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Emerging Treatment Options in Inflammatory Bowel Disease: Janus Kinases, Stem Cells, and More

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Inflammatory bowel diseases · Crohn's disease · Ulcerative colitis · Biologicals · Small molecules · Lymphocyte trafficking · Janus kinase inhibition · Stem cell transplantation

Abstract
Background: Treatment of inflammatory bowel diseases (IBD) has tremendously improved during the last 20 years; however, a substantial fraction of patients does not respond to available therapies or lose response, and new strategies are needed. ***Summary:*** Two pharmacological principles have been successfully used for IBD treatment: inhibition of cellular signaling and interference with leukocyte trafficking. Besides tumor necrosis factor, interleukin (IL)-23 is a promising drug target, and antibodies for the combined inhibition of IL-23 and IL-12 (ustekinumab and briakinumab) or selective IL-23 inhibition (brazikumab, risankizumab, and mirikizumab) seem to be effective in Crohn's disease (CD) with emerging evidence also for ulcerative colitis (UC). Janus kinase (JAK) mediates intracellular signaling of a large number of cytokines. Tofacitinib is the first JAK inhibitor approved for UC, and the JAK inhibitors filgotinib and upadacitinib showed potential in CD. Leukocyte trafficking can be inhibited by interference with lymphocyte integrin-α4β7 or endothelial MadCAM-1. The α4β7 integrin inhibitor vedolizumab is an established treatment in IBD, and long-term data of pivotal studies are now available. Additional molecules with therapeutic potential are α4β7-specific abrilumab, β7-specific etrolizumab, and the α4-specific small molecule AJM300. PF-00547659, an antibody against endothelial MadCAM-1, also showed therapeutic potential in UC. Modulation of sphingosine-1-phosphate receptor (S1PR) activity is necessary for the egress of lymphocytes into the circulation, and S1PR modulation results in lymphocyte trapping in lymphatic organs. Ozanimod, an S1PR1 and S1PR5 inhibitor, has been successfully tested in initial studies in UC. Mesenchymal stem cell therapy has been approved for the treatment of complex, active CD fistula, and mesenchymal stem cell therapy might be a paradigm shift for this condition. Autologous stem cell transplantation (ASCT) has been successfully used in CD case series; however, in a randomized trial, a highly stringent endpoint was not met. However, considering positive effects in secondary endpoints, ASCT might be a future treatment of last resort in severe, refractory CD cases,

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provided that safer protocols can be provided. ***Key messages:*** New IBD treatments are successful for a significant fraction of patients. However, new strategies for patient selection, treatment combinations, and/or additional therapies must be developed to serve the need of all IBD patients.

Introduction

Treatment of inflammatory bowel disease (IBD) has significantly improved within the last 20 years. While initial IBD treatments relied on nonspecific immunomodulatory effects, introduction of specific inhibitors of tumor necrosis factor (TNF) has been a landmark achievement, enabling long-standing remission and modification of the IBD course in a substantial fraction of patients [1]. However, primary nonresponse to TNF inhibitors is observed in approximately 20–40% of patients, and an additional 23–46% lose response, mainly within the first 12 months of treatment [2]. Therefore, new therapeutic options, especially for IBD patients with moderate to severe disease activity, are urgently needed.

For specific drug treatment, efficacy of 2 broad therapeutic principles has been proven: (i) inhibition of cytokine signaling and (ii) inhibition of immune cell trafficking, and newly introduced and emerging therapies fall into one of these categories [3–6]. Newly introduced IBD treatments have been designed with the aim to inhibit specific molecular pathways. This contrasts traditional treatments (steroids, azathioprine, methotrexate, or mesalamine) with a broader immunosuppressive, antimetabolic, or unknown mode of action. Cell-based therapies are an emerging treatment option, aiming to improve the cellular environment in the bone marrow or fistula tract.

New drug therapies are either antibody-based treatments ("biologicals") or small molecules. Disadvantages of biologicals include the long half-life, which limits flexibility in case of infection, surgery, or therapeutic failure. Further, biologicals have inherent antigenicity, which is especially relevant for not fully humanized antibodies. Moreover, biologics need to be applied parenterally, and production costs remain significant [7]. For these reasons, reproduction of pharmacological effects of a biological by a small molecule can also be a significant innovation [6]. A general disadvantage of small molecules is a frequently less specific mode of action. Further, small molecules can reach many cellular compartments by diffusion. This opens the possibility of more unspecific side effects. Cell-based therapies are intended as a one-time treatment, which would facilitate future long-term IBD management. High procedure-related risks of stem cell transplantation and unknown long-term risks for mesenchymal stroma cells (MSCs) make unique risk-benefit calculations necessary.

Both subtypes of IBD, ulcerative colitis (UC) and Crohn's disease (CD), share most but not all genetic and environmental risk factors [8–10]. In line with a similar pathogenesis, many inflammatory cytokines are involved in both, UC and CD, even though differences exist [11]. Therefore, most established and emerging IBD treatments are effective for both IBD subtypes, even though to various degrees. This is illustrated by mesalamine, which is a first-line treatment in UC but only marginally effective in CD [12, 13]. Therefore, regulatory agencies require independent proof of efficacy for both IBD subtypes, CD and UC, separately.

Increasing prevalence of IBD and significant morbidity in affected individuals provide a strong incentive for the development of new therapeutics. The field of IBD treatment remains one of the most exciting and dynamic areas in gastroenterology. However, similar to established treatments, none of the new therapeutics can provide an IBD cure, and all new treatments lack effectiveness in a significant fraction of patients.

