Review Article

Inflammatory Intestinal Diseases

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Mechanism-Based Treatment Strategies for IBD: Cytokines, Cell Adhesion Molecules, JAK Inhibitors, Gut Flora, and More

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Abstract
Background: Although TNF inhibitors revolutionized the therapy of inflammatory bowel disease (IBD), we have been reaching a point where other therapies with different mechanisms of action are necessary. A rising number of elderly IBD patients with contraindications to established therapies and a growing group of patients losing response to anti-TNF therapy compel us to find safer, better-tolerated, and, ideally, personalized treatment options. However, in order to choose the right drug to fit a patient, it is indispensable to understand the pathomechanism involved in IBD. ***Summary:*** The aim of this review is to explain the inflammatory signaling pathways in IBD and how to inhibit them with current and future therapeutic approaches. Next to biologic agents targeting inflammatory cytokines (anti-TNF agents, anti-IL-12/-23 agents, and specific inhibitors of IL-23), biologics blocking leukocyte trafficking to the gut (anti-integrin antibodies) are available nowadays. More recently, small molecules inhibiting the JAK-STAT pathway (JAK inhibitors) or preventing lymphocyte trafficking (sphingosine-1-phosphate modulators) have been approved or are under investigation. Furthermore, modifying the microbiota has potential therapeutic effects on IBD, and autologous hematopoietic or mesenchymal stem cell transplantation may be considered for a highly selected group of IBD patients. ***Key Message:*** Physicians should understand the different mechanisms of action of the potential therapies for IBD to select the right drug for the right patient.

Introduction

In recent years, our understanding of the pathogenesis of inflammatory bowel disease (IBD) with its two main entities, ulcerative colitis (UC) and Crohn's disease (CD), has increased considerably. IBD is a chronic inflammatory disease believed to be triggered by specific or multiple environmental factors in genetically

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susceptible individuals. An impaired mucosal barrier together with disturbed luminal microbiota finally lead to a consecutive dysregulation of the intestinal immune system [1].

Although current strategies connect this knowledge of disease pathogenesis with new mechanisms of action for potential therapies, there is still no cure in sight. Instead, a global increase in the incidence and prevalence of IBD can be observed [2, 3], which is mainly driven by higher incidence rates in Asian and South American countries and due to a demographic shift with a growing, older IBD population [4], inevitably leading to a higher prevalence. Despite the fact that the course of elderly-onset IBD is often mild and associated with a lower use of immunosuppressants [5, 6], these IBD patients represent a difficult-to-treat patient group with many aspects to be considered [7].

Interestingly, the incidence of IBD in Western countries – after a tremendous rise in the past 50 years [8] – finally seems to increase more slowly or reach a plateau. Nevertheless, IBD has still the highest incidence and prevalence (exceeding 0.3%) in North America, Oceania, and Europe [3, 9]. As mentioned above, we experience an increase in the incidence of IBD in Asian countries [3, 8, 10]. Considering China with a population of nearly 1.4 billion and India with 1.3 billion people, the increase in IBD in these countries [11–14] creates huge economic challenges. However, it also provides the opportunity to better understand the epidemiological aspects of IBD and to investigate the factors that lead to IBD, which finally may help us to develop new therapies.

This review highlights novel therapies for CD and UC based on novel insights into the highly complex pathogenesis of IBD, including anti-cell adhesion molecules; therapies capable of blocking proinflammatory cytokines and stopping downstream signaling; molecules preventing lymphocyte trafficking; and strategies influencing the microbiota and stem cell therapy. The available agents and therapies under investigation are summarized in Table 1.

Cytokines

TNF Inhibitors

The proinflammatory cytokine TNF-α plays a major role in the immunopathogenesis of IBD [15]. In IBD, the production of soluble and membrane-bound TNF is significantly increased through CD14+ macrophages, fibroblasts, and T cells [16].

At the turn of the millennium, the advent of infliximab, a chimeric antibody against TNF comprising 25% murine sequence and 75% human sequence, marked an important milestone in the therapy for refractory IBD. In 1997, Targan et al. [17] published the first controlled study demonstrating the efficacy of infliximab in CD patients. More placebo-controlled trials of CD [18, 19] and, later on, of UC [20] followed, so that nowadays infliximab is a mainstay of IBD therapy particularly for patients who do not respond to conventional therapies [21]. In the past decade, three other subcutaneous TNF inhibitors have become available. Adalimumab, a fully human monoclonal antibody, has been shown to induce and maintain remission in moderate-to-severe CD [22–24] and UC [25–27]. For certolizumab, a humanized Fab (antigen-binding fragment) lacking the fragment crystallizable (Fc) region, successful induction and remission could be demonstrated in CD [28, 29] – and, likewise, for golimumab, a fully human antibody, in UC [30, 31].

No randomized controlled trials (RCTs) of certolizumab in UC or golimumab in CD have been published. However, in the last years some retrospective studies have demonstrated the efficacy and safety of golimumab in CD [32, 33]. Furthermore, the first results of an open-label maintenance study with certolizumab pegol showed its effectiveness in UC [34], and a phase II study is still ongoing [35]. Recently, meta-analyses have confirmed the efficacy of TNF inhibitors in CD and UC [36–38].

Interestingly, etanercept – a soluble recombinant TNF receptor also binding to circulating TNF, thereby neutralizing it – failed to show efficacy in CD, leading to the concept that the therapeutic effect of anti-TNFs in IBD must be due to mechanisms other than only TNF neutralization [39]. One explanation for this finding is that both membrane-bound and soluble TNF need to be neutralized to induce T-cell apoptosis in vivo. Blocking soluble TNF alone, as postulated for etanercept, has no therapeutic effect on IBD [16, 40]. However, it has never been investigated in detail whether a soluble TNF receptor fails to block membrane-bound TNF.

