768.
82. Targan SR, Feagan BG, Fedorak RN, Lashner BA, Panaccione R, Present DH, Spehlmann ME, Rutgeerts PJ, Tulassay Z, Volfova M, Wolf DC, Hernandez C, Bornstein J, Sandborn WJ. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. Gastroenterology. 2007;132:1672–83.
83. Sands BE, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, Katz S, Goldblum R, Harrigan R, Hilton D, Hanauer SB. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission whil receiving infliximab. Inflamm Bowel Dis. 2007;13:2–11.
84. Gordon FH, Hamilton MI, Donoghue S, Greenlees C, Palmer T, Rowley-Jones D, Dhillon AP, AmLot PL, Pounder RE. A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to alpha-4 integrin. Aliment Pharmacol Ther. 2002;16:699–705.
85. Prescribing information for Tysabri (natalizumab). 2007. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125104s0576lbl.pdf; https://www.biogen.com.au/content/dam/corporate/en_AU/pdfs/products/TYSABRI/bdptysab11116.pdf.
86. Hyams JS, Wilson DC, Thomas A, Heuschkel R, Mitton S, Mitchell B, Daniels R, Libonati MA, Zanker S, Kugathasan S, International Natalizumab CD305 Trial Group. Natalizumab therapy for moderate to severe Crohn's disease in adolescents. J Pediatr Gastroenterol Nutr. 2007;44:185–91.
87. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. [see comment]. N Engl J Med. 2005;353:369–74.
88. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. [see comment]. N Engl J Med. 2005;353:375–81.
89. Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. [see comment]. N Engl J Med. 2005;353:362–8.
90. Yousry TA, Major EO, Rysckewitsch C, Fahle G, Fischer S, Hou J, Curfman B, Miszkiel K, Mueller-Lenke N, Sanchez E, Barkhof F, Radue EW, Jager HR, Clifford DB. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephaolopathy. N Engl J Med. 2006;354:924–33.
91. Van Deventer SJH, Wedel MK, Baker BF, Xia S, Chuang E, Miner PB. A phase II dose ranging, double-blind, placebo-controlled study of alicaforsen enema in subjects with acute exacerbation of mild to moderate left-sided ulcerative colitis. Aliment Pharmacol Ther. 2006;23:1415–25.
92. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369:699–710.

93. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369:711–21.
94. Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology. 2014;147:618–27.
95. Zoet ID, et al. Successful vedolizumab therapy in a sixteen-year-old boy with refractory ulcerative colitis. J Crohns Colitis. 2015;10(3):373–4.
96. Poster presentation UEGW 2014, P1059, Hanauer S et al., poster presentation UEGW 2014, P1667, Feagan B et al.
97. Milch C, Wyant T, Xu J, Parikh A, Kent W, Fox I, et al. Vedolizumab, a monoclonal antibody to the gut homing alpha-4beta7 integrin, does not affect cerebrospinal fluid T-lymphocyte immunophenotype. J Neuroimmunol. 2013;264:123–6.
98. Lowenberg M, D'Haens G. Novel targets for inflammatory bowel disease therapeutics. Curr Gastroenterol Rep. 2013;15:311.
99. Colombel J-F, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2016;0:1–13.
100. Vermeire S, O'Byrne S, Keir M, Williams M, Lu TT, Mansfield JC, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet. 2014;384:309–18.
101. Pullen N, Molloy E, Carter D, et al. Pharmacological characterization of PF-00547659, an antihuman MAdCAM monoclonal antibody. Br J Pharmacol. 2009;157:281–93.
102. Vermeire S, Ghosh S, Panes J, Dahlerup JF, Luegering A, Sirotiakova J, et al. The mucosal addressin cell adhesion molecule antibody PF-00547,659 in ulcerative colitis: a randomised study. Gut. 2011;60:1068–75.