Inhibition of Cytokine Pathways

New Anti-TNF Agents

TNF inhibitors are the first class of therapeutics with a selective mode of action in IBD that have dramatically changed the management of IBD [1]. However, even in TNF responders, usage of TNF inhibitors is limited due to systemic effects, including immunosuppression and cardiotoxicity, which limit its usage, especially in elderly individuals [14]. Therefore, gut-selective TNF inhibition might increase utility of anti-TNF treatment.

AVX-470 is an orally administered polyclonal anti-TNF antibody derived from cow colostrum (Table 1). Due to a delayed-release formulation, antibodies are released in the small intestine and colon. In these formulations, <1% of antibodies would be TNF-specific. However, bovine milk-derived IgA might be exceptionally safe, as suggested by a long history of milk consumption in infants and adults [15]. AVX-470 has been tested in 36 patients with UC with dosages of 0.2, 1.6, or 3.5 g per day or placebo. Clinical response was observed in 25.9% over all AVX-470-treated patients, compared to 11.1% in the placebo group. No relevant systemic side effects were observed and no anti-bovine antibodies were induced [15, 16].

Table 1. Overview of newly established and emerging drugs for IBD

Drug	Mode of delivery	Clinical efficacy demonstrated	Approval state[a]	Ref
Oral anti-TNF treatment				
AVX-470	Oral polyclonal IgA	Small UC trial (n = 36)	None	[15, 16]
Anti-IL-12 and anti-IL-23 treatments				
Ustekinumab	Anti-p40	Large trials for CD and UC	For CD and UC, psoriasis, and psoriasis arthritis	[21, 22, 24]
Briakinumab	Anti-p40	CD trial failed primary end point	None	[22, 25]
Brazikumab (MEDI2070)	Anti-p19	Phase IIa study in CD	None	[26]
Risankizumab (BI 655066)	Anti-p19	Phase II study in CD	For psoriasis	[27]
Mirikizumab (LY3074828)	Anti-p19	Phase II studies in CD and UC	None	[28–30]
Guselkumab	Anti-p19	No IBD data	For psoriasis	[31]
Tildrakizumab	Anti-p19	No IBD data	For psoriasis	[31]
JAK inhibitors				
Tofacitinib	JAK1/JAK3	For UC, in CD primary end point of a phase IIb study was missed	For UC, rheumatoid arthritis, and psoriasis arthritis	[46–48, 50]
Filgotinib	JAK1	Phase II study in CD	None	[51]
Upadacitinib	JAK1	Phase II studies: successful in UC; primary endpoint failed in CD	For rheumatoid arthritis	[52, 53]
TD-1473	Pan-JAK with only intestinal exposure	Small Ib study in UC	None	[54]
BMS-986165	TYK2	No data in IBD yet	None	[52]
Brepocitinib (PF-06700841)	TYK2 and JAK1	No data in IBD yet	None	[52]
PF-06651600	JAK3	No data in IBD yet	None	[52]
Inhibition of lymphocyte adhesion: integrin and MadCAM-1 inhibitors				
Natalizumab	α4 integrin	CD, very small open label study in UC	For multiple sclerosis, CD (reserve)[b]	[63–66, 113]
Vedolizumab	α4β7 integrin	CD and UC	For CD and UC	[67–69, 71]
Abrilumab	α4β7 integrin	Phase IIb study in UC	None	[72]
Etrolizumab	β7 integrin	Phase II study in UC and phase III study in CD (partially complete)	None	[74, 75]
AJM300	α4 integrin	Phase IIa in UC	None	[76]
PF-00547659	MadCAM-1		None	[77, 78]
Lymphocyte trapping: S1PR modulators				
Fingolimod	S1PR1, 3, 4, and 5	No IBD data	For multiple sclerosis	
Ozanimod	S1PR1 and 5	Phase II studies in UC and CD	None	[84, 85]
Etrasimod	S1PR1, 4, and 5	Phase II study in UC	None	[86]

CD, Crohn's disease; EMA, European Medicines Agency; FDA, Food and Drug Administration; IBD, inflammatory bowel disease; IL, interleukin; JAK, Janus kinase; MadCAM-1, mucosal addressin cell adhesion molecule-1; S1PR, sphingosine-1-phosphate receptor; TYK2, tyrosine kinase 2; UC, ulcerative colitis; TNF, tumor necrosis factor. [a] Specific restrictions might apply, for example, disease severity (usually moderate to severe) as well as unsuccessful treatment or intolerance to anti-TNF medication or other biologicals. For details of the indication, please refer to documentation of FDA and EMA. [b] Approval by FDA if no options by other treatments, no EMA approval.

Expert Opinion

Anti-TNF is the main therapeutic principle applied in IBD patients today, and this new oral formulation might introduce gut specificity to anti-TNF treatment. Oral formulation would increase patient comfort and might actually increase patient safety and at least no additional side effects compared to established anti-TNF treatment would be expected. However, much larger trials are needed to demonstrate efficacy for this interesting new drug.

