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Vedolizumab for the treatment of ulcerative colitis and Crohn's disease

Leon P McLean^{1,2}, Terez Shea-Donohue^{1,2}, and Raymond K Cross^{1,3,*}

¹University of Maryland, Department of Medicine, Division of Gastroenterology & Hepatology, 100, North Greene Street, Lower Level, Baltimore, MD 21201, USA

²University of Maryland, Baltimore, Mucosal Biology Research Center, Baltimore, MD, USA

³Veterans Affairs Maryland Health Care System, Baltimore, MD, USA

Abstract

Crohn's disease and ulcerative colitis are chronic, relapsing inflammatory disorders of the GI tract. In both Crohn's disease and ulcerative colitis, leukocytic infiltration of the mucosa is associated with epithelial damage. Recently, monoclonal antibodies directed against cell adhesion molecules (CAMs) involved in leukocyte extravasation have been developed. Natalizumab, the first drug brought to market targeting CAMs, is clinically effective but is associated with serious adverse effects including the uncommon, but often fatal, neurological disease progressive multifocal leukoencephalopathy. Vedolizumab targets a subset of the CAMs blocked by natalizumab and is currently in Phase III trials to study its efficacy and safety in patients with inflammatory bowel disease. Here, we discuss the current treatment options available for patients with Crohn's disease or ulcerative colitis, the history of CAM inhibitors, the current state of development of vedolizumab and its future role in inflammatory bowel disease, if approved by regulatory agencies.

Keywords

$\alpha_4\beta_7$ antagonist; cell adhesion molecule inhibitor; Crohn's disease; inflammatory bowel disease; LDP-02; MLN-00002; MLN-02; natalizumab; ulcerative colitis; vedolizumab

The inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of the GI tract consisting primarily of two subtypes, ulcerative colitis (UC) and Crohn's disease (CD). In recent years, the incidence of IBD has been increasing, particularly in industrialized nations, although both the incidence and prevalence vary according to region [1, 2]. In the USA and Europe, approximately 3.6 million individuals have IBD [1]. A systematic literature review published in early 2012 found that the prevalence of UC in North America between 1980 and 2008 was 198.1–298.5 cases per 100,000 persons and the prevalence of CD was 135.7–318.5 cases per 100,000 persons. Over the same time period the incidence of UC and CD was 7.72–19.2 cases per 100,000 person-years and 6.39–24.3 cases per 100,000 person-years, respectively (CD prevalence and incidence in California and New York was estimated to be lower than the rest of North America at 48.1–135.6 cases per 100,000 and 3.77–6.38 cases per 100,000 person-years, respectively) [2]. Approximately 30,000 new cases of IBD are diagnosed in the USA each year [3]. Most individuals are diagnosed during the second and third decades of life, although a second smaller peak in diagnoses occurs during the sixth and seventh decades [3, 4]. Epidemiological data suggests that genetics play a

* Author for correspondence: Fax: +1410 706 4330, rcross@medicine.umaryland.edu.

significant role in IBD pathogenesis as first-degree relatives of patients with IBD have a relative risk of at least fivefold for developing CD or UC [4]. In fact, 35% of patients with CD were found to have at least one affected relative [5]. Since many patients are diagnosed at a relatively young age, significant expenditures can occur due to the need to provide decades of medical and/or surgical care [6]. In 2008, the mean cost of treatment for CD and UC was US\$8265 and \$5066 per patient-year, respectively, with the direct costs of IBD care in the USA totaling approximately \$6.3 billion annually [7].

CD is characterized by transmural inflammation of any portion of the GI tract from mouth to anus, whereas UC is limited to the colon and rectum with inflammation typically restricted to the mucosa, although inflammatory involvement of the submucosa may occur in severe cases. Both CD and UC are characterized by an influx of inflammatory cells into gut mucosal tissue. A variety of leukocytes including neutrophils, macrophages, T lymphocytes and dendritic cells participate in the pathogenesis of both of these diseases [8]. Although the pathogenesis of CD and UC is similar, the clinical manifestations of CD and UC differ. Patients with UC present with bloody diarrhea, fecal urgency, incontinence, tenesmus and systemic symptoms. Conversely, the presentation of CD can be heterogeneous. In patients with inflammatory CD, symptoms typically include nonbloody diarrhea, crampy right lower quadrant pain, fecal urgency, incontinence, weight loss and systemic symptoms. Obstructing CD symptoms include intermittent postprandial abdominal pain in the periumbilical region or right lower quadrant, borborygmi, bloating, nausea, vomiting and weight loss. Patients with perforating or penetrating CD present with severe abdominal pain, systemic symptoms, and fistulization through an abdominal wall incision, to the bladder or adjacent intestinal segment, or blindly into the abdominal cavity (abscess). A total of 25% of patients with CD develop perianal involvement, which manifests as 'dog-eared' perianal tags, anal fissures, anal ulcers and stenoses, fistulas or abscesses. Extraintestinal manifestations occur in both disorders, complicating up to a third of cases [9]. In UC, inflammation extends proximally from the rectum whereas the inflammation associated with CD tends to be patchy and segmental, involving the terminal ileum in more than 75% of cases [4]. The diagnosis of both CD and UC is typically confirmed by histopathologic analysis of biopsies obtained during ileocolonoscopy.

Current treatment modalities for UC include 5-aminosalicylates (5-ASAs), corticosteroids, immune suppressants or biologic therapy depending on the severity of a patient's symptoms and whether remission is being induced or maintained. Surgical therapy is indicated for severe disease not amenable to medical management or when complications of disease develop. Approximately 25% of UC patients will undergo surgery within the first decade after diagnosis [10]. Infliximab has typically been reserved for patients with disease refractory to steroids and/or immune suppressants. Although infliximab is highly effective in UC, 40% of patients will not respond to induction therapy [11]. Additionally, either due to blocking antibodies to the drug, accelerated drug clearance or development of aberrant immune pathways, 30–40% of patients will lose response to infliximab over time [12, 13].

