CLINICAL INVESTIGATION

Novel treatment options for ulcerative colitis

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The approved treatment options for patients with ulcerative colitis (UC) are currently limited to mesalamine or immunosuppressants. Patients who do not respond to mesalamine-based therapy can be treated with immunomodulators or anti-TNF antibody therapy. Failure or adverse reactions to these medications leaves the patient with little choice other than colectomy. However, novel insights into the pathogenic drivers of UC have led to new developments in drugs that promise clinical efficacy via modulation of targeted pathways. Given the impending expansion of therapeutic options for patients with UC, clinicians and researchers should be familiar with these mechanisms of action. In addition, the typical 'step-up' treatment paradigm for UC will likely need to be reshaped to allow for a more personalized approach to treating UC.

Keywords: anti-integrins • chemokine inhibitors • clinical drug trials • inflammatory bowel disease therapy • novel therapies • ulcerative colitis

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Inflammatory bowel disease (IBD is an umbrella term that encompasses chronic, idiopathic inflammatory conditions of the small bowel and colon. While the etiology of IBD is unknown, it is presumed to be the result of a complex interaction of intestinal flora, mucosal immune response, environmental factors and genetic makeup [1,2]. The predominant IBDs are Crohn's disease and ulcerative colitis (UC). UC is distinct from Crohn's disease in that the inflammation is isolated to the colon, and typically restricted to the mucosal layer in a uniformed fashion starting at the anorectal verge and extending proximally [3,4]. Extra-intestinal manifestations of IBD can occur in UC including erythema nodosum, pyoderma gangrenosum, uveitis, arthritis and primary sclerosing cholangitis. The natural history of UC is episodes of flares interspersed with periods of quiescence. During a flare, the goal of therapy is to induce clinical and endoscopic remission, followed by continuation of therapy to maintain remission. The hallmark of a UC flare is bloody diarrhea, often associated with tenesmus and urgency. Initial therapy is dependent on severity and extent of disease. Moderate disease is characterized by more than four stools in a day with minimal signs of toxicity, while severe is more than six bloody stools a day with signs of toxicity (tachycardia, fever, anemia or elevated erythrocyte sedimentation rate) [5,6]. For mild-to-moderate disease, 5-aminosalicylic medications, either oral or topical, are the mainstay of treatment. If needed, topical steroids can be added. Occasionally, mild-to-moderate disease will require oral corticosteroids to induce remission [3,6].

Patients with severe colitis or patients who do not respond to, or are intolerant of, treatment for mild-to-moderate colitis will require escalation of therapy. In the case of severe colitis, patients require hospitalization for intravenous steroid management. If there is a response to intravenous steroids, conversion to oral steroids with initiation of an immunomodulator as a steroid-sparing agent is a reasonable course. If patients do not improve with intravenous corticosteroids then salvage therapy with cyclosporine or infliximab are the only medical therapies available with apparent similar short-term efficacy [7]. If salvage therapy is unsuccessful, colectomy is the remaining

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step. While steroids are an effective anti-inflammatory agent, their side-effect profile remains high, especially in the long term [8,9]. Thus, while often used for moderate and severe disease, steroid-sparing therapies are needed.

The natural history of UC is difficult to predict at onset. Examining all patients with UC, the estimated 10-year colectomy rate is approximately 10%, however it is significantly higher in patients with extensive disease or who require steroids [10–14]. In such patients, early and aggressive therapy could alter the natural history of the disease, although evidence to support this in UC is lacking. Ideally, early intervention would lead to mucosal healing, which would lead to a decrease in the frequency of flares as well as potentially a lower risk of colorectal cancer [15–17]. This review will focus on some novel and emerging therapies from the perspective of their pharmacological targets in the UC inflammatory cascade (Table 1). This review is not exhaustive, but focuses on a number of prevalent targets.

Pharmacological targets in UC

UC develops due to an unchecked inflammatory response to antigenic triggers in genetically susceptible individuals. The etiology is unknown, but the inflammatory response is characterized as an atypical type-2 helper T (Th2) cell response. Th2 inflammatory responses are characterized by production of TGF-β and IL-5, but not IL-4 [18–20]. In addition, cytokines such as TNF and IL-1 induce the expression of adhesion molecules on the endothelium of the intestinal vasculature to attract additional lymphocytes to the sites of inflammation. A relative overexpression of Type-17 helper T (Th17) cells compared with T regulatory (Treg) cells has also been implicated in IBD [2]. Th17 cells secrete IL-17, which may be an instrumental pathway in the development of intestinal inflammation [4,21,22]. Recently it has been noted that Th17 cells may act differently in Crohn's disease versus UC, suggesting that therapies that do not work in Crohn's disease may work in UC [23]. A summary of key targets in IBD is shown in Figure 1.

Anti-TNF antibodies

TNF is a proinflammatory cytokine produced predominantly by macrophages and monocytes, although to some degree it is produced by neutrophils, macrophages

Table 1. Novel drugs and mechanisms of disease for ulcerative colitis.

