Clinical Immunology 206 (2019) 9–14

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Biological therapies in inflammatory bowel disease: Beyond anti-TNF therapies

Konstantinos H. Katsanos[a,1], Konstantinos Papamichael[b,1], Joseph D. Feuerstein[b], Dimitrios K. Christodoulou[a], Adam S. Cheifetz[b,*]

[a] Division of Gastroenterology, University Hospital & Faculty of Medicine, School of Health Sciences, University of Ioannina, Greece
[b] Center for Inflammatory Bowel Diseases, Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard University, Boston, MA, USA

ARTICLE INFO

Keywords:
Ulcerative colitis
Crohn's disease
Biologics
Novel therapies
S1P receptors
Integrins
Janus kinases

ABSTRACT

The pharmacological management of inflammatory bowel disease (IBD) over the last two decades has transitioned from reliance on aminosalycilates, corticosteroids and immunomodulators to earlier treatment with anti-tumor necrosis factor (anti-TNF) therapy. Nevertheless, 20–30% of patients discontinue anti-TNF therapy for primary non-response and another 30–40% for losing response within one year of treatment. These undesirable therapeutic outcomes can be attributed to pharmacokinetic (anti-drug antibodies and/or low drug concentrations) or pharmacodynamic issues characterized by a non-TNF driven inflammation. The latter issues necessitate the use of medications with different mechanisms of action. Besides the biologics natalizumab, vedolizumab and ustekinumab that have already been approved for the treatment of IBD new non-anti-TNF therapies are currently under investigation including small molecule drugs against Janus kinase and sphingosine-1-phosphate receptors. This manuscript will review the medications that are in the later stages of development for the treatment of IBD and directed against immune targets other than TNF.

1. Introduction

Inflammatory bowel diseases (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (UC), are chronic, relapsing, immune-mediated inflammatory disorders with significant morbidity and effects on quality of life [1]. The incidence and prevalence of these diseases is increasing worldwide, particularly in the East [2]. Although the exact etiopathogenesis of IBD remains largely unknown, the advent of more advanced molecular and cellular biology techniques has greatly contributed to improving our understanding of the inflammatory pathways that drive tissue damage in these disorders [3]. These discoveries, in turn, have led to more specific and targeted pharmacological treatment of IBD [4].

Anti-tumor necrosis factor (anti-TNF) therapies have revolutionized the treatment of IBD. These agents have been shown to be steroid sparing, to reduce IBD-related hospitalizations and surgeries, induce mucosal healing, and improve patients' quality of life [5]. However, up to 30% of patients show no clinical benefit after induction therapy (primary non-responders), and another 30–40% lose response during the first year of treatment, requiring dose-escalation or a switch to another biologic [6]. These undesired therapeutic outcomes are due to either pharmacokinetic issues, characterized by increased drug clearance mostly due to immunogenicity and development of anti-drug antibodies, or pharmacodynamic issues, characterized by non-TNF driven inflammation [7]. Moreover, although the overall safety profile of anti-TNF is satisfactory, there are some concerns with respect to infusion/injection site reactions, infections and some rare malignancies, such as melanoma and lymphoma [8,9]. Thus it is crucial to develop new biological therapies with different mechanisms of action with equivalent or even improved safety and efficacy profiles. The latter refer mostly to clinical response typically defined as a decrease from baseline of the Crohn's disease activity index by 70 points for CD and the Mayo score by $\geq$30% and $\geq$ 3 points, with decrease in rectal bleeding subscore of $\geq$1 or rectal bleeding subscore of 0 or 1 for UC.

Major advances of knowledge in the immunology and pathophysiology of the intestinal inflammatory processes have helped to identify

Abbreviations: CD, Crohn's disease; CDAI, Crohn's disease activity index; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IL, interleukin; JAK, Janus-activated kinase; JCV, John Cunningham virus; MAdCAM-1, mucosal addressin cell adhesion molecule 1; PML, progressive multifocal leukoencephalopathy; S1P, sphingosine-1-phosphate; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor; SLR, secondary loss of response; UC, ulcerative colitis; RCT, randomized clinical trials.

* Corresponding author at: Center for Inflammatory Bowel Disease, Beth Israel Deaconess Medical Center, 330 Brookline Ave., Rabb 425, Boston, MA 02215, Harvard Medical School, USA.
E-mail address: acheifet@bidmc.harvard.edu (A.S. Cheifetz).
[1] Equal contribution.

https://doi.org/10.1016/j.clim.2018.03.004
Received 19 December 2017; Received in revised form 10 March 2018; Accepted 11 March 2018
Available online 12 March 2018
1521-6616/

Table 1
Non-TNF-related drugs for the treatment of inflammatory bowel diseases.