Targeting IL-23 and IL-12

Besides TNF, a crucial role of interleukin (IL)-23 for IBD pathogenesis has been recognized within the last years [17]. The pathways of IL-23 and IL-12 overlap since

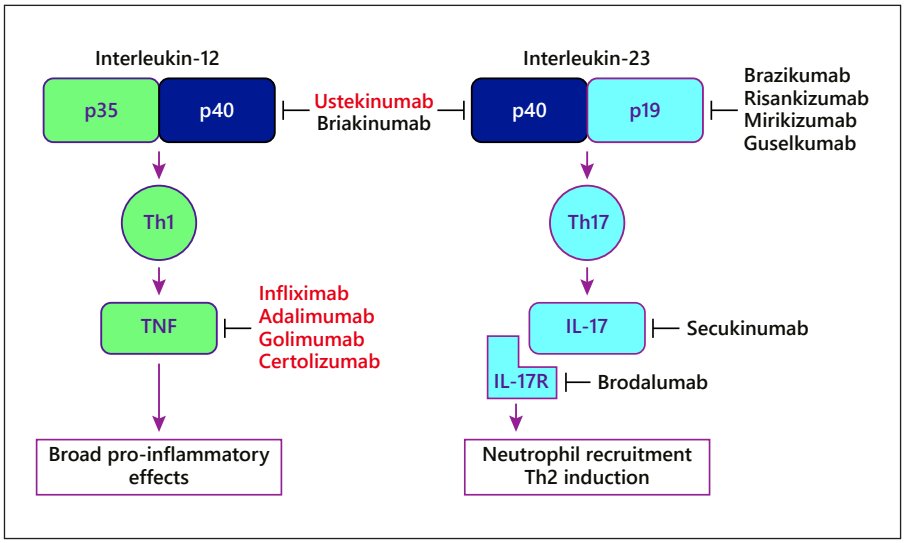

Fig. 1. IL-23 and IL-12 as drug targets in IBD. IL-23 and IL-12 share the p40 subunit. Therefore, the p40-specific antibodies ustekinumab and briakinumab inhibit both IL-12 and IL-23. In contrast, p19-specific antibodies mediate selective IL-23 inhibition. Downstream effectors of IL-12 include TNF. IL-23 mediates Th17 differentiation and IL-17 secretion. However, inhibition of the IL-17 pathway in the gut has pro-inflammatory effects (for details, see text). Figure adapted from [31]. IBD, inflammatory bowel disease; IL, interleukin; TNF, tumor necrosis factor.

IL-23 and IL-12 share a subunit of the cytokine (IL-23 = p19/p40; IL-12 = p35/p40) and a subunit of its receptors (IL-23 receptor = IL-23R/IL-12Rβ1; IL-12 receptor = IL-12Rβ1/IL-12Rβ2). IL-23 has pro-inflammatory activities in the intestine. It promotes generation and maintenance of Th17 cells, which in turn produce IL-17. IL-17 upregulates chemokines, resulting in turn in the recruitment of macrophages, neutrophils, and dendritic cells into the intestine, thus contributing to intestinal inflammation [18, 19]. IL-12 has pro-inflammatory effects in the colon since it promotes T-cell differentiation toward a Th1 phenotype [20]. Several monoclonal antibodies have been advanced (Fig. 1), targeting either p40 (for combined IL-23 and IL-12 inactivation) or p19 (for selective IL-23 inactivation).

Ustekinumab is a monoclonal antibody targeting the p40 subunit of the cytokines IL-23 and IL-12 with effectiveness for the therapy of CD [21, 22], and recent data demonstrate maintenance of remission after 3 years for the majority of patients [23]. Recently, the data of the UNIFI program also indicated effectiveness of ustekinumab in UC [24], and ustekinumab is now an approved drug for both UC and CD.

Briakinumab is another anti-p40 antibody with effectiveness in psoriasis. When tested in CD, numerically higher response rates were found; however, the primary end point of the study was not met [25].

Brazikumab (MEDI2070) is a monoclonal antibody with selective activity against the p19 subunit of IL-23 and no activity against IL-12. In a study with 119 CD patients with TNF failure, clinical response was observed in 49% of brazikumab-treated patients versus 27% with placebo ($p = 0.01$). Higher baseline concentrations of IL-22 (a cytokine downstream of IL-23) were positively associated with treatment response [26]. Risankizumab, another anti-p19 antibody with selective activity against IL-23 antibody, induced remission in 31% of treated CD patients versus 15% with placebo [27]. Similarly, in phase II studies, mirikizumab (LY3074828) seems to be active for the induction and maintenance of UC [28, 29] and CD [30]. Guselkumab and tildrakizumab might be other promising anti-p19 antibodies [31], and studies of guselkumab in IBD are ongoing. Most IL-12/IL-23-inhibiting drugs were initially tested in CD, and, besides mirikizumab and ustekinumab (see above), less experience for p40 or p19 inhibition is available for UC treatment.

Despite the success of multiple antibodies blocking the IL-23 axis (see above), targeting IL-17, a downstream effector of IL-23, does not seem to be effective in IBD [31]. Secukinumab, an anti-IL-17 antibody, and brodalumab, an antibody against the IL-17 receptor subunit IL-17RA, performed worse than placebo or actually aggravated CD in clinical trials [32, 33]. Further, even though successful in psoriasis, side effects of secukinumab treatment included hemorrhagic diarrhea [34]. Detrimental effects of IL-17 inhibition might be due to a role of IL-17 in epithelial barrier maintenance and regulating gut colonization by segmented filamentous bacteria [35, 36].

In summary, combined IL-12/IL-23 inhibition (ustekinumab and possibly briakinumab) and selective inhibition of IL-23 (brazikumab, risankizumab, and mirikizumab) are effective for treatment of CD, and data

