Review Article

Vedolizumab: A novel anti-integrin drug for treatment of inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is the chronic inflammatory disorder of gastrointestinal tract consisting of two subtypes: Ulcerative colitis and Crohn's disease. IBD occurs due to infiltration of leukocytes in intestinal mucosa and derangements in intestinal barrier function. One of the most important steps in pathogenesis of IBD is the interactions between integrins on the surface of leukocyte. The $\alpha_4\beta_7$ integrin expressing T-cell is an important leukocyte involved in pathogenesis and represents a new drug target for the treatment of IBD. Vedolizumab is a humanized monoclonal antibody, which acts against $\alpha_4\beta_7$ integrin heterodimer and blocks the interaction of $\alpha_4\beta_7$ integrin with MAdCAM-1. It prevents leukocyte binding to endothelial surface and its extravasation into affected tissue. The efficacy and safety of the vedolizumab have been established in many clinical studies. It has shown promising results in various clinical studies where a greater percentage of patients as compared to a placebo achieved and maintained clinical response, clinical remission, and corticosteroid-free clinical remission. Vedolizumab has been shown to be well tolerated with slightly higher risk of infections, headache, naspharyngitis as compared to placebo. This review focuses on the potential role of vedolizumab for the treatment of IBD.

Key words: Crohn's disease, inflammatory bowel disease, integrins, ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD) is the chronic inflammatory disorder of gastrointestinal tract (GIT) consisting of two subtypes: Ulcerative colitis (UC) and Crohn's disease (CD). CD is characterized by transmural inflammation of any portion of the GIT 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.[1] IBD is characterized by influx of inflammatory cells into gut mucosal tissue. Leukocytes including neutrophills, macrophages, T-lymphocytes, and dendritic cells participate in pathogenesis of both CD and UC. In UC, inflammation extends proximally from rectum whereas inflammation associated with CD tends to be patchy and segmental, involving terminal ileum in more than 75% of cases.[2]

The incidence of IBD has increased in recent years, especially in industrialized nations, although both incidence and prevalence vary from region to region. It has also been found that that young Asians who were born in Britain are

Access this article online	
Quick Response Code:	Website: www.jnsbm.org
	DOI: 10.4103/0976-9668.175016

How to cite this article: Singh H, Grewal N, Arora E, Kumar H, Kakkar AK. Vedolizumab: A novel anti-integrin drug for treatment of inflammatory bowel disease. J Nat Sc Biol Med 2016;7:4-9.

at a significantly higher risk of developing UC and CD than the indigenous European population.[3] A study in 2012 found that prevalence of UC in North America between 1980 and 2008 was 198.1-298.5 cases per 100,000 persons and prevalence of CD was 135.7-318.5 cases/100,000 persons.[4]

Most of the individuals are diagnosed during second and third decades of life, although a second smaller peak in diagnosis occurs during sixth and seventh decades.[5] Epidemiological data suggests that genetics play a significant role in IBD pathogenesis as first degree relatives of patients with IBD have a relative risk of at least five-fold for developing CD or UC.[2]

INFLAMMATORY BOWEL DISEASE: AN INDIAN PERSPECTIVE

IBD has been considered to be uncommon in India. The data that explains frequency and determinants of disease distribution in India is generally lacking. In general, the Asia-Pacific has been reported to have the lower incidence and prevalence of IBD in than in Europe and North America.[6] The increasing awareness among physicians and public coupled with availability of modern diagnostic facilities may boost the detection of IBD, but despite of this only a few cases have been reported from India in recent years. There is a compelling need to develop uniformity in diagnosis and starting an IBD registry to accumulate accurate and authentic data regarding the epidemiology of this disease in India.

The reported minimum incidence of CD in India is 0.14/105 persons year. Apart from this, studies done in rural Indian subcontinent found that rate of cases having UC rather than CD greater in India and Bangladesh, than in Pakistan, Nepal or Bhutan.[7] In a thorough cross-sectional study in Punjab, the authors reported an incidence figure for UC of 6.0/100,000.[8]

PATHOGENESIS OF INFLAMMATORY BOWEL DISEASE: ROLE OF INTEGRINS

IBD occurs due to infiltration of leukocytes in intestinal mucosa and derangements in intestinal barrier function. One of the most important steps in pathogenesis of IBD is the interactions between integrins on the surface of leukocyte and their ligands on the endothelium. Integrins which consist of α and β chain that together form a heterodimer, bind to ligands on endothelial cells, allowing leukocytes to firmly adhere to endothelial surfaces. Leukocytes then cross the endothelium and enter the mucosa through a paracellular route.[9] $\alpha_4\beta_7$ integrin expressing T-cell is an important factor involved in pathogenesis of IBD. These cells on activation preferentially adhere to their ligand MAdCAM-1 on endothelial surfaces within GIT and associated lymphoid tissues [Figure 1]. Animal studies demonstrated that inhibition of MAdCAM-1 prevents development of ileitis in mice by preventing T-cell adhesion to ileal endothelium.[10] It was realized that a monoclonal antibody targeting $\alpha_4\beta_7$ integrin could prevent or significantly attenuate leukocyte extravasation into affected tissue and thus decrease the severity of IBD.

