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MINIREVIEWS

Review of vedolizumab for the treatment of ulcerative colitis

Michelle SY Lau, Her Hsin Tsai

Michelle SY Lau, Her Hsin Tsai, IBD Unit, Gastroenterology Department, Castle Hill Hospital, HEY NHS Trust, Cottingham HU16 5JQ, United Kingdom

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Correspondence to: Her Hsin Tsai, MD, FRCP, IBD Unit, Gastroenterology Department, Castle Hill Hospital, HEY NHS Trust, Castle Road, Cottingham HU16 5JQ, United Kingdom. hhtsai@doctors.org.uk
Telephone: +44-1482-875875
Fax: +44-1482-622049

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Abstract

The review summarises the key data on the efficacy and the safety of vedolizumab in the management of ulcerative colitis.

Key words: Ulcerative colitis; Vedolizumab; Biological therapy; Pharmacology; Safety and efficacy

Core tip: Vedolizumab appears to be effective in the management of moderate to severe ulcerative colitis with a good safety profile.

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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 100000 person years, and prevalence between 4.9 and 505 cases per 100000 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[4]. 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[5].

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[8].

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 α4β7, which is expressed on T lymphocytes bound on the inflamed gut, but also α4β1, 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 α4β7or a non-therapeutic control monoclonal antibody intramuscularly. The intervention group benefited 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

antibody (MLN02) on 181 patients with active UC. Active disease was defined as a UC clinical score of between 5 to 9 points, with a score of at least 1 on either stool frequency or rectal bleeding, with a modified Baron score of at least 2 on sigmoidoscopy, with the disease extending a minimum of 25 cm from the anal verge. Patients with active UC and either on no therapy or stable doses of mesalazine were eligible for inclusion. Excluded were patients on therapy with oral steroids within 4 wk or *IV* steroids within 6 wk prior to screening, topical therapy with mesalazine or steroids in the preceding 1 wk, immunosuppressive therapy the preceding 3 mo and severe active disease. The patients were randomly assigned to receive either 0.5 mg/kg of MLN02 (n = 58), 2 mg/kg of MLN02 (n = 60), or placebo (n = 63) *IV* on day 1 and day 29.

At week 6, the primary outcome of clinical remission (which was defined as UC clinical score of 0-1 plus a modified Baron score of 0-1 without rectal bleeding) was significantly higher in the MLN02 group as compared to placebo (33% in the 0.5 mg/kg, 32% in the 2 mg/kg and 14% in the placebo only group; P = 0.003).

Secondary outcome of clinical response (which was defined as improvement of UC clinical score by at least 3 points) were significantly higher in the MLN02 group compared to placebo (66% in the 0.5 mg/kg, 53% in the 2 mg/kg and 33% in the placebo only group; P = 0.002).

Endoscopically assessed remission rates at week 6 were observed in 28% in the 0.5 mg/kg MLN02 group, 12% in the 2 mg/kg of MLN02 group, and 8% in the placebo group (P = 0.007). A lower median modified Baron grade was also observed in the MLN02 group compared to placebo (1 *vs* 1.5; P = 0.02). The mean IBD questionnaire scores were significantly higher in the MLN02 group compared to placebo (171.5 *vs* 162.5; P = 0.03).

A further Phase Ⅱ dose ranging, randomised controlled trial was undertaken by Parikh *et al*[15] in 2012, using an improved formulation of vedolizumab made with a substance produced in hamster ovary. The study randomised 47 patients from 11 centres in Canada and Russia. Criteria for inclusion were patients aged 18-70 years who were diagnosed with UC, confirmed histopathologically or endoscopically (partial Mayo score of > 1), with minimum disease length of 10 years. These patients were randomised to receive either vedolizumab (n = 38) [2 mg/kg (n = 13), 6 mg/kg (n = 14), or 10 mg/kg (n = 11)] or just placebo (n = 9) on days 1, 15, 29 and 85, and were followed up for 253 d. This study used higher doses of vedolizumab administered with shorter frequency in between doses compared to previous trials. The aim of the study was to assess the safety, pharmacokinetics, pharmacodynamics and immunogenicity of the new formulation of vedolizumab. Clinical remission and response were assessed by partial Mayo score and faecal calprotectin. The study demonstrated pharmacokinetics which were dose-proportional and vedolizumab maximally saturated $\alpha4\beta7$ 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*[16]. 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 naïve 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

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	66
			2 mg/kg *IV*	32	53
Parikh *et al*[15], 2012	47	II	Placebo	33	22-33
			2 mg/kg *IV*	68-89[1]	> 50[1]
			6 mg/kg *IV*		
			10 mg/kg *IV*		
Feagan *et al*[16], 2012	374	III			
		Induction phase	Placebo	5.4	25.5
			300 mg *IV*	16.9	47.1
		Maintenance phase	Placebo	15.9	23.8
			300 mg *IV* 4 weekly	44.8	56.6
			300 mg *IV* 8 weekly	41.8	52

[1]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],	Placebo	24	15	13	10	7	5	16	5	1	4
2005	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],	Placebo	4		1			4			1	
2012	2 mg/kg *IV*	2		2			4			1	
	6 mg/kg *IV*	1		3			3			0	
	10 mg/kg *IV*	0		2			1			0	
Feagan *et al*[16],	Placebo	58	19	28		10	21	10	25		
2012	300 mg *IV*	97	38	80		33	52	35	56		

IV: Intravenously; UC: Ulcerative colitis.

group, 52% for the vedolizumab 8 weekly group and 20% for the placebo group; $P < 0.001$) compared to placebo. The proportion of patients who were steroid-free at week 52 was also significantly more in the vedolizumab group (45% for the vedolizumab 4 weekly group, 31% for the vedolizumab 8 weekly group, and 14% for the placebo group; $P = 0.012$/$P < 0.0001$). The authors did not find a clear difference in efficacy between the 4 and 8 weekly vedolizumab regimes (Table 1).

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).

CONCLUSION

Vedolizumab is a novel, humanised, monoclonal IgG1-type antibody, developed as a gut selective anti-integrin specifically targeting $\alpha4\beta7$ 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

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

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