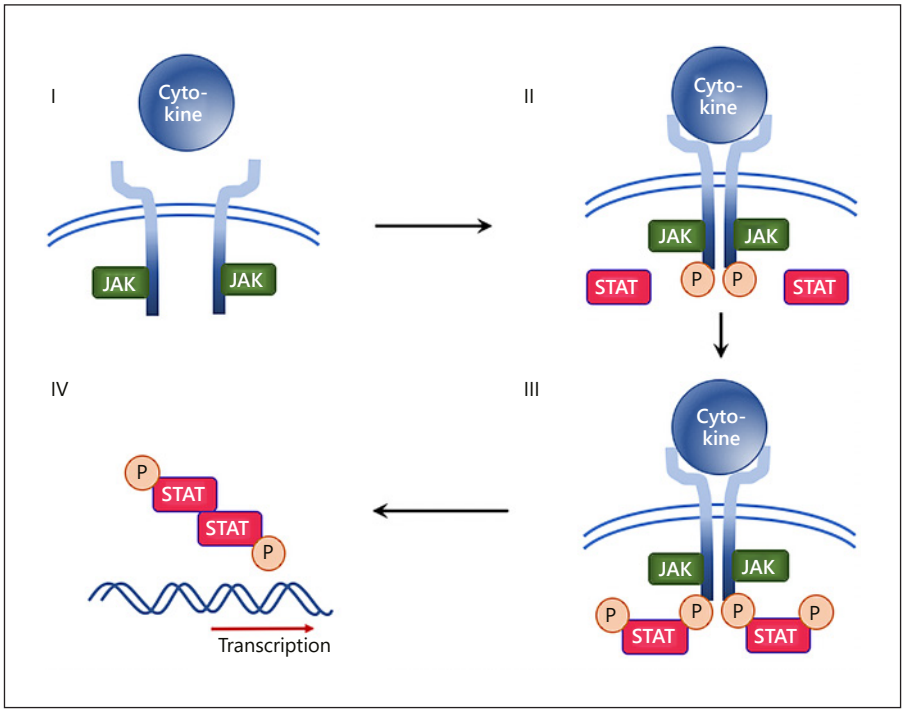

Fig. 2. Inhibition of the JAK-STAT pathway. There are 4 Janus kinase (JAK) family members: JAK1, JAK2, JAK3, and TYK2. JAKs are able to mediate the signaling in a wide range of cytokine receptors. Thereby, the STAT molecules are phosphorylated. Phosphorylated STATs subsequently relocate to the nucleus for activation of gene transcription. Figure adapted from [6]. JAK, Janus kinase; STAT, signal transducer and activator of transcription.

are also accumulating for IL-12/IL-23 inhibition in UC (ustekinumab and mirikizumab). For ustekinumab, long-term data indicate an excellent safety profile in >5,000 patients [37], some of these cover for more than 5 years [38]. Studies are ongoing to further establish the effectiveness and safety of those antibodies [39]. However, inhibition of the IL-23 effector cytokine IL-17 aggravates bowel inflammation.

Expert Opinion

IL-12/IL-23 inhibition is an attractive new treatment option for IBD, especially if the excellent safety profile will be confirmed. So far, there is no indication that the theoretical advantage of the selective p19 inhibition, which would only affect IL-23 (but not IL-12), significantly influences efficacy or side effects. To determine the optimal placement in a rational IBD treatment algorithm will be a special challenge and will need head-to-head trials as well as testing of IL-12/IL-23 inhibitors after failure of other therapies.

Inhibition of JAK-STAT Signaling

Janus kinase (JAK) molecules are important intracellular signaling molecules and comprise the JAK1-3 family members and tyrosine kinase 2 (TYK2). JAK proteins contain a JAK-homology (JH)-1 tyrosine kinase domain and a JH-2 domain with only low-level catalytic activity but negative regulatory activity for JH-1. These dual antagonistic activities within the same molecule prompted the naming according to Janus, the Greek god for duality, beginning, transitions, and ending [40].

JAK proteins mediate the intracellular signaling of a wide range of cytokines. Binding of a cytokine to its receptor leads to receptor dimerization and conformational changes. These changes are translated to receptor-associated JAK molecules, resulting in JAK activation and autophosphorylation [41, 40]. JAK in turn phosphorylates the receptor which recruits 1 of 7 signal transducer and activator of transcription (STAT) family members (STAT1–4, STAT5a/b, and STAT6) [42]. JAK subsequently phosphorylates bound STATs, which oligomerize and translocate into the nucleus for activation of transcription [40, 43] (Fig. 2).

Cytokines using the JAK-STAT pathway include the pro-inflammatory molecules IL-6, IL-12, IL-23, granulocyte-macrophage colony-stimulating factor, interferon (IFN)-α, IFN-β, and IFN-γ but also the anti-inflammatory cytokine IL-10. Overall, the JAK-STAT pathway orchestrates the intracellular signaling of >50 extracellular ligands [43].

The JAK-STAT pathway, therefore, provides broad opportunities for therapeutic intervention; however, the

JAK-STAT pathway also comprises considerable complexity [43]. Depending on the receptor, signaling can be mediated by more than 1 JAK kinase or STAT molecule, resulting in some functional redundancy. For instance, signaling by IL-6 and other cytokines mediated by the common cytokine receptor subunit gp130 activates 3 JAK kinases, JAK1, 2, and TYK2 [44], and the effect of a highly selective inhibitor of only one of those JAK molecules would be limited. Moreover, some JAK molecules mediate signaling for pro- and anti-inflammatory molecules. For instance, JAK1 mediates signaling of pro-inflammatory IL-6 and anti-inflammatory IL-10. Therefore, JAK1 inhibition might shift the balance in both ways, resulting in more or less inflammation [45, 43]. Further, JAK2 inhibition impairs hematopoiesis due to inhibition of cytokines such as erythropoietin, thrombopoietin, and granulocyte-macrophage colony-stimulating factor with the risk for cytopenia [43].

Despite these complexities, JAK inhibitors started to enter the market. Tofacitinib has been the first molecule of this class approved for the treatment of UC. Tofacitinib is a primary JAK1/JAK3 inhibitor with minor JAK2 inhibition. Effectiveness in UC was demonstrated in the large OCTAVE trials (OCTAVE-1: 476 patients, 19% remission with tofacitinib vs. 8% with placebo; OCTAVE-2: 547 patients, remission in 17% with tofacitinib vs. 4% with placebo); response rates were considerably higher [46, 47].

