National Institute for Health and Care Excellence

Vedolizumab for the for the treatment of adult patients with moderately to severely active Crohn's disease after prior therapy [ID690]

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) for Vedolizumab for the treatment of adult patients with moderately to severely active Crohn's disease after prior therapy [ID690].

Vedolizumab (VDZ) received its European licence for the treatment of adults with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD) who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNFα) antagonist on May 22nd 2014, and the technology has been available for use in the UK since June 2014.

RCN IBD Nurse Network involving nurses caring for people with **Crohn's disease** reviewed the documents on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the questions on which comments were requested is set out overleaf:

i) Has all the relevant evidence been taken into account?

The evidence for Vedolizumab is based on four main clinical trials, GEMINI I, GEMINI II and GEMINI III and GEMINI LTS and new emerging evidence. The primary end points in GEMINI II were hard end points, remission at week 6, but there is evidence that the Chronic Disease Activity Index (CDAI) continues to fall, showing continued response.

Vedolizumab Phase 3 CD Study (GEMINI II): CDAI-100 response at 10 and 14 weeks in patients who failed to show a CDAI-70 response at week 6. The graph below shows results for patients who failed to demonstrate CDAI-70 response at week 6 in GEMINI II and who were retained in the study and received Vedolizumab every four weeks, showing continued response in the CDAI.

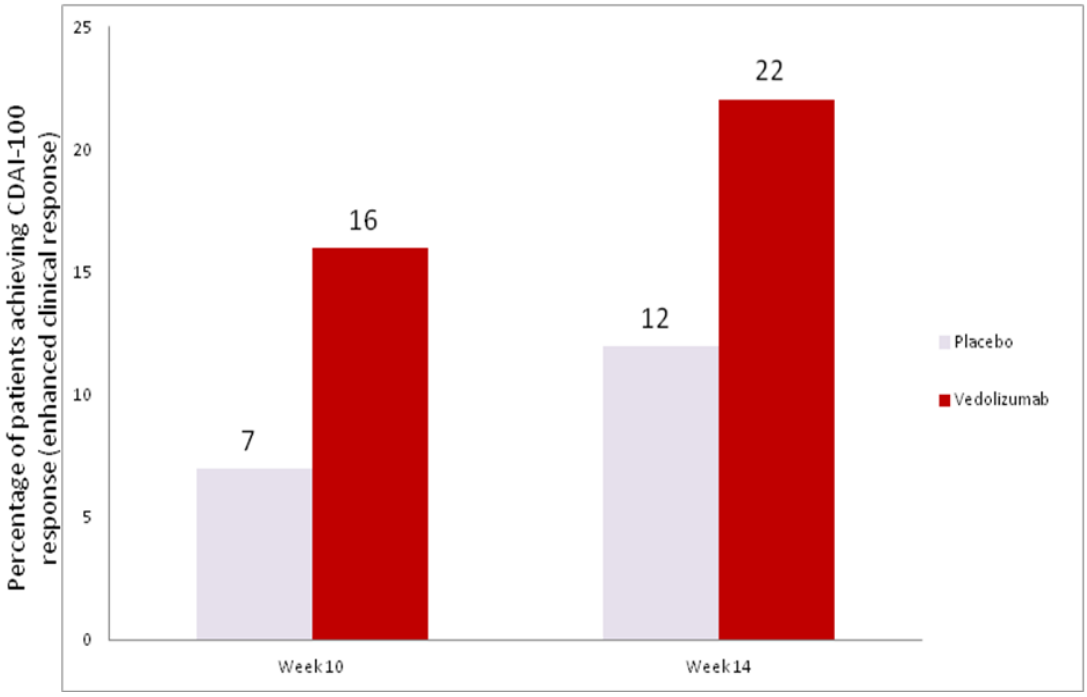

Figure 1: results of patients who failed to to demonstrate CDAI-70 response at week 6 in GEMINI II and who were retained in the study and received Vedolizumab every four weeks

Sandborn WJ et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's disease. NEJM 2013;369:711-721

Although remission was not achieved at 6 weeks in GEMINI II, this appears unrealistic in clinical experience. The ongoing response at 10 and 14 weeks suggest Vedolizumab has a slower effect than anti TNF but patients do continue to respond.

