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DRUG EVALUATION:

Pharmacodynamic assessment of vedolizumab for the treatment of ulcerative colitis

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Abstract

Introduction—Vedolizumab is an anti-integrin approved for the treatment of Crohn's disease and ulcerative colitis. By binding the $\alpha 4\beta 7$ -integrin heterodimer, vedolizumab blocks leukocyte translocation into gastrointestinal tissue.

Areas Covered—This review discusses the chemistry, pharmacologic properties, clinical efficacy, and safety of vedolizumab in ulcerative colitis. Other medications available for the treatment of ulcerative colitis are also discussed.

Expert Opinion—Vedolizumab is a promising new agent for the treatment of ulcerative colitis. Its mechanism of action differs from TNF- α inhibitors and immune suppressants, allowing it to be used in cases of TNF- α inhibitor failure or non-response, or as a first-line biologic drug. Available safety data suggests that vedolizumab is not associated with an increased risk of infection or malignancy; however, additional post-marketing data are required to confirm these initial reports. Vedolizumab is likely to be used in growing numbers of patients over the coming years.

Keywords

anti-integrin; inflammatory bowel disease; ulcerative colitis; vedolizumab

1.0 Introduction

Vedolizumab is a humanized monoclonal antibody directed against the $\alpha 4\beta 7$ integrin heterodimer. The United States (US) Food and Drug Administration (FDA) approved vedolizumab for the treatment of moderate to severe ulcerative colitis (UC) and moderate to severe Crohn's disease (CD) in 2014¹.

UC, along with CD, is a type of inflammatory bowel disease (IBD), which are chronic inflammatory disorders affecting the gastrointestinal (GI) tract. UC, unlike CD, affects only the colon and rectum. In most cases of UC inflammation is limited to the mucosa; however, in severe cases the submucosa can be affected as well. In both UC and CD, inflammatory

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Declaration of Interest

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cells including neutrophils, macrophages, and T lymphocytes are recruited to the GI tract. T cells that express $\alpha 4\beta 7$ are preferentially recruited to GI tissues. By blocking $\alpha 4\beta 7$ vedolizumab decreases leukocyte migration into affected GI mucosa (Figure 1).

Patients with UC typically present with bloody diarrhea, fecal urgency, incontinence, tenesmus, and/or systemic symptoms such as fever, fatigue, or malaise. The diagnosis is suspected based on symptoms and laboratory investigation and is confirmed by histopathologic analysis of biopsies obtained during colonoscopy. Medical options for the treatment of UC include 5-aminosalicylates (5-ASAs), corticosteroids, immune suppressants, or biologic options such as TNF- α inhibitors or anti-integrin agents. The choice of medication is largely based on the severity of presentation, but other factors including side effects and cost are considered. Surgery remains an option for all patients with UC as proctocolectomy is curative. Patients with severe UC, those who fail medical therapy, or those who develop complications of disease may require surgery to achieve symptom control.

2.0 Body of review

2.1 Overview of the market

A variety of safe, effective treatment options exist for patients with mild to moderate UC. However, treatment of moderate to severe UC can be more challenging due to the severity of symptoms as well as potentially life-threatening complications, such as toxic megacolon, that may not respond adequately even to aggressive medical therapy. In such cases, colectomy is indicated. In fact, up to 25% of patients with UC will have surgery within 10 years of diagnosis². Available medical therapies include 5-ASAs, corticosteroids, immune suppressants, TNF- α inhibitors, and anti-integrin agents. Cyclosporine and tacrolimus can also be considered in UC patients who do not respond to intravenous steroids³⁴.

Patients with mild to moderate UC often respond to aminosalicylates, which can be used for both induction and maintenance therapy. A Cochrane Database review of 48 studies that enrolled 7,776 UC patients found that patients treated with placebo did not enter clinical remission as often as those treated with 5-ASA (RR 0.9, 95% CI 0.8 – 0.9)⁵. There was no difference between 5-ASA and sulfasalazine for inducing remission in patients with UC (RR 0.9, 95% CI 0.8 – 1.0)⁵. A second Cochrane Database review of 38 studies and 8,127 patients found that fewer patients receiving 5-ASA for UC maintenance therapy relapsed compared to those receiving placebo (RR 0.7, 95% CI 0.6 – 0.8)⁶. Sulfasalazine was found to be slightly more effective for maintaining remission than 5-ASA (RR 1.1, 95% CI 1.0 – 1.3)⁶. Aminosalicylates are generally well tolerated. However, they can be associated with mild side effects including headache, nausea, abdominal pain, decreased appetite, rash, vomiting, flatulence, and fever. In addition, up to 5% of patients taking 5-ASAs can develop a paradoxical worsening of diarrhea^{7–9}. Rarely, 5-ASAs can trigger interstitial nephritis¹⁰.