Target	Compound (PubChem SID)	Mode of administration	Mechanism of action	IBD type	Study phase	Ref.
Integrins	Vedolizumab (160666632)	i.v.[a]	Humanized IgG1monoclonal antibody that selectively blocks the α4β7 integrin	CD/UC	FDA approved	20–23
Integrins	Etrolizumab (160704152)	s.c.	Humanized IgG1monoclonal antibody that targets the β7 subunit of the heterodimeric integrins α4β7 and αEβ7	UC	III	33, 34
Integrins	Alicaforsen (319360904)	p.r.	Human antisense oligonucleotide which inhibits ICAM-1 and blocks leukocyte recruitment	Chronic pouchitis	III	35
Integrins	AJM-300	p.o.	Orally active α4 integrin antagonist	UC	III	36
Integrins	PF-00547659 (160682419)	s.c.	Human IgG2 monoclonal antibody directed against MAdCAM-1	CD/UC	II	38, 39
Cytokines	Risakizumab (310264703)	i.v.	Humanized IgG1 monoclonal antibody against the p19 subunit of IL23	CD	III	45
Cytokines	Brazicumab (318164812)	i.v.	Human IgG2 monoclonal antibody that targets the p19 subunit of IL23	CD	II	46
Cytokines	Ustekinumab (103771533)	i.v. induction and s.c. maintenance[b]	Human IgG1 monoclonal antibody against the p40 subunit of IL12 and 23	CD	FDA approved	42, 43
Small molecules	Tofacitinib (354281529)	p.o.	JAK1, 3 inhibitor	UC	Awaits FDA final approval	48, 49
Small molecules	Filgotinib (354346952)	p.o.	JAK1 inhibitor	CD/UC	II/III	50
Small molecules	Upadacitinib (350079067)	p.o.	JAK1 inhibitor	CD/UC	II/III	51
Small molecules	Ozanimod (348687948)	p.o.	S1P1, S1P5 receptor agonist	CD/UC	II/III	52
Small molecules	Laquinimod (348926252)	p.o.	Anti-inflammatory properties	CD	II	53

UC: ulcerative colitis; CD Crohn's disease; IL: interleukin; ICAM: intercellular adhesion molecule; ref.: references; messenger RNA; MAdCAM-1: mucosal addressin cell adhesion molecule 1; IBD: inflammatory bowel disease; JAK: Janus Kinase; S1P: sphingosine-1-phosphate; SID: substance identification; p.o.: per os; i.v.: intravenous; s.c.: subcutaneous; p.r.: per rectum; w: week; FDA: Food and Drug Administration.

[a] 300mg at w0, 2, 6 and then q8w.

[b] 260-520 mg at w0 and then 90 mg q8w.

novel molecular targets for drugs and potential new therapeutic approaches for the treatment of IBD. At present, there are only three non-anti-TNF biologics approved for the treatment of IBD; natalizumab (a recombinant humanized monoclonal IgG4 antibody against the integrin subunit α4), vedolizumab (a humanized IgG1 monoclonal antibody that selectively blocks the α4β7 integrin) and ustekinumab (a fully human IgG1 monoclonal antibody directed against the shared p40 subunit of interleukin (IL)-12 and IL23) [10,11]. In addition, there are several new biologics currently under development that are projected to reach the pharmaceutical market in the near future [12,13]. These agents include other anti-adhesion molecule inhibitors (anti-integrins) and anti-IL drugs as well as small molecules, such as Janus kinases (JAK) and sphingosine-1-phosphatase (S1P) receptor inhibitors (Table 1).

The aim of this review is to provide an overview of non-anti-TNF therapies for the treatment of IBD that were studied or are still being studied in clinical trials with an emphasis on the most promising agents already in late-stage clinical development.

2. Anti-adhesion molecule inhibitors (anti-integrins)

2.1. Natalizumab

Natalizumab is a recombinant humanized monoclonal IgG4 antibody against the integrin subunit α4 that blocks both α4β7 and α4β1 preventing the migration of lymphocytes into most tissues, including the intestine, skin and the brain. Natalizumab was the first anti-adhesion molecule inhibitor approved by the Food and Drug Administration (FDA) for CD. The efficacy of natalizumab was demonstrated by the ENACT-2 [14] and ENCORE [15] placebo-controlled randomized clinical trials (RCTs). In the ENACT-2 trial, 339 patients who had responded to induction natalizumab therapy were randomly assigned to receive either 300 mg of active drug or placebo every 4 weeks through week 56. Natalizumab compared to placebo resulted in higher rates of sustained response (61% vs. 28%, $p < 0.001$) and remission (44% vs. 26% $p < 0.003$) at week 36, respectively [14]. In the ENCORE study 509 patients with moderately to severely active CD and active inflammation characterized by elevated C-reactive protein concentrations were randomized to receive either natalizumab 300 mg or placebo at weeks 0, 4, and 8. Natalizumab compared to placebo resulted in higher rates of sustained response (48% vs. 32%, $p < 0.001$) and remission (26% vs. 16% $p = 0.002$) at week 8 through week 12, respectively [15]. Moreover, a recent meta-analysis showed that natalizumab was superior to placebo for the induction of remission in CD [16].

However, natalizumab in some rare cases promoted reactivation of John Cunningham virus (JCV) in the brain and the development of progressive multifocal leukoencephalopathy (PML) due to inhibition of leukocyte migration to the central nervous system [17,18]. Thus, natalizumab was voluntarily withdrawn from the market in the US and Europe but was then reintroduced in the US in combination with a surveillance program and careful monitoring. The use of natalizumab is limited to patients without other immunosuppressive therapy and those who are JCV negative, preferably for short-term treatment (< 2 years) [19]. Monitoring of JCV antibody development on therapy is recommended [19].

2.2. Vedolizumab

Vedolizumab is a humanized IgG1 monoclonal antibody that selectively blocks the α4β7 integrin and mainly targets gut homing leukocytes. Due to the gut-selective nature of the compound and the fact that it does not cross the blood brain barrier, it is not associated with PML. Vedolizumab was approved by the FDA and the European Medicines Agency for the treatment of moderate to severe CD [20] and UC [21]. The efficacy of vedolizumab was confirmed by the GEMINI phase III RCTs.

