Vedolizumab for ulcerative colitis – second or subsequent line

SUMMARY

Vedolizumab is intended to be used as second or subsequent line therapy for the treatment of moderate to severe ulcerative colitis. If licensed, vedolizumab may provide an alternative treatment option for patients resistant or intolerant to conventional therapies, including tumour necrosis factor-alpha (TNF-α) antagonists. Vedolizumab is a humanised IgG1 monoclonal antibody derived from a newly engineered cell line. It is not currently licensed for any other indication.

The prevalence of ulcerative colitis in the UK is estimated to be 243 per 100,000, with an incidence of 10 per 100,000/year. This amounts to approximately 146,000 diagnosed patients in the UK. Ulcerative colitis can present at any age but the incidence has a bimodal age distribution, with peaks between the ages of 15 and 25 years and between 55 and 65 years. Ulcerative colitis is a chronic condition and is associated with significant morbidity. Approximately 25% of people with ulcerative colitis will have one or more episodes of acute severe colitis in their lifetime. Although mortality rates have improved steadily over the past 30 years, acute severe colitis still has a mortality rate of up to 2%3. One hundred and sixty six deaths from ulcerative colitis were registered in England and Wales during 2011.

Treatment of ulcerative colitis depends on the severity of the condition, and is largely focussed on symptom relief rather than cure. Management of ulcerative colitis includes drug therapy (aminosalicylates, corticosteroids, immunosuppressants), attention to nutrition, and surgery for severe or chronic active disease. Vedolizumab has completed phase III clinical trials comparing its effect on clinical response and remission against treatment with placebo. Vedolizumab is also in another phase III trial looking at long term safety. This trial is expected to complete in March 2016.
TARGET GROUP

- Ulcerative colitis: moderate to severe; active; resistant or intolerant to either conventional therapy or tumour necrosis factor-alpha (TNF-α) antagonists - second or subsequent line.

TECHNOLOGY

DESCRIPTION

Vedolizumab (MLN 0002; MLN-002) is a humanised IgG1 monoclonal antibody derived from a newly engineered cell line. It is targeted against the α4β7 integrin, which is expressed in certain white blood cells and is responsible for recruiting these cells to inflamed bowel mucosal tissue. Increased T-cell trafficking is believed to play an important role in the pathogenesis of inflammatory bowel disease. Vedolizumab is administered by intravenous (IV) infusion over 30 minutes at 300mg at weeks 0, 2, 6, and then at 8-week intervals thereafter.

Vedolizumab is also in phase III clinical trials for the treatment of Crohn’s disease.

INNOVATION and/or ADVANTAGES

If licensed, vedolizumab may provide an alternative treatment option for patients resistant or intolerant to conventional therapies, including TNF-α antagonists.

DEVELOPER

Takeda Pharmaceuticals Company Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase III clinical trials.

PATIENT GROUP

BACKGROUND

Ulcerative colitis is the most common type of chronic inflammatory bowel disease (IBD) and causes inflammation and ulcers to develop in the lining of the colon and rectum1. It has a relapsing, remitting pattern and symptoms can vary depending on how much of the colon is affected and the level of inflammation1. The most common symptoms include abdominal cramping, faecal urgency, bloody diarrhoea and weight loss2. The exact cause of ulcerative colitis is unknown but it is thought that genetics and environmental factors are both involved2.

Ulcerative colitis can also be associated with complications outside the gut. Osteoporosis affects 1 in 6 people with ulcerative colitis and develops as a side effect of prolonged use of steroids2. People with ulcerative colitis also have an increased risk of developing bowel cancer especially if the condition is extensive or severe2.
CLINICAL NEED and BURDEN OF DISEASE

The prevalence of ulcerative colitis in the UK is estimated to be 243 per 100,000, with an incidence of 10 per 100,000/year\(^3\). This amounts to approximately 146,000 patients diagnosed in the UK. Ulcerative colitis can present at any age but the incidence has a bimodal age distribution, with peaks between the ages of 15 and 25 years and between 55 and 65 years\(^3\).

Ulcerative colitis is a chronic condition and is associated with significant morbidity. Approximately 55% of patients report a flare-up of symptoms every few months (which may not reflect a true relapse), while 9% have monthly flare-ups and a further 9% experience weekly problems\(^4\). The clinical course of ulcerative colitis is marked by exacerbation and remission, with an estimated 30–60% of people with ulcerative colitis experiencing at least one relapse per year\(^3\). About 80% of these are mild to moderate and about 20% are severe\(^3\).

Approximately 25% of people with ulcerative colitis will have one or more episodes of acute severe colitis in their lifetime\(^3\). Of these, 20% will need a colectomy on their first admission and 40% on their next admission\(^5\). Although mortality rates have improved steadily over the past 30 years, acute severe colitis still has a mortality rate of up to 2%\(^3\). One hundred and sixty six deaths from ulcerative colitis were registered in England and Wales during 2011 (ICD-10 K51)\(^5\).

