Vedolizumab for ulcerative colitis and Crohn’s disease

Steve Chaplin BPharm, MSc, Rishi Goel MRCP, Kamal Patel MRCP and Peter Irving MD, FRCP

Vedolizumab (Entyvio) is licensed for the treatment of moderate to active ulcerative colitis and Crohn’s disease. Here we present the clinical data relating to its efficacy and adverse events and comment on its place in therapy.

**KEY POINTS**

- Vedolizumab (Entyvio) is a monoclonal antibody that inhibits T cell migration to the gastrointestinal tract
- It is licensed for the treatment of moderate to severe active ulcerative colitis and Crohn’s disease in adults after failure of conventional therapy or a TNF-alpha inhibitor
- The recommended dose is 300mg by intravenous infusion at weeks 0, 2 and 6 then every eight weeks or, if the response declines, every four weeks
- The basic NHS price of vedolizumab is £2050 per 300mg vial
- In clinical trials, about 10 per cent of patients discontinued treatment due to adverse events with both vedolizumab and placebo; during long-term treatment, serious adverse events were reported by 19 per cent of patients treated with vedolizumab and 13 per cent of those assigned to placebo.

**Vedolizumab**

Vedolizumab (Entyvio) is a humanised monoclonal antibody that binds to alpha beta integrin, a membrane receptor present on a subset of T helper lymphocytes implicated in causing inflammatory bowel disorders. This inhibits their migration into the gastrointestinal tract and adhesion to target cells.

Vedolizumab is licensed for the treatment of adults with moderate to severe active UC or CD who have had an inadequate response with, lost response to, or are intolerant of, either conventional therapy or a TNF-alpha inhibitor. Treatment should be initiated and supervised by an appropriate specialist and patients should be given the package leaflet and an alert card.

The initial dose for UC and CD is 300mg by a 30-minute intravenous infusion at weeks 0, 2 and 6 then every eight weeks. Patients should be observed during and after the infusion for signs and symptoms of hypersensitivity.

Treatment with steroids may be reduced or discontinued. If there is a decrease in response, reducing the dose interval to four weeks may help. If treatment with vedolizumab is interrupted, the dose interval should be four weeks if it is restarted. Intervals of up to one year occurred in clinical trials.

In patients with UC, treatment should be reconsidered if there is no response after 10 weeks. Patients with CD may benefit from an additional dose at week 10. Induction of remission may take up to 14 weeks in patients with CD, after which treatment should be discontinued if there is no response. Vedolizumab may be less effective in inducing remission in patients with CD who are not taking a steroid.

No dose adjustment is recommended for elderly people. There is no experience of treatment in patients with impaired
renal or hepatic function. As with other biological agents, treatment is contraindicated in patients with active severe infection such as tuberculosis or opportunistic infection.

**Clinical trials**

The trials providing the key evidence for vedolizumab are GEMINI I for UC and GEMINI II and III for CD.

The induction phase of GEMINI I included 374 patients randomised double blind to vedolizumab 300mg at weeks 0 and 2 or placebo, and 521 patients who received non-blinded treatment. Treatment with oral steroids or immunosuppressants continued; about 40 per cent had previously been treated with a TNF-alpha inhibitor. The primary endpoint was the clinical response at week 6, defined as a reduction in the Mayo Clinic score (a composite of change in bowel frequency, bleeding, endoscopy and clinician assessment) of ≥3 points and a decrease of ≥30 per cent from the baseline score, with a decrease of ≥1 point on the rectal bleeding subscale or an absolute rectal bleeding score of 0 or 1.

In the double-blind cohort, significantly more patients treated with vedolizumab had a clinical response compared with placebo (47.1 vs 25.5 per cent). This was associated with significantly higher rates of remission (Mayo Clinic score of ≤2 and no subscore >1) (16.9 vs 5.4 per cent) and mucosal healing (40.9 vs 24.8 per cent). Outcomes were similar in the non-blinded cohort.

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Patients with a response at six weeks were randomised to a trial of maintenance treatment with vedolizumab administered every four or eight weeks, or placebo (n=473). The primary endpoint was clinical remission at 52 weeks.

During maintenance therapy, disease activity worsened among patients assigned to placebo but changed little with vedolizumab (see Figure 1). Remission rates were similar for the vedolizumab regimens (41.8 per cent eight-weekly and 44.8 per cent four-weekly) and were significantly greater than in patients switched to placebo (15.9 per cent). This was associated with higher rates of steroid-free remission than with placebo (31.4 and 45.2 vs 13.9 per cent) and mucosal healing (51.6 and 56.0 vs 19.8 per cent). Health-related quality-of-life scores improved significantly more with vedolizumab than with placebo. There were no differences in response rates between patient subgroups, including prior vs no treatment with a TNF-alpha inhibitor.

The design of GEMINI II (n=1115) was similar to that of GEMINI I; about 60 per cent of patients had previously received a TNF-alpha inhibitor. The primary endpoints were clinical remission (Crohn’s Disease Activity Index score of ≤150 points) and CDAI-100 response (≥100-point decrease in the CDAI score) at week 6.