CD treatment incorporates the use of 5-ASAs, corticosteroids, immune suppressants and/or biologic therapy. Selection of therapy depends on the severity of a patient's symptoms and whether remission is being induced or maintained. Surgery is reserved for refractory cases or patients who develop complications of their disease such as bowel obstructions or intra-abdominal abscesses. Approximately 80% of CD patients will undergo surgery within their lifetime [14]. Biologic therapy, primarily with TNF- α inhibitors such as infliximab, adalimumab and certolizumab pegol, has typically been reserved for patients with symptoms refractory to conventional therapy. However, more recent data have demonstrated that infliximab either alone or in combination with azathioprine is superior to azathioprine alone [15]. As a result, TNF- α inhibitors are being used earlier in the treatment process, especially

in patients with risk factors for disabling CD [16]. Between 20 and 40% of CD patients will not respond to induction therapy with TNF- α inhibitors and 40% of patients will lose response to TNF- α inhibitors over time [12]. Dose escalation can recapture clinical response in 50–70% of patients [13]. Initially, approximately 40–80% of patients who lose response to infliximab may respond to adalimumab. However, after 12 months the response rate drops to 19–68%, suggesting that a proportion of patients who switch to a second TNF- α inhibitor will lose response to that drug as well [13].

Because a significant proportion of patients with UC and CD will not respond to TNF- α inhibitors or will lose response to TNF- α inhibitors over time, a significant need for additional therapies for patients with moderate-to-severe CD and UC exists. Natalizumab, an antibody that prevents leukocyte extravasation, has a definitive role in CD patients meeting these criteria; however, its use has been limited because of patient and provider concerns about the risk of developing progressive multifocal leukoencephalopathy (PML).

A variety of mechanisms have been postulated for the pathogenesis of IBD, all of which ultimately result in leukocytic infiltration of the intestinal mucosa as well as derangements in intestinal barrier function. Extravasation of leukocytes from the blood into stromal tissues is a complex process involving a coordinated sequence of events between leukocytes and vascular endothelial cells. Several steps – tethering/rolling, activation, adhesion and extravasation/migration – occur allowing immune cells to enter stromal tissues (Figure 1). Initially, leukocytes tether to the vascular endothelium through multiple transient interactions between selectins on leukocytes such as PSGL-1 and their ligands on the endothelial surface (P-selectin and E-selectin). This process decreases the speed of leukocytes to facilitate rolling along the endothelial surface. The slower speed of these leukocytes permits interactions to occur between integrins on the surface of the leukocyte and their ligands on the endothelium. Slowing leukocytes also allows chemokines from inflamed tissue to activate them resulting in leukocyte polarization, priming them for extravasation while also enhancing the binding affinity of integrins. Integrins, which consist of an α - and β -chain that together form a heterodimer, bind to ligands on endothelial cells, allowing leukocytes to firmly adhere to endothelial surfaces. Leukocytes subsequently cross the endothelium and enter the mucosa through a paracellular route [17].

An important leukocyte involved in the pathogenesis of both CD and UC is the $\alpha_4\beta_7$ -integrin-expressing T cell. When activated, these cells preferentially adhere to endothelial surfaces within the GI tract as well as the associated lymphoid tissues. Upon activation, $\alpha_4\beta_7$ -integrin-expressing T cells bind to their ligand MAdCAM-1. The tissue specificity of the $\alpha_4\beta_7$ -integrin/MAdCAM-1 interaction has been confirmed through experiments utilizing antibodies to $\alpha_4\beta_7$ and MAdCAM-1 as well as experiments involving knockout mice [18]. Animal studies demonstrated that inhibition of MAdCAM-1 prevents the development of ileitis in mice by preventing T-cell adhesion to ileal endothelium [19]. Based on these observations, it was felt that a monoclonal antibody targeting the $\alpha_4\beta_7$ -integrin could prevent or significantly attenuate leukocyte extravasation into affected tissues, and perhaps decrease the severity of CD and/or UC.

Prior to the development of a specific $\alpha_4\beta_7$ antagonist, integrins involved in cell adhesion were targeted with natalizumab, a monoclonal antibody directed against the α_4 -integrin chain, which blocks the $\alpha_4\beta_1$ -integrin in addition to $\alpha_4\beta_7$. ENCORE demonstrated the efficacy of natalizumab for inducing clinical response and remission in patients with moderately-to-severely active CD who had objective evidence of inflammation [20]. At week 12, 60% of patients receiving natalizumab achieved a clinical response versus 44% of those receiving placebo ($p < 0.001$). The superiority of natalizumab over placebo for achieving clinical response was also demonstrated at weeks four and eight. ENACT-2

demonstrated that, at week 36, patients who responded to initial treatment with natalizumab were more likely to maintain clinical response (61 vs 28%; $p < 0.001$) and remission (44 vs 26%; $p = 0.003$) with continued treatment with natalizumab when compared with patients receiving placebo maintenance [21]. In addition to CD, natalizumab is also used to treat patients with multiple sclerosis. Unfortunately, three patients receiving natalizumab developed PML, a rare and often fatal neurological disease caused by the John Cunningham (JC) virus. Two of these cases occurred in multiple sclerosis patients receiving concomitant therapy with IFN β -1 α and the third case occurred in a CD patient with previous exposure to immune suppressants [22, 23]. As a result, the US FDA withdrew natalizumab from the market. After a safety review was performed the FDA allowed natalizumab to be returned to the market in 2006 under a special prescribing program as monotherapy for multiple sclerosis [24]. Natalizumab gained approval for the treatment of CD in 2008, although patients receiving natalizumab as well as their providers are required to participate in a strict monitoring program [23]. Since then, additional cases of PML have been reported with an incidence of PML in natalizumab-treated patients of 1.44 cases per 1000 patient-years (95% CI: 1.20–1.72). Through May 2011, 124 postmarketing cases of PML have been reported with 23 resultant deaths over a total of 148,800 patient-years of exposure to natalizumab. The risk of developing PML is increased by 2 years of natalizumab therapy, JC virus seropositivity and previous exposure to immune suppressants [24].

