Review of vedolizumab for the treatment of ulcerative colitis

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INTRODUCTION

The prevalence and incidence of inflammatory bowel disease (IBD) have been increasing globally, with the highest incidence in Europe and North America. Ulcerative colitis (UC) remains the commonest type of IBD, the annual incidence varying from 0 to 24 per 100,000 person years, and prevalence between 4.9 and 505 cases per 100,000 worldwide[1]. UC typically causes bloody diarrhoea, urgency and abdominal pain, and runs a relapsing and remitting course. It is associated with significant morbidity, with an estimated 30%-60% of patients experiencing at least one relapse per year, and approximately 20% of patients suffer from severe UC[2].

Conventional treatments for maintenance therapy for UC include 5-aminosalicylates (5-ASA), and additional immunosuppressants such as thiopurine analogues, e.g., azathioprine and 6-mercaptopurine, are used in cases of frequent relapses. Thiopurine analogues have shown to prevent relapse in quiescent UC[3]. Corticosteroids remain the predominant therapy for induction of remission of moderate to severe acute
exacerbation of UC but limited by serious side effects. Over the last two decades, much research has been focussed on understanding the immune processes in the pathogenesis of IBD. More targeted therapies have been developed that specifically inhibit the mediators of gut inflammation, such as monoclonal antibodies, which have revolutionised the treatment for IBD. Infliximab is the first monoclonal antibody inhibitor to be developed which targets the tumour necrosis factor, the key pro-inflammatory cytokine in gut inflammation. The ACT 1 trial showed that patients with moderately to severe UC had a clinical response rate to infliximab of 65.5% at week 8, and almost 50% maintained response at week 30[6]. Adalimumab was subsequently developed, with the ULTRA 2 trial demonstrating a clinical response rate of nearly 50% at week 8, although only 17% patients maintained remission at week 52[15].

**ROLE OF INTEGRINS**

Recent advances in research have led to the development of drugs targeting alternative pathways of inflammation in IBD. One important pathway which propagates gut inflammation in IBD involves recruitment of circulating T lymphocytes into the intestinal vascular endothelial cells[6]. The trafficking of lymphocytes involve a complex adhesion cascade resulting in tethering, rolling, firm adhesion, and finally migration of lymphocytes from the vascular space into inflamed tissue[7]. Integrins play a critical role in the adhesion cascade. They are heterodimeric receptors composed of an α and β subunit, that is expressed on the surface of circulating lymphocytes where they are activated, and bind to their major ligand, the mucosal addressin-cell adhesion molecule (usually abbreviated, MadCAM-1), selectively expressed on the intestinal endothelium. This aids the binding of circulating lymphocytes onto the endothelium and migration into the lamina propria and tissue, contributing to the inflammatory process in IBD[6].

**INTEGRIN ANTIBODY ANTAGONISTS**

Integrin antagonists are monoclonal antibodies that block the trafficking of lymphocytes to the intestinal endothelium. The first integrin antagonist to emerge is Natalizumab, a humanised IgG4 monoclonal antibody eventually leading to inhibition of the α4 integrin. It was approved for use in Crohn’s disease in 2008. The ENCORE trial reported a clinical response rate of nearly 48% for Natalizumab at 8 to 12 wk for Crohn’s disease, compared to 32% in the placebo group[9]. However, the widespread use of Natalizumab was limited by associated increased incidence of progressive multifocal leukoencephalopathy (or PML), a fatal demyelinating disease of the CNS caused by the opportunistic human polyoma John Cunningham (JC) virus[10,11]. Natalizumab inhibits not only α4β1, which is expressed on T lymphocytes bound on the inflamed gut, but also α4β7, which mediates lymphocyte homing exclusively in the central nervous system (CNS).

**VEDOLIZUMAB**

Vedolizumab (previously known as LDP-02 or MLN02, MLN002), a humanised monoclonal IgG1 antibody, was subsequently developed as a gut selective anti-integrin specifically targeting α4β7 integrins in the gut. This paper reviews the safety and efficacy of vedolizumab as a novel therapy in the management of UC.