Corticosteroids are highly effective for inducing remission in UC. A meta-analysis of 20 trials found that corticosteroids are superior to placebo for inducing remission in UC (RR 0.7, 95% CI 0.5 – 0.9)¹¹. Oral prednisone exhibits a dose-response effect between 20 and 60 mg per day, although this increased efficacy is associated with a more significant side effect

profile¹². Potential side effects include the development of cushingoid features, emotional or psychiatric disturbances, increased susceptibility to infection, glaucoma, gastric or duodenal mucosal injury, impaired wound healing, striae, metabolic bone disease, hyperglycemia, electrolyte disturbances, hyperlipidemia, adrenal insufficiency, and atherogenesis¹². Because of the multitude of serious side effects associated with corticosteroid use, long-term use as a maintenance agent is not appropriate.

Immune suppressants such as the thiopurines, 6-mercaptopurine (6MP) and azathioprine (AZA), may be used as steroid-sparing maintenance agents for patients with UC. Their utility is limited by their slow onset of action, which can take up to 6 months^{13, 14}. Because of this, another agent such as a corticosteroid must be used to induce clinical remission. Additional considerations include side effects such as increased susceptibility to serious or opportunistic infection, bone marrow suppression, liver toxicity, hypersensitivity, and pancreatitis¹⁵. Thiopurine therapy is also associated with an increased risk of non-melanoma skin cancer and lymphoma with risk of both conditions increasing with patient age¹⁵. Although their use is associated with fewer hospitalizations, fewer operations, and steroid-free remission¹², a Cochrane analysis concluded that their use as first-line maintenance agents for UC could not be recommended given their less favorable side-effect profile when compared to 5-ASA therapy¹⁶.

Monoclonal antibodies directed against the pro-inflammatory cytokine TNF- α are steroid-sparing and can be used for induction and maintenance of remission in UC. Infliximab is the first TNF- α inhibitor approved for use in patients with IBD. The Active Ulcerative Colitis Trial (ACT) 1 demonstrated that at week 8 infliximab induces clinical response in approximately 65% of patients with moderate to severely active UC compared to 37% in those receiving placebo ($p < 0.01$) with clinical remission in 35% of those receiving infliximab compared to 15% of those receiving placebo ($p < 0.01$)¹⁷. At week 54 clinical response was observed in approximately 45% of those receiving infliximab compared to 20% of those receiving placebo ($p < 0.01$)¹⁷. Other TNF- α inhibitors approved in the US for treatment of moderate to severe UC are adalimumab and golimumab. The Ulcerative Colitis Long-term Remission and Maintenance with Adalimumab (ULTRA) trial demonstrated the efficacy of adalimumab over placebo for inducing and maintaining remission in patients with moderate to severe UC. Patients enrolled did not respond to steroid therapy or immune suppressants. Clinical remission was achieved in 16.5% of adalimumab-treated patients vs. 9.3% of placebo-treated patients at week 8 ($p < 0.05$) and 17.3% vs. 8.5% of patients at week 52 ($p < 0.01$)¹⁸. Response rates were 50.4% vs. 34.6% (adalimumab vs. placebo, $p < 0.01$) at week 8 and 30.2% vs. 18.3% (adalimumab vs. placebo, $p < 0.05$) at week 52¹⁸. Similarly, the Program of Ulcerative Colitis Research Studies Utilizing an Investigation Treatment – Subcutaneous (PURSUIT-SC) study demonstrated the efficacy of golimumab for inducing and maintaining clinical response, remission, and mucosal healing in patients with moderate to severe UC^{19, 20}. Like thiopurines, anti-TNF agents are associated with an increased risk of serious and opportunistic infections. In addition, patients using anti-TNF agents may develop infusion or injection site reactions, paradoxical autoimmune reactions, worsening heart failure, and melanoma skin cancers¹⁵. Importantly, a proportion of patients treated with TNF- α inhibitors either will not respond (primary nonresponse) to anti-TNF therapy or lose response (secondary nonresponse) over time^{21, 22}.

Although total proctocolectomy is curative, many patients do not wish to have a permanent end ileostomy. Patients who elect to undergo an ileal pouch anal anastomosis are subject to complications of the ileal pouch including pouchitis, sexual dysfunction, incontinence, irritable pouch syndrome, and a small risk of developing pouch dysplasia over time^{23, 24}. Patients must also be counseled regarding normal pouch function and should expect 4–8 bowel movements per day.