The reason for these adverse effects may be related to the fact that natalizumab targets the α_4 -integrin monomer, ultimately blocking two integrin heterodimers – $\alpha_4\beta_1$ and $\alpha_4\beta_7$. In addition to preventing the $\alpha_4\beta_7$ /MAdCAM-1 interaction, natalizumab also prevents $\alpha_4\beta_1$ from binding VCAM-1. It has been hypothesized that preventing $\alpha_4\beta_1$ binding to VCAM-1 may result in decreased immune surveillance within the CNS, in turn increasing the risk of developing PML. Unlike natalizumab, vedolizumab specifically targets $\alpha_4\beta_7$ and does not inhibit binding at VCAM-1 [8]. Based on studies performed by Millennium Pharmaceuticals (MA, USA), vedolizumab does not affect levels of T cells in the cerebrospinal fluid of healthy volunteers after a single dose nor does it inhibit immune surveillance of the CNS in nonhuman primates [25, 26].

At present, gastroenterologists lack a safe, effective therapy that can prevent or decrease leukocyte infiltration into intestinal mucosa without a concurrent risk of PML. Vedolizumab is being developed to meet this need.

Overview of the market

Safe, effective treatment options exist for patients with mild-to-moderate CD or UC. However, a significant proportion of patients with moderate-to-severe CD or UC lack effective medical treatment. In addition, although effective in a significant proportion of patients with CD and UC, immune suppressant and biologic therapy (or the combination of an immune suppressant and a TNF- α inhibitor) are associated with uncommon, but serious, side effects. Although patients with mild-to-moderate UC respond well to 5-ASAs, the efficacy of these drugs is limited in patients with severe disease [27]. 5-ASAs have also been used for the treatment of mild-to-moderate CD, although they are less efficacious in this group of patients, particularly in those with small bowel disease [28–31]. The remission rate for UC patients treated with 5-ASAs is approximately 50% and, as a result, an escalation in therapy to corticosteroids, immune suppressants or biologic agents is often required [32].

Corticosteroids are effective for inducing remission, but cannot be used for maintenance due to their significant side-effect profile. Patients that do not respond to 5-ASAs may be maintained on immune suppressants such as 6-mercaptopurine or azathioprine, although

these medications are associated with potentially serious side effects including a fourfold increased risk of lymphoma in patients treated with either of these agents [33]. The clinical utility of these drugs is further limited by their slow onset of action, making them inappropriate for induction therapy. Other agents that have been used to treat patients with refractory disease include cyclosporine and methotrexate. Cyclosporine may be used as a short-term induction agent for UC as a bridge to immune suppressant therapy; however, its use is also complicated by its sideeffect profile. Major adverse events including renal failure, serious infectious complications (bacterial pneumonia, *Pneumocystis jiroveci* pneumonia and venous catheter infections), anaphylaxis and death were reported in 15% of patients included in a retrospective study of 111 IBD patients treated with cyclosporine. Minor effects, such as paresthesias, hypertension, headache and transient liver function test abnormalities, occurred in 20–50% of patients [34]. Methotrexate can be used to achieve clinical response in both CD and UC and is often better tolerated than cyclosporine. A systematic review conducted by the Cochrane Library found data to support the use of intramuscular methotrexate (25 mg/week) for the induction of remission in patients with CD [35, 36]. In a retrospective study of 131 patients who failed or were intolerant to azathioprine/6-mercaptopurine, methotrexate achieved a clinical response rate, defined as steroid withdrawal, normalization of C-reactive protein, or physician's clinical assessment of improvement, of >60% in both CD and UC. In the same study, side effects were observed in 17% of patients and included abnormal liver function tests, dyspnea, nausea and vomiting, and neutropenia [37]. Two multicenter randomized trials are currently underway to determine the efficacy of parenteral methotrexate in patients with UC [38].

The development of monoclonal antibodies against TNF- α has provided physicians with an additional class of drugs for treating patients with CD or UC. Unfortunately, these agents are expensive, may require administration in a monitored setting, and are associated with a number of potentially serious side effects including serious infection, opportunistic infection, lupus-like reactions, psoriaform eruptions and lymphoma. Infliximab, the first TNF- α inhibitor approved for use in IBD, is capable of inducing and maintaining remission in both UC and CD [39–42]. In patients with moderate-to-severe CD who were treated with infliximab, 81% had a clinical response at week 4 compared with 17% who had been treated with placebo [40]. In a follow-up study, patients with active CD who continued maintenance infliximab therapy after responding to a single open-label infusion of infliximab were more likely to maintain clinical remission at week 30 than those receiving placebo (odds ratio: 2.7; 95% CI: 1.6–4.6) [41]. In moderately-to-severely active UC, infliximab induced clinical response in 61–69% of patients at week 8 compared with 37% of those treated with placebo ($p < 0.001$ for both doses tested vs placebo) [39]. Other TNF- α inhibitors include adalimumab and certolizumab pegol, both of which are indicated in the USA for the treatment of patients with moderately-to-severely active CD who do not respond to conventional therapy. Adalimumab is also indicated for the treatment of moderately-to-severely active CD in Europe; however, certolizumab pegol is not. TNF- α inhibitors work well in a significant proportion of patients; however, the remission rate for induction in patients with CD is less than 35% at week 4 and is less than 50% for maintenance therapy (assessed at 20–30 weeks) [32]. ACCENT I followed patients with CD for 54 weeks and demonstrated that infliximab maintained clinical remission at week 54 in approximately 30–40% of patients who responded to infliximab induction by week 2 compared with approximately 15% in those who received placebo after induction ($p < 0.01$ for both doses tested vs placebo) [41]. The Crohn's trial of the fully Human antibody Adalimumab for Remission Maintenance (CHARM) trial demonstrated clinical remission in approximately 50% of patients with moderate-to-severe CD who were maintained with adalimumab after receiving induction therapy compared with approximately 35% of those who received placebo after adalimumab induction ($p < 0.05$ for both weekly and every other week dosing vs placebo) [43]. Certolizumab pegol was shown to maintain clinical remission at week 26

in 29% of patients with moderate-to-severe CD versus 18% of those treated with placebo after open-label induction therapy and has also been shown to result in improvements in work productivity and health-related quality of life in patients with active CD who lost response to or could not tolerate infliximab [44, 45]. Although a variety of medical therapies are available to treat patients with IBD, limitations to current treatment modalities do exist. In addition to the safety concerns described above, certain patients, termed primary nonresponders, do not respond to treatment with TNF- α inhibitors. An additional subset of patients, secondary nonresponders, lose their ability to respond over time. It is thought that the development of endogenous antibodies to these drugs, accelerated drug clearance, ongoing fibrosis or aberrant immune pathways is responsible for this effect [13, 46–48]. Other factors complicating treatment with biologic agents include infusion reactions, occurring in 9–17% of patients receiving infliximab, and injection site reactions, occurring in <5% of patients receiving certolizumab pegol and approximately 10% of those receiving adalimumab [49–51].