Figure 1. UC symptom score during 52 weeks’ maintenance therapy with vedolizumab

Figure 2. Response rates after 52 weeks’ maintenance therapy with vedolizumab in patients with CD

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Few patients were in remission at week 6 (vedolizumab 14.5 per cent vs placebo 6.8 per cent, p=0.02) and CDAI-100 response rates were not significantly different (31.4 vs 25.7 per cent). Response rates were similar in the non-blinded cohort.

Patients who had a clinical response (≥70-point decrease in CDAI score) with vedolizumab at week 6 (n=461) were randomly assigned to continue blinded treatment with vedolizumab every eight or four weeks, or placebo for up to 52 weeks.

The primary endpoint was clinical remission at 52 weeks. This was similar with the two vedolizumab regimens and both were significantly greater than with placebo (see Figure 2). Response rates were similar across patient subgroups. Vedolizumab improved health-related quality of life at 52 but 30 weeks.

In GEMINI III, 416 patients were randomised to treatment with vedolizumab at weeks 0, 2 and 6 or placebo. The primary end-point was clinical remission at six weeks in the subgroup of patients in whom treatment with a TNF-alpha inhibitor had failed (n=315). There was no significant difference in remission rates between vedolizumab and placebo (15.2 vs 12.1 per cent). By week 10, however, the remission rate had increased with vedolizumab (26.6 per cent) but not with placebo (12.1 per cent). This suggests the onset of effect of vedolizumab in patients with CD is slower than with the TNF-alpha inhibitors.

Adverse effects
In clinical trials the most frequent adverse events other than gastrointestinal symptoms included upper respiratory infections, rash, arthralgia, muscle pain, headache and pyrexia. About 10 per cent of patients discontinued treatment due to adverse events with both vedolizumab and placebo. During 52 weeks of treatment, serious adverse events were reported by 19 per cent of patients treated with vedolizumab and 13 per cent of those assigned to placebo. Four per cent of patients reported mild to moderate infusion-related reactions. There were few serious infections (vedolizumab 0.07 per patient-year, placebo 0.06 per patient-year). Ten per cent of patients had antibodies to vedolizumab 16 weeks after the end of treatment.

References
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Declaration of interests
Steve Chaplin has none to declare.

Steve Chaplin is a pharmacist who specialises in writing on therapeutics.

Place in therapy
Rishi Goel, Kamal Patel and Peter Irving

Vedolizumab is a new gut-selective anti-alpha_beta_integrin monoclonal antibody drug recently approved in the USA and Europe for the treatment of UC and CD. The current therapeutic armamentarium for steroid-dependent or steroid-refractory IBD primarily comprises conventional immunosuppressants, such as thiopurines and TNF-alpha inhibitors. Vedolizumab is an attractive alternative although its place in the therapeutic pathway for CD and UC remains to be determined.

Conventionally, UC is managed in a step-wise fashion from mesalazines, through steroids to immunosuppressants and TNF-alpha inhibitors in those parts of the world where it is funded. The GEMINI I trial demonstrates vedolizumab’s efficacy in achieving remission in patients refractory to conventional therapy as well as to TNF-alpha inhibitors. In the UK, TNF-alpha inhibitors are only recommended by NICE as a rescue therapy for acute severe steroid-refractory UC but not for subsequent maintenance in responders; it is not recommended for chronic active UC, although an ongoing multiple technology assessment may change this. Access to vedolizumab, at least for TNF-alpha inhibitor-naive patients appears to be likely based on initial assessment by NICE. The choice of vedolizumab or TNF-alpha inhibitor for chronic active UC may, therefore be driven not by clinical factors but by the decisions of NICE regarding which patient groups have access to which drugs. Vedolizumab is not currently licensed in acute severe UC.

The results from the GEMINI II and GEMINI III trials indicate that vedolizumab is also effective in moderate to severe CD. Its onset of action is slower than TNF-alpha inhibitors and steroids but it is clearly an effective maintenance agent. To date, there is no study which directly compares vedolizumab with TNF-alpha inhibitors, although given the effectiveness of anti-TNF in CD it seems unlikely that vedolizumab will be used much in the first instance in TNF-alpha inhibitor-naive patients with CD; again, the decisions regarding funding by NICE will clearly influence this.

As with any new drug, clinical experience of the effectiveness of vedolizumab in different patient groups as well as its safety profile, which currently looks very promising, will affect how and when it is used.

References

Declaration of interests
Drs Goel and Patel have none to declare.

Dr Irving has received honoraria from several pharmaceutical companies.

Dr Goel and Dr Patel are gastroenterology clinical research fellows at Guy’s and St Thomas’ Hospitals, London, and Dr Irving is a consultant gastroenterologist at Guy’s and St Thomas’ NHS Foundation Trust and an honorary senior lecturer at King’s College London