In the GEMINI I trial 374 patients with moderate to severely active

UC were randomized to either 300 mg of intravenous vedolizumab or placebo at weeks 0, 2 and 6 (cohort 1) and 521 patients received open-label vedolizumab at weeks 0 and 2 (cohort 2), with disease evaluation at week 6. Vedolizumab compared to placebo resulted in higher rates of clinical response (47.1% vs. 25.5%, $p < 0.001$) at week 6. In the trial of maintenance therapy, patients in either cohort who had a response to vedolizumab at week 6 were randomly assigned to continue receiving vedolizumab every 8 or 4 weeks or to switch to placebo for up to 52 weeks. Vedolizumab compared to placebo resulted in higher rates of clinical remission (44.8% vs. 29.1%, $p < 0.001$) for vedolizumab every 4 weeks and (41.8% vs. 15.9%, $p < 0.001$) for vedolizumab every 8 weeks at week 52, respectively. Adverse events were not different between groups [22].

In the GEMINI II trial, 368 patients with moderate to severely active CD were randomly assigned to receive 300 mg vedolizumab or placebo at weeks 0 and 2 (cohort 1) and 747 patients received open-label vedolizumab at weeks 0 and 2 (cohort 2) with disease evaluation at week 6. Vedolizumab compared to placebo resulted in higher rates of clinical remission (14.5% vs. 6.8%, $p = 0.020$) at week 6 (cohort 1). In the maintenance trial, 461 patients from both cohorts 1 and 2 who had had a response to vedolizumab were randomly assigned to receive placebo or vedolizumab every 8 or 4 weeks until week 52. Vedolizumab compared to placebo resulted in higher rates of clinical remission (36.4% vs. 21.6%, $p = 0.004$) for vedolizumab every 4 weeks and (39% vs. 21.6%, $p < 0.001$) for vedolizumab every 8 weeks at week 52, respectively. The incidence of any serious adverse event was higher among patients who received vedolizumab than among those who received placebo (24.4% vs. 15.3%) with nasopharyngitis being the most frequent one [23].

In the GEMINI III trial 315 patient with moderately to severely active CD and previous anti-TNF failure were randomly assigned to receive 300 mg vedolizumab or placebo at weeks 0, 2 and 6 with disease evaluation at weeks 6 and 10. Vedolizumab compared to placebo resulted in higher rates of clinical response (39.2% vs.22.3%, $p = 0.001$) at week 6 and clinical remission (26.6% vs.12.1%, $p = 0.001$) at week 10. Adverse event results were similar in all groups [24].

Recent data from systematic reviews, meta-analyses and post-marketing studies have demonstrated that vedolizumab is a safe drug for the treatment of patients with moderate to severe CD and UC including also those who have previously failed anti-TNF therapy [25–29]. However, it may have a slower onset of action often requiring 10 weeks of therapy or more.

2.3. Etrolizumab

Etrolizumab (rhuMAb b7) is a humanized monoclonal IgG1 antibody that targets the β7 subunit of the heterodimeric integrins α4β7 and αEβ7 and subsequently inhibits lymphocyte trafficking to the gut by blocking a4b7/mucosal address in cell adhesion molecule 1 (MAdCAM-1) and retention of leucocytes in the gut intraepithelial lining by blocking αEβ7/E-cadherin [30,31].

In a phase I trial of patients with moderate-severe UC, etrolizumab was found to be safe and well tolerated with headache being the most common adverse effect followed by fatigue, abdominal pain and nasopharyngitis [32]. In a later phase II RCT, EUCALYPTUS, 124 patients with moderate to severe UC were randomized 1:1:1 to one of two doses of subcutaneous etrolizumab (100 mg at weeks 0, 4, and 8, with placebo at week 2; or 420 mg loading dose at week 0 followed by 300 mg at weeks 2, 4, and 8) or matching placebo. Both the 100 mg (20.5% vs.0%, $p = 0.004$) and 300 mg dosing strategies of etrolizumab (10.3% vs. 0%, $p = 0.048$) were associated with higher rates of clinical remission compared with placebo at 10 weeks. Serious adverse effects were comparable between the etrolizumab groups (12% for etrolizumab 100 mg and 5% for etrolizumab 300 mg) and the placebo group (12%) [33].

A retrospective analysis of pharmacodynamic data collected from 110 patients with UC who participated in the EUCALYPTUS study and 21 patients with UC or without IBD serving as a control group showed that levels of granzyme A and integrin αE messenger RNAs in colon tissues can identify patients with UC who are most likely to benefit from etrolizumab [34]. This could be the first step towards more personalized medicine. Etrolizumab is currently being evaluated in phase III RCTs studies in both CD (NCT02394028) and UC (NCT02100696, NCT02165215, NCT02163759).