**EFFICACY**

**Early clinical trial**

Inhibition of monoclonal antibody to α4β7 integrin was initially reported to be effective at inducing remission of colitis in cotton-top tamarin in a double blinded RCT done by Hesterberg et al[12] in 1996. Cotton top tamarin monkeys, when kept in captivity, can develop chronic colitis, clinically and histologically resembling UC in humans. Eight cotton top tamarin moneys were diagnosed with chronic colitis endoscopically and histologically, before being administered either a cross-reactive antibody to human α4β7 or a non-therapeutic control monoclonal antibody intramuscularly. The intervention group benefitted from a rapid improvement of endoscopic and histological inflammatory activity and stool consistency[12]. These encouraging results propelled the study of vedolizumab in phase 1 clinical trials.

**Phase I trial**

In 2000, Feagan et al[13] conducted a double-blinded, placebo-controlled, ascending dose trial of humanised α4β7 antibody (LDP-02) in 29 patients with moderate to severe UC. Their inclusion criteria included endoscopically verified UC for at least 25 cm from the anal verge, a minimum of 3 bowel motions a day, and a Mayo score of 5 or more. The median Mayo score being 10. Eligible patients (86%) received and continued on a same dose of concomitant 5-ASA for 3 wk or more, and 34% received some oral prednisolone during the study. The patients were administered either a single dose of humanised antibody (LDP-02) in an increasing dose (0.15 mg/kg subcutaneously, 0.15 mg/kg intravenously (IV), 0.5 mg/kg IV, and 3 mg/kg IV) or placebo in a 5:2 ratio in each group. A dose of 0.5 mg/kg IV was found to be sufficient to completely saturate the antibody receptors for up to 30 d, and to give an endoscopic mucosal response at day 30 with at least a two grades improvement in the Baron score[13].

**Phase II trials**

In 2005, Feagan et al[14] conducted a multicentre, double blinded, placebo controlled trial of α4β7
controlled trial was undertaken by Parikh and response were assessed by partial Mayo score and faecal calprotectin. The study demonstrated pharmacokinetics which were dose-proportional and vedolizumab maximally saturated α4β7 receptors over the tested dosing. Multiple doses up to 10 mg/kg were very well-tolerated with no adverse events leading to drug discontinuation. The clinical response rate of those receiving vedolizumab was over 50% compared to 22%-33% in the placebo group. Vedolizumab treatment was also shown to reduce faecal calprotectin levels compared to placebo.

**Phase III trial**

The GEMINI 1 trial was published in 2013 by Feagan et al[13]. This phase III trial was a randomised, double-blinded, placebo-controlled study on the efficacy, safety and tolerability of vedolizumab (MLN002) in patients with moderate to severe UC. The GEMINI 1 trial consisted of 2 separate trials on vedolizumab as both induction and maintenance therapy for UC involving 895 patients in 34 countries. Patients were eligible if they were 18 to 80 years of age with active UC (defined by a Mayo score of 6 to 12, with a sigmoidoscopy sub-score of at least 2, and disease extending 15 cm or more from the anal margin). An additional criteria was previously failed treatment with steroids, immunosuppressives or anti-TNF therapy.

In a trial of induction therapy, 374 patients received either vedolizumab 300 mg (n = 224) or only placebo (n = 149) IV at weeks zero and 2. Results showed a significantly greater percentage of patients receiving vedolizumab achieving clinical response (47% vs 26%; P < 0.001), with clinical remission (17% vs 5%; P = 0.0009) and with mucosal healing (41% vs 25%; P = 0.0012) compared to placebo. The study also included a second group of 521 patients receiving open-labelled vedolizumab in parallel with the first cohort, with similar results. Remission rates and clinical response were higher in the vedolizumab group amongst patients who had been anti-TNF naive and also those who had prior anti-TNF failure, when compared to placebo (Table 1).

In a trial of maintenance therapy, patients in either of above cohorts who had responded to vedolizumab at week 6 were then randomly assigned to continue receiving vedolizumab 300 mg IV at 4 wk intervals (n = 125), vedolizumab 300 mg IV at 8 wk intervals (n = 122), or placebo (n = 126) for 52 wk. The authors assessed outcome measures of clinical remission rate at 52 wk, durable clinical response (defined as a response at weeks 6 and 52), durable clinical remission (which was defined as remission at weeks 6 and 52), mucosal healing at 52 wk and steroid free remission at 52 wk. Results showed that a significantly greater percentage of patients receiving vedolizumab reached clinical remission (45% for the vedolizumab 4 weekly group, 52% for the vedolizumab 8 weekly group, and 16% for the placebo group; P < 0.001) and mucosal healing at 52 wk (56% for the vedolizumab 4 weekly
found no significant difference in the number of serious adverse events of vedolizumab when compared to placebo (Table 2).

