CLINICAL
INVESTIGATION

Vedolizumab for the treatment of inflammatory bowel diseases

Although multiple therapies for IBD currently exist, a substantial proportion of patients do not respond to conventional agents and important safety concerns have emerged regarding the use of broad-spectrum immunosuppression. Given these limitations, development of more specific, gut-targeted therapy is an attractive approach. Vedolizumab specifically blocks trafficking to the gut of a small proportion of circulating T-lymphocytes to prevent the chronic inflammatory response observed in IBD. Several large-scale clinical trials support the efficacy of vedolizumab for the treatment of IBD, and have led to regulatory approval of this agent. However, multiple questions remain regarding the use of vedolizumab in clinical practice. This article will explore several of these issues.

Keywords: Crohn's disease • inflammatory bowel disease • integrin • monoclonal antibodies • treatment • ulcerative colitis • vedolizumab

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The chronic inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD) are complex and poorly understood disorders characterized by dysregulated immune responses to luminal antigens in genetically predisposed individuals [1]. Although multiple therapies for IBD currently exist, a substantial proportion of patients do not respond to conventional agents such as corticosteroids [2–4], antimetabolites [5–8] and tumor necrosis factor (TNF) antagonists [9–14]. Furthermore, important safety concerns exist regarding the use of these broad-spectrum [9,15,16] immunosuppressives [13,17–23]. Specifically, the risks of serious infection and immunosuppression-related cancers such as lymphoma and nonmelanoma skin cancer, are relevant, especially in older patients. Given these limitations, development of more specific, gut-targeted, therapy is an attractive approach.

Vedolizumab, a humanized IgG1 monoclonal antibody that specifically binds to the α4β7 integrin, is a novel gut-selective therapy [24] that has recently been approved for the treatment of adults with moderately to severely active UC and CD [25–29]. Vedolizumab specifically blocks trafficking to the gut of a small proportion of circulating T-lymphocytes [24] that express α4β7, a cell-surface glycoprotein that interacts with the mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) [30] on the intestinal vasculature. Binding of α4β7 to MAdCAM-1 allows firm attachment of these cells to the vascular endothelium which facilitates diapedesis, the process whereby cells exit the bloodstream and enter the tissue compartment. Continued recruitment of effector lymphocytes is a critical factor for sustaining chronic inflammation in IBD.

Following intravenous administration, vedolizumab rapidly binds α4β7, blocks migration of lymphocytes to the gut, and downregulates intestinal inflammation. However, cell trafficking to other organs such as the central nervous system, is unaffected since vedolizumab does not prevent α4β1 integrin-VCAM interactions that govern leukocyte movement at these sites [24,31–34]. This highly specific mechanism of action has the potential to reduce the

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incidence of infectious complications associated with broad spectrum immunosuppression.

Several randomized control trials have assessed the efficacy of vedolizumab in patients with UC and CD. In the GEMINI 1 study [25], 374 patients with UC, approximately 40% of whom had previously failed therapy with TNF-antagonists, were randomized in a 3:2 ratio to receive 300 mg of intravenous vedolizumab or placebo at weeks 0 and 2. A second cohort of 521 UC patients received open-label vedolizumab therapy at the same time points. In both groups patients who responded, defined as a decrease in Mayo clinical score of 3 points and a 30% reduction in total score at week 6 (with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point), were randomized to receive maintenance vedolizumab or placebo infusions every 4 or 8 weeks (with placebo at the 4 weeks intervals) until week 52. At week 6, 47.1% and 25.5% of patients in the vedolizumab and placebo group, respectively, had a clinical response (p < 0.001). The week-52 response rates were 41.8% in patients who received maintenance vedolizumab every 8 weeks, 44.8% for vedolizumab every 4 weeks and 15.9% with placebo (p < 0.001 for either comparison with placebo), respectively. The corresponding remission rates were 16.9% in patients who received vedolizumab and 5.4% the placebo group (p = 0.001). A study of similar design, GEMINI 2 [26], was conducted in 1115 patients with Crohn's disease (CD). As in the GEMINI 1 trial, more than 50% of the participants (57.8%) had failed treatment with a TNF-antagonist. At week 6, 14.5% and 6.8% of patients in the vedolizumab and placebo groups, respectively, had a Crohn's disease activity index (CDAI <150)-defined remission was observed in 39.0% of patients who received maintenance vedolizumab every 8 weeks (p < 0.001 for the comparison with placebo), 36.4% receiving vedolizumab every 4 weeks (p = 0.004 for the comparison with placebo) and 21.6% of the placebo group. These findings have established vedolizumab as an effective treatment option for patients with IBD for both patients who have failed a TNF-antagonist and those who are naive to biologic therapy.