2.2 Introduction to the compound

Vedolizumab is a humanized version of a murine antibody (Act-1) that was originally developed in the 1980s. Act-1 binds the $\alpha 4\beta 7$ -integrin heterodimer²⁵, which facilitates leukocyte extravasation into GI tissues (Figure 1). Vedolizumab has since been reformulated as the rate of antibody development observed in patients receiving earlier versions of vedolizumab was unexpectedly high.

The $\alpha 4\beta 7$ integrin is expressed on T cells and binds to mucosal addressin cell adhesion molecule (MAdCAM)-1, which is found on endothelial cells in venules within the GI tract and on high endothelial venules in gut-associated lymphoid tissue, including Peyer's patches and mesenteric lymph nodes²⁶. MAdCAM-1 plays an important role in leukocyte recruitment to GI tissue as murine studies found that blockade of either MAdCAM-1 or $\alpha 4\beta 7$ inhibits migration of memory and effector T cells to GI tissue²⁷. Other sites of MAdCAM-1 expression in humans include the pancreas and lymphoid tissue with increased expression in inflamed GI mucosa, but not at inflamed extra-intestinal sites²⁶. By blocking the ability of $\alpha 4\beta 7$ and MAdCAM-1 to bind, vedolizumab prevents leukocytes from binding to venules within GI endothelium as well as subsequent leukocyte extravasation into GI mucosa²⁸ (Figure 1).

2.3 Chemistry

The chemical name for vedolizumab is immunoglobulin G1-kappa, anti-human integrin lymphocyte Peyer's patch adhesion molecule 1 (human-Mus *musculus* heavy chain), disulfide with human-Mus *musculus* α -chain, dimer. Prior names include LDP-02, LPD-02, MLN-0002, MLN-002, MLN-02, and UNII-9RV78Q2002. Vedolizumab is currently marketed by Takeda Pharmaceuticals USA, Inc. under the trade name "Entyvio". Vedolizumab's molecular formula is C₆₅₂₈H₁₀₀₇₂N₁₇₃₂O₂₀₄₂S₄₂. It has a molecular weight of 146.837 kDa and its Chemical Abstracts Service (CAS) registry number is 943609-66-3²⁹.

Vedolizumab's specificity for the $\alpha 4\beta 7$ -integrin heterodimer has been established in animal and human studies. A non-human primate chronic colitis model was used to determine the effect of $\alpha 4\beta 7$ blockade on GI inflammation. Animals were treated with a monoclonal antibody directed against $\alpha 4\beta 7$ with subsequent improvement in stool consistency, decreased mucosal infiltration of lymphocytes, neutrophils, and macrophages, and decreased histological inflammation within the GI tract. Importantly, antibodies to $\alpha 4\beta 7$ did not inhibit lymphocyte recruitment to extraintestinal sites³⁰. Human tissue was also used to study the effect of $\alpha 4\beta 7$ blockade. Cells expressing $\alpha 4\beta 7$ were strongly positive in the stomach, small intestine, colon, and spleen, with moderate signal in lymphoid tissues²⁵. Flow cytometry was

used to confirm vedolizumab binding to immune cells rather than other cell types. Vedolizumab was found to bind B cells, naïve CD4 and CD8 T cells, memory CD4 and CD8 cells, natural killer cells, and basophils. Monocyte binding was minimal and binding to neutrophils did not occur. Vedolizumab had the greatest affinity for memory CD4 T cells expressing the $\alpha 4\beta 7$ -integrin heterodimer. It is this T-cell population that is 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 on GI tissue without suppressing the protective effects of these T-cells at extraintestinal sites or the protective effects of other nonpathogenic T-cell subsets^{25, 28}.

2.4 Pharmacodynamics

A prior formulation of vedolizumab was found to promote the development of antidrug antibodies. In Phase II studies, human anti-human antibodies (HAHA) developed in approximately 40% of participants receiving this formulation of vedolizumab³¹. These antibodies were associated with decreased drug binding at $\alpha 4\beta 7$ as well as decreased drug efficacy^{31, 32}. As a result, vedolizumab was reformulated in an effort to produce a less immunogenic antibody. The reformulated vedolizumab underwent testing to reevaluate pharmacodynamics, pharmacokinetics, and drug safety. Binding to $\alpha 4\beta 7$ was nearly 100% in all dosing groups studied (2 mg/kg, 6 mg/kg, and 10 mg/kg). In the presence of detectable vedolizumab, the maximum effect ($E_{\max}$) was > 95% in all treatment arms, indicating near complete saturation at $\alpha 4\beta 7$. Since the $E_{\max}$ was >95% in all treatment arms, the authors were unable to determine a dose or concentration-dependent response relationship because there were no arms in which receptor saturation was not near complete^{28, 32}.

