CLINICAL INVESTIGATION

The emerging role of vedolizumab in the treatment of ulcerative colitis

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Ulcerative colitis is a chronic inflammatory disorder of unknown etiology. Despite current treatments that include aminosalicylates, corticosteroids, antimetabolites and TNF antagonists, many patients fail to respond to conventional medical management and undergo colectomy. Thus, new approaches to treatment are needed. This review discusses the emerging role of vedolizumab, a humanized monoclonal antibody that selectively blocks lymphocyte trafficking to the gut, for the treatment of ulcerative colitis.

Key words: α4β7 integrin • MAdCAM-1 • therapy • ulcerative colitis • vedolizumab

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The idiopathic inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic intestinal inflammation that is thought to result from a pathological interaction between the immune system and gut flora [1]. CD typically causes transmural inflammation of any part of the GI tract, which may result in the complications of strictures and fistulas. In contrast, UC is characterized by superficial inflammation with a variable degree of severity [2,3]. In distinction to CD, where involvement is segmental, inflammation in UC is continuous from the anal verge and is usually restricted to the lamina propria and epithelium of the colon [1,4,5]. Typical symptoms of both conditions include bloody diarrhea, abdominal cramps and fatigue. Current medical therapy features the use of anti-inflammatory drugs and first-line treatment for most patients consists of topical and/or oral 5-aminosalicylic acid formulations. Although these drugs are effective and safe, a substantial proportion of patients fail to respond, and receive systemic corticosteroids such as prednisone [6]. However, corticosteroid therapy has a high incidence of adverse events and lacks a maintenance benefit [7–9]. Although the purine antimetabolites azathioprine and 6-mercaptopurinde are currently recommended in guidelines for the treatment of corticosteroid-dependent or -resistant patients [10], the evidence supporting these recommendations is not robust [11,201]. TNF antagonists such as infliximab, adalimumab and golimumab are effective for inducing and maintaining remission in UC [12–16]; however, these agents are associated with the development of infectious complications from both conventional pathogens and opportunistic organisms such as *Mycobacterium tuberculosis* [17–20]. Furthermore, secondary loss-of-response to TNF antagonists occurs in up to 40% of patients [21]. Consequently, the identification of more durable, selective and safer treatments for patients with corticosteroid resistance or dependence is a research priority [22,23].

The pathophysiology of UC is unclear. Current theory implicates a dysregulated immune response to a yet-to-be-identified luminal antigen in genetically susceptible individuals. However, since specific mechanisms are unknown, therapy is inherently empiric. Conventional anti-inflammatory drugs such as aminosalicylates and corticosteroids target multiple mechanisms. For example,

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glucocorticoids inhibit NF-κB-mediated cytokine expression, granulocyte activity and leukocyte migration into inflamed tissue [24,25]. Likewise, TNF antagonists have wide-ranging effects on immune function including inhibition of leucocyte trafficking [26]. Unfortunately, broad-based activity comes at the cost of systemic immunosuppression and 'off-target' side effects. While TNF antagonists are more selective than corticosteroids and have a better therapeutic index, they also cause systemic immunosuppression since gut inflammation is not directly targeted [27]. Specific intestinal therapy is a new concept that offers a more effective and safer approach to treatment.

In this regard, amplification and perpetuation of the inflammatory cascade in UC requires migration of specific populations of lymphocytes to the colonic mucosa. In the past decade, the molecular mechanisms that regulate cellular trafficking to the intestine have been identified and applied to new drug development in IBD [2,3, 28–30].

This review outlines current understanding of the pathophysiology of UC and describes the emerging role of vedolizumab, a selective antagonist of the α4β7 integrin, for treatment of the disease [31].

Normal gut immunity

In healthy individuals, a precise balance exists between inflammatory and proinflammatory factors, which result in a state of constant, yet controlled intestinal inflammation. Immune homeostasis, a dynamic process that evolves following birth as the neonatal gut is colonized by microbes [32], is governed by both host and environmental factors. The most widely accepted model for the development of IBD hypothesizes that gut immune homeostasis is perturbed by exposure to an environmental factor that results in an inappropriate and pathological immune response to commensal microorganisms.

In health, equilibrium exists between proinflammatory effector T cells (Th1/Th2/Th17 cells) and regulatory T cells that suppress inflammation through the release of cytokines such as IL-10 and TGF-β [33–35]. Theoretically, in this model, any increase in effector T-cell activity or decrease in regulatory T-cell function could result in mucosal inflammation and tissue damage. The innate and adaptive mucosal immune systems provide an integrated defense against harmful antigens. The former depends on multiple, diverse mechanisms such as 'pattern recognition' by toll-like receptors expressed on the surface of epithelial cells and macrophages, natural killer cells, antimicrobial peptides and physical barriers such as the mucous layer [1,36,37]. However, if innate immunity fails to contain a potential pathogen, adaptive cellular and humoral immune responses come into play [38]. Antigen processing by tissue macrophages and dendritic cells and the subsequent generation of specific T-cell responses is the foundation of adaptive immunity. Importantly, it should be noted that the normal gut immune system is characterized by relative anergy [39]. In most circumstances adaptive responses are not mounted to the diverse foreign antigens that we encounter on a daily basis in our diet. However, in the case of sensitization, highly specific humoral and T-lymphocyte responses are generated that are both essential for protection against exogenous pathogens and, as is in the case of IBD, potentially harmful.

