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Review Article

Review Article

An Overview of the Mechanism of Action of the Monoclonal Antibody Vedolizumab

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Abstract

Vedolizumab is a novel therapeutic monoclonal antibody recently approved for the treatment of moderately to severely active ulcerative colitis and Crohn's disease in adults who have failed at least one conventional therapy. An integrin antagonist, vedolizumab binds to the $\alpha_4\beta_7$ integrin which is expressed specifically by a subset of gastrointestinal-homing T lymphocytes. The binding of $\alpha_4\beta_7$ integrin to mucosal addressin cell adhesion molecule-1 expressed on the surface of mucosal endothelial cells is a crucial component of the gut-selective homing mechanism for lymphocytes. In contrast, other monoclonal antibodies approved for the treatment of inflammatory bowel diseases, such as tumour necrosis factor α antagonists and the integrin antagonist natalizumab, act systemically or on multiple targets to reduce inflammation.

The unique gut selectivity of vedolizumab may contribute to the favourable benefit-risk profile observed in vedolizumab clinical trials. In this review, we summarise data from the preclinical development of vedolizumab and describe the current understanding of the mechanism of action as it relates to other biological therapies for inflammatory bowel disease.

Key Words: Crohn's disease; ulcerative colitis; vedolizumab

1. Introduction

Ulcerative colitis [UC] and Crohn's disease [CD] are inflammatory bowel diseases [IBDs] that are characterised by chronic intestinal inflammation involving a pathological response in both the innate and the adaptive immune systems.[1,2] Although the pathogenesis remains unclear, several theories have emerged to characterise the aetiology of IBD including genetic susceptibility, external environmental factors, infectious agents, commensal enteric flora, and immune system dysfunction.[3–5] Regardless of the biological origin of IBD, the trafficking of lymphocytes to the site of inflammation drives the progression of disease.[6] With a diverse array of possible causes, the complex immune response offers many therapeutic targets which are reflected in the wide range of drugs available and in clinical development for UC and CD.[5,7,8]

Conventional nonbiological therapies for the treatment of UC and CD include 5-aminosalicylic acid derivatives, corticosteroids, and immunosuppressants; however, limited efficacy and adverse events associated with these treatments highlight the need for an alternative approach.[9,10] Targeted biological therapies have been developed over the past several years, initially for use in refractory disease. Specifically, monoclonal antibodies against tumour necrosis factor α [anti-TNF α] were designed to target excessive activity of the adaptive immune system, namely cytokine signalling [Table 1].[11,12] Although treatment with these anti-TNF α agents has been successful in many patients, 20% to 40% of patients do not respond to induction therapy; and, of the 20% to 30% of patients who achieve remission, 30% to 40% will eventually lose their response.[10,13] In addition, anti-TNF α agents are associated with serious adverse events, such as systemic infections.[14] These factors, along with the chronic nature of the disease, support the development of new therapies deploying innovative mechanisms of action.

Essential to lymphocyte trafficking, integrin interactions mediate the attachment of lymphocytes to the gut endothelium, promoting migration into inflamed tissue.[7] Integrin antagonists have become an efficacious addition to the armamentarium for the treatment of UC and CD. Several antagonists of integrin interactions are

on the market or in clinical development, including monoclonal antibodies specific for the $\alpha_4\beta_7$ integrin heterodimer, the α_4 integrin, the β_7 integrin, and the mucosal addressin cell adhesion molecule-1 [MAdCAM-1].[15] Etrolizumab, a β_7 integrin antagonist,[16] and PF-00547659,[17] an anti-MAdCAM-1 antibody, are two such compounds in clinical development that may offer gut-selective approaches for reducing inflammation if approved for clinical use. However, monoclonal antibodies inhibiting the $\alpha_4\beta_7$:MAdCAM-1 interaction that are currently under clinical development are beyond the scope of this review, which considers only therapies available in clinical practice.

The only antagonists of integrin interactions that are currently available in clinical practice are natalizumab and vedolizumab, which are integrin antagonists that have been developed to block the attachment of integrins to their endothelial ligands [Table 1]. Natalizumab is a monoclonal antibody to the α_4 integrin, binding both the $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrin heterodimers. Currently, natalizumab is used in the treatment of multiple sclerosis and, in the USA, refractory CD.[7,18–20] Vedolizumab is a monoclonal antibody indicated for the treatment of UC and CD. Specifically targeting the $\alpha_4\beta_7$ integrin, vedolizumab blocks the interaction between $\alpha_4\beta_7$ integrin and MAdCAM-1 [Figure 1], selectively inhibiting gastrointestinal inflammation.[21–25] Here we describe the preclinical development and mechanism of action of vedolizumab, with a focus on selective targeting of leukocyte infiltration into the intestinal mucosa.