In summary, it has to be admitted that the exact mechanism of action of anti-TNF agents in IBD is not fully understood. It is generally assumed that inhibition of the membrane-bound TNF/TNFR2 pathway is crucially involved in inducing T-cell apoptosis [41], consequently inhibiting downstream proinflammatory pathways.

Although TNF inhibitors revolutionized the treatment of IBD, it must be remembered that more than a third of patients are primary nonresponders [42] and that the annual risk for loss of response (LOR) is about 13% per

Table 1. Available agents and therapies for Crohn's disease and ulcerative colitis under investigation

	Crohn's disease	Ulcerative colitis	Remarks
Cytokines			
TNF inhibitors			
Infliximab	✓	✓	
Adalimumab	✓	✓	
Certolizumab	✓	Phase II trial ongoing	
Golimumab	(✓)*	✓	* Retrospective studies in Crohn's disease
Etanercept	Not effective	No data	
IL-23/Th17			
Ustekinumab	✓	Phase III trial ongoing	
Risankizumab	✓ (phase II)	Phase III trial ongoing	
Brazikumab	✓ (phase II)	Phase II trial ongoing	
Mirikizumab	Phase II trial ongoing	✓ (phase II)	
IL-17			
Secukinumab	Not effective*	No data	* Even higher Crohn's disease activity with secukinumab
IL-6			
Tocilizumab	Not effective*		* Only clinical response
PF-04236921	✓ (phase II)*		* Higher rates of perforation
PDE4 inhibitor			
Apremilast	No data	✓ (phase II)	
JAK inhibitors			
Tofacitinib	Not effective (phase II)	✓	
Filgotinib	✓*	Phase III trial ongoing	* Mucosal healing comparable to that with placebo
Upadacitinib	✓ (phase II)	Phase III trial ongoing	
Peficitinib	No data	Not effective*	* Trends for increased remission and response
Anti-trafficking therapies			
Anti-cell adhesion			
Natalizumab	✓	No data (only one open-label trial)	Increased risk of PML
Vedolizumab	✓	✓	
Etrolizumab	Phase III trial ongoing	✓ (phase II)	
Abrilumab	Not effective (phase II)	✓ (phase II)	
Anti-MAdCAM-1			
PF-00547659	Not effective*	✓ (phase II)	* High placebo clinical response and remission rates
Small-molecule integrin antagonists			
AJM300	Not effective	✓	
PTG-100	No data	Phase II trial stopped	Study discontinued due to futility-based outcome
S1P receptor modulators			
Ozanimod	Phase III trial ongoing	✓ (phase II)	
Etrasimod	No data	✓ (phase II)	

patient-year of treatment with infliximab and around 20% per patient-year [43] with adalimumab. Eventually, around 40% of initial responders will definitively lose response to infliximab [44]. Even though we can counteract immunogenicity as the key mechanism in primary nonresponse and LOR by combining infliximab with azathioprine [45, 46], by increasing the dose [47], or by shortening the treatment interval [48], many other unsolved problems remain with TNF inhibitors and their short- and long-term treatment efficacy.

One major concern is the economic burden of biologics. Nowadays, two biosimilars of infliximab, CT-P13 (Inflectra; Remsima) and SB2 (Flixabi), are on the market with an approximately 30% lower price than that of the reference product [49]. Since biosimilars are manufactured with a different cell line and the manufacturing technique may differ slightly from its original product, they are highly similar copy versions of the originators, but not identical. This slight discrepancy between biosimilars has raised substantial caution about their use [50]. In recent years, more real-life data have become available demonstrating no significant differences in efficacy or safety between biosimilars and their reference product [51–53]. A large French equivalence cohort study investigating more than 5,000 CD patients confirmed the equivalent effectiveness of CT-P13 and infliximab [54].

Furthermore, switching from the infliximab originator to CT-P13 can be conducted safely and feasibly without having to expect more serious adverse events [55–58]. Based on the growing number of data on IBD patients treated with biosimilars, the European Crohn's Colitis Organisation (ECCO) states that switching from the originator to a biosimilar in IBD patients is acceptable [59]. Currently, many more biosimilars of adalimumab and infliximab are in the pipeline [49].

Besides the abovementioned immunogenicity and the substantial costs, the two most feared concerns regarding anti-TNF therapy are deleterious adverse events, particularly serious or opportunistic infections and malignancy. Especially in combination therapy with azathioprine, but also less pronounced with anti-TNF monotherapy, there exists a nonnegligible risk of lymphoma [60]. Furthermore, the risk of serious infections in anti-TNF-treated patients is significantly increased [61, 62] and develops at around an annual rate of 2% [63]. The risk is even higher with combination therapy [62] and in elderly patients above 65 years of age, where the absolute risk can be 2- to 3-fold greater than in younger patients [62]. Compared to patients without immunosuppression, the risk of opportunistic infection is approximately 2- to 3-fold increased [64, 65], which is comparable to the infection risk with corticosteroids [64].

Newer biologics and small molecules with a better safety profile and the possibility of being used as "rescue" treatments have been developed and are described below.

IL-23/Th17 Pathway

Recent concepts of the pathophysiology of IBD suggest a disturbed adaptive immune response, with an excessive Th1 immune reaction especially in CD; it is discussed that this is induced by IL-12, leading to the production of large amounts of interferon-γ (IFN-γ), TNF, and IL-6. In contrast, UC is considered a Th2 immune response, with an increased release of IL-5, IL-6, IL-13, and TNF [66]. More recent data have implicated the innate immune system and the IL-23/Th17 axis as being pivotal to the pathogenesis of IBD. A genetic variant of *IL23R*, the gene encoding a subunit of a receptor for IL-23, which is a cytokine involved in the differentiation of Th17 cells, has been found to be significantly associated with CD [67]. Activation of IL-23, with its subunits p19 and p40, triggers the differentiation of naïve T cells into Th17 cells, which then produce IL-17A, IL-17F, and IL-21, thereby suppressing regulatory T-cell activity [16]. Th17 cells are considered to build a bridge between the adaptive and the innate immune system [68]. Interestingly, apoptosis-resistant IL-23R-positive T cells expand in anti-TNF-refractory patients, leading to the hypothesis that IL-23 antagonists are suitable agents for anti-TNF-refractory patients [69].