In contrast, the clinical effectiveness of tofacitinib in CD has not been conclusively established [48]. However, the negative studies in CD had very high placebo responses, possibly due to reliance on the Crohn's disease activity index as an end point, and post hoc analyses using calprotectin measurements and endoscopic scores suggest possible therapeutic effects [49], and recently, a promising open label study was published [50].

Filgotinib is a selective JAK1 inhibitor which has shown significant effectiveness for the induction treatment of CD in a phase II study with 128 patients (47% remission with 200 mg filgotinib vs. 23% with placebo). This difference was even higher in the subgroup with TNF naïve patients (60 vs. 13%) [51]. Upadacitinib, another oral selective JAK1 inhibitor, showed a favorable trend in a phase II study in CD patients even though the primary end point was not reached [52]. Significant improvements in endoscopic and histological outcomes were noted in UC patients [53]. Large trials with filgotinib and upadacitinib are ongoing. Finally, TD-1473 is an orally administered pan-JAK inhibitor with limited resorption and mainly intestinal exposure. A small phase Ib study (20 mg/80 mg/270 mg/placebo) showed endoscopic improvement in 20/30/18 versus 0% for placebo in 40 UC patients [54]. New inhibitors with specificity for TYK2 with a smaller set of downstream kinases and/or JAK1 or JAK3, which would avoid JAK2-mediated side effects, continue to be developed [52]. Examples of compounds in clinical testing include brepocitinib (PF-06700841, a JAK1/TYK2 inhibitor) and BMS-986165 (a TYK2 inhibitor).

In summary, JAK inhibition is a promising treatment principle, and the first drug of this class, tofacitinib, has already been approved for treatment of UC. Side effects include herpes zoster (3.6% of tofacitinib-treated psoriasis patients) [55], cytomegalovirus reactivation, cholesterol elevation [56], and nephrotoxicity. In addition, for a dose of 10 mg tofacitinib bid, an increased risk for pulmonary embolisms has recently been reported [57], and the high tofacitinib dose should be avoided in patients with higher baseline thromboembolic risk. Anemia, as a feared side effect of JAK2 inhibition, occurred rarely (hemoglobin decrease >3 g/dL in <1% of patients) [58].

Expert Opinion

Considering limited treatment options for some IBD patients, JAK inhibition is a welcome addition to the existing treatment armamentarium. Even though no head-to-head trials have been performed, tofacitinib might be a very effective agent in UC with similar effectiveness compared to a TNF inhibitor. However, physicians should bear in mind to give the herpes vaccination before starting treatment (Shingrix®) to prevent herpes zoster and its complications such as post-herpetic neuralgia. Other JAK inhibitors (filgotinib and upadacitinib) are likely to find their place in treatment algorithms of CD. The complexity of JAK signaling makes careful surveillance for side effect especially important, and the list of currently known side effects might well expand in the future and/or specific risks might appear for subsets of patients. The optimal pharmacological profile for JAK inhibition in IBD remains to be determined, but new compounds with better specificity for JAK1 or TYK2 might further optimize the performance of JAK inhibitors.

Phosphodiesterase Inhibitors

Phosphodiesterase 4 catalyzes the breakdown of cAMP, and apremilast, a PDE-4 inhibitor, is approved for treatment of psoriasis [59]. A phase II study in 170 UC patients showed clinical remission in 31.6% of patients treated with 30 mg apremilast versus 13.8% for placebo

[60], but no phase III trials are available to confirm effectiveness, and it is unclear if development of this molecule will be pursued.

Phosphatidylcholine

Normal colonic mucus contains phosphatidylcholine (PC); however, in inflammation, PC is depleted from the mucus, compromising membrane integrity, which could aggravate colitis. The therapeutic principle of PC replacement was tested in a large trial of 156 UC patients, and clinical improvement was observed at the highest dose of 3.2 g PC per day [61]. However, in a recent phase III study, no efficacy could apparently be shown, but the publication of full results of this phase III trial is still pending.

Inhibition of Immune Cell Trafficking

Inhibition of immune cell trafficking has emerged as a major therapeutic principle in IBD. Immune cells circulate within the blood stream and lymphoid organs, and specific mechanisms ensure homing of leukocytes into specific organs. Integrin-α4β7 is specifically expressed on lymphocytes activated in gut lymphatic structures. This integrin interacts with mucosal addressin cell adhesion molecule-1 (MadCAM-1), expressed on blood vessels of the intestinal tract and intestinal lymphatic structures [62]. Therapeutic interference with gut homing offers the promise of a gut-specific mode of action with potentially low systemic immunosuppression.

Natalizumab, a monoclonal antibody targeting the integrin-α4 subunit, is an effective treatment of IBD [63]. However, since the integrin-α4 subunit is also critical for α4β1-dependent central nervous system homing of lymphocytes, natalizumab treatment can be complicated by progressive multifocal leukoencephalopathy (PML) due to JC virus reactivation [64]. Therefore, natalizumab is only rarely, if ever, used for IBD treatment and only in patients with JC-negative serology or with a very strict surveillance framework [65, 66].

Vedolizumab, a monoclonal antibody directed against integrin-α4β7, is an effective and approved treatment for CD and UC [67, 68]. Long-term effectiveness and safety data of the pivotal studies with up to 9 years of follow-up are now available, demonstrating a generally favorable safety profile, with nasopharyngitis as the most frequent side effect [69]. Subcutaneous application seems to be equally effective compared to intravenous treatment, possibly increasing patient comfort [70]. Vedolizumab is the first biological for which a head-to-head study against an established TNF inhibitor (adalimumab) was performed with long-term results at 52 weeks, favoring vedolizumab in UC patients [71]. Abrilumab is another monoclonal antibody, inhibiting integrin-α4β7, which showed some efficacy for the treatment of UC (13.3% remission with 70 mg and 12.7% remission with 210 mg vs. 4.3% with placebo) [72].