Table 1. Biological therapies for the treatment of UC or CD.

Drug	Target	Indication	Gut selectivity[a]
Adalimumab	TNF α	UC, CD	No
Certolizumab pegol	TNF α	CD	No
Golimumab	TNF α	UC	No
Infliximab	TNF α	UC, CD	No
Natalizumab	α_4 integrin	CD	No
Vedolizumab	$\alpha_4\beta_7$ integrin	UC, CD	Yes

CD, Crohn's disease; TNF α, tumour necrosis factor α; UC, ulcerative colitis.

[a]Determined, in principle, based on therapeutic mechanism of action.

2. Therapeutic Targeting of Leukocyte Infiltration into the Mucosal Endothelium to Reduce Inflammation

One mechanism of IBD exacerbation is the extravasation of leukocytes into areas of inflammation within the gut, a process driven by immunosurveillance. As part of the adaptive immune system, naïve T cells monitor secondary lymphoid organs for foreign antigens. Once an antigen has been encountered, naïve T cells differentiate into memory T cells and preferentially recirculate through tissues in which the antigen was first identified. The imprinting of T cells is thought to enhance the efficiency of pathogen response and clearance.[26,27]

To initiate infiltration into the site of infection or inflammation, lymphocytes travelling through the vasculature must adhere to the endothelial lumen and resist the shear stress of venous flow. Tissue-specific adherence is mediated by the interaction of lymphocyte integrins and their endothelial ligands. Integrins are heterodimeric transmembrane receptors expressed on the surface of many cell types, including lymphocytes. To date, 18 α and 8 β integrin subunits have been identified, generating at least 24 characterised heterodimers with largely distinct functions. The expression of specific integrin heterodimers directs the tissue-tropic homing of memory T cells. In particular, the $\alpha_4\beta_1$, $\alpha_4\beta_7$, and $\alpha_E\beta_7$ integrins are expressed by distinct subsets of lymphocytes [Table 2][28,29] with unique patterns of migration.[27,30,31] Lymphocytes expressing the $\alpha_4\beta_1$ integrin migrate to the central nervous system [CNS], bone marrow, and skin through