Next to activation of the IL-23/Th17 pathway through antigen-presenting cells, the induction of other members of the IL-12 family (consisting of IL-12, IL-23, IL-27, and IL-35) [16] is upregulated in intestinal inflammation. Of special interest in CD is IL-12, composed of the subunits p35 and p40, which induces the differentiation of naïve T cells into Th1 cells with concomitant production of TNF and IFN-γ [70]. Several agents interfering with the pathways of IL-23/IL-12 have been developed or are under investigation and show promising results, especially in CD patients. In contrast, attempts to inhibit IL-17A or IL-17R in IBD have remained unsuccessful.

Ustekinumab is a fully human IgG1 monoclonal antibody that blocks the p40 subunit of IL-12/IL-23. Although a phase IIa induction trial failed to show any superiority of ustekinumab over placebo regarding clinical response at week 8 in moderate-to-severe CD (49 vs. 40%, $p = 0.340$), interestingly, in patients who were infliximab experienced, the clinical response was stronger with ustekinumab than with placebo (59 vs. 26%, $p = 0.022$) [71]. The phase III trial (CERTIFI) demonstrated a stronger clinical response in patients receiving 6 mg of ustekinumab per kilogram body weight (39.7 vs. 23.5%, $p = 0.005$), but the rate of clinical remission did not differ significantly between the groups. Furthermore, patients who responded to ustekinumab in the induction phase had increased rates of response and remission in maintenance therapy with ustekinumab [72]. The UNITI-1 (TNF antagonist failures) and UNITI-2 (conventional therapy failures) trials confirmed the previously published data with even better results particularly for anti-TNF-experienced patients, showing significant efficacy in inducing a clinical response in moderately to severely active CD and maintaining remission in patients responding to induction therapy [73]. More recent data support the high maintenance rates in IM-UNITI (a phase III ustekinumab maintenance study in patients with CD) through week 92 without occurrence of serious adverse events, confirming its long-term efficacy and safety in CD patients [74]. A recently performed substudy demonstrated a reduced simplified endoscopic activity score for CD at week 8 and week 44 [75]. Maintenance trough levels of ustekinumab above 4.5 μg/mL after at least 26 weeks of therapy were associated with a stronger endoscopic response (75.9 vs. 40.7%, $p = 0.008$) and a lower mean level of C-reactive protein (12.6 vs. 23.9 mg/L,

$p = 0.040$) [76]. Furthermore, ustekinumab induced a favorable clinical response after 6 months of therapy in a refractory population with chronic pouchitis and CD of the pouch [77]. The first results of a phase III trial showed promising results in moderate-to-severe active UC patients treated with ustekinumab [78].

With risankizumab, a humanized monoclonal IgG1 antibody that selectively targets the p19 subunit of IL-23, another agent influencing the IL-23 signaling pathway is under investigation. The promising results of a randomized, double-blind, phase II study in patients with moderate-to-severe CD, in whom over 70% of the patients had previously received at least two anti-TNF agents, showed higher clinical and endoscopic remission rates (31 vs. 15%, $p = 0.049$, and 17 vs. 3%, $p = 0.002$, respectively) [79]. The extension study confirmed the efficacy of risankizumab in maintaining clinical remission at week 52 and suggests that extended treatment of patients not in deep remission at week 12 increases clinical response and remission rates at week 26 [80]. The most serious adverse events were of gastrointestinal origin [79, 80].

Similar to risankizumab, brazikumab (MEDI2070, formerly AMG 139) is a monoclonal antibody binding selectively to the p19 subunit of IL-23. The first results of a phase IIa study in moderate-to-severe CD patients who failed treatment with an anti-TNF antibody are promising. In the brazikumab group, significantly higher rates of clinical improvement at week 8 could be demonstrated than in the placebo group (49.2 vs. 26.7%, $p = 0.010$) [81].

Although the IL-23 axis is thought to be mainly involved in CD, the first results of a completed induction phase of a phase II study with mirikizumab (LY3074828), a p19-directed anti-IL-23 antibody, showed positive results regarding clinical response and remission at week 12 in moderate-to-severe UC patients [82]. These results have to be confirmed in further studies, but they are encouraging with regard to enlarging the armamentarium for the treatment of UC.

Anti-IL-17

Despite overexpression of IL-17 in CD tissue [83], a known risk polymorphism of IL23R associated with CD [67], and the effect of anti-IL-17 agents in other inflammatory diseases [84, 85], a proof-of-concept study failed to show any efficacy of secukinumab, an IL-17 inhibitor, in CD patients. Patients treated with secukinumab suffered from higher CD activity than patients treated with placebo [86]. Furthermore, some recently published case reports presented the emergence of IBD in patients treated with secukinumab [87]. This deleterious effect with an anti-IL-17 antibody on CD has shown the limitations of our understanding of the complex system of cytokines involved in the pathogenesis of IBD. Nowadays, it is assumed that besides a possible proinflammatory effect, IL-17 acts as an important cytokine for homeostasis in the gut, plays a role in wound repair [88], and maintains intestinal barrier integrity [89]. Blockade of IL-17 can subsequently result in an altered integrity of the gut barrier, which has a more substantial impact on causing colitis than the proinflammatory effect of IL-17 [90].

