Vedolizumab for treating moderately to severely active Crohn's Disease after prior therapy [ID690]

NICE Appraisal Consultation Document, January 2015

Crohn's and Colitis UK response

Summary

- Crohn's and Colitis UK welcomes the Committee's conclusions that the need for an additional treatment for Crohn's Disease was greatest in people whose treatment options were limited and that, for maintenance therapy, vedolizumab was significantly better than placebo for this sub-group.
- Denying access to this novel treatment option condemns those for whom all other treatment options have failed, who have lost response to anti-TNF therapies, or for whom anti-TNF therapies are contraindicated, to ongoing, highly undesirable steroid treatment, debilitating active disease, potentially repeated surgeries and low quality of life.
- We would therefore urge the Appraisal Committee to consider this specific area of unmet need in more detail, with a view to issuing a positive recommendation to this clearly defined sub-group.

About Crohn's and Colitis UK

Crohn's and Colitis UK is the major UK charity offering information and support to anyone in the UK affected by these conditions, which come under the umbrella description Inflammatory Bowel Disease or IBD. Established in 1979, the charity's services include information and support services, a wide range of accredited information sheets and booklets, and a nationwide network of locally-based groups. The charity, which currently has 28,000 members UK-wide, also raises awareness, campaigns for improved health and public service provision for patients and funds vital research.

Introduction

We welcome the opportunity to comment on the Appraisal Consultation Document and the Committee's conclusion that the need for an additional treatment for Crohn's Disease was greatest in people whose treatment options were limited, such as those whose disease had either failed to respond to, or lost response to TNF-alpha inhibitors, or for whom they were unsuitable. We also welcome the Committee's conclusion that, for maintaining remission up to 52 weeks, vedolizumab was significantly better than placebo in the whole population, in the population who had not had a TNF-alpha inhibitor before **and in the population in whom a TNF-alpha inhibitor had failed**. In our submission, we would like to focus on this specific sub-group who effectively have no further treatment options available to them and for whom vedolizumab may offer highly significant benefit. Our comments are illustrated, throughout, by the views and experiences of people affected by Crohn's Disease.

Crohn's Disease

Crohn's Disease can start at any age but usually appears between the ages of 10 and 40. Recent data suggest that new cases of Crohn's are being diagnosed more often, particularly among teenagers and children.[i]

The symptoms of Crohn's Disease vary for each individual, and range from mild to severe, but typically include abdominal pain, diarrhoea (possibly with mucus, pus or blood) and weight loss, with systemic symptoms of malaise, anorexia or fever more common than for Ulcerative Colitis. Crohn's Disease may cause intestinal obstruction due to strictures, fistulae (often perianal) or abscesses. Some people with Crohn's develop conditions affecting the joints, eyes or skin. Crohn's may also lead to bone thinning, liver problems, blood clots and anaemia. There is an increased risk of bowel cancer for those who have had severe Crohn's Disease affecting all or most of the colon for at least eight to 10 years.

Crohn's Disease can develop anywhere in the gut, including in previously healthy sections of the small intestine or colon. Therefore, there is always a chance that Crohn's will reoccur after an operation, either close to the operation site or in another part of the gut. It may be possible to treat these symptoms with medication, and there is some evidence that the newer biological therapies may be particularly effective in helping to treat postoperative Crohn's. At least 50% of patients may require surgical treatment in the first 10 years and approximately 70%-80% may require surgery within their lifetime. Overall mortality is slightly higher than for the normal population and is greatest in the two years after diagnosis. The clinical course is characterised by exacerbations and remission. Crohn's Disease tends to cause greater disability than Ulcerative Colitis and can have a significant impact on ability to work and quality of life.[ii]

"Crohn's Disease is an incurable and relapsing condition, which blights my life. I am an experienced professional teacher and a trustee of a local charity but my ability to contribute to my community, to wider society, and to pay my taxes, is limited by the impact of the disease. It forces me to work part-time when I would otherwise work full-time and I have regular episodes of sick-leave, roughly every 12-18 months. The latest period of sick-leave will last six weeks, which is a burden on my employers. The impact on my family and social life is huge. I haven't been able to travel abroad for over two years."

We have sought to address the areas identified as being of interest to the Appraisal Committee

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid 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?