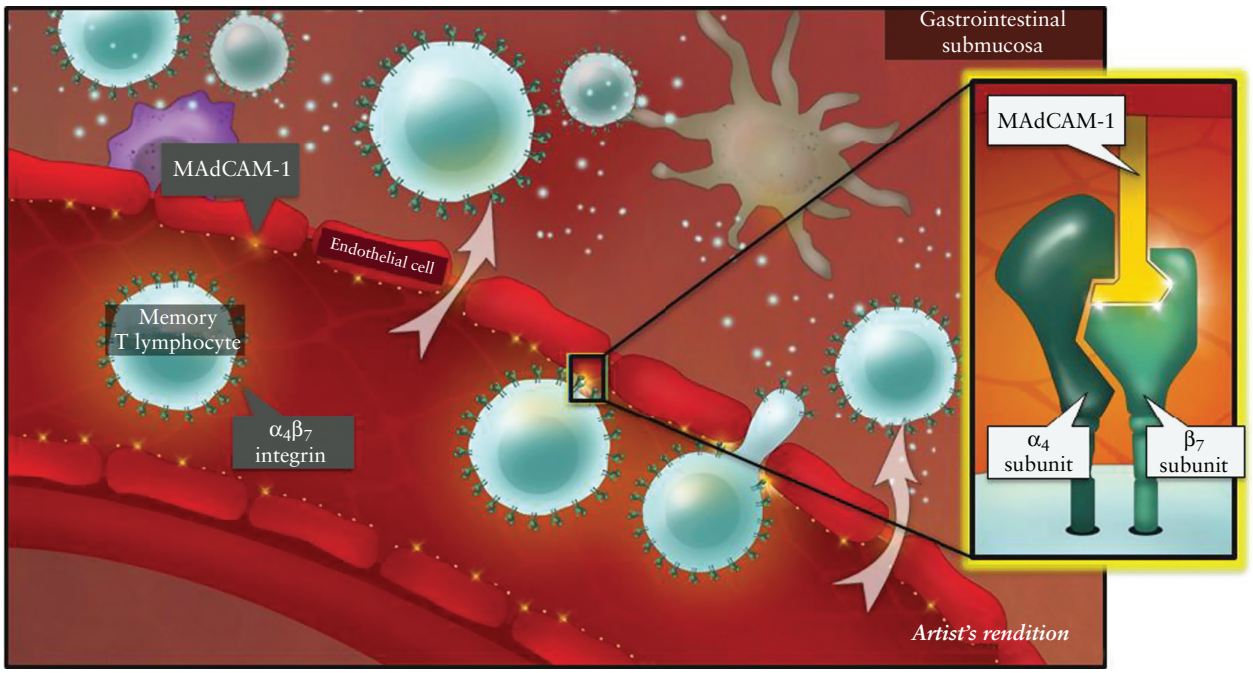

Figure 1. Schematic representation of the interaction between $\alpha_4\beta_7$ integrin and MAdCAM-1. The $\alpha_4\beta_7$ integrin is expressed on the surface of a discrete subset of memory T lymphocytes that preferentially migrate into the gastrointestinal tract. The $\alpha_4\beta_7$ integrin binds to MAdCAM-1 on the surface of endothelial cells to initiate extravasation into gastrointestinal submucosa. Interaction of $\alpha_4\beta_7$ integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of UC and CD. CD, Crohn's disease; MAdCAM-1, mucosal addressin cell adhesion molecule-1; UC, ulcerative colitis.

Table 2. Integrin heterodimers and their function.[28,33]

Integrin heterodimer	Ligands[a]	Cell expression[b]	Integrin antagonists
$\alpha_4\beta_1$	MAdCAM-1, **VCAM-1**, fibronectin, osteopontin, ADAM, ICAM-4, Thrombospondin	Leukocytes	Natalizumab
$\alpha_4\beta_7$	**MAdCAM-1**, VCAM-1, fibronectin	CD4+ and CD8+ naive T cells, **CD4+** and CD8+ **memory T cells**, B cells, eosinophils, natural killer cells	Natalizumab, Vedolizumab
$\alpha_E\beta_7$	**E-cadherin**	T cells, dendritic cells and mast cells in mucosal tissues	N/A

ADAM, a disintegrin and metalloprotease; ICAM-4, intercellular adhesion molecule-4; MAdCAM-1, mucosal addressin cell adhesion molecule-1; N/A, not applicable; VCAM-1, vascular cell adhesion molecule-1.

[a]Preferential ligand in bold.

[b]Expression of $\alpha_4\beta_7$ was identified by vedolizumab binding [cell type with highest level of binding in bold].

adhesion of $\alpha_4\beta_1$ integrin and vascular cell adhesion molecule-1 [VCAM-1].[26,30,32] Despite moderate expression on several types of leukocytes [Table 2], $\alpha_4\beta_7$ is preferentially expressed by a subset of CD4+ memory T cells[33] and mediates gut-selective homing. Memory T cells expressing the $\alpha_4\beta_7$ integrin migrate selectively into the gastrointestinal tract by binding to MAdCAM-1 [Figure 1].[27,30,34,35] The clinical relevance of $\alpha_4\beta_7$ expression on other leukocyte subpopulations has not been directly addressed; however, the relative expression level on other leukocytes was lower than that observed with memory T cells,[33] suggesting minimal clinical implications. In fact, the high level of $\alpha_4\beta_7$ expression observed on memory T cells appears to be critical for the clinical impact of vedolizumab on this cell type specifically, as no functional effect on other leukocyte subtypes such as natural killer cells has been observed.[33,36,37] It should be noted that, although it is well established that the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction is gut selective, the possibility of an alternative mucosal interaction cannot be excluded. Retention of T lymphocytes in tissue epithelium such as the gut, lung, and skin, is mediated by binding of $\alpha_E\beta_7$ on T lymphocytes to E-cadherin expressed by epithelial cells.[38,39] Although each of these integrin interactions can facilitate pathological inflammation, only the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction is selective for the gastrointestinal tract.