In 2011-12, there were 38,745 hospital admissions for ulcerative colitis (ICD-10 K51) in England and Wales\(^6\), resulting in 75,265 bed days and 46,652 finished consultant episodes\(^6\).

The population likely to be eligible to receive vedolizumab could not be estimated from available published sources.

RELEVANT GUIDANCE

NICE Guidance

- NICE technology appraisal. Infliximab for acute exacerbations of ulcerative colitis (TA163). December 2008\(^7\).
- NICE technology appraisal. Infliximab for subacute manifestations of ulcerative colitis (TA140). April 2008\(^8\).
- NICE clinical guideline in development. Management of ulcerative colitis. Expected June 2013\(^3\).
- NICE clinical guideline. Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn’s disease or adenomas (CG118). March 2011\(^9\).
- NICE interventional procedure guidance. Leukapheresis for inflammatory bowel disease (IPG126). June 2005\(^10\).
Other Guidance

- European Crohn's and Colitis Organisation consensus on ulcerative colitis. European evidence based consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. 2012\(^1\).  
- European Crohn's and Colitis Organisation consensus on ulcerative colitis. European evidence based consensus on the diagnosis and management of ulcerative colitis: current management. 2012\(^2\).  
- European Crohn's and Colitis Organisation consensus on ulcerative colitis. European evidence based consensus on the diagnosis and management of ulcerative colitis: special situations. 2012\(^3\).  
- British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. 2011\(^4\).

EXISTING COMPARATORS and TREATMENTS

Treatment of ulcerative colitis depends on the severity of the condition. It is largely focussed on symptom relief rather than cure and involves induction of remission in patients with active disease and subsequent maintenance of remission. Management of ulcerative colitis includes drug therapy, attention to nutrition, and surgery for severe or chronic active disease.

The aim of drug treatment is to reduce symptoms, and depending on which part of the colon is affected, oral, topical, suppositories, or liquid or foam enema formulations are available. Treatment options include\(^5\):  
- Aminosalicylates – mild to moderate ulcerative colitis. These include mesalazine, balsalazide sodium and sulphasalazine.  
- Corticosteroids – moderate to severe relapsing ulcerative colitis. These include prednisolone, beclometasone dipropionate and hydrocortisone.  
- Immunosuppressants – if two or more courses of corticosteroids per year are needed. These include methotrexate, azathioprine and mecaptopurine and are increasingly being used to maintain remission in people with longstanding ulcerative colitis.  
- Ciclosporin – severe ulcerative colitis, not responding to first line intravenous corticosteroids.  
- TNF-\(\alpha\) antagonist – moderate to severe ulcerative colitis refractory to corticosteroids and/or immunosuppressive agents. These include infliximab, which is recommended by NICE for treatment of acute exacerbations where ciclosporin is contraindicated or inappropriate.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>GEMINI I, NCT00783718, C13006; vedolizumab vs placebo; phase III.</th>
<th>GEMINI LTS, NCT00790933, C13008, 2008-002784-14; vedolizumab; phase III.</th>
<th>NCT01177228, C13002; vedolizumab vs placebo; phase II.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Millennium Pharmaceuticals Inc.</td>
<td>Millennium Pharmaceuticals Inc.</td>
<td>Millennium Pharmaceuticals Inc.</td>
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<tr>
<td>Status</td>
<td>Complete and published in abstract</td>
<td>Ongoing.</td>
<td>Published.</td>
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<tr>
<td>Source of information</td>
<td>Abstract(^6), trial registry(^7).</td>
<td>Trial registry(^8).</td>
<td>Publication(^9), trial registry(^9).</td>
</tr>
<tr>
<td>Location</td>
<td>USA, Canada and Latin America.</td>
<td>EU, USA and Canada and other countries.</td>
<td>Canada and Russian Federation.</td>
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<tr>
<td>Participants</td>
<td>(n=895); aged 18-80 years; ulcerative colitis; moderate to severe; inadequate response, loss of response, or intolerance to at least one conventional therapy over 5 years; Mayo score (MS) (\geq 6) and endoscopic score (\geq 2) despite prior therapy. Conventional therapies for IBD permitted.</td>
<td>(n=2,200) (planned); aged 18 years and older; ulcerative colitis; moderate to severe; previously received active treatment in NCT00783718 or NCT00619489 that was well tolerated.</td>
<td>(n=47); aged 18-70 years; ulcerative colitis; disease duration at least 2 years; active; partial MS 1-7; conventional therapies for ulcerative colitis permitted.</td>
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<tr>
<td>Schedule</td>
<td>Cohort 1 ((n=374)): Randomised to vedolizumab 300mg IV induction dose at weeks 0 and 2. Cohort 2 ((n=521)): Participants received open label vedolizumab 300mg on weeks 0 and 2. Those with clinical response from both cohorts (MS reduced (\geq 3) points and (\geq 30%) from baseline, and decrease in rectal bleeding (\geq 1) point or absolute rectal bleeding (\leq 1) point) at week 6 were randomised to vedolizumab 300mg IV at 4 or 8 week intervals, or placebo.</td>
<td>Participants receive vedolizumab 300mg IV as a 30 min infusion every 4 weeks.</td>
<td>Participants receive vedolizumab 2mg/kg, 6mg/kg, 10mg/kg IV or placebo on days 1, 15, 29 and 85. Treatment followed by observation period till day 253. After day 253 patients eligible to enrol on 18 month open-label, long-term safety study (NCT00619489).</td>
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<tr>
<td>Follow-up</td>
<td>Active treatment period up to 1 year.</td>
<td>Active treatment period up to 7 years, follow-up 16 weeks.</td>
<td>Active treatment period 85 days, follow-up until day 253.</td>
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<tr>
<td>Primary outcomes</td>
<td>Clinical response at week 6; clinical remission at week 52; mucosal healing; corticosteroid-free remission.</td>
<td>Safety.</td>
<td>Safety and tolerability; assessment for human anti-human antibodies (HAHA); pharmacokinetics; pharmacodynamics.</td>
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<tr>
<td>Secondary outcomes</td>
<td>Clinical response at week 52; clinical remission at week 6.</td>
<td>-</td>
<td>Partial MS; faecal calprotectin.</td>
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<tr>
<td>Key results</td>
<td>Clinical response at week 6: 47.1% vs 25.5 for vedolizumab ((n=225)) and placebo ((n=149)) respectively; difference vs placebo 21.7 [95% confidence interval (CI) 11.6-31.7]. For vedolizumab every 4 weeks ((n=125)), 8 weeks</td>
<td>-</td>
<td>Most common adverse events ((\geq 5%)) in both vedolizumab and placebo were headache, colitis, upper respiratory tract infection and nasopharyngitis.</td>
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</table>
(n=122) and placebo (n=126) respectively; Clinical remission at week 52: 44.8%, difference vs placebo 29.1 [95% CI 17.9-40.4]; 41.8%, difference vs placebo 26.1 [CI 95% 14.9, 37.2] and 15.9%. Mucosal healing at week 52: 56.0%, difference vs placebo 32.0 [95% CI 24.4-48.3]; 51.6%, vs placebo 32.0 [95% CI 20.3-43.8] and 19.8% respectively.