1. **Has all of the relevant evidence been taken into account?**

While we welcome many of the Committee's conclusions throughout the Appraisal Consultation Document, we do not believe that all the relevant evidence has been taken into account. Uncertainties have been highlighted in relation to quality of life, cost-effectiveness and clinical effectiveness data which bring the ICERs into question. We urge the Committee to consider further the specific sub-group which has the greatest unmet clinical need – those who have had inadequate response to, or lost response to, treatment with a TNF-alpha inhibitor, or for whom this option is contraindicated. This group has no effective medical treatment options, very low quality of life, fear and anxiety over disease progression, increased potential for surgery, risk of complications and of cancer. Yet there is undisputed evidence that vedolizumab was significantly better than placebo for maintaining remission up to 52 weeks and could therefore be of tremendous value to this group in particular.

"I've had Crohn's since 2007 and I've failed every drug so far. My Crohn's symptoms are inflammation of the eyes, joints, skin, extreme tiredness, lots of bowel motions, weight loss and a zero quality of life."

Drugs tried so far:
6 Mercaptopurin: Flu symptoms
Methotrexate: Hepatitus
Infliximab: Rash
Adalimumab: Rash and return of Crohn's symptoms
Thalidomide: Rash extreme tiredness and return of Crohn's

I was so ill that that my only option was to have an ileostomy The thought of there not being a drug as a means of getting me well enough to have more surgery or even better to avoid surgery is very, very scary. To live with active Crohn's really is no life.

For me, when I have a flare is: liquid formula diet for months not days, not going out to socialise in fear of needing the loo, or having embarrassing accidents, unable to walk far as joints are so painful, going to bed early, too tired to work..zero quality of life."

2. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

Sub-group population
As a proportion of the whole population affected by Crohn's Disease, the numbers of those ultimately failing on anti-TNF agents is in the order of 10% or lower (40%-50% of 20%).

The health care costs of the 10% (or lower) of people with Crohn's failing on all currently available therapy are complex and likely to be underestimated, especially given the complexity and extent of surgery and the repeated requirement for numerous ineffective medical interventions maintaining these individuals in a state of chronic ill-health with continuously high health care utilisation rather than a state of clinical remission.

Additionally, for a proportion of those with moderate to severely active Crohn's Disease, anti-TNF therapy treatment is deemed inadvisable, for example, due to previous demyelination, a personal history of cancer, including haematological malignancy or a strong family history of cancer. For these individuals, options are extremely limited and surgery has unacceptable consequences. Vedolizumab provides a safer alternative of acceptable efficacy according to

the most relevant endpoints. The lower infection risk of vedolizumab can also be of particular benefit to those who are more susceptible to infection.

"Long-term use of aminosalicylates and immunosuppressants gives me only partial remission: the disease is currently absent from my colon (where it has been in the past) but remains severely active in my terminal ileum and caecum. The symptoms of the active disease are very debilitating: explosive diarrhoea, excruciating abdominal pain, severe nausea, projectile vomiting and extreme fatigue. At crisis points I have been treated with steroids and antibiotics, which calm things down for a while but cannot be used long term. I have been on an exclusive liquid diet for the last two months and I will shortly be having surgery: an ileo-caecal resection.

If the Crohn's returns after surgery, my consultant's options are very limited. I am intolerant of Azathioprine and 6-Mercaptopurine. I have been on Methotrexate for four years. I cannot be given Infliximab or Adalimumab because they both carry significant cancer risks for me. I had breast cancer four years ago and later learned that I carry the BRCA2 genetic mutation. My gastroenterologist therefore concludes that using anti-TNF drugs in my case would be too dangerous. At the moment, vedolizumab looks like the only other viable option for my further treatment."

Induction response data
We note the Committee's conclusion that using data from later time points in the trials than six weeks, to assess response to induction treatment, could potentially increase the efficacy estimates for vedolizumab.

An exploratory secondary analysis at 10 weeks confirmed this by showing a statistically significant benefit with vedolizumab and clinical experts explained that in clinical practice a patient was likely to have four doses before a decision was made in relation to continuation of treatment. We would therefore suggest this indicates strongly that the data, already shower higher numerical value than placebo, is underestimating the likely efficacy of induction response.

Additionally, as clinical experts have identified, the most significant results for vedolizumab as therapy for Crohn's Disease are seen in the maintenance phase of GEMINI III. They state that, in clinical practice in Crohn's Disease that is refractory to current maintenance strategies including anti-TNF agents and thiopurines, short term induction of remission can often still be achieved with conventional therapy such as corticosteroids, exclusive enteral nutiriton or antibiotics. However, maintenance of clinical remission in this setting can only be achieved with a novel therapeutic agent. Hence, there is a key and absolutely specific role for vedolizumab. We welcome the Committee's recognition that the selective mechanism of action of vedolizumab might be a particular advantage in some people for whom a TNF-alpha inhibitor is contraindicated.