Inhibiting lymphocyte infiltration at the site of chronic inflammation provides a novel approach for the treatment of UC and CD. The monoclonal antibody natalizumab, which targets the α_4 integrin, a key mediator of lymphocyte trafficking, is an example of an initial attempt at pursuing this strategy. However, natalizumab antagonises both the $\alpha_4\beta_1$ and the $\alpha_4\beta_7$ integrins, inhibiting the binding of $\alpha_4\beta_1$ integrin to VCAM-1 as well as of $\alpha_4\beta_7$ integrin to MAdCAM-1, thus exhibiting non-selective anti-inflammatory effects.[6,18] The action of natalizumab on the $\alpha_4\beta_1$:VCAM-1 interaction prevents the infiltration of human T cells through the microvasculature of the murine spinal cord[40] and delays the progression of physical disability in patients, supporting its use in the treatment of multiple sclerosis.[19,20,41] Similarly, natalizumab interferes with the binding of $\alpha_4\beta_7$ integrin to MAdCAM-1, thereby reducing gastrointestinal inflammation in CD.[6,42] However, the use of natalizumab for the treatment of CD has been limited by its association with progressive multifocal leukoencephalopathy [PML], a rare and often fatal opportunistic infection. Caused by the recrudescence of the John Cunningham [JC] virus, PML is characterised by demyelination of white matter and can be attributed to impaired immunosurveillance of the CNS.[43,44,45] It is thought that the association between the inhibition of the $\alpha_4\beta_1$ integrin:VCAM-1 interaction and the risk of PML is caused by an increase in the viral load in the peripheral blood and the inability to clear the JC virus upon entry into the CNS.[43] Despite its efficacy in CD, natalizumab use is restricted to refractory disease because of its safety profile.[19] Safety concerns associated with systemic therapeutic agents such as natalizumab may be overcome with a gut-selective integrin antagonist such as vedolizumab.

3. Mechanism of action of vedolizumab

Creating a monoclonal antibody that blocks the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction in the gastrointestinal tract was proposed as a way to reduce the disease burden of UC and CD and possibly provide a more acceptable safety profile. The initial step in validating this therapeutic premise was to demonstrate specific binding of ACT-1 [the mouse anti-human $\alpha_4\beta_7$ monoclonal antibody from which vedolizumab was derived] with $\alpha_4\beta_7$ integrin. Exposure to the ACT-1 formulation of vedolizumab induced anti-inflammatory effects and disease remission in a proof of concept study in spontaneously colitic cotton-top tamarin monkeys.[46]

Efficacy in the animal model launched the development of humanised versions of ACT-1 [LDP-02, MLN02, MLN0002, and vedolizumab, which we will collectively refer to as vedolizumab throughout this review], which were better suited for chronic exposure in patients with UC and CD. Humanisation was achieved by cloning the binding region of ACT-1 onto a human immunoglobulin [Ig] G_1 [IgG_1] antibody. Immunogenicity with an earlier version of vedolizumab was overcome by altering the formulation process for subsequent versions.[47] To prevent the cytotoxicity associated with the fragment crystallisable [Fc] region, the Fc receptor-binding motif was mutated, which reduced antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity activity.[37] The lack of cytotoxicity *in vitro* and *in vivo* demonstrates that vedolizumab is a non-lytic antibody.[37]

Vedolizumab binds exclusively to the gut-tropic $\alpha_4\beta_7$ integrin and does not bind to any other α_4 or β_7 heterodimers, including the functionally distinct $\alpha_4\beta_1$ or $\alpha_E\beta_7$ integrins.[29,33] The selectivity for $\alpha_4\beta_7$ integrin was confirmed by X-ray crystallography, which elucidated that the vedolizumab epitope resides within the β_7 chain of the $\alpha_4\beta_7$ heterodimer.[48] The lack of specificity of vedolizumab for the $\alpha_4\beta_1$ or $\alpha_E\beta_7$ integrins offers the theoretical advantage of eliminating undesired effects outside the gastrointestinal tract where these integrins might play a more significant role. For example, $\alpha_4\beta_1$ integrin is responsible for leukocyte trafficking across a variety of tissues and, in particular, the migration of T cells to sites of inflammation within the CNS.[49] Consequently, blocking the physiological function of $\alpha_4\beta_1$ integrin can predispose patients to serious adverse events such as the development of PML, as observed with natalizumab.[43,50]

Similarly, vedolizumab does not inhibit $\alpha_E\beta_7$ integrin function despite its β_7 epitope.[29,48] Although $\alpha_E\beta_7$ integrin-positive intraepithelial cells are present in gastrointestinal tissues, binding of $\alpha_E\beta_7$ integrin to E-cadherin occurs in many epithelial tissues, such as the lung and skin.[51,52,53,54,55] It is believed that the function of $\alpha_E\beta_7$ integrin adhesion to E-cadherin is to retain T cells in the epithelia of many tissues such as the gastrointestinal tract, skin, and lungs. Retention in epithelial tissues may be necessary for efficient immunosurveillance of these sites. Thus, inhibition of the $\alpha_E\beta_7$ integrin:E-cadherin interaction suggests a potential broad reactivity. Importantly, the specificity of vedolizumab for the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction and its inability to bind to $\alpha_E\beta_7$ integrin limit the possibility of off-target epithelial effects driven by the disruption of the $\alpha_E\beta_7$ integrin:E-cadherin interaction.