The role of leukocytes & adhesion molecules in the development & regulation of gut inflammation

Immune homeostasis is highly dependent upon the continuous recirculation of leukocytes between peripheral lymphoid organs (regional lymph nodes, liver and spleen) and the gut-associated lymphoid tissue in Peyer's patches and the lamina propria. During this process, T lymphocytes evaluate lumen-derived antigens that evoke either stimulatory or inhibitory responses [40]. Both the intensity and duration of mucosal immune responses rely upon proliferation of lymphocytes in peripheral lymphoid organs and their subsequent homing via the bloodstream to the gut [41]. Although multiple mechanisms facilitate intestinal lymphocyte trafficking, this process is specifically regulated by interactions between a single-chain 60-kDa glycoprotein; the mucosal addressin cell adhesion molecule 1 (MAdCAM-1) [42–45] and its cell surface ligand α4β7 integrin. MAdCAM-1 expressed on the surface of endothelial cells, in mesenteric lymph nodes, the lamina propria of the small and large intestine and, to a lesser extent, in the lactating mammary gland [46,47]. However, several other adhesion molecules such as ICAM-1 and VCAM-1 also participate in leukocyte recruitment to the gut. In active IBD, endothelial cells express a greater density of adhesion molecules on their cell surface [48]. This phenomenon is driven by proinflammatory cytokines, such as TNF, INF-γ and IL-1[49]. In mesenteric lymph nodes and Peyer's patches, activated T cells home to the gut as a consequence of the expression of both the integrin α4β7 and chemokine receptor CCR9 [1,50–54].

As part of the inflammatory process, leukocytes from distant vascular territories rapidly accumulate at sites of intestinal inflammation. As noted previously, the migration of T lymphocytes to the gut is essential in the pathogeneses UC and CD [55]. Leukocyte recruitment requires directed migration across the single layer of endothelial cells. Cells then traverse the interstitial

space to sites of active inflammation [56]. This entire process is under the control of specific molecular mechanisms. During the extravasation cascade, leukocytes make initial tethering and rolling contact with the vascular endothelium. Activation occurs and the cells firmly adhere to target endothelial cells. Finally, they migrate through the vessel wall (a process known as diapedesis) and undergo chemotaxis towards specific tissue regions. As a consequence, activated T cells and monocytes release proinflammatory cytokines that amplify, refine and perpetuate the inflammatory process [57,58].

The initial stages of leukocyte recruitment require coordinated interactions between multiple adhesion and signaling molecules (selectins, integrins and chemokine receptors) on the surface of responding T lymphocytes and their endothelial ligands. These molecules mediate leukocyte attachment\rolling (endothelial [E- & P] selectins, leukocyte [L]-selectin; integrins α4β1/α4β7), subsequent leukocyte arrest (β1 and β2 integrins) and, ultimately, transmigration across the vascular endothelium (Figure 1) [59–63]. The αEβ7 integrin is a recently recognized member of the β7 integrin family. αEβ7 is exclusively expressed on mucosal intraepithelial T lymphocytes and binds selectively to E-cadherin, a receptor located on all epithelial cells. αEβ7 has been implicated in T-cell retention in mucosal tissue, providing a mechanism that facilitates prolonged contact between immune cells and stressed or infected epithelial cells [64–69].

The α4β7 integrin is the therapeutic target for vedolizumab [31,70]. The first preclinical studies that highlighted the importance of antagonizing α4β7 were performed in cotton-top tamarins (*Saguinus oedipus*) [71,72] using a murine homolog of the antibody. Promising results from these studies then led to human trials.

Targeting leukocyte migration: a novel concept for drug development

Multiple strategies have evolved to block key steps in white blood cell trafficking [26,73,74]. The concept of specifically targeting leukocyte migration was based on the notion that interference with the continuing