Drug	Route of administration	Mechanism	Target	Clinical trial number	Phase	Ref.
Golimumab†	sc.	Inhibits TNF-mediated inflammation	TNF	NCT00488631 NCT00487539	III	[216,217]
Vedolizumab	iv.	Inhibits leukocyte migration	α4β7	NCT00619489 NCT00783718 NCT01177228 NCT00790933	II, III	[218–221]
Traficet	p.o.	Inhibits leukocyte migration	CCR9	NCT01658605	II	[203]
Etrolizumab	sc.	Inhibits leukocyte migration	β7	NCT01461317 NCT01336465 NCT00694980	I, II	[222–224]
Anrukinzumab	iv.	Inhibits IL-13-mediated inflammation	IL-13	NCT01284062	II	[205]
Tralokinumab	sc.	Inhibits IL-13-mediated inflammation	IL-13	NCT01482884	II	[206]
Vidofludimus	p.o.	DHODH inhibitor	DHODH	NCT00820365	II	[225]
Tofacitinib	p.o.	Jak inhibitor	Jak (Jak3, Jak1>Jak2)	NCT01465763 NCT01458951 NCT01458574	III	[208–210]
PF-00547659	sc./iv.	Anti-MAdCAM antibody	MAdCAM	NCT01620255 NCT00928681	I, II	[201,202]
BMS-936557	iv.	Anti-IP-10 antibody	IP-10 (CXCL10)	NCT01294410	II	[204]

†Approved by the US FDA for ulcerative colitis.

DHODH: Dihydroorotate dehydrogenase; iv.: Intravenous; p.o.: Oral; sc.: Subcutaneous.