Etrolizumab binds the integrin-β7 subunit, thus blocking integrins α4β7 and αEβ7. This broader specificity would also inhibit the interaction of αEβ7 with E-cadherin, thus blocking homing of $\alpha E\beta 7^{+}$ cells, including dendritic cells into the gut [7, 73]. In a study with 124 patients with moderate to severe UC, etrolizumab induced remission in 21% of patients in the 100-mg group, 10% in the 300-mg group, and none in the placebo group [74]. Etrolizumab might also be effective for the treatment of CD [75]. A study comparing adalimumab and etrolizumab in UC patients is under way. Inhibition of the integrin-α4 subunit is also therapeutically useful since AJM300, a small-molecule integrin-α4 inhibitor, induced a response in 63% of patients versus 26% with placebo at week 8 in a randomized controlled study with 102 UC patients [76].

MadCAM-1, the interaction partner for integrins can also be therapeutically inhibited for IBD treatment. PF-00547659 is a highly specific monoclonal antibody against MadCAM-1. In a first randomized controlled study in UC patients with active colitis, response rates of 52 and 42% compared to 32 and 21% with placebo at weeks 4 and 12, respectively, were observed [77]. PF-00547659 was also effective in a large phase II study with 357 UC patients, 57.4% with previous anti-TNF exposure. Remission rates of 11.3 (7.5), 16.7 (22.5), 15.5 (75), and 5.7% (225 mg) were observed, compared to 2.7% in the placebo group [78]. In a similar study with CD patients, results favored PF-00547659 over placebo, but the difference did not reach statistical significance [79].

Expert Opinion

Anti-adhesion strategies seem to be an effective therapeutic principle, in some situations (comparison vedolizumab vs. adalimumab) at least as efficient as TNF inhibition. However, more direct comparisons, especially in CD, would be interesting. Additional antibodies and small molecules seem to be able to replicate and extend the therapeutic success of vedolizumab. The good safety profile remains the most attractive feature of adhesion inhibitors, especially in elderly and multi-morbid patients and patients with malignancies in their history. Fortunately, besides natalizumab, for none of the newer compounds, cases of PML have been observed. However,

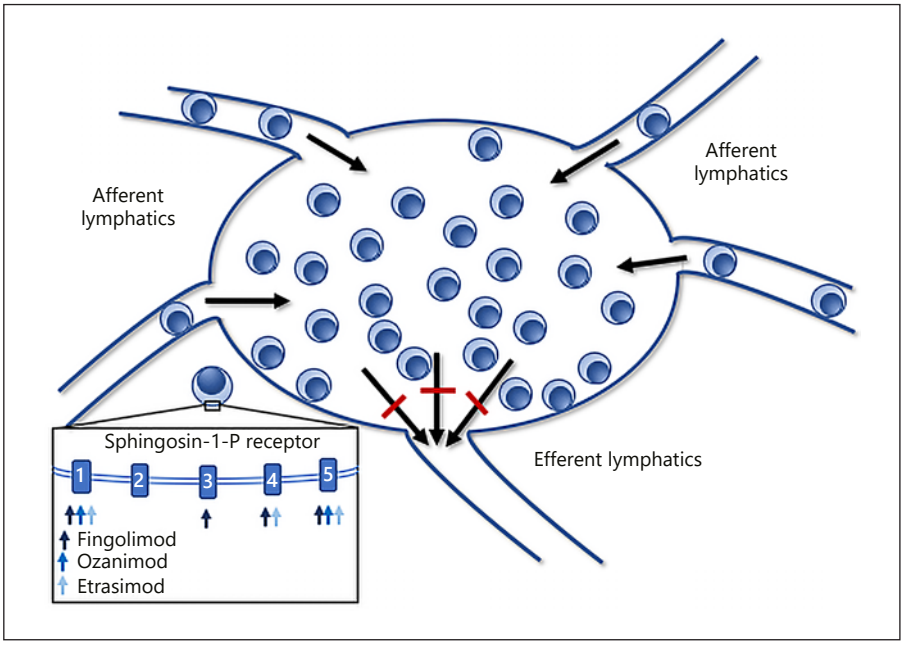

Fig. 3. Lymphocyte trapping by S1PR modulation. Lymphocytes enter a lymph node via afferent lymphatics and leave the lymph node via an efferent lymphatic vessel. For the egress from a lymph node, lymphocytes follow a S1P gradient. Blocking of S1P receptors by filgotinib, ozanimod, or etrasimod (blue arrows) inhibits release of lymphocytes into the circulation and results in lymphocyte trapping within the lymph node. Figure adapted from [6]. S1PR, sphingosine-1-phosphate receptor.

for the newer drugs, the number of cases is still too low to completely exclude a relevant risk.

Lymphocyte Trapping by Sphingosine-1-Phosphate Receptor Modulators

A new class of sphingosine-1-phosphate receptor (S1PR) modulators enables functional inactivation of lymphocytes by trapping them within lymphoid organs (Fig. 3). Sphingolipids are normal constituents of a cell membrane which can be phosphorylated to S1P by sphingosine kinases 1 and 2 [80]. Degradation of S1P by S1P lyase results in a gradient of S1P with higher S1P concentrations in blood but lower concentrations in secondary lymphoid organs. Lymphocyte trafficking along this gradient results in the release of B cells, dendritic cells, and some T-cell subsets into the circulation [80].