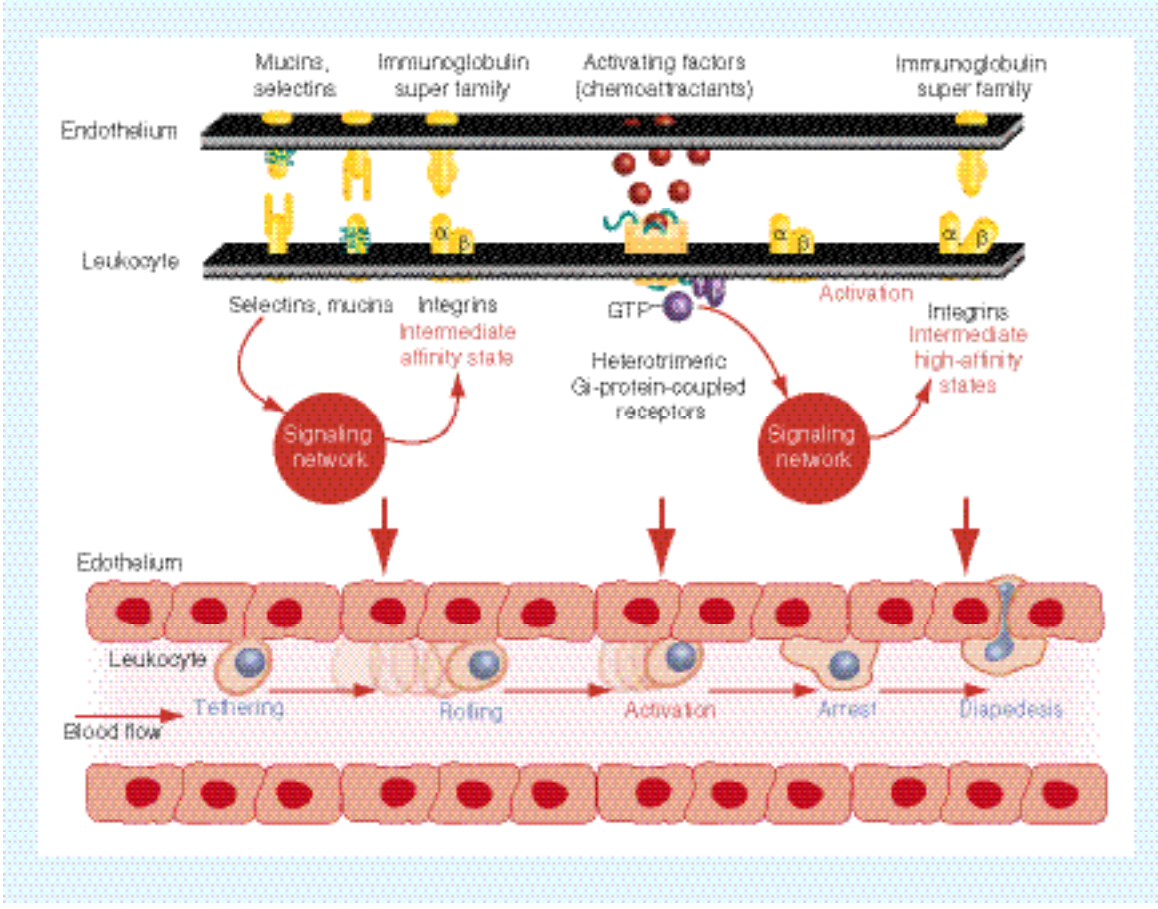

Figure 1. Stages of leukocyte recruitment to inflamed areas of the bowel.
Adapted from [117].

recruitment of cells into the site of inflammation should down-regulate any pathological immune response and restore homeostasis [2,3].

Leukocyte trafficking inhibitors

Broadly speaking, treatments have been either directed towards the integrins α4-integrin, α2-integrin, adhesion molecules (MAdCAM-1, VCAM-1 or ICAM-1) or chemokine receptors (CCR-9) [75]. The α4β7-integrin/MAdCAM-1 interactions have been targeted by four monoclonal antibodies. Natalizumab, a humanized monoclonal antibody that targets the α4-integrin is currently approved in the USA for the treatment of both multiple sclerosis (MS) and CD. Vedolizumab, a monoclonal antibody directed towards the α4β7-integrin, is in late stage clinical development for both UC and CD. RHuMab β7, a humanized monoclonal antibody directed to the β7 integrin and PF-547659, a monoclonal antibody directed to MAdCAM-1, are both in early phase development [2]. Small molecule inhibitors of the α2-integrin/ICAM-1 interaction, alicaforsen (ISIS 2303; ISIS Pharmaceuticals) [76], and of the chemokine CCR9 have also been evaluated in large-scale studies (Figure 2) [77–79].

Natalizumab: the first leukocyte adhesion molecule inhibitor

Natalizumab (Tysabri®, Elan, Biogen)is a humanized IgG4 monoclonal antibody directed towards the α4 integrin [80]. As such, it blocks both α4β7\MAdCAM-1- and α4β1\VCAM-mediated trafficking [81]. Accordingly, natalizumab has broad-spectrum anti-inflammatory activity, and thus was evaluated as a treatment for such diverse diseases as MS and CD. Initial studies of natalizumab in MS showed striking improvement in MRI-defined lesion burden following treatment [82]. Subsequent randomized placebo-controlled trials showed clinically important benefits on relapse rates, progression of disability and visual loss in patients with relapsing MS [83,84]. The impressive results of this successful development program, and the large unmet medical need, led to an expedited review of the drug by regulatory authorities. Natalizumab was subsequently approved for use in multiple jurisdictions and was hailed by most neurologists as a breakthrough treatment for MS.

Natalizumab was initially evaluated in the cotton-top tamarin model of colitis [72]. Efficacy in humans with IBD was subsequently assessed [85–88]. Experience in UC was limited to two small open-label trials [89,90]. However, the subsequent IBD development program that featured multiple large-scale induction and maintenance trials was restricted to CD. A brief review of these results follows.