Anti-IL-6

Due to the fact that IL-6 possesses multiple proinflammatory effects and its production is upregulated in patients with CD [16], it is another potential target for the treatment of IBD. Interestingly, the IL-6 pathway could be a loophole in patients refractory to anti-TNF and anti-integrin therapy. A study investigating biomarkers of vedolizumab (VDZ) resistance demonstrated that patients with IBD failing anti-TNF and VDZ treatment had significantly higher circulating IL-6 levels [91]. Therefore, it is thought that the IL-6 pathway can cause inflammation independently of TNF.

Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor already used in rheumatoid arthritis [92], has been investigated in a randomized pilot trial in active CD, demonstrating a higher clinical response rate than placebo (80 vs. 31%, $p = 0.019$), but neither endoscopic nor histological healing [93]. Since the performance of this small study, no further trials of tocilizumab in CD were performed.

Another fully human IgG2 monoclonal antibody binding and neutralizing IL-6 is PF-04236921. In a double-blind, parallel-group trial in CD patients who failed anti-TNF therapy (ANDANTE I and II), PF-04236921 appeared to be efficient in inducing a clinical response and remission at week 12 (47.4 vs. 28.6%, $p < 0.050$, and 27.4 vs. 10.9%, $p < 0.050$, respectively) [94]. However, it should be noted that gastrointestinal abscesses and perforation were observed with PF-04236921, a known serious adverse event that has also been reported for tocilizumab [95]. Although most of the perforations occurred in patients having diverticulitis and previously taking nonsteroidal anti-inflammatory drugs [96] (therefore being excluded from the ANDANTE trial), the occurrence of perforation was still present [94]. This disastrous event, especially in patients already suffering from a gastrointestinal disease, may compromise a wide spread of IL-6 antagonists and requires special attention in future clinical trials.

Another therapeutic target in TNF-refractory patients is oncostatin M (OSM). OSM belongs to the family of IL-6 cytokines and is highly expressed in active CD and UC patients, particularly with deep ulcerations. Furthermore, a mouse model demonstrated high expression of OSM in TNF-resistant inflamed intestinal mucosa [97]. This finding could lead to a possible new biomarker for therapy responsiveness to TNF treatment, or to a new treatment option.

Anti-IL-9

A further interesting approach is to block IL-9 as a therapeutic target in IBD. Patients with UC have elevated IL-9-expressing T cells and cells expressing the transcription factor PU.1, a key regulator of Th9-cell differentiation. An animal model demonstrated the same findings and could show that IL-9- and PU.1-deficient mice were spared from developing colitis [98]. Therefore, it is assumed that IL-9 negatively alters intestinal barrier function by influencing tight junction molecules [99]. These findings can be used in the development of a new treatment option for UC.

Phosphodiesterase 4 Inhibitor

Phosphodiesterase 4 (PDE4) is a protein highly expressed in immune cells which catalyzes the breakdown of cyclic AMP (cAMP). cAMP is a key player in the intracellular inflammatory cascade [100], and elevated intracellular cAMP levels suppress the production of various proinflammatory mediators [101] and promote the release of anti-inflammatory mediators [102]. By blocking PDE4, cAMP levels rise, which subsequently results in an anti-inflammatory response [100]. Apremilast is an orally administered PDE4 inhibitor showing anti-inflammatory activity in murine models of colitis through reducing TNF-α, IFN-γ, IL-6, IL-13, and IL-9 [103]. A phase II trial with active UC patients treated with apremilast showed an improvement in symptoms, biomarkers, endoscopy results, and mucosal healing compared to placebo at week 12 [104].

Janus Kinase Inhibitors

Janus kinases (JAKs) play a central role in innate and adaptive immune response. Since nearly all cytokines use the JAK signal transducer and activator of transcription (STAT) pathway as a common signaling pathway, JAK inhibitors block the activity of multiple cytokines simultaneously. Cytokines not using the JAK-STAT pathway are TNF, IL-1, IL-8, TGF-β, and macrophage colony-stimulating factor [105].

After binding of a cytokine to its cell surface receptor, the intracellular part of JAK gets activated. Subsequently, JAKs phosphorylate the intracellular part of the cytokine receptor, which allows binding of latent cytoplasmic transcription factors known as STATs. These in turn become tyrosine phosphorylated by the JAKs, dimerize, and translocate to the nucleus to regulate gene expression [106]. Four JAKs are found in humans, namely, JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), as well as seven STATs, that is, STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 [106].

JAK inhibitors are small molecules which differ from antibodies or other biologicals in many ways. Unlike biologicals, small molecules have a short half-life, allowing interference with the immunosuppressive effect in case of infection, surgery, or pregnancy. Furthermore, they are efficient at lower doses; thus, they do not block the entire signaling pathway [107]. Patients often prefer orally administered medication over an injectable therapy [108]; hence, small molecules could improve patient acceptance and may increase adherence. Lastly, due to their small size, they confer a much lower risk of immunogenicity and allergic reactions [109, 110].

Tofacitinib, a small molecule, inhibits JAK1 and JAK3, as well as, to a lesser extent, JAK2 and TYK2, which is why it is considered as pan-JAK inhibitor. JAK1/JAK3 dimerization controls signaling of the cytokines IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [107]. By blocking these signaling pathways, B-cell class switching and differentiation of T cells and NK cells may be suppressed [107, 111].