103. Miner PB, Wedel MK, Xia S, Baker BF. Safety and efficacy of two dose formulations of alicaforsen enema compared with mesalazine enema for treatment of mild to moderate left-sided ulcerative colitis: a randomized, double-blind, active-controlled trial. Aliment Pharmacol Ther. 2006;23:1403–13.
104. Reinisch W, Sandborn W, Danese S, et al. 901a A randomized, multicenter double-blind, placebo-controlled study of the safety and efficacy of anti-MAdCAM Antibody PF-00547659 (PF) in patients with moderate to severe ulcerative colitis: results of the TURANDOT study. Gastroenterology. 2015;148:S-1193.
105. Sandborn W, Lee SD, Tarabar D, et al. 825 anti-MAdCAM-1 antibody (PF-00547659) for active refractory Crohn's disease: results of the OPERA study. Gastroenterology. 2015;148:S-162.
106. Takazoe M, Watanabe M, Kawaguchi T, Matsumoto T, Oshitani N, Hiwatashi N, Hibi T. Oral alpha-4 integrin inhibitor (AJM300) in patients with active Crohn disease – a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2009;136:A-181.
107. Shanahan Jr WR. ISIS 2302, an antisense inhibitor of intercellular adhesion molecule 1. Expert Opin Investig Drugs. 1999;8:1417–29.
108. Yacyshyn BR, Chey WY, Goff J, Salzberg B, Baerg R, Buchman AL, Tami J, Yu R, Gibiansky E, Shanahan WR. Double blind, placebo controlled trial of the remission inducing and steroid sparing properties of an ICAM-1 antisense oligodeoxynucleotide, alicaforsen (ISIS 2302), in active steroid dependent Crohn's disease. Gut. 2002;51:30–6.
109. Yacyshyn BR, Bowen-Yacyshyn MB, Jewell L, Tami JA, Bennett CF, Kisner DL, Shanahan Jr WR. A placebo-controlled trial of ICAM-1 antisense oligonucleotide in the treatment of Crohn's disease. Gastroenterology. 1998;114:1133–42.
110. Yacyshyn B, Chey WY, Wedel MK, Yu RZ, Paul D, Chuang E. A randomized, double-masked, placebo-controlled study of alicaforsen, an antisense inhibitor of intercellular adhesion molecule 1, for the treatment of subjects with active Crohn's disease. Clin Gastroenterol Hepatol. 2007;5:215–20.
111. Schreiber S, Nikolaus S, Malchow H, Kruis W, Lochs H, Raedler A, Hahn EG, Krummenerl T, Steinmann G. Absence of efficacy of subcutaneous antisense ICAM-1 treatment of chronic active Crohn's disease. Gastroenterology. 2001;120:1339–46.
112. van Deventer SJ, Tami JA, Wedel MK. A randomised, controlled, double blind, escalating dose study of alicaforsen enema in active ulcerative colitis. Gut. 2004;53:1646–51.
113. Miner Jr PB, Geary RS, Matson J, Chuang E, Xia S, Baker BF, Wedel MK. Bioavailability and therapeutic activity of alicaforsen (ISIS 2302) administered as a rectal retention enema to subjects with active ulcerative colitis. Aliment Pharmacol Ther. 2006;23:1427–34.
114. Miner P, Wedel M, Bane B, Bradley J. An enema formulation of alicaforsen, an antisense inhibitor of intercellular adhesion molecule-1, in the treatment of chronic, unremitting pouchitis. Aliment Pharmacol Ther. 2004;19:281–6.
115. Pan WJ, et al. Clinical pharmacology of AMG 181, a gut-specific human anti-α4β7 monoclonal antibody, for treating inflammatory bowel diseases. Br J Clin Pharmacol. 2014;78(6):1315–33.
116. Prat A, Stuve O. Firategrast: natalizumab in a pill? Lancet Neurol. 2012;11(2):120–1.
117. A randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of nine-weeks administration of three doses of SB-683699 in subjects with moderately to severely active Crohn's disease. Clinicaltrials.gov. NCT00101946.