S1P signaling is complex and mediated by 5 S1P G-protein coupled receptors (S1PR1–5) with different downstream targets. S1PR1 mediates the egress of T cells from secondary lymphoid organs to the lymphatic vessel, systemic circulation, and inflamed tissues. S1PR1 receptor antagonists keep T cells trapped and sequestered within lymphoid organs. S1PR4 and 5 are involved in different pro- and anti-inflammatory pathways. In contrast, S1PR2 and 3 mediate vasoconstriction and fibrosis and are likely responsible for cardiac side effects such as bradycardia, hypertension, and renal injury. Further, S1PR1–4 are involved in cancerogenic and anti-carcinogenic mechanisms [81]. These pleiotropic effects make selective S1PR inhibition desirable.

The first S1P inhibitor was myriocin, derived from the fungus *Isaria sinclairii*. Further derivatization yielded in generation of the high-affinity ligand fingolimod, which activates S1PR1, 3, 4, and 5. The interaction with S1PR1 is unique, since after an early activation, S1PR1 is internalized, resulting in functional antagonism and downregulation of S1PR1 on T cells, which is responsible for immunomodulatory effects [80]. Fingolimod has been approved for the treatment of multiple sclerosis; however, multiple cardiac side effects [82], varicella zoster encephalitis, abnormal liver function tests, macula edema, and cases of PML limit its use.

Ozanimod has activity for S1PR1 and S1PR5. The TOUCHSTONE study compared 0.5 mg, 1 mg, and placebo treatment in 197 UC patients with moderate to severe disease, resulting in remission in 14, 16, and 6% of participants at week 8 ($p = 0.048$). Mucosal healing rates were higher with ozanimod (34 and 28%, respectively, vs. 12% with placebo). In line with entrapment of lymphocytes as the mode of action for ozanimod, peripheral lymphocyte counts decreased by 49 and 32% in the group with 1 mg and 0.5 mg, respectively. No serious adverse events were observed, but the study was considered too small to assess the safety and efficacy of ozanimod [83]. In an unpublished long-term extension study, 91% (119/131) of patients had little or no active disease based

on physician global assessment and 85% had no rectal bleeding [81]. A large phase III study of ozanimod in UC is planned. Preliminary data indicate efficacy of ozanimod also in CD [84, 85]. Efficacy of etrasimod, another S1PR1, 4, and 5 receptor modulator in UC was suggested in a study with 156 patients, and etrasimod 2 mg resulted in higher rates of endoscopic and histological improvement than the placebo [86].

Expert Opinion

S1P receptor modulation is an attractive new therapeutic principle. Newer S1P receptor modulators might be safer than fingolimod, and if no unforeseen safety issues arise, these drugs would be promising and powerful new agents for the treatment of UC.

Oligonucleotide Therapeutics

Specific inactivation of selected genes involved in disease pathogenesis has been the dream of drug developers. When delivered into the cytoplasm, small RNA oligonucleotides will find the specific complementary mRNA of a target gene and activate the enzyme RNase H, resulting in degradation of the respective mRNA [87, 88]. Therefore, oligonucleotide therapeutics offer the possible advantage for the selective downregulation of a selected gene with potentially fewer side effects. However, clinical experience with oligonucleotide therapeutics in the intestinal tract is very limited.

Oligonucleotide therapeutics have been tested for the transforming growth factor (TGF)-β pathway. Inflammation is typically accompanied by upregulation of both pro- and anti-inflammatory pathways including TGF-β. However, TGF-β signaling is suppressed by the activity of intracellular Smad7. Mongersen is a chemically stabilized oligonucleotide directed against Smad7 and contains cytidine-phosphate-guanosine motives to avoid immune activation (see below). Mongersen is an oral drug, formulated for preferential release in the terminal ileum and right-sided colon for optimal treatment of CD [87, 88]. However, even though phase II studies showed high rates of clinical remission (65 vs. 10% with placebo) [89, 90], a recent large-scale phase III study was stopped due to lack of efficacy, and it remains unclear whether mongersen will ever be applied clinically [91].

Oligonucleotides have also been used for interference with leukocyte trafficking. Intercellular adhesion molecule-1 (ICAM-1) is an endothelial adhesion molecule, upregulated by inflammatory cytokines, including TNF, IL-1, and IFN-γ. ICAM-1 supports leukocyte trafficking into the gut and mucosal inflammation. Alicaforsen can downregulate ICAM-1 expression in an RNAse H-dependent manner. Despite some effects on disease activity, so far, no clinical effectiveness could be convincingly demonstrated in large phase II studies in CD and UC [92–94]; however, a phase III study of alicaforsen enema in pouchitis is ongoing.

Oligonucleotide therapeutics have also therapeutic potential outside gene downregulation. TLRs recognize molecular patterns of pathogens for activation of innate immunity. TLR9 recognizes small oligonucleotide molecules containing cytidine-phosphate-guanosine motives. Even though most TLR molecules have pro-inflammatory activity, TLR9 has anti-inflammatory activity in the gut, and the TLR9 agonist cobitolimod (DIMS0150) can induce expression of IL-10 and type I IFNs. Local application of DIMS0150 via colonoscopy at weeks 1 and 4 did not result in clinical improvement at week 12; however, rates of mucosal healing were greater at week 4 [95]. This suggests that for lasting clinical improvement, ongoing application of the drug is required.

In summary, oligonucleotide therapeutics are potentially highly interesting molecules for the treatment of UC and CD due to its highly selective mode of action. A large number of clinical trials have confirmed the general safety; however, no drug of this class has been approved for IBD treatment yet, but further improvements in drug target selection and/or mode of delivery might deliver promising results.