Even though a variety of medications exist for treating CD and UC, many patients will still require surgery despite utilization of maximal medical therapy. Colectomy is thought to be curative in patients with UC; however, when performed in combination with an ileal pouch anal anastomosis, the procedure is not without complications. Surgery for patients with CD is not curative and these patients often require additional intestinal resections for recurrent disease. Approximately 29% of CD patients in North America undergo surgery within 5 years of diagnosis, although these rates have dropped somewhat in recent years [52]. Approximately 33% of CD patients who undergo one surgery will require at least one additional surgery during their lifetime [53].

Introduction to vedolizumab

Vedolizumab, currently being developed by Millennium Pharmaceuticals, is a humanized version of Act-1, a murine antibody originally developed in the 1980s with activity against the $\alpha_4\beta_7$ -integrin heterodimer [8]. During leukocyte extravasation into tissues, the $\alpha_4\beta_7$ -integrin heterodimer, found on the surface of T cells, binds to its ligand MAdCAM-1, which is expressed on the endothelial surface of venules within the GI tract as well as associated lymphoid tissue [54]. By blocking the interaction of the $\alpha_4\beta_7$ -integrin with MAdCAM-1, vedolizumab prevents leukocyte binding to the endothelial surface and, as a result, extravasation into affected tissue. Unlike natalizumab, which binds the α_4 -chain directly and inhibits the activities of both $\alpha_4\beta_7$ and $\alpha_4\beta_1$, vedolizumab binds to the β_7 -chain only when it is heterodimerized with α_4 [55]. This results in selective inhibition of $\alpha_4\beta_7$ /MAdCAM-1 without affecting the ability of $\alpha_4\beta_1$ /VCAM-1 to function (Figure 1) [8].

Chemistry

The chemical name for vedolizumab is IgG1- κ , antihuman integrin lymphocyte Peyer's patch adhesion molecule 1 (human-*Mus musculus* heavy chain), disulfide with human-*Mus musculus* α -chain, dimer. Previous versions are known as MLN0002, MLN02 and LDP02. Vedolizumab's molecular formula is $C_{6528}H_{10072}N_{1732}O_{2042}S_{42}$, its molecular weight is 146.8 kDa, and its Chemical Abstracts Service (CAS) registry number is 943609-66-3 [56]. The specificity of vedolizumab to the $\alpha_4\beta_7$ -integrin heterodimer was confirmed in both animal and human studies. Nonhuman primates with chronic colitis were treated with a monoclonal antibody to the $\alpha_4\beta_7$ -integrin, resulting in improved stool consistency, decreased mucosal infiltration of lymphocytes, neutrophils and macrophages, and decreased histological inflammatory activity in the GI tract. The same study noted that antibodies to $\alpha_4\beta_7$ did not inhibit lymphocyte homing to tissues outside the GI tract [57]. The specificity of vedolizumab was examined in human tissues by using immunohistochemical and flow

cytometric techniques. Immunohistochemistry demonstrated strong binding to leukocytes in the stomach, small intestine, colon and spleen, with moderate binding at lymphoid tissues [8]. Flow cytometric analysis of human blood revealed that vedolizumab binds to B cells, naive CD4 and CD8 T cells, memory CD4 and CD8 cells, NK cells, eosinophils and basophils. Vedolizumab binds at low levels to a small (~15%) subpopulation of monocytes. Binding to neutrophils was not observed. The highest degree of binding occurred in the memory CD4 T-cell population expressing the $\alpha_4\beta_7$ -integrin heterodimer, which is a T-cell population thought to be pathogenic in IBD. By targeting the $\alpha_4\beta_7$ -integrin heterodimer, vedolizumab is able to inhibit the pathologic effects of this T-cell population without suppressing the protective effects of other nonpathogenic T-cell subsets [8].

Pharmacodynamics

In recognition of an unexpectedly high rate of human antihuman antibody (HABA) development in Phase II trials of MLN02 and MLN0002, Millennium Pharmaceuticals recently generated a new version of vedolizumab while seeking to preserve its original antigen recognition sequence. During Phase II studies, up to 38% of participants receiving vedolizumab developed HAHA [58]. Furthermore, the presence of HAHA (titer >1:125) was associated with reduced saturation of the $\alpha_4\beta_7$ binding site as well as decreased drug efficacy [58, 59]. This new version of vedolizumab prompted the performance of a dose-ranging clinical trial to re-evaluate pharmacodynamics, pharmacokinetics and drug safety.

In this trial, binding to $\alpha_4\beta_7$ was nearly 100% in all dosing groups studied (2, 6 and 10 mg/kg). In the presence of detectable vedolizumab, the maximum effect ($E_{\max}$) was >95% in all dosing groups, indicating near complete saturation of $\alpha_4\beta_7$. Since the $E_{\max}$ was >95% in all dosing groups, the authors could not comment upon a dose- or concentration-dependent response relationship because there were no treatment arms in which receptor saturation was not near complete [59].

Pharmacokinetics & metabolism

Patients received induction doses on days 1, 15 and 29 and their first maintenance dose on day 85. Serum vedolizumab concentrations increased with escalating doses. The maximum serum concentration and area under the curve increased in a linear fashion with increasing doses. Concentrations fell monoexponentially after the final dose until they were between 1 and 10 $\mu\text{g/ml}$ at which point the decline continued in a nonlinear fashion. The mean elimination half-life was 15–22 days [59]. The manner in which vedolizumab is metabolized has not been reported.