In, the United States, vedolizumab is indicated for the both induction and maintenance of clinical response and remission of UC, improvement of mucosal appearance, and for achieving corticosteroid-free remission. In CD, vedolizumab has been granted a label for achieving clinical response, and remission, and corticosteroid-free remission [29]. Collectively the results of these studies provide a basis for the safety and efficacy of this new agent. However, multiple questions remain regarding the use of vedolizumab in clinical practice. This article will explore several of these issues.

How does vedolizumab change our current treatment algorithms?
Treatment of patients refractory to TNF-antagonists

The most obvious rolefor vedolizumab is treatment of patients with either UC or CD who fail to respond or lose response to a TNF-antagonist. Although TNF-antagonists are highly effective therapies for CD [9–14] approximately a third of patients fail to benefit from induction treatment, and up to 40% of responders ultimately relapse on maintenance therapy [35]. Multiple mechanisms are responsible for treatment failure in patients receiving TNF-antagonists including sensitization, the presence of non-TNF-mediated inflammation and inadequate drug concentrations due to rapid clearance of drug. Sensitization, defined as the formation of antidrug antibodies (ADAs) is a cause of treatment failure with biologic drugs. In a cohort study of 272 patients with rheumatoid arthritis treated with adalimumab [36], 28% developed ADAs after 3 years despite concomitant administration of methotrexate in the majority of patients. In those with ADAs, 67% of which were detectable during the first 28 weeks of therapy, higher rates of treatment discontinuation (38 vs 14%; hazard ratio [HR] = 3.0; 95% CI, 1.6–5.5; p < 0.001), lower trough drug concentrations (median, 5mg/l intraquartile range (IQR), 3–9 mg/l compared with 12 mg/l, IQR, 9–16 mg/l, p < 0.001), and decreased rates of sustained remission (4% compared with 34%, p < 0.001) were observed [36]. In patients with secondary failure to a TNF-antagonist, therapeutic drug monitoring with measurement of trough drug concentrations and antidrug antibodies may determine the most appropriate treatment choice.

Although a second TNF-antagonist can be used to treat sensitized patients [37], this approach may be suboptimal [38]. In a large cohort study, RA patients who developed ADAs to a TNF-antagonist and were subsequently treated with etanercept had similar response rates to TNF-antagonist-naive patients. However, in patients without ADAs, response rates to the second TNF-antagonist were significantly lower suggesting that other inflammatory pathways may be dominant in these patients. Likewise non-TNF mediated mechanisms may be an important cause of primary treatment failure.

Vedolizumab is an effective alternative for patients in both of these groups. In a randomized trial that evaluated 315 CD patients who had failed TNF-antagonist therapy 44% of whom were primary failures. Although CDAI-defined remission rates were similar between the vedolizumab and placebo groups at week-6 (15.2% and 12.1%, respectively, p = 0.433), significant differences in remission were observed by week-10 (26.6% and 12.1%, respectively, p = 0.001) [27]. These results,

obtained in a population of patients with treatment refractory severe disease, suggest that a 6-week induction period may be suboptimal for the use of vedolizumab in CD patients who have failed a TNF-antagonist. Accordingly the current prescribing information in the United States suggests that a minimum of 14-weeks is optimal for clinicians to evaluate the benefits of therapy with vedolizumab. It is noteworthy that a relatively slow onset of action was also observed with natalizumab, an $\alpha4$ integrin antagonist, induction therapy [39].