The first placebo-controlled trial randomized 30 patients with active CD (CD Activity Index [CDAI] >150 and <450) to receive either a 3 mg/kg infusion

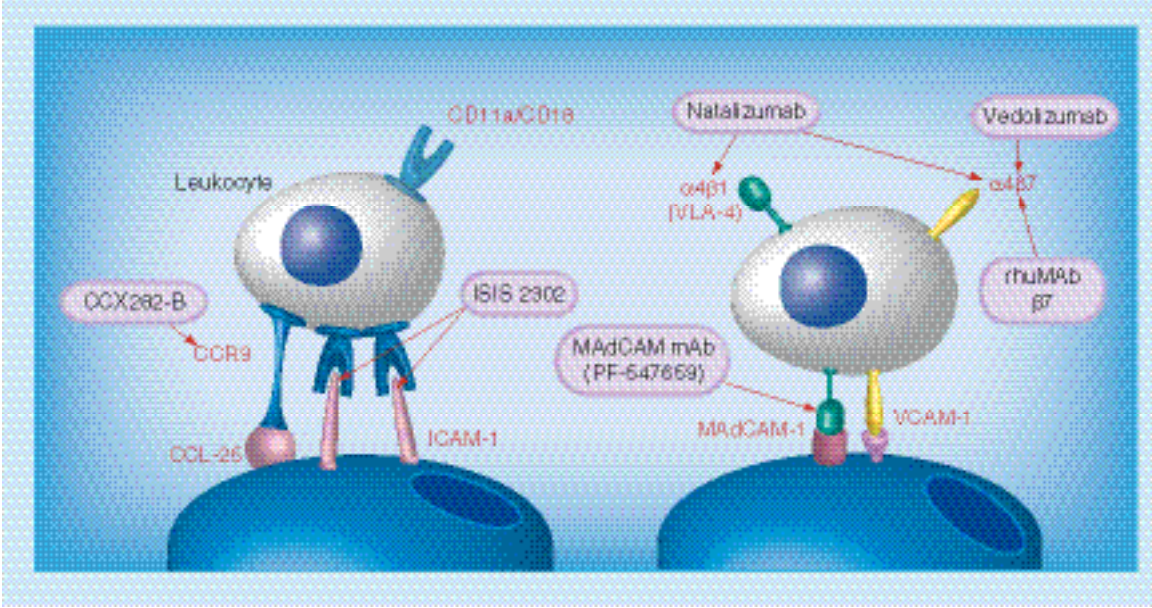

Figure 2. Potential therapeutic targets for the treatment of patients with inflammatory bowel disease.
ICAM-1: Intercellular adhesion molecule-1; MAdCAM-1: Mucosal addressin cellular adhesion molecule-1; VCAM-1: Vascular cellular adhesion molecule-1; VLA-4: Very late activation antigen-4.
Adapted from [2].

of natalizumab (n = 18) or placebo (n = 12). A significantly greater reduction in CDAI scores was demonstrated in patients who received natalizumab in comparison with those assigned to placebo. Furthermore, more natalizumab-treated patients were in remission at week 2 (n = 7; 39%) compared with those treated with placebo (n = 1; 8%) [86]. Subsequently, a larger double-blind, placebo-controlled trial that evaluated 248 patients with moderate-to-severe disease was performed. Patients were randomly assigned to one of four arms. In the first arm, patients received two placebo infusions. In the second arm, an infusion of 3 mg/kg of natalizumab was given followed by a second placebo dose. The third arm evaluated two infusions of 3 mg/kg of natalizumab and two infusions of 6 mg/kg of natalizumab [85]. This study demonstrated a beneficial effect of natalizumab on response and remission end points at multiple timepoints. In 2005, two large-scale, randomized, placebo-controlled trials (ENACT-1 and ENACT-2) that enrolled 905 patients, examined the use of natalizumab for induction and maintenance of remission in patients with active CD. In the first trial, similar rates of clinical response (56 vs 49%; p = 0.05) and clinical remission (37 vs 30%; p = 0.12) at 10 weeks were seen in natalizumab- and placebo-treated patients. However, a clear benefit over placebo was demonstrated for sustained clinical response, remission, and most importantly, sustained corticosteroid-free remission. A subsequent trial performed in 509 patients, which employed rigorous means of controlling the placebo response affirmed the value of natalizumab as an inductive agent in CD [88].

Based on these data, initial reaction to the natalizumab development program was highly positive. Although the drug was perceived by some experts to be less effective than TNF antagonists for induction of remission in active CD [91], the maintenance results were impressive, especially with respect to the benefit for corticosteroid-free remission. Furthermore, the incidence of serious and opportunistic infection seemed relatively low in comparison with that observed with TNF antagonists. However, a subsequent unexpected occurrence had a profound effect on the future use of natalizumab for the treatment of IBD.