2.5 Pharmacokinetics and metabolism

Data regarding the pharmacokinetics of vedolizumab were obtained in the Phase II study described above. Study participants received induction doses of vedolizumab on days 1, 15, and 29 with their first maintenance dose administered 8 weeks later 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 1–10 $\mu\text{g/mL}$ at which point the decline continued in a nonlinear fashion. The mean elimination half-life was 15–22 days. The manner in which vedolizumab is metabolized has not been reported, although it is expected that it is degraded to small peptides and amino acids^{28, 32}.

Phase III trials of vedolizumab reported additional pharmacokinetic data³³. In this study the mean trough concentration of vedolizumab at week 6 was 27.9 ± 15.5 $\mu\text{g per mL}$ with a steady state concentration of 11.2 ± 7.2 $\mu\text{g per mL}$ with vedolizumab administered every 8 weeks. Greater than 95% saturation of $\alpha 4\beta 7$ on CD4+CD45RO+ T cells was observed. Twenty-three (3.7%) patients receiving vedolizumab had anti-vedolizumab antibodies at one point during the trial, with 6 patients (1.0%) having samples that were positive on 2 consecutive samples. The administration of immunosuppressive agents reportedly reduced the formation of anti-vedolizumab antibodies; however, these data were not presented in the referenced study. At present, there is no commercially available assay for measuring vedolizumab levels or antibodies against vedolizumab.

2.6 Clinical efficacy

Vedolizumab was approved for the treatment of moderate to severe UC and CD by the US FDA in 2014 and was also approved by the European Union European Medicines Agency (EMA) for the same indications^{1, 34} in addition to other countries and regions for similar indications. As such, it is currently undergoing post-marketing surveillance with no unexpected safety signals reported to date.

2.6.1 Phase I—Results from a Phase I study of LDP02 (vedolizumab) were presented in abstract form at Digestive Disease Week (DDW) 2000. This double-blind, placebo controlled, ascending dose trial evaluated the safety and efficacy of LDP02 in 29 patients with moderately severe UC (Table 1). Patients were required to have a Mayo Clinic Score (MCS) of at least 5, greater than or equal to 3 bowel movements daily above baseline, and endoscopic evidence of active disease. Placebo or LDP02 at one of four doses (0.15 mg/kg subcutaneous, 0.15 mg/kg intravenous, 0.5 mg/kg intravenous, 2.0 mg/kg intravenous) was administered. MCS and endoscopic disease activity were reassessed at day 30. No acute drug reactions occurred with headache being the most common adverse event reported. Saturation of the $\alpha 4\beta 7$ receptor persisted to day 30 in the 0.5 mg/kg group. The authors concluded that $\alpha 4\beta 7$ blockade persists for at least 30 days after a single dose of LDP02 and that LDP02 was well tolerated³⁵.

2.6.2 Phase II—A multicenter, double-blind, placebo-controlled Phase II trial of MLN02 (vedolizumab) was performed to determine its ability to induce remission in patients with active UC. This study assigned 181 patients to intravenous placebo, MLN02 0.5 mg/kg, or MLN02 2.0 mg/kg administered on day 1 and day 29 (Table 2). The primary endpoint was clinical remission at week 6. Endoscopic disease activity was also determined at that time point. Clinical remission rates were higher in the MLN02 0.5 mg/kg and MLN02 2.0 mg/kg groups (33% and 32%, respectively) than the placebo group (14%, $p < 0.05$). Clinical scores also improved to a greater extent in the MLN02 groups (66% and 53%) than in the placebo group (33%, $p < 0.01$). Mucosal healing was achieved in 28% of subjects receiving MLN02 0.5 mg/kg, 12% of subjects receiving MLN02 2.0 mg/kg, and 8% of subjects receiving placebo ($p < 0.01$). Adverse events were similar in all three treatment arms with exacerbation of UC, nausea, and headache being the most common side effects. A Phase II study examining the efficacy of MLN02 for the treatment of CD also found similar adverse event rates in treatment and placebo arms. Both the UC and CD Phase II studies found no difference in circulating lymphocyte counts between patients receiving MLN02 and those receiving placebo^{31, 36}.

A second Phase II trial designed to examine vedolizumab's pharmacology and safety profile was conducted. This study enrolled 47 patients with endoscopic and/or histopathologically confirmed UC of at least 2 years duration as well as a partial Mayo score of 1 – 7 (Table 2). Participants received placebo, vedolizumab 2 mg/kg, vedolizumab 6 mg/kg, or vedolizumab 10 mg/kg and were followed for 253 days. During this period two serious adverse events were reported (compression fractures of thoracic vertebrae and gastroduodenitis). Both adverse events were determined to be moderate and unrelated to vedolizumab. No systemic opportunistic infections or neoplasms were reported. Maximal saturation of $\alpha 4\beta 7$ occurred

at all drug doses studied. Higher antibody concentrations were detected in lower dose vedolizumab groups with no antibodies detected in the higher dose group. Even though the study was not designed to detect differences in efficacy, participants who received vedolizumab more frequently achieved a clinical response than those receiving placebo³⁷.