In characterising the molecular mechanism of vedolizumab, ligand selectivity is equally important as integrin specificity. Binding of vedolizumab sterically hinders the interaction of the $\alpha_4\beta_7$ integrin with the endogenous ligands MAdCAM-1 [Figure 2] and fibronectin, but not VCAM-1.[33,48] Disruption of the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction selectively inhibits leukocyte migration through the gut mucosal endothelium. In contrast, the inability to block the interaction of $\alpha_4\beta_7$ integrin and VCAM-1 suggests that vedolizumab would not affect lymphocyte trafficking into other tissues.

Although vedolizumab inhibits the binding of $\alpha_4\beta_7$ integrin to fibronectin,[33] the physiological consequences are not understood. In mice, the binding of cells to fibronectin is more highly dependent on the interaction of another integrin α_V and less dependent on α_4 integrin.[56] In addition, fibronectin has many binding partners, suggesting a redundancy that is not present in the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction.[57] Therefore, inhibition of the $\alpha_4\beta_7$ integrin:fibronectin interaction may not contribute significantly to any extra-intestinal effects.

The binding of vedolizumab to $\alpha_4\beta_7$ integrin on the cell surface induces the internalisation of $\alpha_4\beta_7$ integrin;[37] however, removing vedolizumab *in vitro* enables the re-expression of $\alpha_4\beta_7$ integrin within 24 to 48 h, restoring T-cell expression levels to near pre-dose levels.[37] MAdCAM-1 binding to $\alpha_4\beta_7$ integrin is partially restored within 24 h *in vitro* and fully restored after 4 days following removal of vedolizumab.[37] Clinical pharmacokinetic evidence indicates that the linear elimination half-life of vedolizumab is 25.5 days.[58] Thus, the restoration of $\alpha_4\beta_7$ expression *in vivo* is unlikely to occur as quickly as was observed *in vitro*, precluding any patient risk of flare vulnerability between doses. The internalisation of the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction does not affect viability of the cell and is consistent with the lack of any changes observed in the peripheral lymphocyte populations.[22,23,37,49] In addition, vedolizumab does not activate leukocytes and does not affect cytokine production by differentiated T lymphocytes.[37]

Gut selectivity of vedolizumab was demonstrated in a preclinical study investigating the intra- and extra-intestinal effects of vedolizumab on non-human primates.[36] Vedolizumab administered chronically to cynomolgus monkeys had no macroscopic or histological effect on any tissues other than the ileum, consistent with a gut-selective profile. Within the ileum, an overall decrease in mononuclear cell infiltrate and a decrease in β_7 integrin-expressing cells were observed, which inversely correlated with an increase in $\alpha_4\beta_7$ integrin-positive memory T cells in the vasculature. No other changes in vascular cell populations were observed.[36] One potential explanation for these observations is that vedolizumab sequesters gut-homing memory T cells in the vasculature by preventing infiltration into the ileal lamina propria. Further evidence for the gut selectivity of vedolizumab came from analysing a T-cell-dependent antigen response [TDAR] to subcutaneous keyhole limpet haemocyanin, a T-cell antigen in cynomolgus monkeys. Investigators observed no difference in TDAR in cynomolgus monkeys treated with vedolizumab compared with controls, demonstrating a lack of effect on immune response outside the gastrointestinal tract.[36] In contrast, with natalizumab treatment,