INTEGRINS AS NEW DRUG TARGET FOR TREATMENT OF INFLAMMATORY BOWEL DISEASE

Earlier, integrins involved in cell adhesion were targeted with natalizumab which is a monoclonal antibody directed against α_4 integrin chain (blocks $\alpha_4\beta_1$ integrin and $\alpha_4\beta_7$). It is used to treat CD and multiple sclerosis, but is associated with risk of developing progressive multifocal leukoencephalopathy (PML). It has been hypothesized that preventing $\alpha_4\beta_1$ integrin binding to vascular cell adhesion molecule-1 (VCAM-1) may result in decreased immune surveillance within the central nervous system, 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.[1]

CURRENT TREATMENT OPTIONS FOR INFLAMMATORY BOWEL DISEASEAND NEED OF NEW DRUGS

Safe, effective treatment options exist for patients with mild to moderate CD or UC. However, a

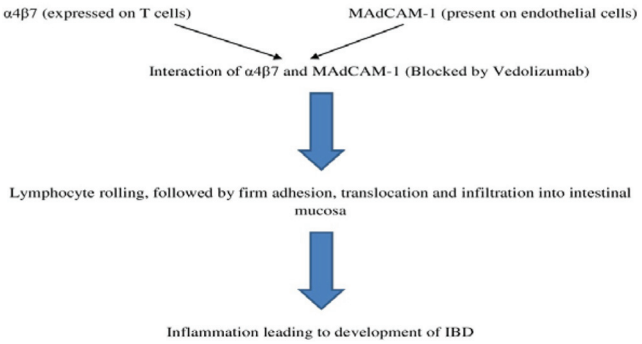

Figure 1: Role of integrins in pathogenesis of inflammatory bowel disease and mechanism of vedolizumab. Interaction of α4β7 and MAdCAM-1 is a crucial step activating the cascade of inflammation in inflammatory bowel disease. Vedolizumab acts by preventing this interaction impairing the inflammatory cascade

significant proportion of patients with moderate to severe CD or UC lack effective medical treatment. Pharmacological treatment options for CD and UC include 5-aminosalicylic acid (5-ASA), corticosteroids, immunnosupressants, or biologic therapy (tumor necrosis factor alpha [TNF-α] inhibitors such as infliximab, adalimumab, certolizumab) depending on severity of patient's symptoms and whether remission is being induced or maintained. Surgical therapy is reserved for severe cases refractory to medical therapy or when complications to disease develop. Efficacy of 5-ASAs is limited to severe cases of UC, though mild to moderate severity patients respond well to it.[11]

The above agents are less efficacious in mild to moderate CD patients, especially those with small bowel disease.[12] Patients not responding to 5-ASAs can be maintained on immunosupressants such as 6-mercaptopurine or azathioprine, although these drugs are associated with serious side effects including four-fold increased risk of lymphoma in patients treated with either of these agents.[13] Corticosteroids are effective for inducing remission, but cannot be used for maintenance because of their significant side effect profile. Biologic therapy with drugs targeting TNF-α are expensive, may require administration in a monitored setting and associated with a number of potentially serious side effects including opportunistic infection, lupus such as reaction, psoriaform eruptions, and lymphoma. With better understanding of mechanisms causing the disease, there is increased possibility of developing drugs with alternate mode of action. Hence, drugs acting against integrins were developed with natalizumab as first member of the class. However, its use was halted as it was associated with serious side effects to be reintroduced under surveillance program.[14] At present, effective and safe therapy is lacking to prevent or decrease leukocyte infiltration into intestinal mucosa without a concern risk of serious adverse effect like PML. Vedolizumab has been developed to address these unmet needs.

In nutshell, we can say that new drugs for IBDs are needed to address the following issues:

- To provide alternative in case of treatment failures to conventional drugs (glucocorticoids, immunomodulators, and/or anti-TNF-α therapies).
- To maintain long-term clinical remission or clinical response.
- To help stop/reduce or sparing glucocorticoids use.
- To provide therapies with better efficacy and safety profile.

