crohn's and colitis UK
Inform Support Research

Vedolizumab for treating moderately to severely active Ulcerative Colitis

NICE Appraisal Consultation Document, December 2014

Crohn's and Colitis UK response

Summary

- Crohn's and Colitis UK very much welcomes the Appraisal Committee's preliminary recommendation of vedolizumab for treating moderately to severely active Ulcerative Colitis in adults
- However, we are concerned that this will not apply to those who have not had a response to, or have lost response to, treatment with a TNF-alpha inhibitor.
- For this sub-group
    - The drug has been shown to be clinically effective
    - The trial data was not powered to determine statistically significant difference so assumptions are based on considerable uncertainty
    - There is particularly high need, with the only alternatives being extended, highly undesirable steroid treatment, debilitating active disease and surgery
- We would therefore urge the Appraisal Committee to reconsider extending the recommendation for vedolizumab to those who have had inadequate response to, or lost response to, treatment with TNF-alpha inhibitors.

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. We very much welcome the preliminary recommendation that vedolizumab is considered to be an effective use of NHS resources for those who have moderately to severely active Ulcerative Colitis (UC) and for whom conventional treatments have failed.

However, we are concerned that this will not apply to those who have had inadequate response to, or lost response to, treatment with a TNF-alpha inhibitor. If upheld, this decision will leave this specific sub-group of patients with moderate to severe Ulcerative Colitis with 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. Patients in this position will be aware of the option of vedolizumab and their inability to access this may lead to further anxiety and distress.

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?

We welcome the Appraisal Committee's conclusion that the different mechanism of action of vedolizumab to other drug treatment options, through suppression of immune activity only in the gut, represents a step-change in the management of Ulcerative Colitis.

Additionally that, based on the data from GEMINI I, vedolizumab is considered to be clinically effective in the whole population, and in both sub-groups (those who have either had or not had prior use of TNF-alpha inhibitors), compared with conventional therapy. Furthermore, that it appears to be safe and well tolerated by patients.

We also welcome the Committee's conclusion that a drug treatment that improves or brings the disease into remission would have a major effect on quality of life and that surgery should be considered a final treatment option for treating moderately to severely active Ulcerative Colitis.

Given these conclusions, **we do not believe that the exclusion of those who have previously had treatment with TNF-alpha inhibitors from vedolizumab as a potential treatment option has been adequately considered**.

a) Clinical and cost effectiveness for this sub-group

Maintenance trial data shows that, in the population who had not had a TNF-alpha inhibitor before, 46% of people having 8-weekly vedolizumab and 19% of people having placebo had clinical remission (percentage difference 26.8, 95% CI 12.4 to 41.2). In the population in whom treatment with a TNF-alpha inhibitor had failed, 37% of people having 8-weekly vedolizumab and 5.3% of people having placebo had remission (percentage difference 31.9, 95% CI 10.3 to 51.4).

It was speculated that the lower percentages in the second sub-group may be due to this group being more difficult to treat. They may have longer disease duration since diagnosis and potential for increased presence of symptoms. However, there is no scientific rationale that they will be more likely to fail vedolizumab than those who are anti-TNF naive. Indeed, the percentage difference between those having vedolizumab and those having placebo is greater than for the anti-TNF naive group. This indicates the significant value of the treatment to those who may have tried anti-TNFs before vedolizumab was available, and have no remaining medical options.

The Appraisal Committee recognised that GEMINI I was not powered to determine whether there was a statistically significant difference in the relative effectiveness of vedolizumab between the two sub-groups. As the Committee considered that there was considerable uncertainty about the extent to which the costs and benefits associated with vedolizumab would be expected to differ between the two sub-groups, it is important to take additional factors into account relating to this sub-group. This analysis should include obtaining a clearer understanding of the population involved and their level of need, as well as the implications of restricting access to this treatment.

b) Population and level of need

Those with moderately to severely active Ulcerative Colitis who have had treatment with TNF-alpha inhibitors fall into three potential groups.

i) Those who have received an induction course of three doses of infliximab for the treatment of acute exacerbations of severely active Ulcerative Colitis in patients in whom ciclosporin is contraindicated or clinically inappropriate. NICE guidance TA163 recommends infliximab as an option for the treatment of acute exacerbations of severely active Ulcerative Colitis in patients in whom ciclosporin is contraindicated or clinically inappropriate. This relates to an induction course of three doses of infliximab.

ii) Additionally, a small proportion of people with moderately to severely active Ulcerative Colitis have been prescribed regular treatment with TNF-alpha inhibitors, with the aim of avoiding hospitalisation and surgery. With NICE guidance shortly to be published [GID-TA357], infliximab, adalimumab and golimumab will be available as treatment options for moderate to severe Ulcerative Colitis. Patients and clinicians may wish to choose one of these over vedolizumab, for a variety of reasons including, for example, the ability to self-inject adalimumab, so avoiding regular visits to hospital for infusions, or the fact that the long-term use of infliximab is better understood, compared to vedolizumab, due to its role in clinical practice over more than a decade.