Following the approval of natalizumab for treatment of MS, three cases of progressive multifocal leukoencephalopathy (PML) were described in patients who had been treated with natalizumab for extended periods [80,92–95]. PML is a severe opportunistic infection of the CNS that is caused by the John Cunningham virus (JCV), a polyoma virus latent in approximately 60% of the adult population. Development of PML was totally unexpected since previous experience was restricted to clinical settings of profound immunosuppression (e.g., HIV, combination chemotherapy for cancer). The development of these cases led to the temporary withdrawal of natalizumab from the market. However, based on a clear unmet medical need and the initiation of a comprehensive risk-management program, natalizumab was reintroduced for the treatment of both MS and CD following extensive regulatory review [16].

In the ensuing years, a tremendous amount of new data have accrued regarding the biology of PML [96]. Important risk factors for the development of the disease include duration of exposure to natalizumab, seropositivity for JCV and, based on retrospective ascertainment of exposure, prior exposure to immunosuppression. Recently, a commercial antibody assay has been developed that is highly predictive of the presence of latent JCV infection [95,97,98]. Although pretreatment serological testing for JCV has potential to greatly reduce the risk of PML, the fear of this complication by patients and physicians has led to very limited use of natalizumab for the treatment of CD. Furthermore, the natalizumab experience with PML has had a negative effect on development of other adhesion molecule antagonists.

Vedolizumab

Vedolizumab (Millennium Pharmaceuticals Inc., Takeda, MA, USA; previous formulations were known as MLN-02, LDP-02 and MLN0002) is a humanized monoclonal IgG-1 antibody to the α4β7 integrin. Two preparations of the antibody have been evaluated in humans. The initial version, an NS0-cell (mouse myeloma cell line)-derived preparation (MLN02, LDP-02 and MLN002), was utilized until completion of the Phase II trials. The newer version that has been evaluated in multiple Phase III trials is manufactured in a Chinese hamster ovary cell-based system. Vedolizumab targets α4β7/MAdCAM-1 binding in a dose-proportional manner. Once serum vedolizumab concentrations decrease below the limit of detection of the assay, α4β7 integrin\MAdCAM-1-mediated trafficking is rapidly restored. Consequently, current intravenous dosing regimens have been selected to ensure near complete saturation of α4β7 for periods of up to 8 weeks [99].

The first animal study that showed the potential of antagonizing the α4β7 integrin was performed by Hesterberg and colleagues, who evaluated a murine monoclonal antibody (Act-1) in the cotton-top tamarins model of UC [71]. These primates, who develop a form of chronic colitis very similar to

UC, responded remarkably well to Act-1 therapy. Subsequently, clinical development programs were initiated in both UC and CD.

Efficacy in UC

Feagan *et al.* performed the first clinical trial examining the use of an anti-α4β7 humanized monoclonal antibody in 29 patients with moderately severe UC [100]. This initial proof-of-concept study revealed that this antibody was well tolerated and that its target on peripheral blood T cells was saturated for up to 30 days after a single dose of drug [100]. The results also confirmed the impression derived from the tamarin studies that a strong relationship exists between serum drug concentrations, receptor saturation on circulating T cells and clinical efficacy. Subsequently, a multicenter study performed in Canada investigated the use of MLN02 as an induction agent in 181 patients with active UC. In this short-term study, adult patients with active disease, as defined by the ulcerative colitis clinical score and modified Baron endoscopic criteria, were randomized to receive 0.5 mg/kg of MLN02, 2.0 mg/kg of MLN02, or placebo in an equal ratio. Patients who required oral corticosteroids within 4 weeks before screening or parenteral corticosteroids within 6 weeks, topical therapy with mesalamine or corticosteroids within 1 week before screening, immunosuppressive therapy within the preceding 3 months or patients with severe disease were excluded. Patients received two intravenous infusions; one at baseline and a second on day 29. Clinical remission at week 6 was the primary outcome measure. At 6 weeks, the group receiving 0.5 mg/kg of MLN02 had a 33% remission rate, compared with 32% in the group receiving 2.0 mg/kg and 14% (9/63) in the placebo group (overall p = 0.03; Figure 3). Each comparison between the MLN02 groups and the placebo group was also significant (p = 0.02 for both contrasts). Corresponding improvements were observed in mucosal healing, histopathology and quality of life. However, antidrug antibodies (ADAs) developed by week 8 in 44% of the patients who received MLN02 with 24% of patients having an antibody titer greater than 1:125. Only one patient developed a clinically significant infusion reaction. The 2.0 mg/kg group had a significantly lower number of patients with ADA than those treated with the 0.05 mg/kg dose. Although the clinical relevance of sensitization was not evaluable in this short-term study, these observations led to the development of an improved formulation of MLN02, otherwise known as vedolizumab [101].