2.6.3 Phase III—A randomized, double-blind, placebo controlled Phase III trial (GEMINI I) examining the effect of vedolizumab on 895 patients with active UC was published in 2013 (Tables 3 & 4). This study reported the results of two integrated trials. The first trial included 374 patients receiving vedolizumab 300 mg or placebo at weeks 0 and 2. The second trial included 521 patients receiving open-label vedolizumab at weeks 0 and 2. Patients were re-evaluated at week 6. Patients who responded to vedolizumab therapy at week 6 were subsequently assigned to either continue to receive vedolizumab every 4 or 8 weeks or placebo. More patients receiving vedolizumab had a clinical response than those receiving placebo (47% vs. 26%, $p < 0.01$) at week 6. Remission was maintained in more patients receiving vedolizumab every 4 or 8 weeks than in those receiving placebo (45% vs. 42% vs. 16%, $p < 0.01$)³³.

An additional Phase III study (GEMINI LTS) is no longer recruiting participants and is scheduled to conclude in 2016. This multicenter, open-label study is designed to determine the safety and efficacy of long-term vedolizumab therapy. Primary outcome measures include adverse events, serious adverse events, results of standard laboratory tests, rates of hospitalization, surgery, or procedure, and changes in quality of life³⁸.

2.6.4 Phase IV/Post-Marketing Surveillance—Vedolizumab is currently undergoing post-marketing surveillance. No unanticipated safety signals have been reported and there have been no cases of progressive multifocal leukoencephalopathy (PML) linked to vedolizumab.

2.7 Safety and Tolerability

In Phase I, II, and III studies there were no differences in the rates of adverse events observed between patients receiving vedolizumab and those receiving placebo. Adverse events that did occur include headache, nausea, diarrhea, abdominal pain, fatigue, and nasopharyngitis³⁹. One case of primary cytomegalovirus infection did occur in a patient who received two doses of vedolizumab; however, the patient improved without antiviral therapy. Although serious infections have occurred in patients receiving vedolizumab, no increase in infection risk, including serious infections and opportunistic infections, has been detected compared to those receiving placebo. In total, 17 patients exposed to vedolizumab were diagnosed with a malignancy. Malignancies developed in 6 (0.4%) of 1434 subjects receiving vedolizumab as part of a clinical trial. One subject (0.3%) out of 297 receiving placebo developed a malignancy⁴⁰. Six deaths were reported during clinical trials evaluating vedolizumab, 5 in patients receiving vedolizumab and 1 in a patient receiving placebo⁴¹. The prescribing information for Entyvio (R) lists nasopharyngitis, headache, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities as the most common adverse reactions⁴¹, although these reactions occur at a similar rate in

patients receiving placebo. Additional data regarding the safety of long-term vedolizumab use will be reported in GEMINI LTS.

With regard to PML, no cases have occurred to date in patients receiving vedolizumab. Unlike natalizumab, which is a humanized monoclonal antibody directed against the $\alpha 4$ integrin, vedolizumab does not cross into the central nervous system because of its increased specificity targeting the $\alpha 4\beta 7$ heterodimer rather than $\alpha 4$ alone (Figure 1). PML is a rare and often fatal neurological disease caused by the John Cunningham (JC) virus. In patients receiving natalizumab, the risk of developing PML is increased by 2 years of natalizumab therapy, JC virus seropositivity, and prior exposure to immune suppressants⁴² with an estimated incidence of 1.44 cases per 1000 patient years (95% CI 1.2 – 1.7)²⁸.

In a Phase II pharmacologic study of reformulated vedolizumab, no changes in white blood cell subsets or counts were observed between participants who received vedolizumab and those receiving placebo. In this same study, HAHA were detected in 4 patients (11%); three patients from the 2 mg/kg cohort and one from the 6 mg/kg cohort. No patients receiving 10 mg/kg developed HAHA. One HAHA positive patient (titer 1:15,625) had accelerated drug clearance. The remaining three HAHA positive patients did not clear drug at an accelerated rate, although their titers were low (1:15). These data suggest that antibodies against vedolizumab can increase drug clearance and, as is observed with infliximab and adalimumab, likely affects drug efficacy³².