Clinical efficacy

Vedolizumab is currently undergoing evaluation for the treatment of CD and UC. To date, Phase I and Phase II trials are completed with several Phase III trials nearing completion. Phase III trials underway are designed to evaluate the effect of vedolizumab on patients with moderately-to-severely active CD or UC as well as its safety profile. The results of completed Phase I–III trials are summarized in Tables 1–5.

A Phase II trial conducted by Feagan *et al.* demonstrated the efficacy of vedolizumab for the induction of clinical and endoscopic remission in 181 patients with active UC [58]. Participants received 0.5 mg/kg of vedolizumab, 2.0 mg/kg of vedolizumab, or placebo intravenously. Infusions were performed on days 1 and 29 and patients were followed for up to 6 weeks with sigmoidoscopy performed at weeks 4 and 6. The primary end point was clinical remission at week 6, which was achieved by 33% of patients in the 0.5 mg/kg group, 32% of patients in the 2.0 mg/kg group, and 14% of patients in the placebo group ($p = 0.03$).

overall; $p = 0.02$ for 0.5 mg/kg group vs placebo as well as 2.0 mg/kg group vs placebo). At week 6, 28% of patients who received 0.5 mg/kg and 12% of patients who received 2.0 mg/kg were in endoscopic remission compared with 8% of patients who had received placebo ($p = 0.007$ for vedolizumab groups vs placebo). The rate of adverse events was similar in all three treatment groups with exacerbation of UC, nausea and vomiting being the most common. There were no differences in lymphocyte counts between patients treated with vedolizumab and those who received placebo [58].

A second Phase II trial conducted by Feagan *et al.* examined the efficacy of vedolizumab for the induction of clinical response and remission in 185 patients with active CD [60]. In this study, patients were treated with 0.5 mg/kg of vedolizumab, 2.0 mg/kg of vedolizumab, or placebo intravenously. Infusions were performed on days 1 and 29. At day 57, 37 and 30% of patients treated with 2.0 mg/kg and 0.5 mg/kg, respectively, of vedolizumab achieved clinical remission compared with 21% of patients receiving placebo ($p = 0.04$ for 2.0 mg/kg vs placebo). There was no significant difference in the proportion of patients achieving clinical response at day 57 among the three treatment groups. Rates for clinical response, defined as a decrement of 70 points in the Crohn's Disease Activity Index, were 53, 49 and 41% in the 2.0 mg/kg, 0.5 mg/kg and placebo groups, respectively. Rates for the secondary end point of enhanced clinical response, defined as a decrement of 100 points in the Crohn's Disease Activity Index, were 47, 43 and 31% in the 2.0 mg/kg, 0.5 mg/kg and placebo groups, respectively ($p < 0.05$ for 2.0 mg/kg vs placebo). The rate of adverse events was similar in all three treatment groups. There was no difference in lymphocyte counts between patients treated with vedolizumab and those treated with placebo [60].

The safety and efficacy of vedolizumab are being investigated further in Phase III trials (GEMINI I, II, III and LTS). GEMINI I and II are randomized, blinded, placebo-controlled, multicenter trials examining the efficacy of vedolizumab for induction and maintenance in moderate-to-severe UC and CD, respectively. Results of the induction phase of GEMINI I were presented at the annual meeting of the American Gastroenterological Association in San Diego, CA, USA in May, 2012. This trial evaluated 374 patients with moderately-to-severely active UC who had failed at least one prior therapy (corticosteroids, purine antimetabolites and/or TNF- α inhibitors). Vedolizumab was found to be more effective than placebo for achieving clinical response, clinical remission and mucosal healing. The maintenance phase of this trial was treated as an independent study with results unavailable at the time of this review. Patients were randomized to 300 mg intravenous vedolizumab or placebo, given on days 1 and 15. The primary outcome was clinical response at 6 weeks. Secondary outcomes were clinical remission and mucosal healing at 6 weeks. A total of 225 patients received vedolizumab and 149 received placebo. A significantly greater proportion of vedolizumab-treated patients achieved clinical response (47.1 vs 25.5%; $p < 0.0001$), as well as clinical remission (16.9 vs 5.4%; $p = 0.001$), and mucosal healing (40.9 vs 24.8%; $p = 0.0013$), when compared with those receiving placebo. Of the 374 patients studied, 39% had been previously exposed to TNF- α therapy. Within this population, both clinical response (39.0 vs 20.6%) and clinical remission (9.8 vs 3.2%) were higher in vedolizumab-treated patients than in those who received placebo. The authors also evaluated the development of adverse events and found no significant difference in the rate of adverse events or serious infections between patients treated with vedolizumab and those receiving placebo [61].

The remainder of the Phase III trials evaluating the efficacy of vedolizumab are in progress, with additional results forthcoming. GEMINI II is targeted to be completed during the second quarter of 2012; however, a press release from Takeda in May 2012 reported that GEMINI II, which evaluated 1115 patients with moderately-to-severely active CD who have failed at least one conventional therapy, demonstrated that vedolizumab was superior to

placebo for meeting the primary end point of clinical remission for both induction and maintenance [101]. GEMINI III, a randomized, blinded, placebo-controlled, multicenter study with an expected completion date of June 2012, will examine the safety and efficacy of vedolizumab for the induction of clinical response and remission in approximately 400 patients with moderately-to-severely active CD. Finally, GEMINI LTS is a 2-year open-label study designed to determine the long-term safety and efficacy of vedolizumab in patients with UC and CD. GEMINI LTS has an estimated completion date of March 2016 [62, 102–105].

Safety & tolerability

In total, 579 patients or volunteers have participated in either Phase I or Phase II trials with 415 patients having received at least one dose of vedolizumab [62]. There is limited information regarding an additional 374 patients participating in GEMINI I, a Phase III trial [61]. There was no significant difference in adverse events between patients receiving vedolizumab and those receiving placebo. The most common adverse events reported have been headache, nausea, exacerbation of UC, abdominal pain, fatigue and nasopharyngitis [62]. Importantly, no cases of PML have been reported. A retrospective study examining 800 subjects from nine clinical trials, including ongoing Phase III trials, reported no association between exposure to vedolizumab and JC viremia in patients receiving up to 19 doses for up to 2.5 years [63]. Furthermore, no increased risk of serious infection, systemic opportunistic infection or malignancy was reported in these short-term studies. However, one case of primary cytomegalovirus infection occurred in a patient who received two doses of vedolizumab. The patient improved without the need for antiviral therapy [58]. There have been no on-study deaths reported.