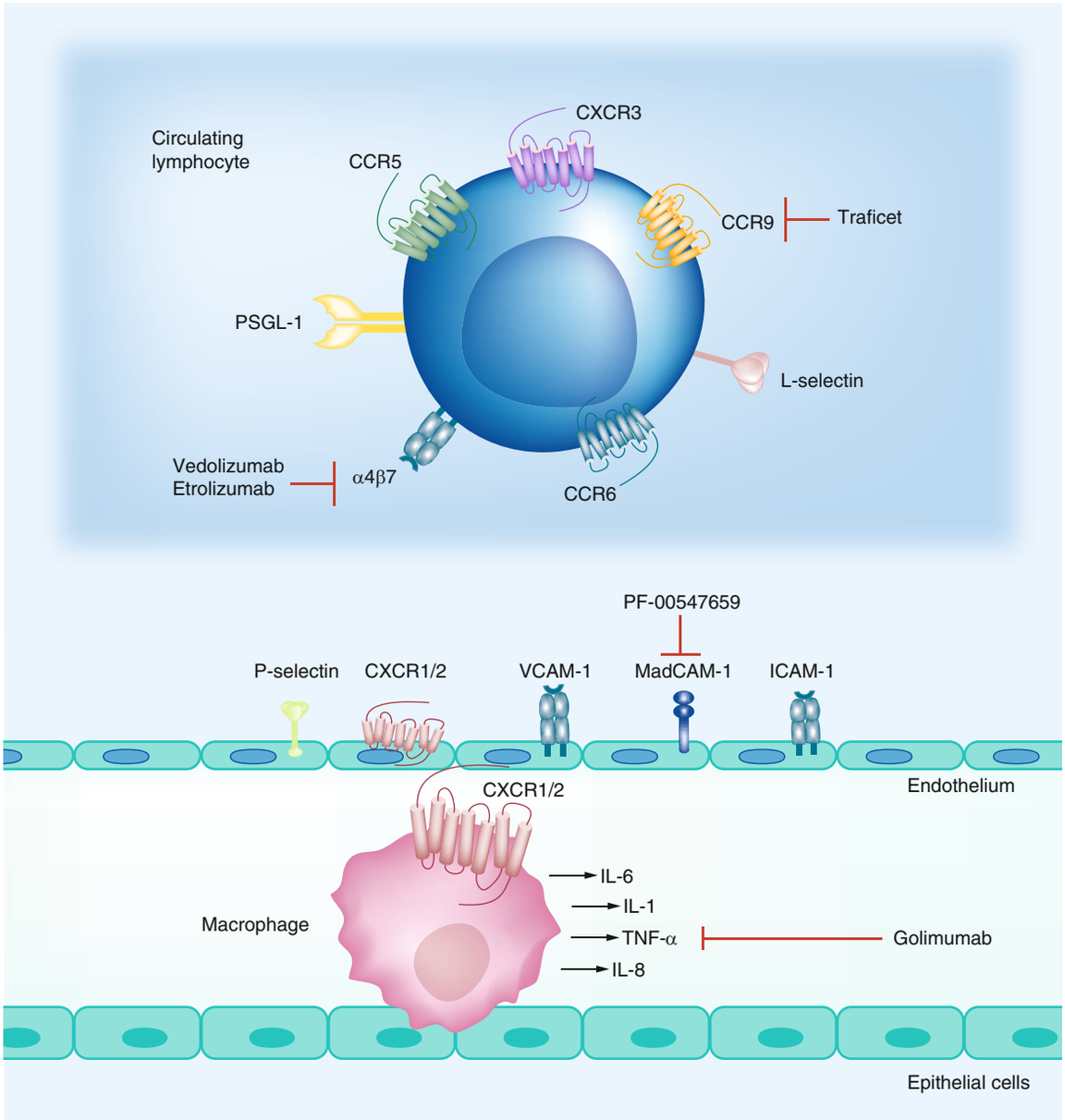

Figure 1. Select targets for novel therapies in ulcerative colitis.
Adapted from [43].

and fibroblasts. It can be released by almost any type of cellular stress including endotoxins, proinflammatory cytokines, various antigens and even osmotic stress [24]. Early studies in children showed significant elevation of TNF levels in relapsed UC compared with remission [25]. Immunohistochemistry of surgical specimens from patients with UC revealed an abundance of high-density TNF producing cells in the lamina propria; this finding correlated well with elevated stool TNF found during relapse of colitis [26,27]. Beyond just a marker of active disease, TNF was soon identified as having a role in producing chronic inflammation in the intestine [28,29]. TNF can affect cells as a transcription factor to induce the production of other proinflammatory cytokines, as well as act on the tissue level, increasing the production of endothelial adhesion molecules to recruit inflammatory cells [24].

A chimeric mouse–human monoclonal IgG1 antibody to TNF was developed and led to the approval of infliximab (Remicade®, Janssen Pharmaceutica, [PA, USA]) for UC in 2005 [30]. Two randomized controlled trials demonstrated the efficacy of infliximab for the induction and maintenance of remission in UC [31]. Notably, patients treated with

infliximab (5 and 10 mg/kg) in these trials had a lower cumulative incidence of colectomy (10%) when compared with patients treated with placebo (17%), although this was not statistically significant [32]. In 2012, the US FDA approved the fully human anti-TNF antibody adalimumab (Humira®, AbbVie Inc. [IL, USA]) for the treatment of UC. It was shown to be effective in induction and remission of UC with a short and long term remission rate of approximately 20%, with a similar adverse events profile to placebo [33,34]. A small portion (~10%) of patients who had previously been exposed to infliximab were able to have a sustained response to adalimumab at 52 weeks [34]. Unfortunately, over time, infliximab looses efficacy with approximately half of patients loosing effect at 30 weeks, requiring a change to another anti-TNF, a different medication or prompting surgery [31]. Most recently, in 2013, another fully humanized IgG1 anti-TNF antibody, golimumab (Simponi®, Janssen Biotec, [PA, USA]), was FDA approved for treatment of patients with moderate-to-severe UC. In the PURSUIT-SC study, rates of clinical response were higher in patients who received the high dose of golimumab compared with placebo (55 vs 30%, respectively) at 6 weeks [35,36].

In general, the anti-TNF medications as a class are well tolerated. Side effects include infusion reactions with infliximab and injection reactions with adalimumab and golimumab [37]. One concerning class effect from anti-TNFs are infections, especially the reactivation of tuberculosis or hepatitis B, thus all patients need to be tested for latent tuberculosis and assessed for hepatitis B status prior to anti-TNF therapy [38,39]. Aside from tuberculosis, infections in general are increased with anti-TNFs [40]. There may be an increase in lymphoma and skin cancer with anti-TNFs, although the absolute magnitude of the increased risk would be small [41]. There is a risk of exacerbation of congestive heart failure with anti-TNFs as a class as well. Specifically with golimumab, adverse events occur in similar frequencies to other anti-TNFs, although it has been suggested that injection site reactions are less than other injectable anti-TNFs [42].

Anti-integrin antibodies

In order for chronic inflammation to occur, inflamed tissue must 'call for reinforcements' from the blood to perpetuate the inflammatory process. Noninflamed endothelium acts as a barrier to leukocytes, preventing migration from the blood into the underlying tissue. However, when activated via a cascade of cytokines, tissue inflammation results in a change of the endothelium to allow leukocytes to adhere to and transmigrate through the endothelium. Specifically, in response to a proinflammatory signal, the endothelium will up-regulate selectins, VCAM-1, ICAM-1 along with other various adhesion molecules [43]. Proinflammatory cytokines released in the tissue such as IL-1 and TNF increase a cell's surface adhesion molecules. Increased activity of the NF-κβ also results in increased expression of endothelial cell surface adhesions.