118. Digital Oral Presentation, ECCO 2015.
119. Koga Y, Kainoh M. PP-065-15 effect of an orally active small molecule alpha4beta1/alpha4beta7 integrin antagonist, TRK-170, on experimental colitis in mice. International Immunology Meeting Abstracts. Kobe. 2010.
120. Nelson DR, Tu Z, Soldevila-Pico C, Abdelmalek M, Zhu H, Xu YL, Cabrera R, Liu C, Davis GL. Long-term interleukin 10 therapy in chronic hepatitis C patients has a proviral and anti-inflammatory effect. Hepatology. 2003;38:859–68.
121. McInnes IB, Illei GG, Danning CL, Yarboro CH, Crane M, Kuroiwa T, Schlimgen R, Lee E, Foster B, Flemming D, Prussin C, Fleisher TA, Boumpas DT. IL-10 improves skin disease and modulates endothelial activation and leukocyte effector function in patients with psoriatic arthritis. J Immunol. 2001;167:4075–82.
122. Maini R, Paulus HE, Breedveld FC. rHuIL-10 in subjects with active rheumatoid arthritis (RA): a phase I and cytokine response study. Arthritis Rheum. 1997;1997:S224.
123. Smeets TJ, Kraan MC, Versendaal J, Breedveld FC, Tak PP. Analysis of serial synovial biopsies in patients with rheumatoid arthritis: description of a control group without clinical improvement after treatment with interleukin 10 or placebo. J Rheumatol. 1999;26:2089–93.
124. van Deventer SJ, Elson CO, Fedorak RN. Multiple doses of intravenous interleukin 10 in steroid-refractory Crohn's disease. Crohn's disease Study Group. Gastroenterology. 1997;113:383–9.
125. Fedorak RN, Gangl A, Elson CO, Rutgeerts P, Schreiber S, Wild G, Hanauer SB, Kilian A, Cohard M, LeBeaut A, Feagan B. Recombinant human interleukin 10 in the treatment of patients with mild to moderately active Crohn's disease. The Interleukin 10 Inflammatory Bowel Disease Cooperative Study Group. Gastroenterology. 2000;119:1473–82.
126. Schreiber S, Fedorak RN, Nielsen OH, Wild G, Williams CN, Nikolaus S, Jacyna M, Lashner BA, Gangl A, Rutgeerts P, Isaacs K, van Deventer SJ, Koningsberger JC, Cohard M, LeBeaut A, Hanauer SB. Safety and efficacy of recombinant human interleukin 10 in chronic active Crohn's disease. Crohn's disease IL-10 Cooperative Study Group. Gastroenterology. 2000;119:1461–72.
127. Fedorak R, Nielsen O, Williams N, Malchow H, Forbes A, Stein B, Wild G, Lashner B, Renner E, Buchman A, Hardi R, The Interleukin-10 Study Group. Human recombinant interleukin-10 is safe and well tolerated but does not induce remission in steroid dependent Crohn's disease. Gastroenterology. 2001;120:A-127.
128. Tilg H, van Montfrans C, van den Ende A, Kaser A, van Deventer SJ, Schreiber S, Gregor M, Ludwiczek O, Rutgeerts P, Gasche C, Koningsberger JC, Abreu L, Kuhn I, Cohard M, LeBeaut A, Grint

P, Weiss G. Treatment of Crohn's disease with recombinant human interleukin 10 induces the proinflammatory cytokine interferon gamma. [see comment]. Gut. 2002;50:191–5.
129. Colombel JF, Rutgeerts P, Malchow H, Jacyna M, Nielsen OH, Rask-Madsen J, Van Deventer S, Ferguson A, Desreumaux P, Forbes A, Geboes K, Melani L, Cohard M. Interleukin 10 (Tenovil) in the prevention of postoperative recurrence of Crohn's disease. Gut. 2001;49:42–6.