**CONCLUSION**

Vedolizumab is a novel, humanised, monoclonal IgG1-type antibody, developed as a gut selective anti-integrin specifically targeting α4β7 integrins in the gut. Clinical studies have demonstrated efficacy in the induction and the maintenance of response and remission in UC. This places it amongst the biologicals that are currently available for treatment of UC. This includes the anti-TNF antibodies of infliximab, adalimumab and golimumab. It has a different target and thus represents a new front for the suppression of the inflammatory process that fuels colitis. It does not appear to have the same safety issues as natalizumab with no reports of PML.

Vedolizumab's role in the management algorithm of moderately to severe UC remains unclear. Further trials would be needed to answer several questions. Firstly, should vedolizumab be used as the primary biologic after failure of conventional treatment? Secondly, is vedolizumab effective in patients who are primary anti-TNF failures? Finally does it have a role in patients who...

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### Table 1  Principal trial results

| Ref. | Sample size (n) | Phase of trial | Treatment arms (n) | Clinical remission (%) | Clinical response (%) |
|------|-----------------|----------------|-------------------|------------------------|----------------------|
| Feagan et al[14], 2005 | 181 | II | Placebo 14 | 33 |
| | | | 0.5 mg/kg IV | 33 |
| | | | 2 mg/kg IV | 32 |
| Parikh et al[15], 2012 | 47 | II | Placebo 33 | 22.33 |
| | | | 2 mg/kg IV | 68-89\* |
| | | | 6 mg/kg IV | > 80\* |
| | | | 10 mg/kg IV | |
| Feagan et al[16], 2012 | 374 | III | Induction phase | Placebo 5.4 | 25.5 |
| | | | 300 mg IV | 16.9 |
| | | | 6 mg/kg IV | 47.1 |
| | | | 10 mg/kg IV | 52.8 |
| | | Maintenance phase | Placebo 15.9 | 23.8 |
| | | | 300 mg IV 4 weekly | 44.8 |
| | | | 300 mg IV 8 weekly | 41.8 |

\*Collective results for all vedolizumab groups combined. IV: Intravenously.

### Table 2  Adverse events

| Ref. | Group | UC aggravated | Nausea/vomiting | Headache | Frequent bowel movement | Fatigue | Upper respiratory tract infection | Abdominal pain | Arthralgia | Dizziness | Rash |
|------|-------|---------------|-----------------|----------|-------------------------|---------|-------------------------------|----------------|------------|-----------|-------|
| Feagan et al[14], 2005 | Placebo | 24 | 15 | 13 | 10 | 7 | 5 | 16 | 5 | 1 | 4 |
| | 0.5 mg/kg IV | 29 | 21 | 12 | 10 | 8 | 8 | 10 | 4 | 6 | 6 |
| | 2 mg/kg IV | 22 | 13 | 11 | 5 | 5 | 8 | 6 | 7 | 4 | 4 |
| Parikh et al[15], 2012 | Placebo | 4 | 1 | 2 | 0 | 2 | 1 | 2 | 1 | 1 | 0 |
| | 2 mg/kg IV | 2 | 2 | 2 | 4 | 1 | 4 | 1 | 0 | 0 | 0 |
| | 6 mg/kg IV | 1 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 |
| | 10 mg/kg IV | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Feagan et al[16], 2012 | Placebo | 97 | 38 | 80 | 10 | 21 | 10 | 25 | 35 | 56 |
| | 300 mg IV | 97 | 38 | 80 | 10 | 21 | 10 | 25 | 35 | 56 |

IV: Intravenously; UC: Ulcerative colitis.

ADVERSE EFFECTS

Vedolizumab displays a relatively benign adverse effect profile. The large GEMINI 1 trial[16] reported the most common adverse effects included an exacerbation of colitis, headache and nasopharyngitis. A similar set of adverse effects were reported by Parikh et al[15]. However, overall the frequency for which these events occur are uncommon. Certainly Parikh et al[15] reported no withdrawal from their clinical trial as a consequence of adverse effects. The concern regarding PML has also not proven to be of significance[15,16]. There is yet to be an index case accountable to vedolizumab. Overall, it is reassuring that meta-analyses of several RCTs have found no significant difference in the number of serious adverse events of vedolizumab when compared to placebo (Table 2).

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have had secondary loss of response to anti-TNFs? These answers would greatly help the clinician treat UC more effectively.

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