Integrins are a family of cell surface adhesion molecules that are responsible for cell–cell interactions, cell–pathogen interactions and cell–extracellular matrix (e.g., fibrin) interactions. They represent a key target for the movement of inflammatory cells into the tissue [44]. Each integrin is a heterodimer with an α and β subunit. Vertebras have 18 different α subunits and eight different β subunits allowing at least 24 different heterodimeric combinations. For the most part, each subunit consists of a large extracellular domain, a transcellular domain and a small cytoplasmic tail [45]. Integrins are expressed constitutively on leukocytes and bind to MAdCAM-1 and VCAM-1 expressed on endothelial cells to facilitate rolling and adhesion and eventually migration [44]. The α4 subunit is particularly important as it is preferentially expressed on lymphocytes and monocytes. The β7 subunit is important in homing leukocytes to the gut. As such, the α4β7 heterodimer seems to be necessary for the migration of leukocytes into the gut epithelium. Activated or naive lymphocytes expressing α4β7 will bind to MAdCAM-1 on the endothelium and preferentially home to the intestine [46,47]. Additional support for the gut-specificity is that the α4β7 integrin is expressed by >95% of intestinal epithelial lymphocytes and <2% of circulating lymphocytes [48]. Thus, while the α4 subunit is essential for lymphocyte migration through the endothelium, the β7 subunit is a key regulator in homing of lymphocytes to the intestine.

Vedolizumab

Vedolizumab is a humanized monoclonal antibody that is specific for the α4β7 heterodimer. It is distinct from prior integrin inhibitors (e.g., natalizumab) that were specific only to the α4 subunit. In theory, this allows intestinal specific inhibition of leukocyte migration, while not affecting leukocyte migration to other organs. In 2005 Feagan *et al.* reported the results of a randomized trial of vedolizumab (MLN02) versus placebo in patients with UC. While the study duration was short, there was a significant increase with patients achieving clinical remission at 6 weeks versus placebo (33 vs 14%; p = 0.03) [49]. An interesting component of this study was the observation that in patients who received the drug, over 90% of the circulating $CD4^+CD45RO^+$ T cells had saturation

of α4β7 integrin at 6 weeks. The level of saturation also correlated with antibody formation and clinical response. Further study into the mechanism of vedolizumab led to two interesting observations. First, while vedolizumab inhibited α4β7 binding to MAdCAM-1 and fibronectin, it did not inhibit binding to VCAM-1, which typically binds to α4β1 [50]. Thus there does not appear to be significant crossover inhibition of other integrins, reinforcing the gut-selectivity of vedolizumab inhibition. In addition, it was noted that type of T cell inhibited by vedolizumab were $CD4^+$ memory cells that were specifically thought to be pathogenic in IBD, as well as a subset of Th17 cells that express α4β7 [50,51]. Th17 cells are postulated to contribute significantly to many autoimmune diseases including IBD [21,52]. Thus by inhibiting the binding of T cells that express high levels of α4β7, vedolizumab seems to inhibit both memory and effector T cells from migrating to the intestine while allowing nonpathogenic immune cells to continue their path to the intestine.

Recently a Phase II trial was published for the treatment of active UC with vedolizumab [53]. Initial trials of vedolizumab in UC and Crohn's disease resulted in high levels of antibody formation (44%), which resulted in less drug binding to T cells and decreased clinical response [49,54]. Thus a new formulation of vedolizumab was undertaken using a Chinese hamster ovary cell based system (instead of a mouse myeloma cell line). This resulted in similar *in vitro* activity as the prior formulation; however, clinically, there was less antibody formation (11%) [53]. Recently the results of a large Phase III trial, the GEMINI trial, were released. This large trial examined patients with active UC and found that more patients were in clinical remission at week 6 compared with placebo (17 vs 5.4% respectively; $p = 0.001$) and at 1 year (45 vs 16% respectively; $p < 0.001$) [55]. Overall, the side effect profile was similar to placebo. However, in a parallel trial of vedolizumab for Crohn's disease, there were more serious adverse events in the vedolizumab arm including more serious infections, one case each of latent tuberculosis, carcinoid tumor and squamous and basal cell carcinoma [56]. The authors note that as of February 2013, approximately 3000 patients had been exposed to vedolizumab and there have been no reported cases of progressive multifocal leukoencephalopathy. Despite these recent large Phase III trials, determining adverse events related to vedolizumab will require more patients and longer follow-up time to accurately quantify the risk of infection and malignancy.

