



Royal College
of Physicians

Setting higher medical standards

Telephone [REDACTED]
Textphone [REDACTED]
Facsimile [REDACTED]

[REDACTED]
Technology Appraisals Project Manager
National Institute for Health and Clinical Excellence
[REDACTED]

[REDACTED]
From The Registrar
[REDACTED]

Telephone extension [REDACTED]
Direct facsimile [REDACTED]

7th October 2008

Dear [REDACTED]

Re: Appraisal Consultation Document (ACD), Infliximab (review) and adalimumab for the treatment of Crohn's disease (including a review of technology appraisal guidance 40)

The Royal College of Physicians is grateful for the opportunity to respond to the above ACD. We would like to make the following comments:

There are a number of major concerns about the appraisal consultation and draft guidance which centres on the following:

1. Validity of the health economic modelling
2. Clinical problem of allowing patients to suffer worsening symptoms to justify re-treatment with a therapy which could maintain remission either completely or partially
3. Lack of recognition of clinical response without conventional remission as a clinically meaningful end point
4. Benefit of maintenance therapy particularly in a relatively small group of patients in whom there are very limited treatment options

Recognition should clearly be made that the appraisal committee has tried to be fair and allow clinical freedom in some areas.

Validity of Health Economic model

There is clear general agreement that there is a lack of meaningful data on clinical course of disease with conventional medical therapy and that the economic models we have available are far from ideal. Much of the data are based on a single study by Silverstein et al 1999. There are several recognised flaws in this study. Firstly the cohort of CD patients is small (174), the clinical data were retrospective and from case notes and are therefore likely to underestimate significantly the number of relapses per patient and also lack quality of life data. Furthermore, the number of patients with severe drug non-responsive disease (i.e. the group that might require anti-TNF- α) is small. Likewise patients with fistulas are not specifically mentioned and there is evidence that they have nearly doubled health care costs compared to CD patients without fistulas (Cohen et al Inflamm Bowel Dis 2008). The major difference was in the rate of hospitalisation and surgery.

The problems with the models used are as follows:

1. Over-estimates the effect of surgery, in particular re-do surgery in CD. There is very good data showing that subsequent resectional surgery has a markedly reduced efficacy.



2. Does not recognise that there are patients in whom surgery is never an option (e.g. pan-enteric disease) or an extremely risky option (malnourished, low albumin, multiple previous operations or multiple co-morbidities). In these patients anti-TNF- α is the only or the best option for induction of remission and maintenance.
3. Underestimates the relapse rate in severe CD.
4. Does not recognise the clinical benefit of reduction in symptoms but not remission. In fact remission (CDAI<150) can be very difficult to achieve particularly in patients who have had previous surgery in whom diarrhoea is common.
5. Underestimation of the cost of standard care.

Clearly this is a difficult area in which to achieve a united path forward. However we feel that it requires further work to improve the economic modelling. In particular to include a gastroenterologist with a background in health economics and experience in managing IBD, of whom there are some we could recommend.

Problem with allowing patients to relapse to justify further therapy

For us this is the most troubling aspect of the decision not to allow scheduled maintenance anti-TNF- α . It is unfair and unnecessary to provide care for a patient that deliberately needs this treatment to suffer recurrent severe symptoms to justify further treatment which has previously been successful. For example a patient with severe disease (on immunosuppression and steroids) has induction of remission with 2 doses of anti-TNF- α ; eight weeks later she develops recurrent diarrhoea and pain however her CDAI is only 240. Her symptoms remain like this for 4 weeks and on the 5th week worsen further and CDAI is 300 but the clinician decides to give further anti-TNF- α which is given one week later. This approach has allowed her to have 6 weeks of symptoms with the concomitant effects on her and family's quality of life. Furthermore this pattern could be repeated with the next induction of remission. This could happen if PCTs take a strict interpretation of the guidance particularly the word 'normally' CDAI above 300'. There are clear benefits to maintenance therapy:

- anti-TNF- α therapy often has a dramatic effect in improving (or gaining complete remission) CD and can maintain this effect with maintenance therapy.
- patients much prefer maintenance therapy because of better disease control, convenience and reassurance. Relapse, or fear of relapse, has a major effect on the quality of life in people with CD.
- anti-TNF- α may be the only therapy option. Many patients who have relapsed and had previous resectional surgery do not want further surgery (which is likely to have less effect than their initial surgery in maintaining remission). Some people, understandably, do not want to have temporary or permanent stoma and in some cases surgery can be avoided with maintenance therapy with anti-TNF- α .
- scheduled regimes can be very flexible and allow patients choice when they have their infusions e.g in the early evening after work. With 'prn' infusions choice is limited as patients usually (and justifiably) want the anti-TNF- α as soon as possible.
- what will happen to patients already on maintenance therapy? It is difficult to estimate the % of the total are on maintenance therapy at present. From our institution I would estimate more than 50%.
- a reasonable approach might be to continue maintenance therapy for 6 months in those with a significant positive effect to induction therapy (remission or fall in CDAI of 70 points). Thereafter in those that maintain response discuss a trial of drug withdrawal. Those that relapse rapidly would require regular maintenance whilst those with prolonged response could have further induction therapy on a as required basis.
- the UK IBD community has been remarkably cautious and restrained in the use of anti-TNF- α therapy. In the National IBD Audit, 5% of CD patients admitted with CD (the majority of whom had

severe disease) had anti-TNF- α during admission. Maintenance therapy is the international norm and recommended as best practice

Benefit of maintenance therapy particularly in a relatively small group of patients in whom there are very limited treatment options

It is not recognised in the appraisal that there are certain groups of patients in whom there are no, or very limited, treatment options. These include patients with pan-enteric disease (more common in children and young adults) and those with multiple resections in whom further surgery would result in short bowel syndrome. Another larger group is those who have had 2 or more resections in whom further surgery would entail a high degree of risk with limited benefit. Patients who have multiple operations are also understandably reluctant to have further resections because of the adverse effects of surgery- time off work, pain, risk of temporary or permanent stoma.