2.4. Alicaforsen

Alicaforsen (ISIS 2302) is a human antisense oligonucleotide, which inhibits ICAM-1 and blocks leukocyte recruitment. In an open-label, uncontrolled study, 12 patients with chronic, unremitting pouchitis were treated with 240 mg alicaforsen antisense enema nightly for 6 weeks with clinical evaluation and endoscopy performed at weeks 3, 6 and 10. After 6 weeks of nightly alicaforsen enema, a statistically significant reduction in the Pouchitis Disease Activity Index from baseline to week 6 (11.42 vs. 6.83, $p = 0.001$, respectively) was observed. Ten of the 12 patients achieved a mucosal appearance score of 0 or 1 at endoscopy. The alicaforsen enemas were well tolerated and no serious side-effects were noted [35]. The alicaforsen enemas are currently being evaluated in a phase III study for chronic antibiotic refractory pouchitis (NCT02525523).

2.5. AJM300

AJM300 is an orally active α4 integrin antagonist. In a phase IIa RCT 102 patients with moderately active UC who had inadequate response or intolerance to mesalamine or corticosteroids were randomly assigned to receive 960 mg AJM300 or placebo 3 times daily for 8 weeks. AJM300 compared to placebo resulted in higher rates of clinical response (62.5% vs. 25.5%, $p < 0.001$), clinical remission (23.5% vs. 3.9%, $p = 0.001$), and mucosal healing (58.8% vs. 29.4%, $p = 0.001$), respectively. No serious adverse event, including PML, was reported [36], although as AJM300 lacks specificity to gut, the potential risk for PML cannot be diminished. AJM300 is now being evaluated in a phase III RCT for UC.

2.6. Pf-00547659

PF-00547659 is a fully human monoclonal IgG2 antibody directed against MAdCAM-1. In the first placebo-controlled RCT regarding 80 patients with active UC who were randomized to receive single or multiple (3 doses at 4-week intervals) doses of 0.03–10 mg/kg PF-00547659 or placebo and were followed through week 12. PF-00547659 was well tolerated and safe [37]. In the subsequent phase II OPERA RCT, 265 patients with active moderate-to-severe CD were randomized to PF-00547659 22.5 mg, 75 mg or 225 mg or placebo. Clinical endpoint differences between PF-00547659 and placebo at weeks 8 or 12 did not reach statistical significance. No safety signal was seen [38]. In the phase II TURANDOT RCT, 357 patients with moderate to severe UC were randomly assigned to receive a subcutaneous injection of 7.5 mg, 22.5 mg, 75 mg, or 225 mg PF-00547659 or placebo. PF-00547659 7.5 mg (11.3% vs. 2.7%, $p = 0.045$), 22.5 mg (16.7% vs. 2.7%, $p = 0.001$) and 75 mg (15.5% vs. 2.7%, $p = 0.012$) resulted in higher rates of clinical remission compared to placebo, respectively. No safety issues were observed [39].

The safety study TOSCA evaluated PF-00547659 in 39 adult patients with moderate to severe CD with prior treatment with both anti-TNF and immunosuppressants (thiopurines or methotrexate). In patients who received a full induction course of the highest clinical dose of PF-00547659, there was no change in cerebrospinal fluid lymphocyte cell count after treatment, suggesting that PML under PF-00547659 may be a lesser concern [40]. While waiting for the long-term efficacy and safety data of PF-00547659 from the RCT OPERA II trial in CD and the

TURANDOT II trial in UC, phase III RCTs have already been planned.

3. Anti-interleukin drugs

3.1. Ustekinumab

Ustekinumab is a fully human IgG1 monoclonal antibody directed against the shared p40 subunit of IL12 and IL23 which leads to a down-regulation of cytokine expression in both the Th1 and Th17 pathways [41]. In the phase IIb CERTIFI RCT, 526 patients with moderate-to-severe CD who were resistant to anti-TNF therapy were randomly assigned to receive intravenous ustekinumab (at a dose of 1, 3, or 6 mg per kilogram of body weight) or placebo at week 0. Ustekinumab (6 mg/kg) compared to placebo was associated with a higher rate of clinical response (39.7% vs. 23.5%, p = 0.005) at week 6. During the maintenance phase, 145 patients who had a response to ustekinumab at 6 weeks underwent a second randomization to receive subcutaneous injections of ustekinumab (90 mg) or placebo at weeks 8 and 16. Ustekinumab compared to placebo was associated with a higher rate of clinical response (69.4% vs. 42.5%, p < 0.001) and remission (41.7% vs. 27.4%, p = 0.030) at week 22. Serious infections occurred in 7 patients (6 receiving ustekinumab) during induction and 11 patients (4 receiving ustekinumab) during maintenance [42].

The phase III RCTs UNITI, randomized patients with moderately to severely active CD who failed TNF (UNITI-1, n = 741) or who were biologic naïve (UNITI-2, n = 628) to receive a single intravenous dose of ustekinumab (130 mg or approximately 6 mg per kilogram of body weight) or placebo. In UNITI-1, ustekinumab (130 mg or approximately 6 mg per kilogram of body weight) compared to placebo was associated with a higher rate of clinical response (34.3% or 33.7% vs. 21.5%, p = 0.003 for both comparisons) at week 6, respectively. In UNITI-2, ustekinumab (130 mg or approximately 6 mg per kilogram of body weight) compared to placebo was associated with a higher rate of clinical response (51.7% or 55.5% vs. 28.7%, p < 0.001 for both comparisons) at week 6, respectively. Patients who completed these induction trials then participated in IM-UNITI, in which the 397 patients who had a response to ustekinumab were randomly assigned to receive subcutaneous maintenance injections of 90 mg of ustekinumab (either every 8 weeks or every 12 weeks) or placebo. In IM-UNITI, ustekinumab (either every 8 weeks or every 12 weeks) compared to placebo was associated with a higher rate of clinical response at week 44 (53.1% or 48.8% vs. 35.9%, p = 0.005 or p = 0.040, respectively). Adverse effects were similar in the groups [43]. Another advantage of ustekinumab was shown in an observational study where almost two thirds of patients with CD refractory to anti-TNFs were able to be spared of steroids for a period of almost a year [44].