Etrolizumab

Etrolizumab (rhuMAb β7, or RG7413) is a humanized monoclonal antibody specific for the β7 integrin heterodimer [1,4]. As stated above, the β7 dimer provides the specificity to the gut, as blockade of α4 alone will result in inhibition of leukocytes to numerous tissues. There are only two integrins that utilize the β7 subunit: α4β7 and αEβ7. αEβ7 T lymphocytes are abundant in the gut; however, they are also present in other mucosal epithelial surfaces, such as the lungs. Animal studies indicate that blockade of β7 predominantly inhibit lymphocyte tracking into the gut and do not inhibit homing of nonmucosal tissue [3,6]. In contrast to α4β7, which is responsible for homing of lymphocytes to the gut, αE seems to be expressed after the lymphocyte is in the tissue and thus acts to retain lymphocytes in the intestine [5,6]. In addition, αEβ7 binds to E-cadherin on endothelial cells as opposed to α4β7, which binds MAdCAM-1. Inhibition of the β7 heterodimer inhibits both the α4β7 and αEβ7 integrin function. It is unclear if this is useful; on one hand there is potentially more inhibition of T cells in the intestine, while on the other hand it may prevent T cell migration to other tissues resulting in infections or reduced tumor surveillance. Interestingly, animal models suggest there is no effect on β7 inhibition in mouse models of encephalitis [3,9]. More human data will be needed to determine the effect on the CNS and other organs.

A Phase I randomized trial of etrolizumab versus placebo demonstrated that the drug was, overall, well tolerated. The pharmacokinetics of the drug was noted to be similar to typical human IgG1 monoclonal antibodies. While this was a Phase I trial, there was some indication that the drug had clinical efficacy with a trend towards clinical improvement compared with placebo [8]. Indeed, in a subset of patients treated monthly, 67% had a clinical improvement at 10 weeks and 20% were in remission. There are currently two Phase II trials underway to further assess the clinical effect in UC (Table 1). In the Phase I trial, there was a slightly higher rate of adverse events in the treatment arm; however, the majority of adverse events were mild [8]. Obtaining an accurate risk profile for this drug will likely require large Phase III trials to see a significant signal in any one adverse event.

PF-00547,659

As previously mentioned, α4β7 integrins bind to MAdCAM. MAdCAM is expressed on vascular endothelium in the intestinal lamina propria. In animals, blocking MAdCAM has been shown to decrease the number of lymphocytes entering the colon as well as decrease the severity of colitis [11,13,16,17]. Importantly, blocking MAdCAM seems to have minimal impact on VCAM, which is involved in leukocyte trafficking to other organs. PF-00547,659 is a fully

humanized IgG2 monoclonal antibody to MAdCAM. While inhibiting leukocyte migration, it differs from natalizumab and vedolizumab in that it is blocking the endothelial cell receptor and not the integrin. The potential advantage of this is selective blockage of leukocyte migration to to the gut. Specifically, MAdCAM does not seem to be expressed in the CNS and thus there should be no inhibition of leukocyte movement to the CNS [10,19]. In 2011, the first-in-human trial of PF00547,659 was undertaken. This small study did not show any serious adverse events related to the drug [2,15]. The trial was not powered to detect clinical end points; however, there was a trend towards clinical improvement and improved fecal calprotectin, both at week 4. Two Phase II trials are currently underway [201,202].

Chemokine inhibitors

Chemokines, a subset of cytokines, are a group of small polypeptides that are involved in trafficking of lymphocytes from the blood to areas of inflammation. Approximately 40 different chemokines have been described in humans acting on neutrophils, lymphocytes, monocytes and eosinophils [4,18,20–22]. There are two main subfamilies of chemokines, CXC and CC, which are defined by the arrangement of the N-terminal cysteine residue [57]. Chemokine receptor 9 (CCR9) is a chemokine receptor that is induced through dendritic cell activation of a T cell or other proinflammatory signal. Its role is in homing of lymphocytes to the gut. Specifically, CCR9 binds solely to CCL25, which is expressed in the small intestine (and thymus), although not in the noninflamed cecum or colon [58]. CCL25 is expressed at higher concentrations in the proximal intestine compared with distal and is significantly upregulated in inflamed tissue. CCR9 regulation is not specific to T cells but also includes dendritic cells and plasma cells. Specifically, plasmacytic dendritic cells express CCR9 and may play a role in the pathogenesis of IBD via increased secretion of TNF-α [59]. While CCL25 is expressed in the small intestine, CXCL10 (also known as IFN-γ-inducible peptide [IP10]) is expressed in the colon and is a receptor for $CXCR3^+$ immune cells [47]. More so, IP-10 has been shown to be expressed at high levels in colonic tissue from patients with active UC [51]. In fact, mice in response to nonsteroidal anti-inflammatory drug injury, or in IL10-/- mice, anti-IP-10 antibody decreases naive T-cell priming and blocks Th1 cell recruitment to the colon [52,53]. It has also been reported that this pathway is significant in modulating Th17 inflammatory cell recruitment [54]. Another difference from CCR9 is the binding specificity of its ligand. CCR9–CCL25 is unique in that it is a nonpromiscuous chemokine receptor pair, whereas IP-10 modulates effects that are unrelated to CXCR3 binding [50].