Specific points on appraisal document

The numbering refers to consultation document (for clarity we have copied the relevant paragraph in bold).

1.2 For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally but not exclusively corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more.

This is a new definition of severe Crohn's disease and not one that has been validated. It has not been a stratification in any clinical trial of which we are aware nor analysed as a secondary end point. It is likely that the higher the CDAI the *less* likely it is that remission (CDAI <150) would be achieved.

A CDAI of >300 represents a heterogeneous group of patients. Some may have new disease, are treatment naive and respond promptly to conventional therapy (antibiotics, enteral nutrition, corticosteroids), others may be on steroids or other therapy and still have very active disease, whilst another group may have complications of CD, in particular intra-abdominal or other abscess. Anti-TNF- α would be contraindicated in the latter group.

Those patients with a CDAI of 220-300 are also a heterogeneous group. A patient can have disease significantly impairing quality of life and on maximum conventional therapy and therefore anti-TNF- α is an excellent treatment option.

It is not clear why this cut off has been chosen and the evidence-base for this decision.

The inclusion of weight loss as a factor is also not evidence-based and again it is not clear the basis for this decision. Increasingly people with CD in line with the rest of the population have increased BMI and weight loss is less of a feature. It needs to be remembered that the CDAI is based on standardised weights from 1976. This skews the CDAI in those who are overweight and means CDAI are lower with equivalent disease activity if no weight loss. A recent paper (Hass et al Clin Gastroenterol Hepatol. 2006) shows overweight patients with CD probably have a more complicated course of disease and require surgery earlier in their disease course.

1.6 Infliximab and adalimumab are not recommended for regular maintenance treatment (treatment given continually at regular intervals) to prevent relapse of Crohn's disease.

See comments made earlier.

2.8 Between 50 and 80% of people with Crohn's disease will require surgery at some stage. The main reasons for surgery are strictures causing obstructive symptoms, lack of response to medical therapy, and complications such as fistulae and perianal disease. Maintenance therapy after surgical resection has been found to prolong remission of the disease, although symptoms recur on average in about 35% of patients within 5 years and in about 73% of patients within 20 years.

The evidence that maintenance therapy prolongs surgical remission is weak. Regular 5-ASA at high doses may increase the time in remission in about 7% of patients. Many people are unable to remain adherent to the dosing regimen.

4.1.5 The study of infliximab induction therapy in fistulising disease compared infliximab at a dose of 5 mg/kg or 10 mg/kg with placebo. Follow up extended to at least week 18. The primary outcome was a 50% reduction in the number of draining fistulae; the rate difference between infliximab 5-mg/kg and placebo groups was 0.42 (95% CI 0.19 to 0.64). The secondary outcome was complete absence of fistulae; the rate difference between the infliximab 5-mg/kg and placebo groups was 0.42 (95% CI 0.21 to 0.63). Infliximab groups had statistically significant improvements in CDAI and PCDAI scores at week 2.

A slight error in terminology here as it is the perianal disease activity index (PDAI) rather than the Paediatric Crohn's disease Activity index (PCDAI). The same typo is in section 4.1.11.

4.2 Cost Effectiveness

See comments made previously.

Conclusions

There are major concerns about the appraisal document, although it is appreciated that the committee has tried to be flexible and receptive to individual clinical judgement. The main concerns are over the cost effectiveness model and its lack of validity. This erroneously inflates the cost per QALY. The other major concern is the unnecessary, unfair and illogical hardship that lack of maintenance with anti-TNF- α therapy will cause for many patients with severe Crohn's disease who require such therapy. We also have concerns that this guidance will be difficult to implement at a local level with regards to how responsive and flexible an organisation will be to deal on a week to week basis to patients having 'as required' anti-TNF- α . It is a genuine worry that the guidance as it stands would lead to widely different interpretation and thus to inequality of treatment of CD in the UK at a time when we are striving to provide good quality care throughout the UK. We would like to propose the following:

- A reassessment of the health economic model. This should involve gastroenterologists with a track record in health economics methodology.
- Survey of current practice and number of patients on maintenance therapy in the UK.
- The UK IBD community to continue and expand the research work required (outlined in section 6).
- Collaborative working between NICE and the interested parties (NACC, BSG, ACP, RCP) to formulate fair and reasonable guidance.

This response was coordinated by: Dr Keith Leiper, Consultant Gastroenterologist, Royal Liverpool University Hospital, on behalf of the Royal College of Physicians, London.

Relevant Clinical Experience: Large IBD practice, personal experience in prescribing and managing patients on infliximab and adalimumab, clinical lead in National IBD Audit, clinical trial experience with infliximab and adalimumab.

Conflict of interest: Dr Leiper has no current conflict of interest and am not on any clinical advisory boards. He has been a member of an advisory board on one occasion in 2005 for Schering Plough. He is a principal investigator in a multi-national clinical trial of adalimumab and previously been involved in multi-national clinical trials of infliximab in Crohn's disease and ulcerative colitis.

I trust these comments will be of use.

Yours sincerely

Dr [REDACTED]
Registrar