In a dose-ranging study of vedolizumab, two out of 37 patients developed pyrexia. No patients developed other signs of an infusion reaction. Two patients experienced serious adverse events that were determined later to be unrelated to vedolizumab (osteoporosis and gastroduodenitis; one patient with a history of osteoporosis who was randomized to the 10-mg/kg group developed compression fractures of multiple thoracic vertebrae. One patient with a history of chronic gastroduodenitis who was randomized to the 2-mg/kg group developed gastroduodenitis 169 days after her last dose of vedolizumab. Esophagogastroduodenoscopy revealed esophagitis and an exacerbation of her gastroduodenitis). There were no cases of opportunistic infections, including PML. Additionally, there were no changes in white blood cell subsets or counts between individuals treated with vedolizumab and those receiving placebo. In this Phase II trial, HAHAAs were detected in four patients studied (11%), three from the 2 mg/kg cohort and one from the 6 mg/kg cohort. One HAHA-positive patient (maximum titer 1:15, 625) from the 2-mg/kg cohort was found to have accelerated clearance of vedolizumab. The remaining three HAHA-positive patients did not clear the drug at an accelerated rate, although their titers were 1:15. All patients completed the study. There were no infusion reactions observed [59].

Regulatory affairs

Upon completion of Phase III trials, Millennium Pharmaceuticals plans to seek registration from the FDA and EMA for the use of vedolizumab for the treatment of moderate-to-severe CD and moderate-to-severe UC in patients who have had an inadequate response to one or more therapies.

Conclusion

Biologic therapy for the treatment of IBD continues to evolve. Phase I and Phase II studies demonstrate the efficacy of vedolizumab for the induction of clinical remission in both CD and UC [58, 60]. Furthermore, Phase II studies suggest that short-term vedolizumab use is safe with an adverse event rate in vedolizumab-treated individuals no higher than that observed in patients receiving placebo. Emerging Phase III studies support the use of vedolizumab in patients with moderately-to-severely active UC who have failed at least one prior therapy including prior TNF- α inhibitors [61]. Although the total number of patients studied remains relatively small, no cases of JC viremia or PML have developed as a result of vedolizumab therapy. One case of primary cytomegalovirus did occur, but the patient improved without antiviral therapy. Upon completion of the remaining Phase III studies and pending approval from the FDA, vedolizumab may represent a promising new alternative treatment for moderate-to-severe cases of UC and CD. Importantly, vedolizumab will become an attractive treatment option for UC patients not responsive to, or losing response to, infliximab, and for CD patients not responsive to, or losing response to, one or more TNF- α inhibitors. Since vedolizumab, like natalizumab, targets leukocyte adhesion molecules, adoption of vedolizumab for treatment of patients not previously exposed to TNF- α inhibitors may initially be limited due to concerns regarding the safety of anti-integrin molecules, although evidence to date suggests that vedolizumab is unlikely to be associated with PML. If there continues to be no association with PML with long-term use and the safety profile continues to be excellent, vedolizumab is likely to supplant natalizumab for the management of CD patients previously exposed to TNF- α inhibitors and offer an additional option for the treatment of UC patients previously exposed to infliximab or immune suppressants. As physician and patient comfort with this more selective agent grows, vedolizumab may also be used for the treatment of patients with UC or CD without prior exposure to TNF- α inhibitors, rather than as a second-line agent.

Future perspective

Considerable attention has been given to developing new biologic agents that take advantage of molecular events that contribute to the pathogenesis of CD and UC. As noted, multiple new medications that target leukocyte extravasation are being developed as a means to achieve clinical remission and improve mucosal healing (Table 6). The development of natalizumab was an important first step in this class of medications, as it demonstrated that targeting leukocyte extravasation can induce clinical remission and response in patients with CD. Unfortunately, natalizumab has the potentially fatal side effect of decreasing immune surveillance within the CNS, resulting in PML. This often fatal adverse event, although extremely rare, has limited the widespread use of natalizumab.

Vedolizumab, which selectively targets the $\alpha_4\beta_7$ -integrin, is a promising new medication that also targets leukocyte extravasation. It is currently undergoing Phase III trials and, assuming it gains FDA approval for the treatment of UC and possibly CD, will provide clinicians with a newer, potentially safer leukocyte traffic inhibitor. Although significant advances have been made in IBD therapy in recent years, current therapies remain ineffective in a significant number of patients. The introduction of a new, highly selective class of medication that targets a different pathway from TNF- α inhibitors and other more traditional agents is a promising next step towards being able to successfully medically manage an even greater proportion of patients with IBD.

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Executive summary

Background

- Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing inflammatory conditions of the GI tract that may be managed medically except for severe cases requiring surgical resection.

Overview of the market

- Biologic therapy directed against endogenous TNF- α is used to induce and maintain remission in patients with inflammatory bowel disease; however, a significant proportion of patients do not respond to therapy or lose responsiveness over time.
- TNF- α inhibitors are associated with potentially serious adverse events including serious infections, opportunistic infections and lymphoma.

Introduction to vedolizumab

- The induction and maintenance of clinical remission have been achieved with antibodies that target cell adhesion molecules, although less-specific agents are associated with serious adverse events including fatal cases of progressive multifocal leukoencephalopathy.
- Vedolizumab selectively targets cell adhesion molecules responsible for leukocyte trafficking to the GI tract; the improved specificity of vedolizumab compared with other medications targeting cell adhesion molecules should minimize off-target effects such as progressive multifocal leukoencephalopathy.