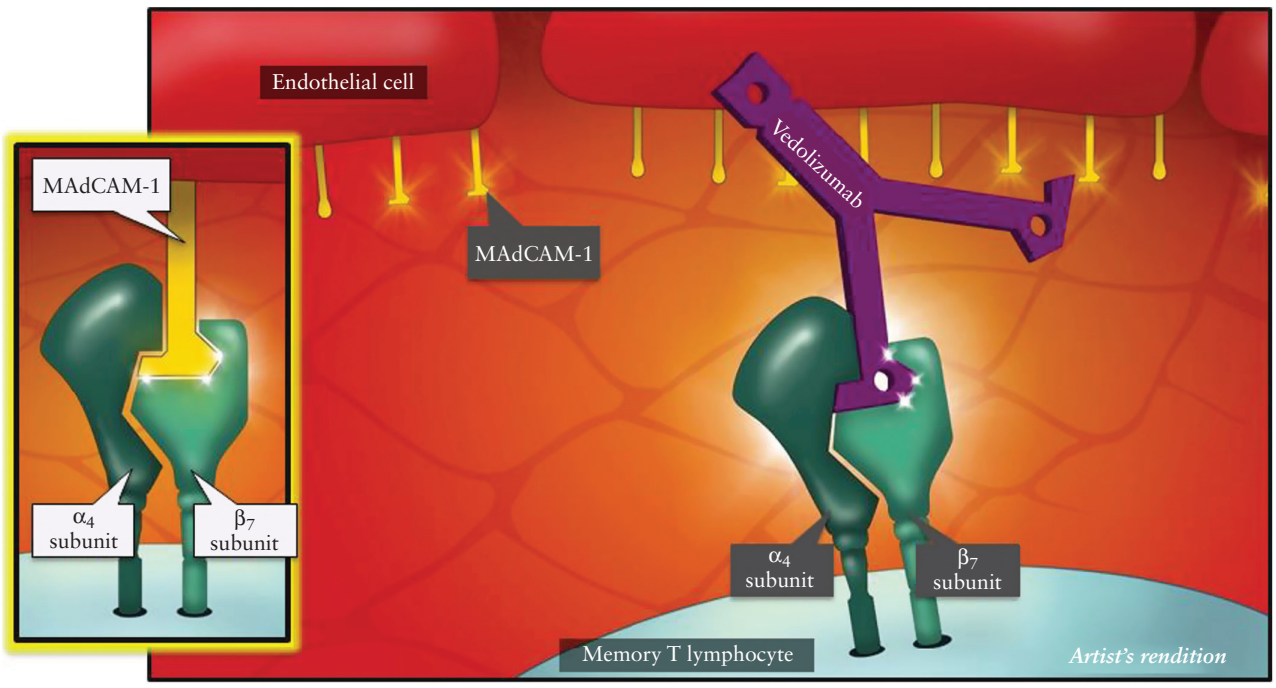

Figure 2. Schematic representation of the interaction between $\alpha_4\beta_7$ integrin and vedolizumab. Vedolizumab, a humanised monoclonal antibody, binds to the $\alpha_4\beta_7$ integrin receptor expressed on the surface of a discrete subset of memory T lymphocytes and blocks the interaction of these cells with MAdCAM-1. Vedolizumab binds to the specific conformation of the $\alpha_4\beta_7$ heterodimer with an epitope for the β_7 subunit. Inset: the adhesion molecule MAdCAM-1 is shown interacting with $\alpha_4\beta_7$ integrin. MAdCAM-1, mucosal addressin cell adhesion molecule-1.

a decreased TDAR was observed as well as an increase in the peripheral levels of a number of leukocyte subsets.[36] These observations are consistent with a systemic mechanism of action for natalizumab and a tissue-selective mechanism for vedolizumab.

The selectivity of vedolizumab for the mucosal system, and particularly the gastrointestinal tract, has also been confirmed by clinical research. In a double-blind phase 1 trial, 127 healthy participants were randomised to a single 750-mg intravenous dose of vedolizumab or placebo.[59] After 4 days, participants began intramuscular hepatitis B vaccine and oral cholera vaccine regimens. The results demonstrated that vedolizumab attenuated the immune response to the enteral antigen challenge [i.e. oral cholera vaccine], but did not affect the immune response to the parenterally administered antigen challenge [i.e. intramuscular hepatitis B vaccine] within the same subjects.[59] It was concluded that vedolizumab has a gastrointestinal-selective mechanism of action.