2.8 Regulatory Affairs

Vedolizumab is approved by both the US FDA and the EMA for the treatment of patients with moderate to severe CD or moderate to severe UC who have had an inadequate response to, loss of response to, or were intolerant to either conventional therapy or TNF- α inhibitor therapy^{1, 34}. Health Canada approved vedolizumab for the treatment of patients with moderate to severe UC who have had an inadequate response, loss of response to, or were intolerant to either conventional therapy or infliximab⁴³. Vedolizumab has also been approved in variety of other countries and regions in addition to the US, EU, and Canada.

3.0 Conclusion

Although multiple agents exist for the treatment of patients with UC, a proportion of patients will not respond even to maximal medical therapy with traditional immune suppressants or with TNF- α inhibitors. As a result, medical therapies for the treatment of both UC continue to evolve. Vedolizumab is the first anti-integrin agent approved by the US FDA for the treatment of patients with moderate to severe UC. Although vedolizumab only recently gained regulatory approval, other anti-integrin agents are in various stages of development⁴⁴ and will likely join the market in coming years.

Phase I, Phase II, and Phase III studies have all established the safety and efficacy of vedolizumab for treatment of patients with moderate to severely active UC^{31, 33, 36, 37}. Importantly, PML has not been reported to date, either in clinical trials or in post-marketing surveillance. Safety data continues to emerge and additional findings from long-term prospective studies will increase our understanding of any potential complications associated

with long-term vedolizumab use. Currently, vedolizumab is well-positioned for use in UC patients not responding to, or losing response to, one or more anti-TNF agents. Vedolizumab may also be used for maintenance therapy in patients not previously exposed to anti-TNF agents, particularly in older patients or in others who may be at increased susceptibility for infection.

3.1 Expert Opinion

Vedolizumab is a promising new agent recently approved for the treatment of patients with moderate to severely active CD or UC who have had an inadequate response to, lost response to, or are intolerant of anti-TNF or immunomodulator therapy, or who have an inadequate response, are intolerant of, or who are corticosteroid dependent. Previously, patients who did not respond to 5ASA therapy, immune suppressants, and anti-TNF therapy required colectomy. By targeting the $\alpha 4\beta 7$ integrin heterodimer, vedolizumab prevents leukocyte migration into GI tissue, thereby reducing inflammation without affecting systemic immune surveillance and is approved for improving endoscopic appearance of mucosa and achieving corticosteroid-free remission in UC in addition to achieving clinical response, clinical remission, and corticosteroid-free remission in CD. Natalizumab, approved for the treatment of patients with CD, is a monoclonal antibody with less specificity than vedolizumab. It does affect systemic immune surveillance, particularly CNS immune surveillance, and is associated with PML. In addition, vedolizumab likely offers an enhanced safety profile compared to thiopurines and anti-TNF agents as blockade of leukocyte migration is largely restricted to GI tissues, rather than blunting the immune response systemically. Unlike anti-TNF agents, vedolizumab has a slower onset of action and co-induction with corticosteroids may be required in patients with more severe symptoms.

Vedolizumab is approved for the treatment of patients with moderate to severely active UC (vedolizumab is also approved for the treatment of patients with moderate to severely active Crohn's disease). In moderate to severely symptomatic patients, remission may be induced with anti-TNF agents or corticosteroids (intravenous or oral) with transition to a maintenance agent. If remission is successfully induced with an anti-TNF agent, that drug should be continued for maintenance therapy. For patients who undergo corticosteroid induction, options for maintenance therapy include anti-TNF agents, immune suppressants, combination therapy (anti-TNF therapy with immune suppressant), or anti-integrin therapy with or without an immune suppressant. Determining which maintenance agent to use is based on patient factors (i.e., disease severity, adverse reactions), convenience (i.e., route of delivery, frequency of dosing), whether the ability to perform therapeutic drug monitoring is desired, and cost. In addition to using vedolizumab as a maintenance agent after corticosteroid induction, vedolizumab may be considered in patients with primary non-response to anti-TNF induction or in patients who develop secondary non-response to one or more anti-TNF agents. Finally, vedolizumab may be considered in patients with a history of infectious, paradoxical autoimmune, and malignant complications on other immune suppressants or biologic agents, in patients with prior malignancy, or in patients at increased risk for infection such as older patients since gut selective anti-integrin antibodies were not

associated with an increased risk of infection (RR 1.6, 95% CI 0.2 – 14.8) in a meta-analysis of placebo-controlled anti-integrin trials⁴⁵.

Vedolizumab use has steadily increased in our clinical practice and we expect that its use at academic tertiary medical centers as well as in community practices will continue to grow. As stated previously, vedolizumab not only adds to the number of agents available for use in UC¹, it expands our ability to treat inflammation associated with IBD by targeting the $\alpha 4\beta 7$ integrin, a receptor not previously subject to antibody blockade in patients with UC. Some physicians may continue to steer patients towards anti-TNF agents since they have been used in the US since 1998. As such, we are approaching 20 years of post-marketing data with a good understanding of the side effect profile associated with these agents. Vedolizumab, however, has only recently been approved for use in the US and other regions. Assuming no unanticipated safety signals emerge in the post-marketing surveillance period, including a continued absence of PML in patients receiving vedolizumab, its use in patients with UC will continue to expand.