Role in TNF-antagonist naive patients

Traditional algorithms have featured TNF-antagonists for the management of moderate to severely active UC that is refractory to aminosalicylates, corticosteroids and thiopurines, however, compelling evidence supports the safety and efficacy of vedolizumab for this indication. This raises the important question of whether treatment with TNF-antagonists or vedolizumab is the preferred strategy in these patients. In the ACT trials [40], TNF-antagonist naive patients with moderate to severely active UC were randomized to placebo, 5 mg/kg of infliximab, or 10 mg/kg of infliximab at weeks 0, 2, 6, then every 8 weeks. In ACT 1, 37, 69 and 41% of patient in these groups had a clinical response at week-8 compared with placebo (p < 0.001 for both comparisons). Notwithstanding that comparisons across trials are of questionable validity, it is notable that a similar effect size was observed with vedolizumab in the GEMINI 1 trial in a population that included a substantial proportion of patients who had failed a TNF-antagonist. Recently two subcutaneously administered TNF-antagonist, adalimumab and golimumab have been approved for the treatment of UC. In ULTRA 1, 390 patient with moderate to severely active UC were randomized 1:1:1 to induction with 160 mg of subcutaneous adalimumab at week 0, 80 mg at week 2, then 40 mg at weeks 4 and 6; 80 mg at week 0, then 40 mg at weeks 2, 4, 6; or placebo. At week 8, nonsignificant differences were observed in Mayo score-defined response between these groups (54.6, 51.5 and 44.6%, respectively) [41]. ULTRA 2 [42] was a randomized, double-blind, placebo-controlled trial in which patients with moderate to severe ulcerative colitis were randomly assigned to receive adalimumab 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week or placebo. At week 8, 16.5% of patients in the adalimumab group and 9.3% in the placebo group (p = 0.019) displayed a Mayo score-defined clinical response. Similarly induction and maintenance studies of golimumab have been conducted in patients with moderately to severely active ulcerative colitis [43,44]. In the Phase III portion

of PURSUIT-SC [43], 761 patients were randomly assigned to receive subcutaneous golimumab 2 weeks apart at doses of: 400 mg then 200 mg; or 200 mg then 100 mg; or placebo. At week 6, 54.9% (p < 0.0001 compared with placebo), 51.0% (p ≤ 0.0001 compared with placebo), and 30.3% of patients achieved a Mayo score-defined response.

Our interpretation of the data is as follows: first, vedolizumab and the TNF-antagonist have all demonstrated efficacy for the treatment of patients with moderate to severely active UC. Although remission rates are higher with infliximab than the other TNF-antagonists these studies were performed approximately 6 years before the pivotal trials of the other agents and did not include patients who had failed other TNF-antagonists. Therefore, the differences in remission rates that seem to favor infliximab over the subcutaneous TNF-antagonists may be more apparent than real. Second, the efficacy observed with vedolizumab, in a more severe population of patients than was studied with the other agents, is at least similar to these drugs. Corticosteroid-sparing in the long-term seems to be a particular strength of vedolizumab. Significant differences from placebo were observed in this important outcome in distinction to the lack of efficacy observed with TNF-antagonists. Furthermore, as discussed below, mechanistic and empiric data suggest that vedolizumab may be a safer choice for many patients, notwithstanding that longer term data are relatively sparse. Thus in UC a strong case can be made for the use of vedolizumab as a first line therapy in biologic naive patients. This argument may be particularly cogent in groups of patients who are at special risk for infection such as the elderly and those with multiple co-morbidities.