Parikh *et al.* subsequently studied this formulation (vedolizumab) in a randomized, controlled, Phase II dose-ranging study that enrolled 46 patients [99]. The aim of the study was to evaluate the clinical pharmacology, safety and efficacy profiles of Chinese hamster ovary cell-derived vedolizumab, given more frequently and in higher doses than in the previous MLN-02 study. Adults with active UC, based on a minimum partial Mayo score of 1, were randomized in a 4:4:4:3 ratio to receive one of three doses of vedolizumab (2, 6 or 10 mg/kg) or placebo. Patients treated with cyclosporine, tacrolimus or infliximab within 60 days of enrollment or patients with proven dysplasia or colorectal cancer were excluded from this study. Participants received their assigned dose of study drug on days 1, 15, 29 and 85 and were followed through day 253. After day 253, patients were eligible to enroll into an 18-month open-label, long-term safety study. The multiple doses (2, 6 or 10 mg/kg) of vedolizumab evaluated in this study demonstrated approximately dose proportional pharmacokinetics and maximally saturated the α4β7 receptor over the tested dose range. Multiple dosing up to 10 mg/kg was well tolerated and was associated with improved clinical signs and symptoms. The pharmacokinetic

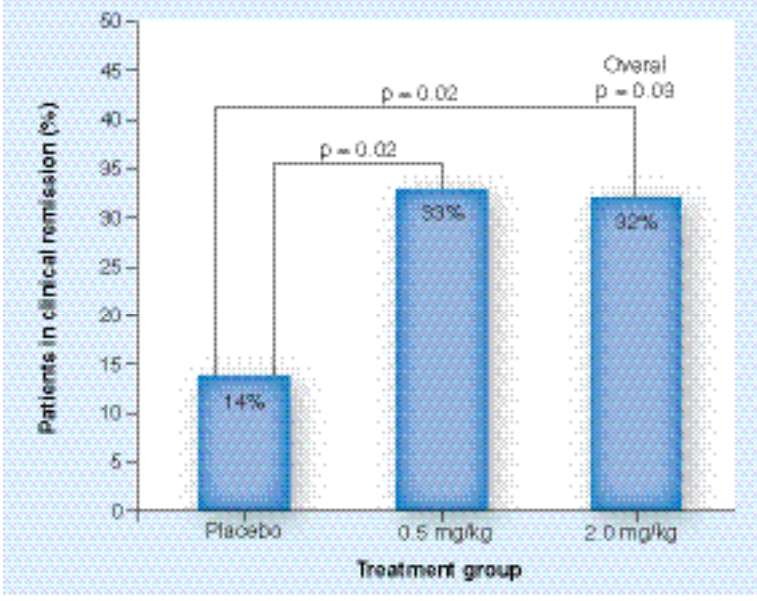

Figure 3. Clinical remission rates at week 6 by treatment group in the Phase II trial of vedolizumab in active ulcerative colitis.
Reproduced with permission from [101].

profile of vedolizumab was proven to be linear over the tested dose range for both C_{max} and AUC parameters. It was also noted that the pharmacokinetic profile did not change after repeated dosing; however, there was evidence of drug accumulation in the serum. This trial was not powered to evaluate efficacy but throughout the study the percentage of responders in the combined vedolizumab cohort was consistently 50%, compared with a range of 22–33% in the placebo group. In contrast to the results observed with the previous formulation, only 11% of the patients treated with vedolizumab developed ADAs by week 8 with no reported infusion reactions. The latter findings were considered clinically relevant in terms of both safety and long-term efficacy. The decreased immunogenicity of the improved formula was thought to be due to both an improved manufacturing process and the administration of a higher and potentially tolerizing drug-induction regimen. These results were encouraging and suggested that large-scale Phase III trials of the drug would yield positive results [99].

Complete reports from trials evaluating the use of vedolizumab in both induction and maintenance of remission in patients with active UC have not been published in manuscript form. However, the results of a large-scale induction trial have recently been reported as an abstract [102]. In the study, the design of which is shown in Figure 4, 374 patients were randomized to receive either 300 mg of vedolizumab or placebo at weeks 0, 2 and 6 [202]. The trial showed very encouraging efficacy results and low rate of sensitization. Furthermore, vedolizumab was shown to be highly effective for maintenance therapy and corticosteroid sparing in a population of patients who had, in approximately 40% of the cases, failed TNF antagonist therapy. Highly anticipated results of studies performed in CD also indicate a benefit of vedolizumab therapy [203]. It is anticipated that applications for review by regulatory authorities are likely to proceed during the first quarter of 2013.

Safety profile of vedolizumab

Extensive safety experience in both UC and CD has accumulated over the past decade. In the Phase II UC induction-trial study, no important differences were observed between the three treatment groups in the occurrence of adverse events. No deaths, cancers, or opportunistic infections were reported. Interestingly, one patient developed a primary cytomegalovirus infection that presented as a fever of unknown origin that resolved despite the presence of a therapeutic serum concentration of vedolizumab. This 'n of 1 study' argues strongly against a systemic immunosuppressive effect of the drug [101]. In distinction to natalizumab, vedolizumab therapy was not associated with any hematological, biochemical or liver-test abnormalities. Specifically, the peripheral lymphocytosis that has consistently been observed