Studies are now emerging, including meta-analyses of placebo-controlled anti-integrin trials, in an attempt to expand the data available regarding the side effect profile of these agents. One meta-analysis included data from 12 trials (4 natalizumab, 6 vedolizumab, 2 etrolizumab) and found that the risk of developing an opportunistic infection was not increased with either gut-specific (RR 1.6, 95% CI 0.2 – 14.8) or gut-nonspecific (RR 2.3, 95% CI 0.1 – 108) anti-integrin agents⁴⁵. Gut-specific (RR 0.8, 95% CI 0.2 – 4.0) and gut-nonspecific (RR 1.6, 95% CI 0.2 – 12.7) anti-integrin agents were not associated with higher rates of malignancy⁴⁵. Large prospective studies will, however, be required to more clearly establish risk of infectious complications and malignancy in patients treated with anti-integrin agents for extended periods of time. Furthermore, although mechanistically vedolizumab should not cause PML, continued vigilance and monitoring for this unlikely complication is warranted.

Anti-integrin agents continue to be developed. Over the next 5 years we expect that other anti-integrin agents will gain regulatory approval and enter the market⁴⁴. A commercially available assay for drug monitoring will permit gastroenterologists to adjust dosing to ensure adequate drug levels in patients receiving vedolizumab. As serum biomarkers improve and advances are made in the realm of personalized medicine, it is likely that drug therapy will be tailored to the individuals, permitting physicians to choose agents that will have optimal effect in a particular patient while minimizing risks of adverse reactions. Until then, vedolizumab will remain a very reasonable choice for maintenance therapy in patients either intolerant of or not responding to anti-TNF agents or as first-line maintenance therapy in patients with UC.

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Drug Summary Box**Drug name**

Vedolizumab

Phase

Post Marketing Surveillance

Indication

US/EU: Patients with moderate to severe UC or CD who have had no response, lost response, or were intolerant to conventional therapy or TNF- α inhibitor therapy.

Canada: Patients with moderate to severe UC who have had no response, lost response, or were intolerant to conventional therapy or TNF- α inhibitor therapy.

Pharmacology description/mechanism of action

Humanized monoclonal antibody directed against $\alpha 4\beta 7$ -integrin heterodimer. Prevents $\alpha 4\beta 7$ binding to MAdCAM-1 thereby preventing leukocyte adherence to vascular endothelium and migration into GI mucosa.

Route of administration

Intravenous

Chemical structure

Humanized monoclonal antibody

Pivotal trials

GEMINI I³³

Figure 1.

Mechanisms of α -integrin blockade. (A) Mechanisms of leukocyte recruitment into the gut mucosa and the proteins involved. Natalizumab (B) is less selective than vedolizumab (C), with the same effects on cell recruitment, but more systemic effects. PSGL: P-selectin glycoprotein ligand.

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Table 1

Phase I Trials of Vedolizumab in Ulcerative Colitis

Study/Phase	Sample Size	Treatment Arms	MCS ¹ (day 30)	Endoscopic Response ² (day 30)	Anti-Drug Antibodies	Adverse Events	Follow-Up Period	Conclusion	Reference
Feagan <i>et al.</i> Phase I	29 patients with moderately severe UC with minimum Mayo clinic score (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	α 4 β 7 blockade lasts at least several weeks after 1 dose. Well tolerated. Complete clinical & endoscopic remission only occurred in patients receiving drug	³⁵

Adapted from⁴⁴

¹Median initial MCS was 10 for all subjects who participated

²Defined as 2 grade improvement in modified Baron score

³2/5 patients in this group had complete endoscopic and clinical remission (Baron's score = 0, MCS = 0)

Table 2

Phase II Trials of Vedolizumab in Ulcerative Colitis

Study/Phase	Sample Size	Treatment Arms (n)	Clinical Remission	Clinical Response ⁴	Anti-Drug Antibodies ⁵	Adverse Events	Follow-Up Period	Conclusion	Reference
Feagan <i>et al.</i> Phase II	181 patients with active UC	Placebo (63) 0.5 mg/kg (58) 2.0 mg/kg (60)	14% 33%* 32%*	33% 66%** 53%**	38% 11%	Rates similar between treatment groups 1 infusion reaction ⁶ 1 CMV infection ⁷ 1 lobar pneumonia ⁸	6 weeks	“[M]ore effective than placebo for the induction of clinical and endoscopic remission” ⁹	31