Ustekinumab is an effective and safe therapy for CD, although several questions remain to be answered regarding the efficacy of ustekinumab for the treatment of extra-intestinal manifestations and perianal fistulizing CD. The phase III RCT UNIFI which will evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in patients with moderately to severely active UC is currently underway (NCT02407236).

3.2. Risankizumab

Risankizumab (BI 655066 or ABBV-066) is a humanized IgG1 monoclonal antibody against the p19 subunit of IL23. In a phase II RCT, 121 patients with moderate to severe CD were randomized 1:1:1 to receive intravenous 200 mg or 600 mg risankizumab, or placebo, at weeks 0, 4, and 8. Risankizumab (combined 200 and 600 mg group) compared to placebo was associated with a higher rate of clinical remission (31% vs. 15%, p = 0.049) at week 12. Adverse effects were similar among the groups. The most common adverse event was nausea and most common serious adverse event was worsening of underlying CD [45]. A phase III RCT investigating the efficacy and safety of risankizumab in subjects with moderately to severely active CD is currently underway (NCT03105128).

3.3. Brazikumab

Brazikumab (AMG 139 or MEDI2070) is a human IgG2 monoclonal antibody that targets the p19 subunit of IL23. In a phase IIa RCT 119 patients with moderate to severe CD who previously failed anti-TNF therapy were randomly assigned 1:1 to receive brazikumab (700 mg) or placebo intravenously at weeks 0 and 4. Brazikumab compared to placebo was associated with a higher rate of clinical response at week 8 (49.2% vs. 26.7%, p = 0.010). Adverse effects were similar between groups. Higher baseline serum concentrations of IL22, a cytokine whose expression is induced by IL23, were associated with greater likelihood of response to brazikumab compared to placebo [46].

4. Small molecules

4.1. Tofacitinib

Tofacitinib is a small molecule drug that inhibits JAK1 and JAK3. This inhibition blocks signaling for a large subset of inflammatory cytokines such as IL2, 4, 6, 7, 9, 15, 21 and interferon-γ [47]. In a phase II RCT, 194 patients with moderately to severely active UC were randomized to receive tofacitinib at a dose of 0.5 mg, 3 mg, 10 mg, or 15 mg or placebo twice daily for 8 weeks. Clinical remission at week 8 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. There was a dose-dependent increase in both low-density and high-density lipoprotein cholesterol [48].

In a subsequent phase III RCTs 598 (OCTAVE 1; failed conventional therapy) and 541 (OCTAVE 2; failed anti-TNF) patients with moderately to severely active UC were randomly assigned to receive induction therapy with tofacitinib (10 mg twice daily) or placebo for 8 weeks. In OCTAVE 1, tofacitinib compared to placebo was associated with a higher rate of clinical remission (18.5% vs. 8.2%, p = 0.007) at week 8. In OCTAVE 2, tofacitinib compared to placebo was associated with a higher rate of clinical remission (16.6% vs. 3.6%, p < 0.001) at week 8. In the OCTAVE Sustain RCT, 593 patients who had a clinical response to induction therapy were randomly assigned to receive maintenance therapy with tofacitinib (either 5 mg or 10 mg twice daily) or placebo for 52 weeks. Clinical remission at week 52 occurred in 34.3% of the patients in the 5-mg tofacitinib group and 40.6% in the 10-mg tofacitinib group versus 11.1% in the placebo group (p < 0.001 for both comparisons with placebo). In the OCTAVE Induction 1 and 2 trials, the rates of overall infection and serious infection were higher with tofacitinib than with placebo. In the OCTAVE Sustain trial, the rate of serious infection was similar across the three treatment groups, and the rates of overall infection and herpes zoster infection were higher with tofacitinib than with placebo. Herpes zoster infection occurred in 3 patients (1.5%) in the 5-mg tofacitinib group, 10 (5.1%) in the 10-mg tofacitinib group, and 1 (0.5%) in the placebo group. Across all three trials tofacitinib was associated with increased lipid levels [49].

4.2. Filgotinib

Filgotinib (GLPG0634, GS-6034) is an oral small molecular that selectively inhibits JAK-1. In a phase II RCT, 174 patients with moderate-to-severe CD were randomly assigned (3:1) to receive filgotinib 200 mg once a day or placebo for 10 weeks. After week 10, patients were assigned, based on responder status, to filgotinib 100 mg once a day, filgotinib 200 mg once a day, or placebo for an observational period lasting another10 weeks. Filgotinib compared to placebo was associated to a higher rate of clinical remission at week 10 (47% vs. 23%, p = 0.008). In a pooled analysis of all periods of filgotinib and

placebo exposure over 20 weeks, serious treatment-emergent adverse effects were reported in 14 (9%) of 152 patients treated with filgotinib and three (4%) of 67 patients treated with placebo [50]. Phase III RCTs for both CD (NCT02914561, NCT02914600, NCT03077412) and UC (NCT02914522) are currently underway or planned to start soon.