Clinical efficacy

- Phase I studies demonstrated that $\alpha_4\beta_7$ blockade lasts for at least several weeks after only one dose of vedolizumab and that the medication is well tolerated.
- Phase II studies demonstrated that vedolizumab is more effective than placebo for inducing clinical and endoscopic remission in patients with active UC. Studies have also demonstrated that vedolizumab is effective at inducing clinical remission in patients with active CD.
- Phase III studies demonstrated that vedolizumab is more effective than placebo for achieving clinical response, clinical remission and mucosal healing at 6 weeks in patients with moderately-to-severely active UC who have previously been treated with corticosteroids, purine antimetabolites and/or TNF- α inhibitors.

Safety & tolerability

- The safety of vedolizumab was demonstrated in Phase II trials with a maximum follow-up period of 253 days. Adverse events were mild and included headaches, nausea, exacerbation of UC, abdominal pain, fatigue and nasopharyngitis. One known case of primary cytomegalovirus infection occurred in a prior Phase II trial. The patient improved without the need for antiviral therapy. There were no reported cases of progressive multifocal leukoencephalopathy.

Regulatory affairs

- Millennium Pharmaceuticals is conducting Phase III studies to confirm vedolizumab's clinical efficacy as well as its safety profile. To date, results from

Phase III trials have demonstrated the efficacy of vedolizumab for the induction of clinical remission, clinical response and mucosal remission in patients with moderately-to-severely active UC previously treated with other agents [61]. Pending completion of Phase III trials, we expect Millennium Pharmaceuticals to submit a Biologics License Application to the US FDA for the use of vedolizumab for moderate-to-severe CD and UC.

Figure 1. Blockade of α -integrins inhibits leukocyte migration into gut mucosa

(A) Tethering/rolling, activation, adhesion and extravasation/migration of leukocytes into gut mucosa occurs through interactions between leukocytes and endothelial cells. (B) Natalizumab prevents leukocyte migration by targeting both the $\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrins whereas (C) vedolizumab targets only the $\alpha_4\beta_7$ integrin, minimizing potential off-target effects such as progressive multifocal leukoencephalopathy, while continuing to inhibit leukocyte migration into gut mucosa.

PSGL: P-selectin glycoprotein ligand.

Reproduced with permission from [64].

Summary of Phase I trials of vedolizumab.

Table 1

Author	Sample size	Treatment arms	MCS [†] (day 30)	Endoscopic response [‡] (day 30)	Antidrug antibodies	Adverse events	Follow-up period	Conclusion	Ref.
Feagan <i>et al.</i> (2000)	29 patients with moderately severe UC with minimum MCS of 5, 3 bowel movements per day over baseline, endoscopic evidence of active UC	Placebo 0.15 mg/kg sc. 0.15 mg/kg iv. [§] 0.5 mg/kg iv. 2.0 mg/kg iv.	4.5 7 10 1 7	2 of 8 1 of 5 0 of 5 3 of 5 1 of 5	Not reported	No acute reactions Headache most common	30 days	$\alpha_4\beta_7$ blockade lasts at least several weeks after one dose. Well tolerated. Complete clinical and endoscopic remission only occurred in patients receiving drug	[65]

[†]Median initial MCS was 10 for all subjects who participated.

[‡]Defined as 2-grade improvement in modified Baron score.

[§]Two out of five patients in this group had complete endoscopic and clinical remission (Baron score = 0, MCS = 0).
iv.: Intravenous; MCS: Mayo Clinic score; sc.: subcutaneous; UC: Ulcerative colitis.

Table 2

Summary of Phase II trials of vedolizumab.

Author	Sample size	Treatment arms (n)	Clinical remission (%)	Clinical response (%) [†]	Antidrug antibodies (%) [‡]	Adverse events	Follow-up period	Conclusion	Ref.
Feagan <i>et al.</i> (2005)	181 patients with active UC	Placebo (63) 0.5mg/kg(58) 2.0 mg/kg (60)	14 33 [*] 32 [*]	33 66 ^{**} 53 ^{**}	38 11	Rates similar between treatment groups One infusion reaction [§] One CMV infection [¶] One lobar pneumonia [#]	6 weeks	"More effective than placebo for the induction of clinical and endoscopic remission" ^{††}	[58]

* $p < 0.05$ vs placebo;** $p < 0.01$ overall.[†] Defined as change in UC score of ≥ 3 points.[‡] Titer 1:125.[§] Human antihuman antibody titer 1:3125.[¶] Resolved without antiviral therapy.[#] 3 days postspinal surgery.^{††} Endoscopic remission rates were 12% (2.0 mg/kg) vs 28% (0.5 mg/kg) vs 8% (placebo), $p = 0.007$ for vedolizumab groups vs placebo.

CMV: Cytomegalovirus; UC: Ulcerative colitis.

Table 3

Summary of Phase II trials of vedolizumab.

Author	Sample size	Treatment arms (n)	Clinical remission (%) [†]	Clinical response (%) [‡]	Antidrug antibodies (%)	Adverse events (%)	Follow-up period	Conclusion	Ref.
Feagan <i>et al.</i> (2008)	185 patients with endoscopic, histologic or radiologic CD of the ileum and/or colon plus a CDAI of 220–400	Placebo (58) 0.5 mg/kg(62) 2.0 mg/kg (65)	21 30 37 [*]	41 49 53	34 12	86 94 91	57 days	"Suggestive of dose-dependent beneficial effect ... on clinical remission"	[60]

^{*} p < 0.05 vs placebo.

[†] Defined as CDAI 150.

[‡] Defined as 70-point decrease in CDAI from baseline.

[§] Rate of neurologic adverse events (headache, dizziness, confusion and ataxia) similar in placebo and treatment groups.

CDAI: Crohn's Disease Activity Index; CD: Crohn's disease

Summary of Phase II trials of vedolizumab.