Unlike natalizumab, vedolizumab does not affect immunosurveillance of the CNS. Both vedolizumab and natalizumab inhibit $\alpha_4\beta_7$ integrin binding to MAdCAM-1 to achieve efficacy in CD. However, the efficacy of natalizumab in multiple sclerosis is a direct result of the inhibition of the $\alpha_4\beta_1$ integrin:VCAM-1 interaction, which is critical to the migration of lymphocytes into the CNS.[6,26,60,61,62] Preclinical and clinical data demonstrated that vedolizumab inhibition of the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction had no effect on T cell trafficking to the CNS. In a non-human primate model of experimental autoimmune encephalomyelitis [EAE], natalizumab [i.e. $\alpha_4\beta_1$ and $\alpha_4\beta_7$ antagonism] prevented the onset of EAE. Conversely, vedolizumab [i.e. $\alpha_4\beta_7$ antagonism] did not delay or stop EAE from developing in these animals. Collectively these data demonstrate that the infiltration of lymphocytes into the CNS was dependent on $\alpha_4\beta_1$ integrin and not $\alpha_4\beta_7$ integrin.[49] In addition, clinical data have shown that natalizumab had the ability to reverse the ratio of CD4:CD8 T cells and to decrease the number of cells in the cerebrospinal fluid [CSF] in as little as a single dose.[63,64] In contrast, data from a phase 1 healthy volunteer clinical trial of vedolizumab demonstrated no changes in the CD4:CD8 ratio or overall cell populations in the CSF after vedolizumab was given as a single dose of 450 mg intravenously.[65] To further demonstrate that the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction does not affect the migration of cells into the CSF, an anti-MAdCAM-1 antibody was used to treat patients with moderately to severely active CD. Similar to the results seen with vedolizumab,[65] no effect on the CD4:CD8 ratio or T cell numbers was observed in the CSF of patients treated with an anti-MAdCAM-1 antibody.[66] Taken together with data demonstrating a lack of MAdCAM-1 expression on CNS tissue,[62] these results suggest that the $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction does not play a role in CNS immunosurveillance. The absence of a $\alpha_4\beta_7$ integrin:MAdCAM-1 interaction in the CNS further validates the gut selectivity of vedolizumab.

Assessing the safety of vedolizumab is essential to the characterisation of this compound. Because of the targeted, gut-selective mechanism of action of vedolizumab, the benefit-risk profile for patients with moderately to severely active UC or CD is favourable. Several phase 2 and phase 3 clinical trials have illustrated the efficacy and safety of vedolizumab in the treatment of both UC and CD.[22,23,24,25,67,68] In particular, PML was closely monitored in these studies because of the association between natalizumab and PML. Both vedolizumab and natalizumab promote immunosuppression, but the gut-selective mechanism of action of vedolizumab appears to restrict this activity to the gastrointestinal tract, thereby reducing the risk of PML. In fact, there has been no PML case to date associated with vedolizumab treatment in clinical trials.[24,25,68] With natalizumab, over 500 cases of PML have been confirmed among at least 138,800 patients—primarily with multiple sclerosis—as reported over 9 years as of June 2015.[69] In addition, infusion-related reactions were infrequent, rarely resulting in discontinuation, and a low risk of malignancy [< 1%] was observed among vedolizumab-treated patients in induction and maintenance phase 3 clinical trials.[24,25,68,70] Although a low risk of infection has been observed in the vedolizumab induction and maintenance phase 3 clinical trials [2% for UC and 6% for CD],[24,25] long-term evaluations of gut-associated infections are still ongoing. Post-marketing risk assessments include monitoring of gut-specific adverse events and the risk of PML. The overall safety profile of vedolizumab correlates with a gut-selective mechanism of action.

4. Therapeutic targeting of TNF α signalling to reduce mucosal inflammation

TNF α signalling is a component of the pathogenesis of IBD. Although both membrane-bound and soluble TNF α are deregulated in IBD, membrane-bound TNF α signalling appears to play a more significant role in promoting gastrointestinal inflammation. The development of anti-TNF α agents [e.g. infliximab, adalimumab, certolizumab, golimumab] to neutralise TNF α signalling has dramatically improved the treatment of UC and CD [Table 1].[8] Anti-TNF α agents block pro-inflammatory signalling and induce apoptosis through a phenomenon called reverse or outside-in signalling.[71] Binding of anti-TNF α agents to membrane-bound TNF α induces the recruitment and activation of a death domain, which subsequently activates a caspase-8 cascade, leading to apoptosis of the cell.[72,73,74]

In addition to the induction of apoptosis, reverse signalling has been shown to reduce the expression of cytokines, including inflammatory cytokines, thereby reducing overall inflammation. Although all anti-TNF α agents bind to transmembrane TNF α, not all induce lymphocyte apoptosis or repress cytokine signalling. Etanercept, a fusion protein of TNF α receptor 2 with an IgG_1 Fc domain, did not induce reverse signalling, suppression of cytokine production, or apoptosis of activated lymphocytes despite binding to transmembrane TNF α.[71,75] Since etanercept is not effective in CD,[76] it is possible that the efficacy of other anti-TNF α agents in the treatment of UC and CD is driven by the apoptosis of lymphocytes and the reduction in cytokine production. A more in-depth discussion on the various mechanisms of anti-TNF α agents has been published previously by Tracey *et al.*[71] Unfortunately, despite their efficacy, anti-TNF α agents have several limitations including a loss of response over time and the potential for systemic infections. For these reasons, the evolution of drugs with novel targets such as vedolizumab has improved the therapeutic landscape of UC and CD.