After a positive phase II trial in moderate-to-severe UC patients [112], three phase III trials with tofacitinib (OCTAVE Induction 1 and 2 and OCTAVE Sustain) followed, which confirmed its efficacy in induction and maintenance therapy compared to placebo in patients with moderately to severely active UC [113] (remission at week 8 in OCTAVE Induction 1 and 2: 18.5 vs. 8.2%, $p = 0.007$, and 16.6 vs. 3.6%, $p < 0.001$, respectively; remission at week 52 in OCTAVE Sustain: 34.6% (5 mg) and 40.6% (10 mg) vs. 11.1%, $p < 0.001$). Observed adverse events were herpes zoster infection and increased lipid levels [113]. The reason for the significantly higher incidence of herpes zoster infection is not known [114]. However, JAK inhibitors block the IL-6 signaling pathway, which may explain the frequent increase in lipid levels also observed with tocilizumab [115], a selective IL-6 antagonist.

A safety analysis up to 8.5 years showed no more adverse events over time than what had been observed in

previous studies [116]. It has to be mentioned, though, that the US Food and Drug Administration (FDA) recently published a warning after an ongoing safety trial had found an increased risk of pulmonary embolism and death among patients with rheumatoid arthritis treated with 10 mg tofacitinib twice daily [117]. A systematic review of studies on rheumatic arthritis patients treated with tofacitinib, however, did not find an increased risk for malignancy [118].

Despite the fact that no head-to-head trials exist, a systematic review suggested that tofacitinib should be ranked highest for induction of remission and mucosal healing as a second-line agent for patients with moderate-to-severe UC previously treated with an anti-TNF agent [119]. Since a recently published study confirmed the rapid onset of action with significant improvement already within 3 days after starting tofacitinib [120], this drug could possibly be utilized for UC patients in need of a fast-acting agent.

In contrast, in moderately to severely diseased CD patients treated with tofacitinib, clinical remission rates were not significantly different from those with placebo in a phase IIb trial [121]. Interestingly, filgotinib, another orally administered JAK inhibitor selectively targeting JAK1, demonstrated a significantly higher rate of clinical remission and response in CD patients than placebo (47 vs. 23%, $p = 0.0077$, and 59 vs. 41%, $p = 0.0453$, respectively) in a phase II RCT (FITZROY study) [122]. Anti-TNF-naïve patients had higher remission and response rates than anti-TNF-experienced patients. Nevertheless, endoscopic mucosal healing at week 10 was comparable to that in the placebo group. It may be argued that the optimal timing for endoscopic assessment using JAK inhibitors is unknown and the time of endoscopy at week 10 is too early to observe differences in mucosal healing.

Another JAK inhibitor, currently investigated in a phase II study on anti-TNF-experienced CD patients, is upadacitinib (ABT-494). In this trial, upadacitinib, which inhibits JAK1, demonstrated higher rates of clinical response, remission, and endoscopic improvement than placebo [123]. Although the safety profile was comparable to that of placebo, further studies are needed to confirm the safety and efficacy of upadacitinib.

Peficitinib, another oral JAK inhibitor, targets JAK3 6-fold more frequently than JAK1 and JAK2. In a phase IIb trial on patients with moderate-to-severe UC [124], peficitinib failed to show a dose response at week 8 according to the Mayo score, but trends for increased remission and response rates were observed with doses ≥75 mg. Since serum and fecal inflammation markers were not different from those with placebo, it is doubtful whether the peficitinib dose was high enough to reach a biological effect.

Further JAK inhibitors under development for IBD are BMS-986165 and TD-1473. BMS-986165 is a specific Tyk2 inhibitor, blocking the IL-12, IL-23, and Th1 pathway [125] and is under investigation in an ongoing phase II study on moderate-to-severe CD subjects [126].

TD-1473 is a novel orally administered pan-JAK inhibitor that selectively inhibits JAK in the gastrointestinal tract [127]. In a phase Ib study on patients with moderately to severely active UC, TD-1473 was well tolerated and showed low plasma exposure confirming gut selectivity and signals for clinical and biomarker activity [128].

Although the development of JAK inhibitors is still in its infancy, our understanding of the JAK-STAT pathway is increasing, which could lead to more specific JAK inhibitors in the future.

Anti-Trafficking Therapies

Anti-Cell Adhesion Molecules

After activation of the innate and acquired immune systems by luminal contents and intestinal microbes, multiple inflammatory mediators are released that attract further activated immune cells. The perpetuation of the inflammatory response in the mucosa is supported by the migration of activated lymphocytes and monocytes into the inflamed area [1]. Leukocytes roll along the vascular endothelium and transmigrate through the endothelium to the inflamed mucosa [129]. To achieve adhesion of a leukocyte to endothelial cells, interaction between cell-expressed integrins on the surface of leukocytes and tissue-expressed adhesion molecules is important. The $\alpha_4\beta_7$ integrins on the surface of leukocytes and the mucosal addressin cell adhesion molecule (MAdCAM) on the vascular endothelium play a pivotal role in the migration of gut-homing leukocytes. To inhibit local inflammation, this pathway may be blocked at many sites by different drugs, such as VDZ (specific IgG1 antibody blocking $\alpha_4\beta_7$), natalizumab (targeting the α_4 subunit of the $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins), etrolizumab (blocks the β_7 integrin subunit), and MAdCAM inhibitors [111].

Natalizumab, a monoclonal antibody directed against the α_4 subunit, inhibits gut and brain lymphocyte migration through blocking $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrin-mediated interactions [130]. Induction therapy failed to show superiority of natalizumab over placebo in moderate-to-

severe CD (ENACT-1 trial, 56 vs. 49%, $p = 0.05$), but demonstrated efficacy in sustaining remission in patients who had responded to natalizumab (ENACT-2 trial, 61 vs. 28%, $p < 0.001$) [131]. However, a post hoc analysis of the ENACT-1 trial showed efficacy in patients with active disease. The ENCORE trial confirmed the efficacy of natalizumab in inducing remission in patients with moderately to severely active CD and active inflammation [132].