Within these groups, there will be those who:

- Have responded positively to the induction doses of TNF-alpha inhibitor, but may subsequently require retreatment
- Have needed longer-term treatment and responded, but who may ultimately lose response, for example, due to the development of antibodies or allergens
- Have not found conventional therapy or TNF-alpha inhibitors to be effective in managing their condition

For these specific groups, should they be denied access to vedolizumab, there are significant implications for quality of life, potential emergency surgery, hospitalisation and complications, including cancer risk.

c) Implications of restricting access

i. Quality of life

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. 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.

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.[i]

Anxiety and depressive illness is higher in people with IBD[ii], with mood disorders at least in part a consequence of the IBD itself[iii] and its medical treatment (e.g. corticosteroid therapy), surgery, including specifically colectomy and stoma formation. 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]

ii. Surgery

With no other satisfactory options available to them, people will be forced to consider surgery, potentially as an emergency. However, it has been established that patients and clinicians would wish to avoid this unless all drug treatment options had failed. As clinical experts outlined, ileo-anal pouch surgery for ulcerative colitis usually requires two to three major operations and some people may need further operations if they have complications from surgery. Complications are documented to occur in around one third of inpatients with Ulcerative Colitis (National Clinical Audit of Inpatient Care for Adults)[v] and include:

- Fecundity (fertility) in women is reduced by 40%-50%
- Nocturnal seepage (of faeces) is 8% after one year, rising to 15.4% at 20 years (other studies have suggested this may be as high as 32%)
- Median frequency of defecation is five per 24 hours, once at night (some studies have put this higher)
- Up to 50% of patients who undergo ileal pouch surgery for ulcerative colitis suffer from pouchitis (inflammation of an ileo-anal pouch) – reported risk factors include younger age at colectomy and extensive Ulcerative Colitis
- Increased risk of thromboembolic events

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.

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

- Potential second or third operations (e.g. restorative protocolectomy with ileoanal pouch is usually undertaken as two operations; colectomy with ileostomy may be followed by pouch surgery at a later date or permanent ileostomy)
- Ongoing stoma care and appliances (estimated at £5,000 per year by Clinical Commissioning Groups for up to 50 years for younger patients)
- 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.[vi]

iii. 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]

The risk of colorectal cancer increases with the extent of disease, severity of inflammation, the age of onset and duration of the disease.[viii]

All the above factors need to be reflected appropriately in the modelling and any subsequent interpretation of these.

The devastating impact of chronic active Ulcerative Colitis is illustrated below:

"I have pan-ulcerative colitis which, since my diagnosis in June 2000, has been extremely difficult to control. I was steroid dependent and all conventional UC therapies failed – including anti TNF (Infliximab). Long term steroid use resulted in osteoporosis at age 28. I was house bound for many years due to UC and was unable to work. Quality of life was zero."

By striking contrast, the value of vedolizumab to the same individual is described here.

"I began this treatment in January 2009 and it has given me my life back. I have been in an uninterrupted remission for the entire past 6 years. I am no longer house bound. I am able to go to work. It has taken away the crippling pain and allowed me to sleep at night. It has stopped me bleeding every time I have a bowel motion. I no longer have to ensure I am always near a toilet due to diarrhoea, which is a defining feature of UC. I can travel and see friends and family, something I could never do before I had this treatment. My mental health was suffering from years of flaring from UC and this has been completely resolved since I went into remission on this treatment. I am no longer reliant on harmful steroids and this alone has been a benefit that is completely immeasurable. In the past I have spent weeks in hospital wards with serious flare-ups of UC. This has never happened in the six years that I have been on this treatment."

It is important to note that vedolizumab would not be available to this person or to others in the same position if the provisional recommendations are upheld as they currently stand.

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

Overall, we believe that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. In particular, we welcome the Appraisal Committee's recognition of the debilitating nature of the condition, the potential value of vedolizumab as a step-change in its management and their understanding that surgery should not be considered as an acceptable alternative to medical treatment, except where the individual patient has made this decision.

However, as outlined above, we have serious concerns about excluding access to vedolizumab to those who have previously had exposure to anti-TNF therapy, and for whom this has been shown to be clinically effective on the basis of:

- The data available, which is acknowledged to be insufficiently-powered to determine statistically significant differences between sub-groups
- The lack of a clear scientific rationale for why this sub-group may be considered less likely to respond to vedolizumab
- The level of need in this group, for whom no other medical treatment options are available and the implications of denying access

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

If the option of treatment with vedolizumab is extended for this sub-group, we would consider the provisional recommendations are a sound and suitable basis for guidance to the NHS. As currently set out, we do not believe they fully meet this objective.

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?

While not a defined comparator, by restricting access to vedolizumab to those who have chronic active Ulcerative Colitis and have no remaining medical treatment options, it is highly possible that surgery may be required which might otherwise have potentially been avoided. As described in 1c)ii), pouch surgery can affect fertility and, as such, discriminates against young people who may not yet have a family and who are in the peak diagnosis group for this condition. Active disease which is not responding to conventional treatment is likely to force a need for surgery, so this cannot be dismissed. For certain religious groups, such as Muslims, the impact of active disease and the effects of pouch surgery may interfere with religious practices and cause particular distress, which would be alleviated by the option of medical therapy.[ix]

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For further information, please contact

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