4.3. Upadacitinib

Upadacitinib (ABT-494) is a selective JAK1 inhibitor. In the phase II RCT CELEST, 220 patients with moderately to severely active CD were randomized to receive upadacitinib at doses of 3, 6, 12, 24 mg twice daily or 24 mg once daily or placebo for 16 weeks, followed by blinded extension therapy for 36 weeks. Significantly more patients receiving upadacitinib doses greater than or equal to 6 mg twice daily achieved endoscopic response compared to placebo ($p \leq 0.01$ for all comparisons). Serious adverse events and discontinuations were similar in all groups, except for numerically greater events in the 12 mg twice daily group [51]. A phase III RCT for UC is currently underway (NCT02819635).

4.4. Ozanimod

Ozanimod (RCP-1063) is a novel orally administered small molecule that is a S1P1 and S1P5 receptor modulator which leads to lymphocyte sequestration in lymph nodes and presumably reduces circulating lymphocytes and migration to the gastrointestinal tract. In the phase II RCT TOUCHSTONE, 197 patients with moderate-to-severe UC were randomized to receive ozanimod 0.5 mg/day or 1 mg/day or placebo for up to 32 weeks. The most common adverse events were anemia and headache. Ozanimod 1 mg/day compared to placebo was associated with a higher rate of clinical remission (16% vs. 6%, $p = 0.048$) at week 8 [52]. A Phase II study in CD (NCT02531113) is currently ongoing, while a phase III RCT is underway in UC.

4.5. Laquinimod

Laquinimod (TV-5600, previously ABR-215062) is an oral, synthetic, small molecule with anti-inflammatory properties. In a phase IIa RCT 180 patients with active moderate-severe CD were randomized to receive laquinimod doses of 0.5, 1, 1.5 or 2 mg/day or placebo ($n = 45$ per cohort randomized in a 2:1 ratio) for 8 weeks with 4-week follow-up. Treatment with laquinimod 0.5 mg showed consistent effects on clinical remission (48.3%) versus placebo (15.9%). Adverse events were similar among groups [53].

5. Therapeutic drug monitoring of non-anti-TNF drugs

Numerous exposure-response relationship studies have demonstrated a positive correlation between anti-TNF drug concentrations and therapeutic outcomes, suggesting that it is maybe the time to go beyond a treat-to-target to a treat-to-trough therapeutic approach [54–58]. However, this seems to be the case also for drugs with different mechanisms of action, such as vedolizumab and ustekinumab [22,23,43,59,60]. Williet et al. in a prospective study of patients with IBD receiving induction therapy, low trough levels of vedolizumab at week 6 (< 19 μg/mL) were associated with need for additional doses (given at week 10 and then every 4 weeks) [59]. Maintenance trough concentrations of ustekinumab > 4.5 μg/mL at week 26 or later were associated with inflammatory biomarker reduction and endoscopic response [60]. On the other hand, anti-drug antibodies have been associated with undesirable therapeutic outcomes in IBD, such as primary non-response and secondary loss of response [54–58]. However, immunogenicity appears to be rather low for non-anti-TNF drugs. Antibodies to vedolizumab were noted only in 3.7–4.1% of patients in GEMINI 1 and 2 RCTs of which 0.4–1% were persistently positive [22,23]. Antibodies to ustekinumab were even lower reported only in 0.7–2.3% of patients in CERTIFI and UNITI RCTs [42,43]. Therapeutic drug monitoring both proactive and reactive could be a great tool for optimizing not only anti-TNF therapy but also other than anti-TNF biologics, especially when assays will be extensively available [61–64].

6. Conclusion

A number of new therapeutic options for IBD have recently been approved and more are in later stages of development. These non-anti-TNF agents may potentially provide valuable treatment options for patients that fail anti-TNF therapy. Although, the position of the aforementioned drugs in the clinical armamentarium is still unknown, it is likely that many of them will find their place in the treatment algorithm of IBD in the upcoming years. It will be of great clinical importance to be able to identify genetic, serologic or tissue markers that predict response/remission to individual agents or mechanisms and better personalize care.

Conflicts of interest

K.H·K: received honoraria for consulting services (educational services, scientific articles, participation in advisory boards, clinical trials, other) from AbbVie, Aenorasis, Ferring, Jannsen, MSD, Nestle, Shire and Takeda; A.S·C: received consultancy fees from AbbVie, Janssen, Takeda, Ferring, Miraca, AMAG, and Pfizer. The remaining authors have no conflict of interest to disclose.