■ Traficet

Traficet-EN (CCX282) is the first of a new class of drugs targeted to CCR9. Specifically it is a chemokine that acts as an antagonist to CCR9 [60]. It has shown promise in the treatment of Crohn's disease in a Phase II study with a significant reduction in both Crohn's disease activity index and Crohn's disease endoscopic index of severity versus placebo at 12 weeks and additionally maintenance of remission at 36 weeks [61,62]. As stated above, CCR9 binds to CCL25, which is expressed in the small intestine and not the colon. However, murine models of acute DSS colitis, which mimics UC in mice, have shown a benefit with interference of the CCR9–CCL25 pathway. The role may be related to dendritic cell and peritoneal macrophage trafficking to inflamed areas of the colon [63]. Thus a Phase II trial of Traficet is currently underway for patients with active UC [203]. Thus far, there is not enough information to comment on any specific adverse events related to this drug.

■ BMS-936557/anti-IP-10 antibody

BMS-936557 (previously MDX-1100) is a fully human anti-IP-10 antibody. Blockade of IP-10 results in inhibition of IP-10-dependent chemotaxis of activated T cells to the target tissue. BMS-936557 is specific for the IP-10-CXCR3 interaction and does not interfere with other receptor interactions for CXCR3 such as CXCL9 and CXCL11 which are involved in trafficking of lymphocytes to other organs [64]. A Phase II randomized trial was recently completed for BMS-936557 in which the pre-specified primary and secondary end points of clinical response and clinical remission at day 57 were not met [65]. The trial was underpowered to detect a statistical difference in the primary outcome. When the data were re-examined in a *post hoc* analysis, the study drug had a significantly higher rate of clinical response versus placebo [65]. In addition, there was histologic improvement in patients with elevated trough levels of BMS-936557 even if there was no significant improvement in clinical scores. In this particular study there was an increase in the number of adverse events, including significant adverse events and serious infections, in the study drug arm. However, prior studies in rheumatoid arthritis have not detected any significant difference in adverse events with BMS-936557 compared with placebo [66]. Thus, this pathway is promising, but more information is needed regarding efficacy and safety. A second Phase II trial for induction and maintenance is currently underway for patients with moderate-to-severe UC [204].

Anti-IL-13 antibodies

Natural Killer (NK) T cells are a subset of T cells that have a controversial role in the pathogenesis of IBD. Mouse models have demonstrated some conflicting data regarding a protective or pathogenic role for NK cells, which ultimately may be related to pleotropic effects of NK cells [67]. In humans, an increase in NK cells has been found in the lamina propria of patients with UC. These NK cells were shown to produce high levels of IL-13 when simulated in culture [68]. In oxalazone induced colitis, NK cells have been shown to play a role in the inflammatory response. Specifically, after an initial IL-4 increase (typical of a Th2 response), there is a large increase in IL-13. This excess of IL-13 is produced from NK T cells in the lamina propria [69]. Inhibition of IL-13, as well as depleting mice of NK T cells, attenuates colitis in this model [70,71]. IL-13 is a potent stimulator of B cells to secrete IgE. It is also involved in the chemotaxis of eosinophils and other immune responses to environmental antigens in other organs such as the lungs [72].

Anrukinzumab

Anrukinzumab is a fully humanized IgG1 antibody to IL-13. In April 2013 a Phase II, randomized, placebo-controlled trial evaluating three doses of anrukinzumab was completed in patients with active UC [205]. The primary outcome of the trial is change in baseline fecal calprotectin level at week 14. At the time of this review's preparation, results had not yet been published.

Tralokinumab

Tralokinumab is a fully humanized IgG4 antibody to IL-13 is currently in a Phase II clinical trial. This trial is examining tralokinumab versus placebo as an adjunct therapy to a current, stable medical regimen (5-aminosalicylic, low dose steroids or purine analogs) for patients with moderate-to-severe UC [206]. The primary outcome is clinical response at 8 weeks. The trial was completed in June 2013 and the results have not been published at the time of this writing.

Other novel immunomodulators

Vidofludimus

Vidofludimus (4SC-101, SC12267) is a novel oral treatment for inflammatory diseases. It is a small molecule that inhibits dihydroorotate dehydrogenase. Dihydroorotate dehydrogenase is a key step in the *de novo* synthesis of pyrimidines. Lymphocytes are distinct in that they rely on *de novo* synthesis of pyrimidines and do not utilize salvage pathways. Vidofludimus has been shown to decrease activated lymphocyte proliferation, decrease IL-17 release and attenuate DSS colitis in mice [73]. Interestingly, it seems to selectively inhibit IL-17 production without an effect on TNF, IL-1 or IL-6.

Clinically, vidofludimus has been tested in a mix of Crohn's disease and UC patients unable to wean off steroids in the ENTRANCE study. The ENTRANCE study was a Phase IIa, prospective open-label cohort of patients in remission on steroids. The investigators found that for UC, a total of 91.7% of patients were able to decrease their steroid dose and remain in remission, and 50% were in steroid-free remission at 12 weeks [74]. The drug has lost some momentum as a Phase IIb trial for rheumatoid arthritis failed to reach a significant improvement in the primary end point [75]. At the time of writing, no further trials in UC are registered at clinicaltrials.gov.