In Crohn's disease the situation is more complex given the relatively weak 6 week induction data. However, safety considerations may be a critical factor in decision-making. Existing data indicate that extending the induction period and using sufficient corticosteroid therapy to control symptoms during this time are important strategies that have potential to overcome this limitation. Certainly, the vedolizumab maintenance data and especially the corticosteroid-free remission rates observed in CD are compelling reasons to consider the preferential use of the drug over the longer term. Nevertheless, we expect many clinicians will continue to use TNF-antagonists as first-line agents in biologic naive CD patients until they gain greater personal experience with the drug. Furthermore, the well-established role of TNF-antagonists in the treatment of fistulizing CD and extraintestinal manifestations is unlikely to be challenged by vedolizumab in the short term [14,45,46].

Is vedolizumab truly gut-specific?

Although concerns regarding risks of infection and malignancy are inherent to the development of any new immunosuppressive, the gut-selective mechanism of action of vedolizumab may mitigate the risk of systemic adverse events associated with the use of conventional agents. However, multiple questions remain regarding this property as a critical advantage over existing agents. It is well established that TNF-antagonist therapy is associated with important infectious risks from both conventional and opportunistic pathogens [13,21–23]. In the TREAT registry, which followed 6273 patients for a mean of 5.2 years, 3420 patients were treated with infliximab yielding 17,712 patient-years of exposure. In this database, infliximab use was independently associated with an increased risk of serious infection (HR 1.43, 95% CI 1.11, 1.84; p = 0.006) [47]. Since the potential risk of serious infection with TNF-antagonists is a relevant concern to both patients and physicians vedolizumab may be viewed as a safer alternative.

As noted previously, the gut selectivity of vedolizumab is founded on a unique mechanism of action. The migration of leukocytes from the intestinal vasculature to mucosa is essential to propagate the dysregulated inflammatory responses in UC and CD [48]. Vedolizumab binds the $\alpha 4\beta 7$ integrin found on a subset of lymphocytes. It prevents these cells binding to MAdCAM-1, which are mainly expressed on gut endothelial cells, however it does not interact with integrins that lead to lymphocyte migration to other organ systems, such as $\alpha 4\beta 1$ in the central nervous system [24,29,31–33,49].

Data from a recently published study, which evaluated T-cell-dependent immune responses to oral and parenteral vaccines in 127 healthy subjects, provide strong evidence for the gut selectivity of vedolizumab. Participants were randomized to receive placebo or 750 mg of intravenous vedolizumab. Following this therapy, subjects received intramuscular recombinant hepatitis vaccine (HBVAXPRO) on days 4, 32 and 60 and inactivated oral cholera vaccine (DUKORAL) on days 4 and 18. On day 74, the mean serum vedolizumab concentration was 20.1 μg/ml, which was sufficient to saturate peripheral lymphocytes. Vedolizumab had no significant effect on systemic hepatitis B virus seroconversion rates (90.3% for placebo and 88.5% for vedolizumab in the vedolizumab, absolute difference, -1.8%, 95% CI -12.7% to 9.1%) and the mean hepatits B antibody titres were equivalent in the two experimental groups [50]. However, therapy with vedolizumab was associated with a lower seroconversion rate to oral cholera vaccine (82.5 and 96.8%, absolute difference -14.2%; 95% CI -24.6 to -3.9%) and both IgG and IgA

concentrations were significantly lower in subjects that received vedolizumab. These results are consistent with a gut-selective mechanism of action and underscore the lack of systemic immunosuppression with this agent.