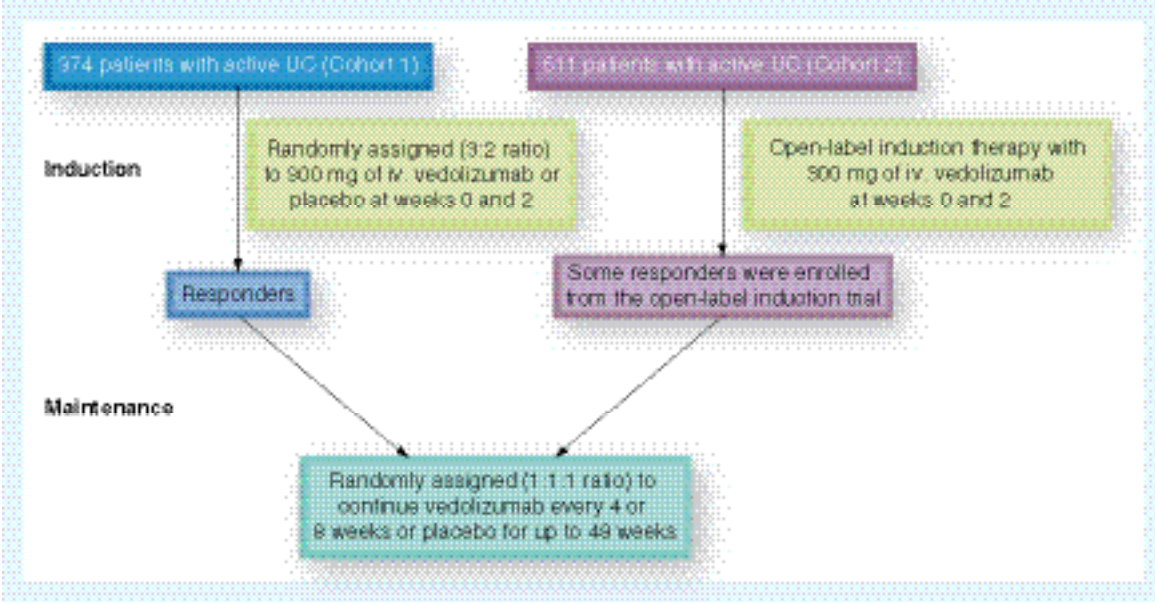

Figure 4. Design of the Phase III trial of vedolizumab for induction and maintenance therapy in ulcerative colitis.

iv.: Intravenous; UC: Ulcerative colitis.

Reproduced with permission from [202].

following administration of natalizumab [85,103] has not been observed vedolizumab. Although the relative absence of lymphocytosis does not preclude that vedolizumab could cause PML, it provides strong *prima facie* evidence of a more selective effect on cellular trafficking [104,105]. Similar to the findings of the initial trial, no neoplasms or serious or opportunistic infections were observed. Importantly, no cases of PML were reported. Preliminary data from the Phase III trial performed in patients with UC also showed no differences in rates of serious adverse events or serious infections between patients assigned to vedolizumab and those who received placebo [102].

As noted previously, the risk of PML is a potential safety concern for all drugs that block lymphocyte trafficking. PML occurs in approximately 2 patients per 1000 treated with natalizumab for MS or CD [204]. At the time of writing, approximately 2500 patients have been exposed to vedolizumab for a period of up to 6 years and no cases of PML have been observed. These findings are consistent with the concept that the gut selectivity of vedolizuamb is protective against the development of PML [99,101,106]. Caution should, however, be taken in interpreting these results as rare side effects can appear after a larger number of patients are exposed to new drugs in clinical practice. Results from the previously mentioned larger randomized control trial as well as long-term extension studies of the participants in the Phase II and III studies, are required to fully evaluate the safety of vedolizumab.

Other agents currently under development

Multiple drugs that interfere with lymphocyte trafficking are currently under development.

■ Etrolizumab (rhuMAb-β7)

Etrolizumab (rhuMabβ7, anti-β7, PRO145223, RG-7413; manufactured by Genentech) is an IgG-1 monoclonal antibody targeted against the β7 subunit of integrins α4β7 and αEβ7 [101]. The theoretical advantage etrolizumab is thought to have over other novel therapies is its dual-blocking mechanism of action targeting both the α4β7/MAdCAM-1 interaction and the inhibition of gut intraepithelial leukocytes retention via the αEβ7/E-cadherin interaction [64].

One Phase I randomized, double-blind, placebo-controlled trial recently examined the safety and efficacy of etrolizumab in 48 patients with moderate-to-severely active UC (Mayo Clinical Score ≥ 5). In this study (n = 20), a single ascending-dose of etrolizumab of 0.3, 1, 3 or 10 mg/kg intravenous, 3 mg/kg subcutaneous or placebo was initially evaluated for safety. This phase was followed by a multidose stage in a different group of patients in which three doses of etrolizumab 0.3, 1.5, 3.0 mg/kg subcutaneous, 4.0 mg/kg intravenous or placebo were given monthly (n = 18). Results at weeks 6, 43 and 71 were promising with regards to clinical response, clinical remission and steroid tapering [107]. Additional large randomized trials are planned to further evaluate the potential efficacy of this antibody.