A serious adverse event of therapy with natalizumab is the occurrence of progressive multifocal leukoencephalopathy (PML) due to JC polyomavirus [131, 133, 134]. However, patients unexposed to immunosuppressive therapy and negative for JC virus antibodies had a very low PML incidence rate of <0.11 per 1,000 [134].

A recently published Cochrane review suggests the effectiveness of natalizumab in induction of clinical remission and response in moderate-to-severe CD [135]. However, the increased risk of PML and the availability of alternative agents limit its use as second-line medication for CD patients. Nevertheless, in retrospective case reviews, natalizumab was used in difficult-to-treat CD patients who had previously failed TNF inhibitor treatment, and it showed efficacy and safety in these patients [136, 137]. Therefore, it could still be an option for difficult-to-treat CD patients and used under a surveillance program (TOUCH Prescribing Program) [138]. Another potential indication is CD with concomitant multiple sclerosis in patients who have never been exposed to immunosuppressants [139].

A further anti-integrin antibody is VDZ, a humanized monoclonal antibody that blocks the entire $\alpha_4\beta_7$ heterodimer. Compared to natalizumab, VDZ selectively prevents leukocyte trafficking to the gut without targeting $\alpha_4\beta_1$ integrin, which modulates brain trafficking. The GEMINI 1 and 2 studies demonstrated that VDZ is more effective than placebo as induction and maintenance therapy in moderate-to-severe UC [140] and CD [141]. In TNF-naïve UC patients, the efficacy is greater than in patients who have previously failed TNF antagonist treatment. However, it is still an alternative for patients who have previously failed TNF antagonist therapy [142]. The same results were obtained for CD [143], but the efficacy was only statistically superior in previously TNF-treated patients after 10 weeks of VDZ. This indicates that VDZ needs more time to induce a response, especially in previously TNF-treated patients [143]. Data from the GEMINI long-term safety (LTS) study show the long-term efficacy and safety of VDZ in maintenance of remission in UC [144] and CD [145] over more than 3 years.

The elevated risk of PML with natalizumab was not observed under VDZ treatment [144–146], probably because VDZ does not inhibit $\alpha_4\beta_1$. In addition, due to the gut-selective blockade of $\alpha_4\beta_7$, VDZ has an excellent safety profile without any risk of serious or opportunistic infections [147]. Recently published real-world data support the safety and efficacy of VDZ, even in refractory IBD patients [146, 148], and demonstrate a cumulative rate of deep remission in 30% of patients [149–152].

As with all biologicals, VDZ has the potential for immunogenicity [153], albeit at a low level with an incidence rate of LOR to VDZ of 47.9 per 100 person-years of follow-up in CD and of 39.8 per 100 person-years of follow-up in UC [154]. Patients who have experienced a LOR to an anti-TNF therapy before use of VDZ have a 2-fold increased risk of LOR to VDZ [155]. Interestingly, immunogenicity is higher for anti-TNF antibodies than for VDZ [153], but the rate of LOR to VDZ is not lower than that to anti-TNF therapy [154]. Among patients with LOR to VDZ, shortening of the interval and intensification of the dose lead to a clinical response in around 50% of patients [154, 155].

Despite a lack of head-to-head trials comparing anti-TNF and VDZ therapy, its efficacy and safety profile makes VDZ an interesting first-line biologic, especially for elderly UC patients [156], and can be considered as first-line agent for CD patients when safety is more important than a fast response to therapy [157]. Interestingly, a simulation model regarding the positioning of VDZ in IBD therapy predicts the greatest potential benefit in quality-adjusted life-years due to higher remission rates when VDZ is used prior to anti-TNF therapy [158]. The model therefore considers VDZ as the first-line steroid-sparing medication. However, when choosing the most suitable first-line biological, many aspects have to be considered. In patients with extraintestinal manifestation or patients with acute severe colitis requiring a fast effect of therapy, anti-TNF treatment probably still is the better choice [156, 159]. Although exploratory analyses of the data from the GEMINI 2 trial have confirmed the efficacy of VDZ in fistula closure in patients with fistulizing CD [160], robust data regarding this selective group of patients are lacking. A recently finished placebo-controlled study will hopefully clarify this unanswered question [161].

Etrolizumab is a humanized IgG1 antibody selectively targeting the β_7 integrin subunit. Besides inhibition of leukocyte trafficking to the gut by blocking $\alpha_4\beta_7$/MAdCAM-1 interactions, it further blocks $\alpha_E\beta_7$ E-cadherin interactions, which is believed to be an important mecha-

nism in retention of lymphocytes in the intraepithelial compartment. In a double-blind, placebo-controlled, randomized phase II study, etrolizumab achieved clinical remission at 10 weeks in a significantly higher number of patients with moderate-to-severe UC than did placebo (21% [300 mg] vs. 0%, $p < 0.010$, and 10% [300 mg plus loading dose] vs. 10%, $p = 0.048$) [162]. The side effect profile is similar to that of VDZ. Currently, phase III clinical trials are ongoing to confirm the efficacy and safety of etrolizumab.

Other than VDZ, abrilumab (AMG 181) is a completely human antibody against $\alpha_4\beta_7$ integrin. A recently published phase IIb trial did not meet the primary endpoint (clinical remission at week 8) in patients with moderate-to-severe CD [163]. In the phase IIb UC study, higher rates of remission at week 8, response, and mucosal healing could be demonstrated [164].

Anti-MAdCAM-1 (PF-00547659)

Anti-MAdCAM-1 is a fully humanized IgG2 antibody targeting MAdCAM-1, an intestinal endothelial cell adhesion molecule. It prevents gut homing in lymphocytes carrying the $\alpha_4\beta_7$ integrin on their surface. The phase II TURANDOT trial demonstrated higher remission rates with PF-00547659 among moderately to severely active UC patients having failed at least one conventional therapy [165]. In contrast, anti-MAdCAM antibody did not reach statistically significant results for clinical response in patients with moderate-to-severe CD who had previously failed anti-TNF or immunosuppressive therapy (phase II OPERA trial), though, unexpectedly, high clinical response and remission rates were observed with placebo [166]. The most common adverse events identified were nasopharyngitis, arthralgia, and headache [165].