Although the efficacy and safety of VDZ was established in the GEMINI II trial, the proportion of patients with durable clinical remission (a secondary endpoint defined as Crohn's Disease Activity Index [CDAI] score ≤150 points at 11 of 13 [80%] visits from weeks 6-52) was not significantly different between VDZ and placebo (PBO), this study defined alternative post-hoc endpoints for evaluating the effects of VDZ on durable clinical remission. In patients who responded at week 6, and continued to receive Vedolizumab 8 weekly, VDZ led to durable clinical remission as defined by multiple clinically relevant alternative endpoints in patients with CD, **including those with previous TNF antagonist failure.**

	VDZ		**PBO n=153**
	Q8W n=154	**Q4W n=154**	
Durable remission based on 60% (8/13) of visits* ***P* value**	49 (31.8) 0.003	42 (27.3) 0.022	30 (19.6) -
Remission at weeks 6 and 52† ***P* value**	30 (57.7) 0.040	26 (60.5) 0.020	22 (39.3) -
Durable remission based on 10 of 12 visits from weeks 10-52 ***P* value**	37 (24.0) 0.060	33 (21.4) 0.044	24 (15.7) -

Table 1: effects of durable clinical remission

The data on anti TNF experienced patients show improving response at 10 weeks also. In comparison to the initial anti TNF trials, patients included perhaps were more refractory to conventional therapies prior to inclusion in the GEMINI trials. It could presumably be extrapolated that these patients would do less well than patients treated at an early stage of their disease course.

ii) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Vedolizumab α4β7 integrin–MAdCAM-1 interactions help mediate selective lymphocyte trafficking to the gut. This is important in that

there is no systemic immunosuppressive action of this biologic drug, it is gut selective, and, therefore, has potential safety benefits in some groups of patients, such as the elderly where there is concern re opportunistic infections, evidenced in the safety and efficacies (SAEs) of anti TNFs. In this instance it may be used as a 1st line biologic for safety reasons.

In Section 2.36 Table 1 of the ACD document - Table 1- **Summary of network meta-analysis for induction treatment: population who had not had aTNF-alpha inhibitor before.** We do not think the comparison should be made with an induction dose regime of 80/40mg Adalimumab given that the 4th Round National IBD Audit has now recommended an induction dose regime of 160/80/40mg be used for all patients. This increases the cost nominally and may have a better remission rate.

Referencing sections 3.41 and 3.58 in the ACD document please note; the induction dose regime for Adalimumab is now recommended to be 160/80/40mg not 80/40mg

We would also ask that the summaries of the clinical and cost effectiveness of this appraisal be aligned to the clinical pathway followed by patients with Crohn's disease. The preliminary views on resource impact and implications should be in line with established standard clinical practice.

iii) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

There is long experience of anti TNF therapy in the UK which often means that many patients with moderate to severely active Crohn's Disease will have previously been treated with anti TNFs. Those who are immunomodulator refractory and have failed or developed allergy / hypersensitive reactions to anti TNF, or those patients whose disease is not driven by TNF (primary non responders to anti TNF) require another medical option.

As Some Crohn's disease can be difficult to manage, we feel Vedolizumab should be available to patients irrespective of whether they have previously "…responded inadequately to, or lost response to,

either conventional therapy or a TNF-alpha inhibitor, or who cannot tolerate these treatment types" (Section1.1 page 3 ACD Document). This should be considered especially for patients who have already had several previous surgeries on the small bowel making them at risk of short bowel syndrome, which in itself carries a considerable cost both financially to the provider but also in terms of a compromised quality of life to the patient

It is reasonable to offer these groups of carefully selected patients Vedolizumab for a period of up to 14 weeks with the expectation the patient will be appropriately assessed, and therapy only continued if response is adequate. Exit strategy in keeping with those of anti TNF guidance should be adopted with Vedolizumab.

iv) Are there any aspects of the recommendations that need particular consideration to ensure that NICE avoids unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

We have commented on the benefit of this technology to some groups, particularly the elderly and those who have failed anti TNF therapy of whose disease is not driven by TNF. We are not aware of any other specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.