VEDOLIZUMAB AS A NOVEL ANTI-INTEGRIN THERAPY

Vedolizumab is a humanized version of act-1, a murine antibody originally developed in 1980s with activity against $\alpha_4\beta_7$ integrin heterodimer (Developed by Millennium Pharmaceuticals). By blocking interaction of $\alpha_4\beta_7$ integrin found on surface of T-cells with MAdCAM-1 which is expressed on endothelial surface of venules within GIT tract and associated lymphoid tissue see [Figure 1], vedolizumab prevents leukocyte binding to endothelial surface and its extravasation into affected tissue.[1]

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. Its molecular formula is $C_{6528}H_{10072}N_{173202042}S_{42}$ and molecular weight is 146.8 kDa.[15]

CLINICAL PHARMACOLOGY

Blockade of $\alpha_4\beta_7$ receptors on T-lymphocytes has been shown to occur for several weeks after a single dose of vedolizumab.[16] The drug concentration following the infusion has been shown to be dose related with a mean maximum concentration of 12.5 μg/ml in those receiving 0.5 mg/kg of vedolizumab and 52.0 μg/ml in those receiving 2 mg/kg. The serum half-life of these two doses was 9-12 days respectively and saturation of $\alpha_4\beta_7$ receptors on T-lymphocytes was >90% at both 4-6 weeks following infusion. In a dose ranging study, the serum drug concentrations increased with increasing dose and when regular induction infusions were used (on day 1, 15, 29 and 85), the serum half-life was between 15 and 22 days across all groups.[17] This saturation of receptors has been shown to be related to the development of antibodies. Over the longer term, trough levels of vedolizumab at one infusion every 8 weeks remained steady and detectable throughout the study, with nearly full inhibition of $\alpha_4\beta_7$ receptors. Trough levels were dose proportional. Vedolizumab is given as fixed 300 mg intravenous (IV) Infusion, administered at week 0, week 2, and week 6 and then every 8 weeks for maintenance therapy.[18]

MAJOR CLINICAL TRIALS INVOLVING VEDOLIZUMAB

Various phase I, II, and III clinical trials involving vedolizumab are given in Tables 1 and 2.

Table 1: Major phase I and II clinical trials of vedolizumab

Trial	Study design	Treatment arms	Efficacy	Safety
Phase I trial Efficacy of vedolizumab after a single dose in patients with UC[19]	Double-blind placebo controlled ascending dose study	Vedolizumab (0.15 mg/kg SC, 0.15, 0.5, 2.0 mg/kg IV) Placebo	$\alpha_4\beta_7$ blockade lasts several weeks after one dose Complete endoscopic and clinical remission was seen only in patients receiving the drug	Well tolerated No acute drug reactions reported Headache was the most common AE reported
Phase II trial Efficacy of vedolizumab in patients with active UC[16]	Multicenter double-blind placebo controlled trial	Vedolizumab (0.5, 2.0 mg/kg) Placebo	Vedolizumab more effective than placebo for the induction of clinical and endoscopic remission	AE similar between treatment groups Aggravation of UC was the most common AE reported Three SAE were attributable to vedolizumab
Phase II trial Efficacy of vedolizumab in patients with active CD[20]	Randomized double-blind placebo controlled trial	Vedolizumab (0.5, 2.0 mg/kg) Placebo	Dose dependent beneficial effects of MLN002 therapy seen on clinical remission	Therapy was well tolerated 92% of the patients reported at least one AE 13% experienced atleast one SAE Most common SAE was worsening of CD OI occurred during the study
Phase II trial Pharmacodynamic and pharmacokinetic study of reformulated vedolizumab in patients with active UC[17]	Randomized placebo controlled dose-ranging study	Vedolizumab (2, 6,10 mg/kg) Placebo	Near complete saturation of $\alpha_4\beta_7$ occurred at all doses tested Treated patients had higher rate of clinical response than those receiving placebo	Vedolizumab was well tolerated Two serious AE reported Most common AE in both groups were headache, colitis, upper RTI and nasopharyngitis No systemic OI occurred

AE: Adverse events, CD: Crohn's disease, OI: Opportunistic infections, SAE: Serious adverse events, UC: Ulcerative colitis, IV: Intravenous, RTI: Respiratory tract infection