Small-Molecule Integrin Antagonists

AJM300 is an oral integrin-targeting agent currently in the pipeline for treatment of IBD. AJM300 is a small-molecule inhibitor targeting the α_4 integrin subunit [167] and was tested in moderately active UC patients in whom higher rates of clinical response at week 8, clinical remission, and even mucosal healing could be demonstrated [168]. Available in abstract form only, a randomized, double-blind trial demonstrated no significant difference in clinical response in active CD patients [169]. Due to the shared mechanism with natalizumab in blocking α_4 integrin, there is a potential risk of PML. Although the published data show the efficacy of AJM300 in UC and have not yet demonstrated any risk of PML [168], it remains uncertain whether AJM300 will get a foothold in IBD treatment algorithms.

Another oral anti-integrin is PTG-100 (an $\alpha_4\beta_7$ antagonist peptide). However, a phase IIb study (PROPEL) was discontinued following an interim analysis [170].

Sphingosine-1-Phosphate Receptor Modulator

Sphingosine-1-phosphate (S1P) is a signaling molecule that regulates the traffic of lymphocytes out of the lymphoid organs into the bloodstream and to inflamed tissue. Ozanimod belongs to the group of S1P modulators, which are small molecules downregulating S1P receptor subtypes 1 and 5 on lymphocytes and prevent lymphocyte trafficking out of the lymph nodes to the site of inflammation [171, 172]. In a phase II RCT [173] of moderate-to-severe UC, ozanimod applied in two doses (0.5 and 1.0 mg per day) showed significant improvement in clinical response and remission within the group receiving 1 mg ozanimod per day compared to placebo (16 vs. 6%, $p = 0.048$). Although the rate of endoscopic remission was significantly higher in both treatment groups, no significant difference in histologic remission could be observed at week 8. Probably, as with VDZ, the onset of action occurs later because lymphocytes already present in the inflamed tissue do not get blocked through ozanimod. The frequency of severe adverse events was comparable to that with placebo. However, findings observed with fingolimod, a nonselective S1P receptor modulator, demonstrated multiple adverse events such as viral infections [174], bradyarrhythmias [175], macular edema [176], and respiratory events, which may be explained by its specific mode of action as a S1P modulator. Additionally, several cases of PML during treatment with fingolimod occurred [177].The long-term safety of ozanimod, including the risk of PML, still needs further evaluation.

Etrasimod (APD334) is another selective S1P receptor modulator under investigation for UC treatment. After two randomized double-blind studies on healthy individuals had demonstrated its safety and a rapid decrease in T-helper and -naïve cells [178], phase II (randomized, double-blind, parallel-group) trials in UC patients were recently completed [179, 180]. The first results of the OASIS induction study showed, at week 12, a greater change in Mayo score (difference, 0.99 points; 90% CI, 0.30–1.68; $p = 0.009$), a bigger endoscopic improvement (41.8 vs. 17.8%, $p = 0.003$), and more patients in clinical remission (33.0 vs. 8.1%, $p < 0.001$) among patients treated with 2 mg etrasimod compared to a placebo group [181].

Intestinal Mucosa and Gut Flora

Besides a dysfunction of the adaptive immune system, the innate immune response is impaired in IBD. The body's first defense to luminal antigens in the gut consists of epithelial cells, which are protected by an adherent, hydrophobic mucus layer. This mucus layer is mainly composed of phosphatidylcholine, and to a much lower extent of lysophosphatidylcholine, which both show significantly decreased levels in UC patients [182]. This impaired mucus layer can lead to increased permeability of the intestinal barrier and, consecutively, to mucosal barrier dysfunction in IBD patients [183]. After a proof-of-concept study showing the safety of an orally administered phosphatidylcholine (LT-02) and its efficacy in induction of clinical remission in UC patients compared to placebo [184], two further studies followed [185, 186], and a multicenter trial confirmed these results [187]. Despite previous positive results, a phase III trial has recently been stopped due to lack of efficacy [188]. As the patients in this study were taking mesalazine simultaneously with phosphatidylcholine, it was hypothesized that the topical bioavailability of phosphatidylcholine to the colonic mucus was reduced [189]. Nevertheless, this interesting approach could evolve into a new effective treatment for UC patients, with a favorable safety profile.

Modifying the Microbiota

Patients with IBD have an altered microbiome with a reduction of microbial diversity, which is more pronounced in CD than in UC [190]. This low diversity comes with low amounts of short-chain fatty acid-producing bacteria, higher levels of proteobacteria producing the endotoxin lipopolysaccharide, and a higher potential for mucus-degrading processes [191–193]. These changes can disrupt intestinal barrier integrity and subsequently activate innate immune responses. Therefore, interventions aiming at modifying the microbiota of IBD patients are under investigation. In addition to the highly complex attempt to positively change the microbiota in IBD patients through dietary interventions [194, 195], various options to alter the microbiota in IBD patients are under investigation, namely, administration of probiotics and antibiotics as well as fecal microbiota transplantation (FMT).