References

[1] C. Abraham, et al., Inflammatory bowel disease, N. Engl. J. Med. 361 (2009) 2066–2078.
[2] C.N. Bernstein, Review article: changes in the epidemiology of inflammatory bowel disease-clues for aetiology, Aliment. Pharmacol. Ther. 46 (2017) 911–919.
[3] R.J. Xavier, et al., Unraveling the pathogenesis of inflammatory bowel disease, Nature 448 (2007) 427–434.
[4] M.F. Neurath, Current and emerging therapeutic targets for IBD, Nat. Rev. Gastroenterol. Hepatol. 14 (2017) 269–278.
[5] L. Peyrin-Biroulet, et al., Review article: remission rates achievable by current therapies for inflammatory bowel disease, Aliment. Pharmacol. Ther. 33 (2011) 870–879.
[6] K. Papamichael, et al., Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse, Inflamm. Bowel Dis. 21 (2015) 182–197.
[7] S. Ben-Horin, et al., Review article: loss of response to anti-TNF treatments in Crohn's disease, Aliment. Pharmacol. Ther. 33 (2011) 987–995.
[8] M. Lemaitre, et al., Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease, JAMA 318 (2017) 1679–1686.
[9] S. Bonovas, et al., Biologic therapies and risk of infection and malignancy in patients with inflammatory bowel disease: a systematic review and network meta-analysis, Clin. Gastroenterol. Hepatol. 14 (2016) 1385–1397.
[10] T. Lobatón, et al., Review article: anti-adhesion therapies for inflammatory bowel disease, Aliment. Pharmacol. Ther. 39 (2014) 579–594.
[11] A. Jauregui-Amezaga, et al., Next generation of biologics for the treatment of Crohn's disease: an evidence-based review on ustekinumab, Clin. Exp. Gastroenterol. 10 (2017) 293–301.
[12] S. Danese, New therapies for inflammatory bowel disease: from the bench to the bedside, Gut 61 (2012) 918–932.
[13] P. Olivera, et al., Next generation of small molecules in inflammatory bowel disease, Gut 66 (2017) 199–209.
[14] W.J. Sandborn, et al., Natalizumab induction and maintenance therapy for Crohn's disease, N. Engl. J. Med. 353 (2005) 1912–1925.
[15] S.R. Targan, et al., Natalizumab for the treatment of active Crohn's disease: results of the ENCORE trial, Gastroenterology 132 (2007) 1672–1683.
[16] A.K. Chandar, et al., Efficacy and safety of natalizumab and vedolizumab for the management of Crohn's disease: a systematic review and meta-analysis, Inflamm. Bowel Dis. 21 (2015) 1695–1708.
[17] G. Van Assche, et al., Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease, N. Engl. J. Med. 353 (2005) 362–368.
[18] A. Langer-Gould, et al., Progressive multifocal leukoencephalopathy in a patient treated with natalizumab, N. Engl. J. Med. 353 (2005) 375–381.
[19] G. Bloomgren, et al., Risk of natalizumab-associated progressive multifocal leukoencephalopathy, N. Engl. J. Med. 366 (2012) 1870–1880.
[20] B.G. Feagan, et al., Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin, Clin. Gastroenterol. Hepatol. 6 (2008) 1370–1377.
[21] B.G. Feagan, et al., Treatment of ulcerative colitis with a humanized antibody to the