■ Anti-MAdCam antibody

PF-547659 is an IgG-2 monoclonal antibody directed to MAdCAM-1, which has been studied in an initial randomized, double-blind, placebo-controlled trial that evaluated 80 patients with active UC. Preliminary results suggested a favorable side-effect profile and efficacy superior to placebo. In this study, response rates were higher with PF-547659 at week 4 (52 vs 32%, respectively; p = 0.10) and week 12 (42 vs 21%, respectively; p = 0.15) as well as remission rates at both week 4 (13 vs 11%) and week 12 (22 vs 0%). Larger studies of longer duration are currently being conducted to further assess the safety and long-term efficacy of PF-547659 in UC [78,205–207].

Alicaforsen

Alicaforsen (ISIS 2303; ISIS Pharmaceuticals) is an antisense oligonucleotide to ICAM-1, which can hybridize to mRNA and, as a result, prevent the translation of the protein [90]. Both intravenous and subcutaneous formulas have been studied in CD with disappointing results [108–112]. In UC, a rectal formulation has been studied in mild left-sided disease with promising results [113,114]. Rectal alicaforsen showed a more sustainable effect compared with mesalamine enemas [115]. Additional trials are planned in pouchitis.

Anti CCR9 (Traficet™)

CCX282-B (GSK-1607586), Traficet-EN, or vercirnon, the recent US Adopted Name, and CCX-025 (also manufactured by GlaxoSmithKline) are small molecules that selectively target CCR9, a chemokine thought to play a pivotal role in T-cell migration to inflamed mucosa by binding the integrin CCL-25 (also known as TECK) [77,116]. Data have been reported from a recently completed pivotal CD maintenance study (Study 004, PROTECT-1), a multicenter, randomized, double-blind, placebo-controlled trial that assigned over 600 patients with moderate-to-severely active CD to once or twice daily dosing with Traficet-EN or placebo. The primary end point of this trial, CDAI-defined clinical remission was not statistically different among the treatment groups. However, at week 36, more patients receiving active drug were in clinical remission than those who received placebo.

Traficet-EN is currently undergoing four large Phase III clinical trials for the treatment of patients with moderate-to-severe CD (SHIELD-1/2/3/4). If successful, this approach has the advantages over monoclonal antibodies of oral administration, low potential for immunogenicity and a relatively short drug half-life [208]. There are however no current trials examining the efficacy of Traficet-EN in UC and it is currently controversial as to whether sufficient expression of the target integrin (CCL-25) exists in the colon to warrant development for this indication.

Conclusion & future perspective

A large, unmet medical need exists in the treatment of patients with UC whose disease is refractory to aminosalicylates, antimetabolites and corticosteroids. Vedolizumab (MLN0002) offers a novel therapeutic approach that is based upon the concept of local immunosuppression of the GI tract with minimal or no systemic effect. This paradigm holds out the possibility of efficacy with improved safety in comparison to systemically active agents such as TNF antagonists. The initial promising results indicate that vedolizuamb may ultimately enter UC treatment algorithms as an important option for patients who are failing either corticosteroids or TNF-antagonist treatment. The treatment of choice in the former group of patients is currently unclear and direct comparisons between TNF antagonists and vedolizumab will be required to answer this important question. Finally, the relatively favorable side-effect profile with no cases of PML observed to date is reassuring, and consistent with the mechanism of action, but will require confirmation by large-scale observational studies. Whether the previously mentioned risk factors for development of PML in patients treated with natalizumab are risks in patients treated with vedolizumab is unknown, however it is relevant to point out that in every jurisdiction except the USA that regulatory authorities have allowed concurrent treatment with immunosuppressives in the vedolizumab trials.

Executive summary

- Pharmacological treatment for inflammatory bowel disease (IBD) is limited by a lack of drug therapies that have sustained benefit with a low risk of serious side effects such as infection.
- The balance that exists between pro- and anti-inflammatory cytokines found in the gut of healthy individuals is disturbed in IBD.
- Leukocyte trafficking plays an important role in the pathophysiology of IBD.
- Leukocyte trafficking is mediated by interactions between adhesion molecules located on the surface of circulating white blood cells and the vascular endothelium.
- Targeting leukocyte migration by integrin inhibitors is a novel concept based on the idea that interruption of white blood cell trafficking will facilitate the restoration of immune homeostasis.
- Natalizumab, a first-generation leukocyte-trafficking inhibitor, is not gut selective and although effective in Crohn's disease, is associated with the development of progressive multifocal leukonecephalopathy.
- Second-generation leukocyte-trafficking inhibitors such as vedolizumab are gut selective and are therefore unlikely to interfere with T-cell trafficking to the CNS, a key factor in the pathogenesis of progressive multifocal leukoncephalopathy.
- Vedolizumab, a humanized monoclonal IgG-1 antibody to the α4β7 integrin, has a promising safety and efficacy profile.
- Vedolizumab is likely to become an important new therapy for ulcerative colitis and Crohn's disease.
- Other novel leukocyte trafficking inhibitors are under development.

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