Tofacitinib

'Janus' is the Roman god of doors or gates, and is also the name of a specific subgroup of tyrosine kinases that are not associated with a receptor. The Janus kinases (Jaks) are fundamental for controlling numerous cytokines related to proliferation and other processes. Erythropoetin, thrombopoetin, growth hormone, prolactin and leptin all use the Jak signaling pathway and therefore they are truly gatekeepers in many cells [76]. While Jak3 is limited to lymphoid cells, Jak1, Jak2 and Tyk2 are found in all mammalian cells [77,78]. Proliferation of certain cytokines such as interferon, IL-2 and others are strongly related if not dependent on Jaks [79]. Thus, inhibition of the Jak pathway has the potential to decrease proinflammatory cytokines as well as decrease cellular proliferation.

An oral Jak inhibitor, tofacitinib (CP690,550 and PF-00547659), inhibits the production of cytokines such as IL-2, -4, -7, -9, -15 and -21 though inhibition of Jak3, Jak1 and to a lesser extent Jak2 [80]. *In vivo*, tofacitinib has been shown to decrease IL-2 dependent differentiation of Type 2 and Th17 cells. It also seems to interfere with the induced immune response to lipopolysaccharide [77,80].

A double bind, placebo controlled trial by Sandborn *et al.* assessed the efficacy of tofacitinib in moderate-severely active UC. The primary outcome of a clinical response at 8 weeks occurred in 78% of patients on 15 mg (highest dose used) compared with placebo ($p < 0.001$). While other doses were not significantly different than placebo, there was a dose response effect seen with increasing dose. The secondary end point of clinical remission was seen in 33% of patients on 3 mg, 48% on 10 mg, and 41% on 15 mg all of which were significantly higher than the 10% on placebo. Similar results were seen with endoscopic remission and response [81]. Infection was the most common adverse event. However, also noted was an increase in both

LDL and HDL. The increases in LDL and HDL were dose dependent and reversed by 4 weeks after discontinuation of the drug. Both LDL and HDL increased by about 12 mg/dl in the 15-mg arm, although the variations of LDL increase were greater than HDL. The dyslipidemia effect of tofacitinib is postulated to be related to inhibition of IL-6 [76]. It is unclear what clinical effects this will have, but it will require further evaluation. Another Phase II trial [207] and three Phase III trials [208–210] are currently underway in UC.

Novel nonimmunosuppressive therapies

Stem cells

While predominantly pharmacologic therapies are on the horizon for UC, other therapies are being explored as well. In the early 1990s, it was observed that patients with autoimmune diseases including Crohn's disease and UC who underwent hematopoietic stem cell transplant for other indications would have improvement and occasionally remission of their disease [82,83]. Hematopoietic stem cell transplantation carries a significant morbidity and even mortality limiting its use. On the other hand, mesenchymal stem cells (MSC) can be harvested from virtually any connective tissue and are multipotent stromal cells that have potential for tissue repair and immune modulation [84].

The exact mechanism of action for the beneficial effect of MSC is unknown. In fact, 95% of MSC are trapped in the lung after systemic infusion and <5% are present in distal tissue at 24 h [85]. Proposed mechanisms of effect include secretion of soluble factors to target tissue or release of a small number of MSC from lung to target tissue is enough to cause effect [86]. In mouse models of DSS colitis, systemic infusion of bone marrow-derived MSC improved clinical histological outcomes compared with controls and downregulated proinflammatory cytokines such as TNF [87]. Similarly preclinical animal studies have shown benefit in a wide range of inflammatory conditions such as graft versus host disease, ischemic limb injury, myocardial infarction and traumatic brain injury [88]. In Crohn's disease, early Phase I trials in humans demonstrated safety of infusions and injections of MSC. Clinical efficacy and safety are difficult to assess given small numbers of patients in early trials, although there appears to be some benefit for luminal and fistulizing disease [89–91]. A Phase II randomized placebo-controlled trial for MSC infusion in UC is currently underway [211].

Fecal microbiota transplant

Targeting the microbiota is a logical choice given the evidence of a strong association for dysbiosis in UC. First, in essentially all mouse models of colitis, enteric bacteria are required for colitis to develop [92]. Second, probiotics (such as VSL#3) have been shown to have a small but clinically significant improvement in UC [93]. While there does appear to be an association with probiotics and UC, it is not clear if the role is for induction or maintenance of remission [94]. Finally, analysis of the microbiota of inflamed areas in patients with IBD have shown decreased floral diversity and bacterial count [95]. While not causal, the association is strong and warrants study.

Fecal microbiota transplant (FMT) is a novel area of therapy first explored as a treatment for recurrent *Clostridium difficile* with excellent effect [96]. Early case series in UC demonstrated a good response with clinical remission occurring for up to 13 years after transplant in one patient [97]. An interesting observation from a large trial of FMT for *C. difficile* demonstrated that patients with IBD did well with FMT and no enhanced colitis activity was seen after FMT [98].