Table 2: Major phase III trials of vedolizumab

Trial	Study design	Treatment arms	Efficacy	Safety
GEMINI I Integrated induction and maintenance trials of vedolizumab in patients with moderately to severely active UC in whom one prior therapy had failed[21]	Randomized double-blind placebo-controlled trial	Vedolizumab (300 mg iv on days 1 and 15) Placebo	Vedolizumab was more effective than placebo as induction and maintenance therapy for UC	Frequency of AE was similar in both groups Most common AE in both groups were colitis, headache and nasopharyngitis
GEMINI II Integrated induction and maintenance trials of vedolizumab in patients with moderately to severely active CD in whom one prior therapy had failed[22]	Randomized parallel-group, double-blind, placebo-controlled trial	Vedolizumab (300 mg IV on days 1 and 15) Placebo	Vedolizumab-treated patients were more likely than patients receiving placebo to have a remission, but not a CDAI-100 response, at week 6 Patients with a response to induction therapy who continued to receive vedolizumab were more likely to be in remission at week 52	Vedolizumab, as compared with placebo, was associated with a higher rate of SAE, infections, and serious infections

AE: Adverse events, CD: Crohn's disease, SAE: Serious adverse events, UC: Ulcerative colitis, IV: Intravenous, CDAI-100: Crohn's Disease Activity Index

ONGOING CLINICAL TRIALS OF VEDOLIZUMAB

GEMINI is a phase (III), randomized, blinded, placebo-controlled, multicenter study in patients with moderately to severely active CD to establish the efficacy and safety of vedolizumab for the induction of clinical response and remission. The enrolled patients received vedolizumab or placebo as an IV infusion at weeks 0, 2 and 6. After completing the study, patients may be eligible to enroll in a long term safety study with continued access to vedolizumab.[23,24]

GEMINI LTS is a 2 years 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. Enrolled patients will receive vedolizumab (MLN0002) every 4 weeks, starting at week 0, for up to a maximum of 7 years. The dosing period will be followed by a 16 weeks posttreatment observation and safety assessment period. Patients will also receive safety phone calls at 6 months intervals for 2 years following receipt of the last dose.[23,25]

ADVERSE EFFECTS OF VEDOLIZUMAB

As the postmarketing experience with this drug is minimal (recently approved), the adverse effect profile in general population is not well established but the most common adverse events observed during phase I and phase II trials were headache, nausea, exacerbation of UC, abdominal pain, fatigue, and nasopharyngitis.[26] No cases PML and no increased risk of serious infection, systemic opportunistic infection, or malignancy have been reported. In dose ranging study of vedolizumab, no signs of infusion reaction were observed except pyrexia in two out of 37 patients. During phase III clinical trials higher rate of serious adverse events, infections, and serious infections were found in vedolizumab group as compared to placebo.[21,22]

CURRENT STATUS AND ANTICIPATED ROLE IN CLINICAL PRACTICE

In June, 2013 The Biologic License Application was filed to the US Food and Drug Administration (FDA) for use in both CD and UC[27] and in September, 2013, vedolizumab was granted a priority review status.[28]

On 20 May 2014, The US FDA approved vedolizumab (under the brand name Entyvio) for treatment of both moderate-to-severe UC and CD.[29] One week later i.e., May 27, 2014 the vedolizumab was also approved by the European Commission for the same indication.[30] Vedolizumab is meant to use when the adequate response cannot be obtained with one or more standard therapies (corticosteroids, immunomodulators, or tumor necrosis factor blocker medications).

Approval was based on promising results shown by the vedolizumab in various clinical studies where a greater percentage of patients as compared to a placebo achieved and maintained clinical response, clinical remission, and corticosteroid-free clinical remission.

Currently, vedolizumab is indicated in IBD when the adequate response cannot be obtained with one or more standard therapies such as corticosteroids, immunomodulators, or tumor necrosis factor blocking drugs.

Results from clinical trials clearly demonstrated the corticosteroid-sparing effects of vedolizumab because of its ability to produce corticosteroid-free remission. It has been shown to be well tolerated as a maintenance therapy with no increased risk of PML, which was a serious concern with the use of natalizumab. When compared to placebo, no higher rates of serious infection were observed. Since the drug has recently been approved (May 2014), the real world performance of this drug cannot be commented on and to address this question, data from large post-marketing trials and observational studies will be needed.

CONCLUSION

Vedolizumab is the second anti-integrin drug approved for the treatment of IBD. The drug has shown promising results in various clinical studies in terms of inducing and maintaining the clinical response and remission. Unlike natalizumab, the first anti-integrin drug, vedolizumab seems to be safe in respect to the risk of severe infections like PML but continuous and careful monitoring of patients is needed to explore its full safety profile.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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