Only a few studies demonstrated a benefit of probiotics for UC patients. Probiotics seem to be effective in maintaining remission in UC patients with pouchitis treated with VSL#3 [196] and maintaining remission with *Escherichia coli* Nissle [197]. In active CD, probiotics do not show any efficacy [198]. Interestingly, probiotic bacteria induce human beta defensin 2 [199], which is an endogenous antimicrobial peptide that is part of innate immunity. Defensins are produced out of epithelial surfaces, "professional phagocytes," and Paneth cells and regulate host immunity in the gastrointestinal tract [200]. Reduced levels of alpha defensins are shown in ileal CD and reduced levels of beta defensins are seen in colonic CD patients [201, 202]. Only recently, a study demonstrated that orally administered human beta defensin 2 increased the microbiota and significantly improved health in a dextran sulfate sodium-induced colitis mouse model [203]. This result supports a therapeutic application of defensins for IBD patients.

Regarding antibiotics, the data are more limited and controversial [204]. Metronidazole plays a role in prophylaxis of postoperative CD [205] or treatment of perianal CD [204] and, like ciprofloxacin, in pouchitis [206].

Another method of altering the gut microbiota of a patient is to infuse a fecal solution from a donor via the upper or lower gastrointestinal tract of the recipient. FMT gained attention due to excellent results in treating recurrent *Clostridium difficile* infections [207, 208]. Many case reports and observational studies have suggested a favorable outcome when treating refractory UC with FMT [209]. Furthermore, a systematic review and meta-analysis [210], including four RCTs, suggests a significant efficacy of FMT in UC compared to placebo. Since the only RCT with negative results used a nasoduodenal approach and only two treatment sessions [211], a repetitive colorectal approach is more advisable when treating UC with FMT. This could be demonstrated in an RCT on UC in which an intensive-dosage FMT (1 infusion at the first colonoscopy with following enema 5 days a week for 8 weeks) was compared to placebo [212]. Steroid-free clinical remission and response could be seen in 44 and 54%, respectively, of the FMT-treated patients (vs. 20%, $p = 0.021$, and 23%, $p = 0.004$, in the placebo group). In addition, the endoscopic response rate was significantly higher in the FMT group (32 vs. 10%, $p = 0.016$), even if there was no difference in endoscopic remission rate between the two groups (12 vs. 8%, $p = 0.48$). The currently available data do not show any difference regarding adverse events [210, 212]. It is important to mention that the response to FMT in most cases is only temporary, and that FMT is not a cure for UC [213].

Although FMT shows promising results, further long-term studies are needed to support its safety and efficacy in treating refractory UC patients.

Stem Cell Therapy

As a last salvage therapy, for highly selected refractory CD patients in whom a surgical procedure is not possible, autologous hematopoietic stem cell transplantation (AHSCT) may be considered [214]. The concept is to reset the immune system through a conditioning regimen that stops inflammation, as well as to restore immune tolerance.

The ASTIC trial, a controlled trial of a large cohort of refractory CD patients undergoing AHSCT who had failed at least three immunosuppressive/biological treatments, demonstrated significant improvement with AHSCT in respect to clinical and endoscopic remission 1 year after AHSCT. Serious adverse events, including one death, occurred due to infections associated with pancytopenia induced by the conditioning regimen [215, 216]. During long-term follow-up over a median time of 3.4 years, 44% of these highly refractory CD patients with multiple previous therapies (a median of 6 previous lines of therapy) were still in remission, and 27% of the patients required no medical therapy [217]. The mortality risk (around 1%) and the rates of infective complications (around one-third) seemed to be comparable to those of other indications for HSCT. Since the patients with the greatest complications were current smokers and patients with perianal disease [216, 217], special precautions must be taken with regard to this subgroup. For patients with an identical twin, an interesting approach regarding safety issues is syngeneic HSCT instead of AHSCT. Due to avoidance of mobilization chemotherapy, the risk of neutropenia and infectious complications can be avoided. One case report of a patient with refractory CD treated with syngeneic HSCT demonstrated that 4 years after transplantation, clinical remission without specific therapy for CD could be possible [218].

Another approach in stem cell therapy is the use of mesenchymal stem cells (MSCs) derived from adipose tissue or bone marrow for treating refractory perianal fistulas in patients with CD. It could be shown that adipose-derived MSCs are as efficacious as bone marrow-derived MSCs [219–222], which leads to the conclusion that the origin of the cells is not that important. An encouraging proof-of-concept study in which allogeneic, expanded adipose-derived MSCs (Cx601) were locally injected into the surrounding tissue of complex perianal fistulas present in CD patients [223] supports the hypothesis of anti-inflammatory and immunomodulatory features of adipose-derived MSCs. Hence, a subsequent phase III randomized, double-blind controlled trial was performed [224]. CD patients with complex perianal fistulas treated with Cx601 significantly more often achieved the primary endpoint defined as combined remission (clinical assessment of closure and absence of collections >2 cm confirmed by MRI) at week 24 than those treated with placebo (51 vs. 36%, $p < 0.021$) [224]. There were no serious adverse events in the Cx601 group. Long-term data over 1 year confirm the safety and efficacy of Cx601 in fistulizing CD [225] with a combined remission rate of 56.3% (vs. 38.6% in controls; $p = 0.010$). It is important to mention that patients who were on treatment with anti-TNF or another immunosuppressant were to be maintained on stable doses during the study. Whether these patients could stop their immunosuppression after injection of Cx601 was not addressed.

Although there still are some unanswered questions, it can be assumed that MSC therapy is a safe and minimally invasive option for a highly selected group of CD patients with fistulas unresponsive to biologics.

Conclusions

The anti-TNF era brought hope for the therapy of refractory IBD patients; however, after two decades, several problems are still unsolved and new therapies are urgently needed. Our understanding of the involved cytokines and their downstream pathways has helped us to develop new treatment strategies with different target points within the pathogenesis of IBD. Furthermore, our growing understanding of genetic factors and the microbiome yields further targets for the treatment of IBD and can help us in understanding the onset of the disease and, thereby, in developing prevention strategies.

Statement of Ethics

The authors have no ethical conflicts to disclose.

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