Study/Phase	Sample Size	Treatment Arms (n)	Clinical Remission ¹⁰	Clinical Response ¹¹	Anti-Drug Antibodies (n) ¹²	Adverse Events	Follow-Up Period	Conclusion	Reference
Parikh <i>et al.</i> Phase II <i>Note: This goal of this study was to examine vedolizumab's pharmacology and safety. It was not powered to detect differences in efficacy.</i>	47 patients with endoscopically and/or histopathologically confirmed UC for 2 years and a partial Mayo score (PMS) of 1–7	Placebo (9) 2 mg/kg (12) 6 mg/kg (14) 10 mg/kg (11)	25–50% 68–89% ¹³ Day 43: 50% placebo 58% Vedolizuma ^b ¹³	22–33% 50% ¹³ Change in PMS at day 43: ¹⁵ –0.4 (placebo) vs. –1.9 (vedolizumab) ¹³	None 25% (3) 7% (1) None	2 serious AEs occurred, not related to study drug No systemic opportunistic infections reported	253 days	Near complete saturation of α4β7 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	32

* p < 0.05 versus placebo;

** p < 0.01 overall

Adapted from⁴⁴⁴ Defined as change in UC score of 3 points

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⁵ Titer 1:125

⁶ HABA titer 1:3125

⁷ Resolved without antiviral therapy

⁸ 3 days post spinal surgery

⁹ 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

Adapted from Immunotherapy, 2012, Vol. 4, No. 9

¹⁰ 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.

¹¹ 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.

¹² One patient had a peak titer of 1:15,625 (days 113 and 141) and exhibited accelerated drug clearance with accelerated desaturation of $\alpha 4\beta 7$. HABA titers in the other 3 patients ranged from 1:5 – 1:10. These titers were not associated with changes in drug clearance or $\alpha 4\beta 7$ saturation.

¹³ Rate for combined vedolizumab groups

¹⁴ Rates apply only to patients with a baseline PMS of 4–7

¹⁵ End of induction period

Table 3**Phase III Induction Trial of Vedolizumab in Ulcerative Colitis**

Study/Phase	Sample Size	Treatment Arms (n)	Clinical Remission ¹⁶ Week 6	Clinical Response ¹⁷ Week 6	Follow-Up Period	Conclusion	Reference
Feagan <i>et al.</i> Phase III	374 patients with moderate to severely active UC previously treated with corticosteroids, purine antimetabolites, or TNF- α inhibitors with mean baseline MCS of 8.5–8.6 521 patients with moderate to severely active UC previously treated with corticosteroids, purine antimetabolites, or TNF- α inhibitors with mean baseline MCS of 8.6	Placebo (n=149) 300 mg IV on days 1 and 15 (n=225) Open-label vedolizumab	5.4% 16.9% 19.2%	25.5% 47.1% 44.3%	6 weeks	Induction with vedolizumab more effective than placebo for clinical response and clinical remission in previously treated patients	33

¹⁶Complete Mayo score of 2 points and no individual subscore >1 point¹⁷Reduction in complete Mayo score of 3 points and 30% from baseline, with a decrease in rectal bleeding subscore of 1 point or an absolute rectal bleeding subscore of 1 point

Table 4

Phase III Maintenance Trial of Vedolizumab in Ulcerative Colitis

Study/Phase	Sample Size	Treatment Arms (n)	Clinical Remission ¹⁸	Durable Clinical Remission ¹⁹	Durable Clinical Response ²⁰	Adverse Events	Follow-Up Period	Conclusion	Reference
Feagan <i>et al.</i> Phase III	373 patients who responded to induction therapy	Placebo (n=126) Vedolizumab every 4 wk (n=125) Vedolizumab every 8 wk (n=122)	15.9% 44.8% 41.8%	8.7% 24.0% 20.5%	23.8% 52.0% 56.6%	No differences in commonly reported AEs or in serious infections No PML Three drug discontinuations due to infusion reactions. Two of these had anti-vedolizumab antibodies	52 weeks	Maintenance with vedolizumab more effective than placebo for clinical response and clinical remission in previously treated patients	33

¹⁸Complete Mayo score of 2 points and no individual subscore >1 point

¹⁹Response at week 6 and week 52. Percentages listed are the proportion of responders (44.8% of participants who received vedolizumab every 4 weeks and 41.8% of participants who received vedolizumab every 8 weeks) who attained a durable clinical remission.

²⁰Remission at week 6 and week 52. Percentages listed are the proportion of responders (44.8% of participants who received vedolizumab every 4 weeks and 41.8% of participants who received vedolizumab every 8 weeks) who attained a durable clinical response.