Quality of life data
We are extremely concerned about the quality of life data, which is of crucial importance and are profoundly disappointed that the Committee was unable to form a conclusion on vedolizumab's effect on quaity of life using the EQ-5D scores because of uncertainty in how these had been reported.

In cases where both conventional and anti-TNF treatment has been unsuccessful, it is likely that individuals will return to treatment which has already been established to be inadequate, in particular, highly undesirable long-term steroid use, surgery of limited value, unproven unconventional therapy or, where available, the uncertain outcome of a clinical trial.

Inadequate control of symptoms including abdominal pain, diarrhoea, rectal bleeding, weight loss, nausea, vomiting and extraintestinal features such as fatigue, arthritis or ocular symptoms will have a profound effect on quality of life.

"I'm an active divorced 60 year old woman now who feels the impact of my symptoms have precluded me from having a regular social life and finding a partner. On the surface I'm a confident outgoing woman but emotionally I'm crying inside and feel completely isolated. I work full time, my employers are aware of my condition and are tolerant. I still travel but with all of my fingers and toes crossed and exercise as much as I can. I gave up my gym membership because my symptoms include constant flatulence which is embarrassing beyond words but not to be beaten, I walk outdoors on my own instead to clock up my 10,000 steps a day. This terrible disease has robbed me of my life in many ways and at times I have felt living on into my even older age is pointless, but my saving grace is that I have three boys whom I want to see marry and be happy. I'd hate for any of them to be diagnosed with this disease but am aware it may be a possibility.

Nobody truly understands what it's like to have Crohn's unless they themselves are patients. My friends can't comprehend why a 'woman like me never remarried'. It's easy, I'm too embarrassed to even contemplate sharing a house with a man. The psychological effects keep me in like a hermit crab at the weekends."

Social function may be substantially impaired in terms of inability to work, attend school, participate in leisure activities, or have intimate relationships. Emotional function may be affected by difficulty in coping with personal lives and feelings of anger, embarrassment, frustration, sadness, and fears of needing surgery or developing cancer.[iii] Additionally, most reports indicate that stress may be involved in triggering relapse.

Patients with active and quiescent IBD often report symptoms of fatigue. Studies have demonstrated that fatigue measurement scores in patients with IBD are comparable to scores reported in cancer patients.[iv]

Surgery can also have an associated profound psychological and social impact, for example, in terms of body image and self-esteem. For those who are facing this at an age when they have just begun to form relationships and do not yet have a family, this can be especially difficult.

Costs of surgery

If surgery is required, full account of the costs needs to be taken into consideration, including:

- Ongoing stoma care and appliances
- Potential fertility treatment for young women after surgery
- Hospital costs for the treatment of infections and other complications
- Psychological support – IBD-related surgery or hospitalisation is associated with a significant risk for depression and anxiety.[v]

There are various different potential types of surgery that might apply for Crohn's Disease. Due to the nature of the condition, and the fact that it can occur anywhere in the gastrointestinal tract, having surgery once does not preclude the potential need to have surgery again.[vi]

Individuals who are receiving treatment with anti-TNF drugs tend to have extensive disease. This means that there are further potentially very costly and highly undesirable consequences of surgery that need to be considered. One is short bowel syndrome and the other, in more extreme cases, is total or partial lifelong dependence on parenteral nutrition. The need for the latter is fortunately rare, but if there is a drug that can be used to prevent the surgery which precipitates it, it should clearly be tried.

"No amount of surgery can remove Crohn's due to its ability to occur anywhere in the GI tract - in fact surgery tends to make matters worse as sections repeatedly get removed till you end up with lifelong symptoms, and expenses involved in treatment, caused by a shortage of bowel. I have been in that situation for 15 years having had two major surgeries and had every drug available, yet still the illness persists. My outlook at present is to be condemned to never working again, having no social life, depression and having a diet limited to less than ten food items. My current intake of 16,376 tablets and 30 injections every year will just roll over year after year after year unless a new drug treatment is successful."

Complications

Both osteoporosis and vitamin D deficiency are common in IBD. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity.[vii] Aggressive disease may also impact on fertility. The risk of colorectal cancer increases with the extent of disease, severity of inflammation, the age of onset and duration of the disease.[viii]

"I was diagnosed 12 years ago, aged 28 with Crohns. Following 3 months on various steroids, I was rushed to hospital to have a right sided hemicolectomy due to complete breakdown of my bowel. On leaving hospital I was prescribed Azathioprine, which made me sick daily for 4 years and I lost several teeth. On stopping this, I then developed a fistula which has resulted in 12 operations over the last 8 years.