Anti-TNF α agents initiate inflammatory clearance through apoptosis, whereas integrin antagonists block the infiltration of additional inflammatory cells responsible for disease exacerbation. Understanding the relationship between these two distinct mechanisms of action might provide insight into the clinical impact of sequential use of these two classes of therapeutic agents. In the pathogenesis of IBD, the inflammatory signalling cascade induces the expression and release of TNF α, which in turn perpetuates inflammation. Preclinical data identifying the TNF α-driven induction of MAdCAM-1 expression[77,78,79] is consistent with clinical evidence demonstrating an increase in MAdCAM-1 expression in UC and CD patients.[80,81]

Recent clinical data have confirmed that treatment with anti-TNF α agents decreases the expression of MAdCAM-1 and increases levels of circulating $\alpha_4\beta_7$ integrin-positive cells.[82] Conversely, individuals who did not respond to infliximab had high levels of MAdCAM-1

expression and lower percentages of β_7 integrin-positive cells in the periphery.[82] Interestingly, these results are consistent with observations from vedolizumab clinical trials in which the mean percentage of $\alpha_4\beta_7$ integrin-positive memory T cells was lower in moderately to severely active UC and CD than that observed with either healthy volunteers or individuals with mild to moderately active UC.[83] Since patients with moderately to severely active disease are more likely to have been previously exposed to anti-TNF α agents, it is possible that the decrease in $\alpha_4\beta_7$ integrin-positive T cells in this population may be attributed to compromised TNF α signalling. In addition, the reduced number of circulating $\alpha_4\beta_7$ integrin-positive cells implies that more cells are sequestered within tissues; these cells would be required to cycle back into the vasculature before vedolizumab would have a more extensive effect. Taken together with the fact that vedolizumab does not directly affect inflammatory clearance, the regulation of MAdCAM-1 by TNF α may contribute to the apparent gradual induction of a clinical response observed with vedolizumab, especially in the TNF antagonist failure subset of patients.[68]

5. Conclusions

Unlike other monoclonal antibodies approved for the treatment of UC and CD, vedolizumab has a mechanism of action that selectively inhibits the migration of gut-homing memory T cells into the gastrointestinal submucosa. Vedolizumab antagonises the interaction of $\alpha_4\beta_7$ integrin with its ligand MAdCAM-1, but not VCAM-1.[33] In contrast, natalizumab, an integrin antagonist for the treatment of multiple sclerosis and CD, produces a broader effect by targeting both the $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins and inhibiting adhesion to both MAdCAM-1 and VCAM-1, respectively.[6,18] Although the mechanism of action of natalizumab is effective for the treatment of multiple sclerosis and CD,[41,42,84] it has been associated with the development of PML, a relatively rare and often fatal opportunistic infection.[43] Similarly, anti-TNF α agents exhibit broader effects on inflammation, increasing the propensity for systemic adverse events. The gut-selective mechanism of action of vedolizumab may preclude the adverse safety profile associated with systemic therapeutics.

Indeed, the current safety research supporting vedolizumab reflects the selectivity for the gastrointestinal tract. A detailed summary of the safety data from six vedolizumab clinical trials is forthcoming.[85] To date, no cases of PML have been associated with vedolizumab treatment during clinical trials. In addition, vedolizumab has been shown to have a similar adverse event profile relative to placebo in patients with moderately to severely active UC and CD in clinical trials.[24,25,68] Post-marketing pharmacovigilance and risk management programmes are in place to monitor the long-term safety of vedolizumab. In fact, the conclusion of the ongoing phase 3 GEMINI long-term safety study [ClinicalTrials.gov ID, NCT00790933] in 2016 will provide much anticipated information about the benefit-risk profile with long-term sustained vedolizumab treatment. Importantly, the gut-selective mechanism of action of vedolizumab demonstrates efficacy while maintaining a favourable safety profile and provides a unique alternative therapeutic option for the treatment of UC and CD.

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Conflict of Interest

All authors are employed by Takeda.

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Author Contributions

TW contributed to the study designs, acquisition of data, and the analysis and interpretation of data presented in this review, was the primary author of the review, and had final approval of the manuscript. EF contributed to the study designs, acquisition of data, and the analysis and interpretation of data presented in this review, provided critical review and co-authorship of the manuscript, and had final approval of the manuscript. BA contributed to the interpretation of data presented in this review, provided critical review and co-authorship of the manuscript, and had final approval of the manuscript.

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