130. Steidler L, Hans W, Schotte L, Neirynck S, Obermeier F, Falk W, Fiers W, Remaut E. Treatment of murine colitis by Lactococcus lactis secreting interleukin- 10. Science. 2000;289:1352–5.
131. Steidler L, Neirynck S, Huyghebaert N, Snoeck V, Vermeire A, Goddeeris B, Cox E, Remon JP, Remaut E. Biological containment of genetically modified Lactococcus lactis for intestinal delivery of human interleukin 10. Nat Biotechnol. 2003;21:785–9.
132. Huyghebaert N, Vermeire A, Neirynck S, Steidler L, Remaut E, Remon JP. Evaluation of extrusion/spheronisation, layering and compaction for the preparation of an oral, multi-particulate formulation of viable, hIL-10 producing Lactococcus lactis. Eur J Pharm Biopharm. 2005;59:9–15.
133. Huyghebaert N, Vermeire A, Neirynck S, Steidler L, Remaut E, Remon JP. Development of an enteric-coated formulation containing freeze-dried, viable recombinant Lactococcus lactis for the ileal mucosal delivery of human interleukin-10. Eur J Pharm Biopharm. 2005;60:349–59.
134. Braat H, Rottiers P, Hommes DW, Huyghebaert N, Remaut E, Remon JP, van Deventer SJ, Neirynck S, Peppelenbosch MP, Steidler L. A phase I trial with transgenic bacteria expressing interleukin-10 in Crohn's disease. Clin Gastroenterol Hepatol. 2006;4:754–9.
135. Comi G, Jeffery D, Kappos L, Montalban X, Boyko A, Rocca MA, et al. Placebo-controlled trial of oral laquinimod for multiple sclerosis. N Engl J Med. 2012;366:1000–9.
136. D'Haens G, Sandborn WJ, Colombel JF, Rutgeerts P, Brown K, Barkay H, Sakov A, Haviv A, Feagan BG. A phase II study of laquinimod in Crohn's disease. Gut. 2015;64(8):1227–35. doi:10.1136/gutjnl-2014-307118. Epub 2014 Oct 3.
137. Creed TJ, Lee RW, Newcomb PV, di Mambro AJ, Raju M, Dayan CM. The effects of cytokines on suppression of lymphocyte proliferation by dexamethasone. J Immunol. 2009;183:164–71.
138. Musch E, et al. Topical treatment with the toll-like receptor agonist DIMS0150 has potential for lasting relief of symptoms in patients with chronic active ulcerative colitis by restoring glucocorticoid sensitivity. Inflamm Bowel Dis. 2013;19:283–92.
139. Lofberg R, Neurath M, Ost A, Pettersson S. Topical NFκB p65 antisense oligonucleotide in patients with active distal colonic IBD: a randomized, controlled, pilot trial. Gastroenterology. 2001;122(Suppl 41):503A.
140. Kuznetsov NV, et al. Biomarkers can predict potential clinical responders to DIMS0150 a toll-like receptor 9 agonist in ulcerative colitis patients. BMC Gastroenterol. 2014;14:79.
141. Gonzalez-Cabrera PJ. S1P signaling: new therapies and opportunities. F1000Prime Rep. 2014;6:109.
142. Masopust D, Choo D, Vezys V, et al. Dynamic T cell migration program provides resident memory within intestinal epithelium. J Exp Med. 2010;207:553–64.
143. Safety and efficacy of APD334 in patients with ulcerative colitis (clinical trials.gov NCT02447302).
144. Sandborn W. New targets for small molecules in inflammatory bowel disease. Gastroenterol Hepatol. 2015;11(5):338–40.
145. Sandborn W, Feagan BG, Wolf DC, et al. 445 the TOUCHSTONE study: a randomized, double-blind, placebo-controlled induction trial of an oral S1P receptor modulator (RPC1063) in moderate to severe ulcerative colitis. Gastroenterology. 2015;148:S-93.