Adalimumab worked for approx. 1 year and then my CRP increased to 70 so I was transferred onto infliximab for approximately 5 rounds of infusions. This caused infliximab-induced hepatitis. I am now on methotrexate, which is also not really controlling my Crohn's and results in extreme fatigue for 2 days after taking it, and am having investigations for Crohn's-induced arthritis and oral abscesses. I have continued to work throughout and am the sole earner in my household which is added pressure, so any drug which could induce remission would be welcomed as I do not have any other options."

All the above factors need to be reflected appropriately in the modelling and any subsequent interpretations based on this.

3. **Are the provisional recommendations a sound and suitable basis for guidance to the NHS?**

As detailed above, we do not believe that the provisional recommendations are a sound and suitable basis for guidance to the NHS. We strongly urge that final recommendations address the specific area of high unmet clinical need that has been identified.

"I am the mother of one Crohn's patient and the aunt of another and I know what this disease does to young people, and what the amazing new drugs can achieve. Both of my family members have been on infliximab and on adalimumab: one is on infliximab now. The one on infliximab has changed from someone who was in constant pain and exhausted to someone who is doing brilliantly at Oxford University. Adalimumab had also helped her a great deal but it eventually failed and she ended up in hospital. As soon as she started her infliximab, she began to fly again. She was energised and without pain most of the time. She follows a careful diet and takes great care of herself, but it is the drug which keeps her going. If she develops an intolerance of infliximab - which I understand is likely- what will happen?

My other relative is now unable to take either of the two drugs I have mentioned as he is intolerant of them. But when he could take them, he was able to enjoy his life and contribute to society. Without them, he is in constant pain and mainly confined to bed. There is no alternative for this patient NOW. His doctors are not able to offer him anything else."

4 Are there any aspects of the recommendations that need particular consideration to ensure we avoid 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?

Where an additional medical treatment option, which has been shown to have significant benefit over placebo, is not made available to those who have exhausted all other medical therapies, this may result in surgery that could potentially have been avoided. In this case, there can a significant impact on fertility, primarily for women, so should be considered in terms of potential gender discrimination. This impact is exacerbated given the peak diagnosis period in the teens and twenties and surgery also carries particular issues for those following certain religious practices.[ix]

Summary

- Crohn's and Colitis UK welcomes the Committee's conclusions that the need for an additional treatment for Crohn's Disease was greatest in people whose treatment options were limited and that, for maintenance therapy, vedolizumab was significantly better than placebo for this sub-group.
- Denying access to this novel treatment option condemns those for whom all other treatment options have failed, who have lost response to anti-TNF therapies, or for whom anti-TNF therapies are contraindicated, to ongoing, highly undesirable steroid treatment, debilitating active disease, potentially repeated surgeries and low quality of life.
- We would therefore urge the Appraisal Committee to consider this specific area of unmet need in more detail, with a view to issuing a positive recommendation to this clearly defined sub-group.

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[i] Crohn's Disease, Crohn's and Colitis UK, http://www.crohnsandcolitis.org.uk/Resources/CrohnsAndColitisUK/Documents/Publications/Booklets/Crohns-Disease.pdf

[ii] Mowat C, Cole A, Windsor A et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011; 60:571-607

[iii] Cosnes J, Gowerrousseau C, Seksik P, and Cortot A. Epidemiology and natural history of inflammatory bowel diseases. *Gastroenterology*. 2011; 140(6):1785–1794.

[iv] Minderhoud IM, Oldenburg B, van Dam PS et al. High prevalence of fatigue in inflammatory bowel disease is not related to adrenal corticol insufficiency. Am J Gastroenterol 2003; 98;1088-93.

[v] Ananthakrishnan AN, Gainer VS, Cai T *et al.* Similar risk of depression or anxiety following surgery or hospitalization for Crohn's disease and ulcerative colitis. *Am J Gastroenterol.* 2013 Apr; 108(4):594-601.

[vi] Surgery for Crohn's Disease, Crohn's and Colitis UK, http://www.crohnsandcolitis.org.uk/Resources/CrohnsAndColitisUK/Documents/Publications/Info-Sheets/Surgery-for-Crohns--Disease.pdf

[vii] Mowat C, Cole A, Windsor A et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2011; 60:571-607.

[viii] Cairns S et al. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut. 2010; 59, 666-690.

[ix] Iqbal F, Zaman S, Bowley D and Vaizey C. Quality of life after restorative protocolectomy in Muslim patients. *Gut* 2014; 63:1197-1198.