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<tr>
<th>Adverse effects (AEs)</th>
<th>Most common AEs (&gt;10%) in both vedolizumab and placebo were colitis, headache and nasopharyngitis.</th>
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<th>As above.</th>
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<tr>
<td>Expected reporting date</td>
<td>-</td>
<td>Primary completion date reported as Mar 2016.</td>
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**Trial**
NCT00619489, C13004; vedolizumab; phase II.

**Sponsor**
Millennium Pharmaceuticals Inc.

**Status**
Completed but unpublished.

**Source of information**
Trial registry<sup>20</sup>.

**Location**
Canada.

**Design**
Non-randomised.

**Participants**
n=80 (planned): aged 18-75 years; ulcerative colitis; active.

**Schedule**
Participants with no previous exposure to vedolizumab received vedolizumab 6mg/kg IV on days 1, 15, and 43 then every 8 weeks thereafter for up to 78 weeks. Participants with previous exposure to vedolizumab received vedolizumab 2mg/kg IV on days 1, 15, and 43 then every 8 weeks thereafter for up to 78 weeks.

**Follow-up**
Active treatment period up to 78 weeks, follow-up 90 days.

**Primary outcome/s**
Safety; assessment for HAHA.

**Secondary outcome/s**
Safety.

**Key results**
Not reported.

**Adverse effects (AEs)**
Not reported.

**Expected reporting date**
Previously reported as Aug 2010.

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**ESTIMATED COST and IMPACT**

**COST**

The cost of vedolizumab is not yet known. The costs of other selected treatments for ulcerative colitis are as follows<sup>21</sup>: 
**Impact - Speculative**

**Impact on Patients and Carers**

- Reduced mortality/increased length of survival
- Reduced symptoms or disability
- Other: No impact identified

**Impact on Services**

- Increased use of existing services
- Decreased use of existing services
- Re-organisation of existing services
- Need for new services
- Other: None identified

**Impact on Costs**

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs:
- Other reduction in costs:
- Other: uncertain unit cost compared to existing treatments
- None identified

**Other Issues**

- Clinical uncertainty or other research question identified: It will be important to define which patients have good responses, as this may impact on the economic assessment of vedolizumab.
- None identified

**References**


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*a Assumes wastage, and based on average adult bodyweight of 77.9kg.
*b Expert personal communication*