Cell-Based Therapies

Autologous Stem Cell Transplantation

Since almost 30 years, small case series reported success of autologous stem cell transplantation (ASCT) for CD [96]. Approximately 70% of patients achieved remission or disease activity could be controlled with standard therapy for CD [97, 98]. ASCT has subsequently been tested in the ASTIC trial, in which stem cells were mobilized in all patients with immediate transplantation in one arm and delayed ASCT after ≥1 year in the control group [99]. ASTIC recruited patients with severe CD despite ≥3 therapies including steroids, not amendable to surgery. ASTIC further used a highly stringent composite end point of clinical remission (Crohn's disease activity index < 150 for ≥3 months) 1 year after ASCT without steroids, immunosuppressants or biologics, and no radiologic or endoscopic evidence of disease activity. The study was negative since the primary end point was met by only 2 out of 23 patients in the treatment group versus 1 out of

22 controls. However, some benefits were suggested regarding secondary end points. Furthermore, long-term data from both treatment arms of this trial showed improvements regarding quality of life and endoscopic activity [100]. Severe side effects, mainly infections, were frequent after therapy, and 1 patient in the ASTIC trial died of sinusoidal obstruction syndrome.

Expert Opinion

ASCT is a relevant treatment option for the most severe CD cases, refractory to all treatments. However, this option should be reserved for highly experienced centers. Development of safer treatment protocols remains the most important challenge.

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is an established treatment option for childhood IBD (very early-onset IBD) with most patients suffering from inherited mutations in signaling pathways including IL-10R1 and IL-10R2 [101, 102]. However, even though potentially effective, due to high risks, allogeneic transplantation is rarely considered in adult IBD.

Mesenchymal Stroma Cell Therapy

Treatment with MSCs might be a paradigm shift in the treatment of fistulizing CD. MSCs are adherent cells with a fibroblast-like phenotype with reservoir function as stem cells for adipocytes, osteoblasts and chondrocytes [96, 103, 104]. MSCs constitute up to 1% of the cellular content of the adipose tissue but can also be found in the bone marrow and other tissues. Upon stimulation by pro-inflammatory cytokines, MSCs secrete a variety of immunosuppressive molecules, thus decreasing overall inflammation [105, 106]. In addition, MSCs can promote wound healing and tissue regeneration by secretion of TGF-β and fibroblast growth factor, and MSCs are also able to differentiate into fibroblasts or endothelial cells for formation of granulation tissue [106–108]. Thus, MSCs combine anti-inflammatory and regenerative properties, and both of these properties would be of value for the treatment of fistulizing CD. MSCs do not express MHC II, and only low amounts of MHC I, and do not stimulate T cells, thus enabling escape from immune surveillance and low rejection after transplantation [104, 109].

MSCs have been successfully used for the treatment of active complex perianal fistula in CD patients. In a large study with 212 patients, 120 million adipocyte-derived MSCs were injected into the fistula tract and the primary end point of absence of fistula discharge, and lack of large fluid collection on MRI >2 cm was met in 50% of patients in the treatment group versus 34% with placebo [110]. A recent meta-analysis demonstrated an effect of MSC treatment with an OR for fistula persistence of 0.21 [111]. Overall, treatment of MSCs has found to be generally safe even though long-term data are still lacking. Malignant transformation of stem cells would be a potential concern since protumorigenic effects have been observed in mice [112, 113]. However, to the best of our knowledge, no cases have been reported in humans. MSCs have been approved for the treatment of fistulizing CD in various countries and provide an attractive treatment option for the subgroup of CD patients with treatment-refractory perianal fistula. In contrast, systemic use of MSCs for the treatment of luminal CD is less established, and future studies would be needed [96, 104].

Expert Opinion

Mesenchymal stem cell therapy is an innovative therapy for CD fistula with surprisingly high success rates in this very hard-to-treat patient population. While MSC therapy is currently established in large centers, costs, logistical challenges, and lack of long-term data so far limit wide-spread application.

Conclusion

The field of IBD therapeutics has seen tremendous improvements, and the efficacy of new drug targets such as IL-12/IL-23, the JAK/STAT pathway, and S1P has been established. The JAK inhibitor tofacitinib has recently been approved for UC, and further drugs of the same class are expected. Similarly, ustekinumab has been approved for CD and UC in Europe, with additional anti-IL-12/IL-23 drugs in clinical testing. Ozanimod is the S1P inhibitor most advanced in clinical testing. However, efficacy of all drugs is limited to approximately 15–40% over placebo, depending on the stringency of the endpoint and rates of placebo response in the respective study. This suggests that no single molecule will enable cure for all patients. One way forward could be the identification of biomarkers predicting cure in subsets of patients, enabling a more specific "personalized medicine." Alternatively, drugs could be combined to maximize the chances of success in patients. In this respect, it is assuring that the rates of side effects have been very low for most modern drugs, and well-tolerated drugs should be selected and systematically combined. Mesenchymal stromal cells are a promising treatment option for fistulizing CD, and ASCT might be

established as a last-resort treatment option for most severe CD, refractory to all other treatment options in the future.

In any case, the clinical observation of spontaneous remission and even resolution of disease activity for longer periods of time or even indefinitely in a subset of patients suggests that a cure for IBD is theoretically possible. However, even though currently no obvious strategy for IBD cure exists, a better understanding of IBD mechanisms should enable such efforts in the future.

Disclosure Statement

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Author Contributions

B.M. did the literature research and prepared the figures and the table. B.M. and S.B. wrote the manuscript. S.B. and the other co-authors contributed to the interpretation of data, critically revised the manuscript, all figures, and the table for important intellectual content. All authors read and approved the final version of the manuscript. S.B. is the guarantor of this article.

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