Although no differences in adverse events were observed between placebo and vedolizumab in a Phase III trials of ulcerative colitis [25], this targeted immunosuppression carries the potential risk of enteric and respiratory infections. An increased risk of nasopharyngitis has been observed in trials of induction therapy for CD [25,26] which may be due to expression of MadCAM in the orophaynx. Over the past decade, enteric infection with *Clostridium difficile* has increased in frequency in patients with IBD [51,52]. Alterations to enteric immunity, from gut-targeted immunotherapies has the potential for greater infectious complications. Based on clinical trial data, the time-adjusted incidence of *C. difficile* infection, per 1000 patient years, was 0.00 and 7.11 in patients who received placebo and vedolizumab, respectively [53]. However, additional data from Phase IV, postmarketing registries, will determine if this potential complication manifests in clinical practice.

The risk of progressive multifocal leukencephalopathy (PML) is a potential safety concern for anti-integrin therapies. Natalizumab, an IgG4 antibody directed to the $\alpha 4$ integrin subunit, was the first anti-integrin therapy used in IBD [54]. However, this agent is encumbered by the risk of progressive multifocal leukoencephalopathy (PML) [55,56], which has been attributed to blockade of the $\alpha 4\beta 1$ integrin that is involved in leukocyte trafficking to multiple organ systems, including the CNS [57]. Interference with T-cell trafficking is a critical mechanism for the development of PML. As a result of the experience with natalizumab, the potential risk of PML emerged as an important concern for vedolizumab during the development program. However, the lack of effect of vedolizumab on T-cell trafficking to the central nervous system has been well-established by several lines of evidence. First, unlike natalizumab, vedolizumab interacts with the $\alpha 4\beta 7$ integrin, which binds with MadCAM which is mainly expressed on gut endothelial cells [30]. Second, in a trial examining the effect of treatment on the development of experimental autoimmune encephalomyelitis, cynomolgus monkeys were randomized to receive natalizumab, vedolizumab, or placebo [58]. Monkeys treated with either placebo or natalizumab developed CNS lesions, whereas monkeys in the vedolizumab group did not develop the disease. These results suggest that vedolizumab, unlike natalizumab, does not affect leukocyte trafficking to the CNS. Third, patients treated with natalizumab develop lymphocytosis due to the diffuse impairment

of leukocyte trafficking [59–61]. A similar increase in leukocyte count is not observed following treatment with vedolizumab, resumably due to its selective blockage of a minority of cells that affect leukocyte trafficking to the gut [24,33,58]. Based on the number of patients exposed to vedolizumab, a several cases of PML would have been expected, however, no cases have been observed to date. The USA FDA Advisory Committeel concluded that routine testing for the ubiquitous John Cunningham Virus (JCV), the causative agent of PML, is not required prior to initiating vedolizumab.

In summary currently available data are consistent with a gut-specific effect of vedolizumab, however long-term, Phase IV, registry data are required to monitor for gut infections and to confirm the lack of systemic adverse effects. Accordingly, vedolizumab may establish a role in the treatment of patients with contraindications to systemic immunosuppression or TNF-antagonist therapy.

What is the risk of sensitization?

The risk of sensitization to recombinant human proteins is well documented and the use of concomitant systemic immunosuppression, to reduce this during vedolizumab treatment, may limit the benefit of gut-selectivity. Antibodies to factor VIII, interferon alpha [62], and TNF antagonists [40,63] have been associated with decreased clinical response. Up to 20% of patients treated with TNF-antagonist monotherapy develop antidrug antibodies (ADAs) [64]; however, this can be reduced to 4% with concomitant methotrexate therapy. In clinical trials of vedolizumab approximately 4% of patients developed ADAs up to week 52 [25,26]. Concomitant immunosuppression was associated with a decrease in rates of antibody formation [25,26]. Three percent of patients receiving immunosuppressants and 18% of those not receiving immunosuppressants were reported to have developed antivedolizumab antibodies in a post-hoc analysis of data from the pivotal ulcerative colitis and Crohn's disease trials [65,66]. However, co-administration of a systemic immunosuppressive such as azathioprine or methotrexate with vedolizumab might offset the safety benefits of gut-selectivity. One potential solution is the use of low-dose methotrexate to inhibit antibody formation. Clinical trials to quantify the efficacy of this combination therapy, to establish a therapeutic index, to define the pharmacokinetic profile of vedolizumab and to determine the prevalence of ADAs with long-term therapy are required.