alpha4beta7 integrin, N. Engl. J. Med. 352 (2005) 2499–2507.
[22] B.G. Feagan, et al., GEMINI 1 study group. Vedolizumab as induction and maintenance therapy for ulcerative colitis, N. Engl. J. Med. 369 (2013) 699–710.
[23] W.J. Sandborn, et al., Vedolizumab as induction and maintenance therapy for Crohn's disease, N. Engl. J. Med. 369 (2013) 711–721.
[24] B.E. Sands, et al., Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed, Gastroenterology 147 (2014) 618–627.
[25] M.H. Mosli, et al., Vedolizumab for induction and maintenance of remission in ulcerative colitis: a Cochrane systematic review and meta-analysis, Inflamm. Bowel Dis. 21 (2015) 1151–1159.
[26] A. Amiot, et al., Effectiveness and safety of vedolizumab induction therapy for patients with inflammatory bowel disease, Clin. Gastroenterol. Hepatol. 14 (2016) 1593–1601.
[27] A. Parikh, et al., Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease, Inflamm. Bowel Dis. 19 (2013) 1691–1699.
[28] J.F. Colombel, et al., The safety of vedolizumab for ulcerative colitis and Crohn's disease, Gut 66 (2017) 839–851.
[29] P. Luthra, et al., Systematic review and meta-analysis: opportunistic infections and malignancies during treatment with anti-integrin antibodies in inflammatory bowel disease, Aliment. Pharmacol. Ther. 41 (2015) 1227–1236.
[30] S. Zundler, et al., Blockade of αEβ7 integrin suppresses accumulation of CD8(+) and Th9 lymphocytes from patients with IBD in the inflamed gut in vivo, Gut 66 (2017) 1936–1948.
[31] E.G. Stefanich, et al., A humanized monoclonal antibody targeting the b7 integrin selectively blocks intestinal homing of T lymphocytes, Br. J. Pharmacol. 162 (2011) 1855–1870.
[32] P.J. Rutgeerts, et al., A randomised phase I study of etrolizumab (rhuMAb b7) in moderate to severe ulcerative colitis, Gut 62 (2013) 1122–1130.
[33] S. Vermeire, et al., Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial, Lancet 384 (2014) 309–318.
[34] G.W. Tew, et al., Association between response to etrolizumab and expression of integrin alphaE and Granzyme A in colon biopsies of patients with ulcerative colitis, Gastroenterology 150 (2016) 477–487.
[35] H.P. Miner, et al., An enema formulation of alicaforsen, an antisense inhibitor of intercellular adhesion molecule-1, in the treatment of chronic, unremitting pouchitis, Aliment. Pharmacol. Ther. 19 (2004) 281–286.
[36] N. Yoshimura, et al., Safety and efficacy of AJM300, an oral antagonist of alpha4 integrin, in induction therapy for patients with active ulcerative colitis, Gastroenterology 149 (2015) 1775–1883.
[37] S. Vermeire, et al., The mucosal addressin cell adhesion molecule antibody PF-00547,659 in ulcerative colitis: a randomised study, Gut 60 (2011) 1068–1075.
[38] W.J. Sandborn, et al., Phase II evaluation of anti-MAdCAM antibody PF-00547659 in the treatment of Crohn's disease: report of the OPERA study, Gut 60 (2011) 1068–1075, http://dx.doi.org/10.1136/gutjnl-2016-313457 (Gut 2017 Oct 5. pii: gutjnl-2016-313457, Epub ahead of print).
[39] S. Vermeire, et al., Anti-MAdCAM antibody (PF-00547659) for ulcerative colitis (TURANDOT): a phase 2, randomized, double-blind, placebo-controlled trial, Lancet 390 (2017) 135–144.
[40] G. D'Haens, et al., Effect of PF-00547659 on central nervous system immune surveillance and circulating β7+ T Cells in Crohn's disease: Report of the TOSCA study: MADCAM-1 antibody and CNS immune surveillance, J. Crohns. Colitis. 12 (2) (2018) 188–196, http://dx.doi.org/10.1093/ecco-jcc/jjx128 (Jan 24, Epub ahead of print).
[41] P. Deepak, et al., Ustekinumab in treatment of Crohn's disease: design, development, and potential place in therapy, Drug. Des. Devel. Ther. 10 (2016) 3685–3698.
[42] W.J. Sandborn, et al., CERTIFI study group. Ustekinumab induction and maintenance therapy in refractory Crohn's disease, N. Engl. J. Med. 367 (2012) 1519–1528.
[43] B.G. Feagan, et al., Ustekinumab as induction and maintenance therapy for Crohn's disease, N. Engl. J. Med. 375 (2016) 1946–1960.
[44] P. Wils, et al., Subcutaneous ustekinumab provides clinical benefit for two-thirds of patients with Crohn's disease refractory to anti-tumor necrosis factor agents, Clin. Gastroenterol. Hepatol. 14 (2016) 242–250.
[45] B.G. Feagan, et al., Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomized, double-blind, placebo-controlled phase 2 study, Lancet 289 (2017) 1699–1709.
[46] B.E. Sands, et al., Efficacy and safety of MEDI2070, an antibody against interleukin 23, in patients with moderate to severe Crohn's disease: a phase 2a study, Gastroenterology 153 (2017) 77–86.
[47] S. Banerjee, et al., JAK-STAT signalling as a target for inflammatory and autoimmune diseases: current and future prospects, Drugs 77 (2017) 521–546.
[48] W.J. Sandborn, et al., Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis, N. Engl. J. Med. 367 (2012) 616–624.
[49] W.J. Sandborn, et al., Tofacitinib as induction and maintenance therapy for ulcerative colitis, N. Engl. J. Med. 376 (2017) 1723–1736.
[50] S. Vermeire, et al., Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial, Lancet 389 (2017) 266–275.
[51] W.J. Sandborn, et al., Safety and efficacy of ABT-494 (Upadacitinib), an oral JAK1 inhibitor, as induction therapy in patients with Crohn's disease: Results from CELEST, Gastroenterology 152 (2017) S1308–S1309.
[52] W.J. Sandborn, et al., Ozanimod induction and maintenance treatment for ulcerative colitis, N. Engl. J. Med. 374 (2016) 1754–1762.
[53] G. D'Haens, et al., A phase II study of laquinimod in Crohn's disease, Gut 64 (2015) 1227–1235.
[54] K. Papamichael, et al., Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis, Clin. Gastroenterol. Hepatol. 14 (2016) 543–549.
[55] K. Papamichael, et al., Post-induction adalimumab concentration is associated with short-term mucosal healing in patients with ulcerative colitis, J. Crohns. Colitis. 11 (2017) 53–59.
[56] K. Papamichael, et al., Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of serum concentrations of infliximab, Clin. Gastroenterol. Hepatol. 15 (2017) 1580–1588.
[57] M.G. Ward, et al., Infliximab and adalimumab drug levels in Crohn's disease: contrasting associations with disease activity and influencing factors, Aliment. Pharmacol. Ther. 46 (2017) 150–161.
[58] B. Ungar, B, et al., optimizing anti-TNF-α therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases, Clin. Gastroenterol. Hepatol. 14 (2016) 550–557.
[59] N. Williet, et al., Association between low trough levels of vedolizumab during induction therapy for inflammatory bowel diseases and need for additional doses within 6 months, Clin. Gastroenterol. Hepatol. 15 (2017) 1750–1757.
[60] R. Battat, et al., Association between ustekinumab trough concentrations and clinical, biomarker, and endoscopic outcomes in patients with Crohn's disease, Clin. Gastroenterol. Hepatol. 15 (2017) 1427–1434.
[61] A. Cheifetz, Overview of therapeutic drug monitoring of biologic agents in patients with inflammatory bowel disease, Gastroenterol. Hepatol. (NY). 13 (2017) 556–559.
[62] K. Papamichael, et al., Therapeutic drug monitoring in IBD: the new standard-of-care for anti-TNF therapy, Am. J. Gastroenterol. 112 (2017) 673–676.
[63] N. Vande Casteele, et al., Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease, Gastroenterology 148 (2015) 1320–1329.
[64] B.P. Vaughn, et al., Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study, Inflamm. Bowel Dis. 20 (2014) 1996–2003.