Table 4

Author	Sample size	Treatment arms (n)	Clinical remission (%) [†]	Clinical response (%) [‡]	Antidrug antibodies (%) [§]	Adverse events	Follow-up period	Conclusion	Ref.
Parikh <i>et al.</i> (2012)	47 patients with endoscopically and/or histopathologically confirmed UC for 2 years and a PMS of 1–7 were randomized	Placebo (9) 2 mg/kg(12) 6 mg/kg (14) 10 mg/kg(11)	25–50 50 [¶] 68–89 [¶] Day 43: [#] 50 (placebo) 58 (vedolizumab)	22–33 50 [¶] Change in PMS at day 43: ^{††} –0.4 (placebo) vs –1.9 (vedolizumab)	None 25(3) 7(1) None	Two occurred, not related to study drug No systemic opportunistic infections reported	253 days	Near complete saturation of $\alpha_4\beta_7$ occurred over all doses tested. Dosing up to 10 mg/kg well tolerated. Treated patients had higher rate of clinical response than those receiving placebo	[59]

The goal of this study was to examine vedolizumab's pharmacology and safety. It was not powered to detect differences in efficacy.

[†]Remission defined as a PMS of 2 with no subscore >1. Reported only for subgroup with baseline PMS of 4–7. Rates reflect days 29–253.

[‡]Response defined as decrease in PMS of 2 points and 25% with a decrease in the subscore for rectal bleeding of 1 point or an absolute subscore of 0 or 1 for rectal bleeding. Rates reflect days 29–253.

[§]One patient had a peak titer of 1:15,625 (days 113 and 141) and exhibited accelerated drug clearance with accelerated desaturation of $\alpha_4\beta_7$. Human antihuman antibody titers in the other three patients ranged from 1:5 to 1:10. These titers were not associated with changes in drug clearance or $\alpha_4\beta_7$ saturation.

[¶]Rate for combined vedolizumab groups.

[#]Rates apply only to patients with a baseline PMS of 4–7.

^{††}End of induction period.

PMS: Partial Mayo score; UC: Ulcerative colitis.

Table 5

Summary of completed Phase III trials of vedolizumab.

Author	Sample size	Treatment arms	Clinical remission (%) [†]	Clinical response (%) [‡]	Antidrug antibodies	Adverse events	Follow-up period	Conclusion	Ref.
Feagan <i>et al.</i> (2012)	374 patients with moderately-to-severely active UC previously treated with corticosteroids, purine antimetabolites or TNF- α inhibitors with mean baseline MCS of 8.6	Placebo 300 mg iv. on days 1 and 15	5.4 16.9	25.5 47.1	Not reported	Equal rates of adverse events and infection in placebo and vedolizumab groups	6 weeks	Induction with vedolizumab more effective than placebo for clinical response, clinical remission and mucosal healing in previously treated patients	[61]

[†]Complete MCS of 2 points and no individual subscore > 1 point.
[‡]Reduction in complete MCS of 3 points and 30% from baseline, with a decrease in rectal bleeding subscore of 1 points or an absolute rectal bleeding subscore of 1 points.
iv.: Intravenous; MCS: Mayo Clinic score; UC: Ulcerative colitis.

Table 6

Other leukocyte traffic inhibitors undergoing development for the treatment of ulcerative colitis and/or Crohn's disease.

Name	Molecule	Molecular targets	Efficacy	Adverse effects	Status	Developer
Etolizumab (anti- β_7 , rHuMab- β_7) [66,67]	Humanized monoclonal IgG ₁ antibody directed against β_7 -integrin	β_7 ($\alpha_4\beta_7$, $\alpha_5\beta_7$)	Clinical response [†] in 10/15 patients with moderately-to-severely active UC versus 2/3 treated with placebo Clinical remission [‡] in 3/15 patients with moderately-to-severely active UC versus 0/3 treated with placebo	Headache (most common), two with UC exacerbation requiring urgent colectomy	Phase II trials [106]	Genentech
Natalizumab (Tysabri®; Antegren®; anti- α_4) [20,66]	Recombinant humanized monoclonal IgG ₄ antibody targeting α_4 -integrin	α_4 ($\alpha_4\beta_7$, $\alpha_4\beta_1$)	Induces clinical response and remission in patients with moderately-to-severely active CD with objective evidence of inflammation	Increased risk of PML [22,23]	Postmarketing surveillance	Biogen Idec, Elan Pharmaceuticals
AJM 300 (anti- α_4) [66,68]	Orally active α_4 -integrin inhibitor	α_4	Greater decrease of CDAI from baseline (21.6 ± 84.9 [240 mg] vs 5.2 ± 71.0 [placebo]) No significant difference in clinical response	Not described, but not dose-dependent	Phase II trials [107]	Ajinomoto
GSK-1605786 (CCX282-B, anti-CCR9, Traficet-ENTM) [66,69]	Orally active selective CCR9 antagonist	CCR9	Awaiting publication of results from multicenter, randomized, double-blind placebo-controlled trial of patients with moderately severe CD	Unknown	Phase III trials [108]	GlaxoSmithKline, ChemoCentryx
PF-00547659 (anti-MAdCAM) [66,70]	Subcutaneously administered humanized IgG2 monoclonal antibody against MAdCAM	MAdCAM	Randomized, double-blind, placebo-controlled study of 80 patients with active UC Clinical response at week 4: 52 vs 32% in placebo. Clinical remission at week 12: 22 vs 0% in placebo	Abdominal pain and tenderness most common. Six gastrointestinal infections, one occurring in placebo group. 'Infrequent' respiratory tract infections. No deaths. Nine serious adverse events in three patients with one possibly related to treatment [§]	Phase II trials [109]	Pfizer
Alicaforsen (ISIS 2302, anti-ICAM-1) [66]	Rectally administered phosphorothioate antisense oligonucleotide inhibitor of ICAM-1	ICAM-1	Did not meet primary end points in randomized, double-blind, placebo-controlled trials for CD. Enema formulation had comparable efficacy to mesalamine for left-sided UC	Unknown	Phase II trials	Isis

[†] Decrease in Mayo Clinic score of 3 points + 30% reduction from baseline and a 1 point decrease in rectal bleeding or absolute bleeding score of 0 or 1.

[‡] Absolute Mayo Clinic score 2 + no individual subscore >1.

[§]Potentially drug-related adverse events described as rectal hemorrhage, physical health deterioration, ankle abscess, wound infection, elevated leukocyte count and anemia.

CDAI: Crohn's Disease Activity Index; CD: Crohn's disease; PML: Progressive multifocal leukoencephalopathy; UC: Ulcerative colitis.