What is the role for therapeutic drug monitoring?

In patients with secondary loss of response to TNF-antagonist therapy, measurement of serum drug and antidrug antibody (ADA) concentrations can guide subsequent therapy by identifying four groups of patients [67]. Patients with suboptimal drug concentrations at trough, without ADAs, comprise Group 1. These patients may benefit from dose intensification. The second and third groups of patients are sensitized with ADAs, either in the presence or absence of adequate trough drug concentrations. Switching therapeutic agents, within class, is recommended. A study from the Mayo clinic demonstrated that in patients with subtherapeutic drug concentrations, intensification of the infliximab dose was superior to switching to another TNF-antagonist (86 vs 33% response, p < 0.02). However, in patients with detectable ADAs, switching to a second TNF-antagonist was superior to dose escalation (92 compared with 17% response, p < 0.004) [68]. Group 4 consists of patients with adequate trough concentrations in the absence of ADAs. These individuals are unlikely to respond to additional dose intensification, and may benefit from an out-of-class agent. This recommendation is supported by data from a study of patient with rheumatoid arthritis, which demonstrated that response to the second TNF-antagonist was significantly lower in patients with loss of response in the absence of ADAs [38]. It has been suggested that increased drug clearance or non-TNF mediated processes may be involved in stimulating disease activity in these patients. As vedolizumab is the first non-TNF-antagonist biologic therapy that is available for the treatment of IBD, this will establish a third, and important, indication for this drug.

Similar to the TNF-antagonists, measurement of serum drug and antibody concentrations may guide vedolizumab dosing in clinical practice. In clinical trials correlations have been observed between drug concentrations and response [25,26]. Although these results underscore the value of a commercial assay to optimizing dosing regimens, optimal trough concentrations have not been identified and controlled data are not available to demonstrate that dose intensification in patients with low trough concentrations results in greater efficacy.

Use of vedolizumab in early disease

The role of vedolizumab early in the treatment of IBD remains unanswered. Nevertheless the notion that prompt introduction of highly effective therapy may result in better long-term outcomes than our traditional 'step care' approach is well established. Recently, a cluster randomization trial that compared an algorithm of early combined immunosuppression (ECI) to the conventional management (CM) of CD, in 39 community gastroenterology practices. In this study, which assessed outcomes in 1982 patients

followed for up to 2 years, combined immunosuppression was implemented earlier in ECI-sites compared with CM-sites. Despite the fact that the investigators evaluated a relatively low-risk patient population, the composite rate of surgery, hospitalization, and serious disease-related complications was lower 27.7% and 35.1% (absolute difference 7.3%, hazard ratio [HR]: 0.73; 95% CI 0.62–0.86, p < 0.001) in ECI-sites at 12-months [69]. No differences in the rates of serious infection were noted between ECI and CM sites. These results underscore the potential of early use of biologic. If the presumed safety profile of vedolizumab is proven in clinical practice, it will be an attractive option to minimize systemic immunosuppression in a patient population with mild disease. However, the cost of vedolizumab may be prohibitive to the wide spread use in practice.

Conclusion

Vedolizumab has a unique mechanism of action, with proven efficacy in the treatment of IBD. In the short-term, it will likely become the first-line therapy for moderate to severely active UC, provide additional therapeutic options for CD, and provide an out-of class therapy for non-TNF mediated disease. Several avenues of active research will continue to influence the clinical applications of this therapeutic class in IBD. Vedolizumab is administered intravenously, and development of subcutaneous and oral formulations are underway. Additional anti-integrin molecules include etrolizumab, a β7-antagonist, has already shown promise [70] for the treatment of UC. Although emerging data will continue to refine the optimal use of this agent, vedolizumab will establish a prominent role in the treatment of IBD.