Currently two Phase II trials and one Phase II/III trial are underway to assess the impact of FMT on UC. Trials range in the mechanism of donation and include infusion into duodenal bulb or mid-gut [212,213] and fecal retention enema [214].

New formulations of standard therapies

Novel formulations of old drugs allow delivery directly to the colon. This provides new therapeutic options in UC for drugs that previously carried systemic toxicities limiting their use.

Budesonide

Controlled release budesonide (Entocort®, AstraZeneca, DE, USA) is a potent corticosteroid that has minimal systemic effect owing to approximately 90% first pass metabolism to inactive metabolites in the liver. Its primary target is ileal and right colon, which limits its use in UC [99]. Budesonide MMX® (Cosmo Pharmaceuticals Spa, Lainate, Italy) is a new formulation allowing dispersion of budesonide throughout the colon. The CORE I and CORE II trials found budesonide MMX to be safe and effective compared with placebo in inducing remission and more effective than placebo in the combined outcome of clinical and endoscopic remission in patients with mild-to-moderately active UC [100,101].

Cyclosporine

Traditionally, cyclosporine has been used for UC as rescue therapy when steroid refractory. This process involves hospitalization and cyclosporine via intravenous line [102]. In the 1990s, cyclosporine retention enemas were tried in patients with UC and found to be safe with low systemic levels of cyclosporine [103,104]. However, in a placebo-controlled trial, the

retention enemas failed to show a benefit for patients with mild-to-moderately active UC [105]. A novel formulation of oral, controlled minicapsule formulation of cyclosporine (CyCol, Sigmoid Pharma, Dublin, Ireland) was tested against placebo in patients with active UC [215]. The primary outcome was efficacy at induction of remission at 4 weeks. Notably the drug was safe; no cyclosporine was detected in the blood of patients. While not statistically significant, more patients achieved the primary outcome of remission on oral cyclosporine than placebo (13.6 vs 6.3%) [106]. Given the prior failure of topical cyclosporine via retention enema, it is not clear if cyclosporine must be systemic for its effect, or if more proximal colonic release will provide a benefit. Trials for CyCol in moderate-to-severe UC are planned but not yet underway.

Conclusion

Currently, the treatment for patients with moderate-to-severe UC failing mesalamine is limited to thiopurines, antimetabolites and TNF inhibitors. Up to half of these patients have required colectomy over time, which can be associated with significant morbidity. The advent of novel targeted therapies for UC may allow clinicians to reduce colectomy rates in this patient population with more severe disease. Additionally, targeted therapy ideally comes with less systemic side effects, although novel mechanisms of immune modulation will likely have some unanticipated consequences that will need to be borne out in larger cohorts of patients. Further observational studies will be required to identify those at higher risk of complicated UC, including those who fail to achieve mucosal healing on current therapy, and those who develop refractory disease. For these patients, novel therapies that influence specific steps in the pathogenesis of UC hold the promise of improved outcomes and quality of life.

Future perspective

The lessons from Crohn's disease suggest that stratification of individuals using pathway-specific biomarkers would permit targeting of agents to prevalent inflammatory mechanisms, rather than our traditional 'blanket immunosuppression' approach. With the evolving landscape of treatment for UC, it is likely that we will be able to think of UC as an umbrella term for the clinical end point of a number of different pathway-driven processes. Thus the common phenotype of UC will start to be understood in terms of disease mechanisms, rather than manifestations. With this shift, we will aspire to identify certain patients who will respond to a specific class of therapy based on mechanism of action. Changing the paradigm to pathway-targeted treatment will involve reshaping the classic step-up pyramid of treatment, and away from a 'one size fits all' approach. In the long-term, the goal will be to alter the natural history of this disease, and prevent colectomy in many more patients.

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Executive summary

Anti-TNF antibodies

- Three anti-TNF therapies are now US FDA-approved for ulcerative colitis (UC). Optimization of pharmacokinetics in practice remains a challenge with this class.

Anti-integrin antibodies

- Vedolizumab is an antibody specific to α4β7, which inhibits homing of lymphocytes to the intestine.
- Inhibiting α4β7 does not appear to inhibit lymphocytes to other organs, notably the CNS.
- Other targets to inhibit lymphocyte homing to the intestine include β7 and mucosal addressin cell adhesion molecule.

Chemokine inhibitors

- Traficet-EN is an antagonist to CCR9, which may mediate proinflammatory cells migrating to inflamed areas of the colon.

Small molecule inhibitors

- Tofacitinib is a novel oral therapy for UC that inhibits Janus kinases, decreasing production of proinflammatory cytokines.
- Tofacitinib had a dose dependent increase of HDL and LDL that resolved after therapy in clinical trials.

Nonimmunosuppressive therapies

- Multipotent stromal stem cell infusion and manipulation of the microbiome through fecal microbiome transplantation are two novel therapies with promise in UC.

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