Executive summary

Background
- Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory conditions.
- Traditional therapies consist of broad-spectrum immunosuppression which are encumbered by safety concerns including infection and malignancy.
- Development of vedolizumab, a more specific, gut-targeted, therapy is an attractive approach.
- Vedolizumab is a humanized IgG1 monoclonal antibody to the $\alpha 4\beta 7$ integrin that specifically blocks trafficking of a small proportion of circulating T-lymphocytes to the gut.
- Multiple randomized control trials, including GEMINI 1 and GEMINI 2 have confirmed the efficacy of vedolizumab in IBD.

How does vedolizumab change our current treatment algorithms?
- Treatment of patients refractory to TNF-antagonists
  - Approximately one third of IBD patients fail to benefit from induction treatment with a TNF-antagonist, and up to 40% of responders ultimately relapse on maintenance therapy, often due to sensitization.
  - Vedolizumab is an effective alternative for patients with both primary and secondary nonresponse.
  - In a randomized trial that evaluated 315 CD patients who had failed TNF-antagonist significant differences in remission were observed between the vedolizumab and placebo groups by week-10 (6.6% and 12.1% respectively, p = 0.001).
  - The current prescribing information suggests that a minimum of 14-weeks is optimal for clinicians to evaluate the benefits of therapy with vedolizumab.

Executive summary (cont.)

Role in TNF-antagonist naive patients

- Vedolizumab and the TNF-antagonist have all demonstrated efficacy for the treatment of patients with moderate to severely active UC.
- The efficacy observed with vedolizumab, in a more severe population of patients than was studied with the other agents, is at least similar to these drugs.
- Vedolizumab leads to long-term corticosteroid-sparing.

in UC a strong case can be made for the use of vedolizumab as a first line therapy in biologic naive patients, we expect many clinicians will continue to use TNF-antagonists as first-line agents in biologic naive CD patients.

Is vedolizumab truly gut-specific?

- Vedolizumab binds the $\alpha 4\beta 7$ integrin found in the intestinal mucosa, however it does not interact with integrins in other organ systems, such as $\alpha 4\beta 1$ in the central nervous system.
- Although no differences in adverse events were observed between placebo and vedolizumab in a Phase III trials of ulcerative colitis, this targeted immunosuppression carries the potential risk of enteric and respiratory infections.
- Multiple lines of evidence indicate that vedolizumab does not carry a risk of PML.
- Long-term, Phase IV registry data are required.

What is the risk of sensitization?

- In clinical trials of vedolizumab approximately 4% of patients developed ADAs up to week-52.
- Concomitant immunosuppression was associated with a decrease in rates of antibody formation (3% and 18%).
- Co-administration of a systemic immunosuppressive with vedolizumab might offset the safety benefits of gut-selectivity.

What is the role for therapeutic drug monitoring?

- Similar to the TNF-antagonists, measurement of serum drug and antibody concentrations may guide vedolizumab dosing in clinical practice.
- In clinical trials correlations have been observed between drug concentrations and response, however optimal trough concentration have not been identified.

Use of vedolizumab in early disease

- The role of vedolizumab early in the treatment of IBD remains unanswered.
- If the presumed safety profile of vedolizumab is proven in clinical practice, it will be an attractive option to minimize systemic immunosuppression in a patient population with mild disease.
- The cost of vedolizumab may be prohibitive to the wide spread use in practice.

Conclusion

- Vedolizumab has a unique mechanism of action, with proven efficacy in the treatment of IBD. In the short-term it will likely become the first line therapy for moderate to severely active UC, provide additional therapeutic options for CD, and provide an out-of class therapy for non-TNF mediated disease. Several avenues of active research will continue to influence the clinical applications of this therapeutic class in IBD. Vedolizumab will establish a prominent role in the treatment of IBD.

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