

Abbott's response to the Appraisal Consultation Document 3 of adalimumab and infliximab for the treatment of Crohn's disease

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD3) prepared by the Committee for the appraisal of adalimumab and infliximab for the treatment of Crohn's disease. Abbott's comments are set out under section headings containing the questions NICE asks consultees to comment on for the ACD.

Executive Summary

Abbott considers that the recommendation that all patients should stop therapy at 1 year regardless of their clinical status is not an appropriate recommendation for the treatment of severe patients with Crohn's disease. The previous recommendation in ACD2 allowing the flexibility of clinicians and patients to discuss the need to continue therapy is pragmatic and appropriate as this would allow patients at high risk of relapse and hospitalisation or surgery to continue therapy based on a full consideration of the risks and benefits of treatment continuation. It should be noted that the Bodger *et al.* modelling study indicated that maintenance therapy with adalimumab and infliximab would reach a cost per QALY of £30,000 at 34 years continuous therapy and 4 years respectively. Despite being based on the Olmsted County cohort of mixed severity patients discussed extensively in previous correspondence, the results of this analysis indicate that maintenance therapy beyond 1 year would be cost effective. Therefore, Abbott considers that on cost effectiveness grounds restricting treatment to 1 year of maintenance therapy is unwarranted and overly restrictive.

Abbott considers it unlikely that treatment of CD patients using infliximab would be less costly than treating patients with adalimumab, and that on average infliximab is likely to be significantly more costly. Based on an indirect comparison of the largest RCTs of maintenance for adalimumab and infliximab, the evidence is not supportive of a requirement for greater dose escalation for patients with adalimumab.

The ACD3 currently states: "*Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active non-fistulising Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*" This recommendation is not in line with the adalimumab licence or the available evidence. The licence for adalimumab does not specify a sub-group of severe patients with non-fistulising disease; it instead encompasses all patients with severe disease, a proportion of whom will have fistulising disease. Therefore, Abbott requests that when the Committee prepares the Final Appraisal Determination, that the wording in paragraph 1.1 is amended to: "*Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe, active Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*"

1. Do you consider that all of the relevant evidence has been taken into account?

As previously indicated in comments on the ACD2 for this appraisal, Abbott considers it unlikely that treatment of CD patients using infliximab would be less costly than treating patients with adalimumab, and that on average infliximab is likely to be significantly more costly¹.

Consultation received by the Institute on ACD2 highlighted that dose escalation with adalimumab may mean that infliximab may be the less costly treatment option. Section 1.1 below sets out supportive evidence not previously seen by the Committee that adalimumab is not associated with greater rates of dose escalation than infliximab and that therefore adalimumab is likely to be significantly less costly than infliximab.

It also appears that there is a concern regarding the long term effectiveness and safety of anti-TNF agents. Section 1.2 highlights the available data for periods of treatment greater than one year with adalimumab.

1.1 Impact of dose escalation on comparative cost of adalimumab and infliximab

As highlighted in the ACD3 document, adalimumab is a lower cost treatment option than infliximab at the recommended maintenance dose of 40mg every other week compared to 5mg/kg for infliximab. However, comments made in consultation have questioned whether the cost difference would be reduced by a greater requirement to dose escalate in patients receiving adalimumab. There are a number of important points that Abbott wishes to highlight in relation to this issue.

It is unclear why the dose escalation rates available from the CHARM study of maintenance therapy have not been considered as this is the largest, randomised maintenance trial of adalimumab in Crohn's Disease (n=854) as is the most appropriate for comparison with the ACCENT I maintenance study for infliximab. In CHARM, 27% of patients escalated to adalimumab weekly dosing by week 56 compared to 30% of infliximab patients in the ACCENT RCT by week 54. Therefore, based on an indirect comparison of the largest RCTs of maintenance for adalimumab and infliximab, the evidence is not supportive of a requirement for greater dose escalation for patients with adalimumab.

Two other aspects of the CHARM data are also worthy of further consideration when considering the likely dose escalation of the two anti-TNFs. Firstly, 49.6% of patients receiving adalimumab in the CHARM trial had been previously treated with infliximab². Given the refractory nature of this segment of the patient population in CHARM compared to ACCENT, it would be expected that a greater proportion of adalimumab patients would dose escalate in CHARM compared to infliximab patients in ACCENT, which was not the case. Secondly, available data indicate that some patients in CHARM having a disease flare were able to regain disease control without escalating to weekly therapy.

It is important to consider additional evidence on dose escalation rates with adalimumab and infliximab. A survey of use of adalimumab in 61 patients across centres in England and Ireland indicated that 16% of patients required dose escalation with adalimumab³. An observational study has considered dose escalation rates with adalimumab and infliximab in privately insured CD patients in the US⁴. Importantly, this analysis was restricted to anti-TNF naïve patients for both drugs to allow a fair comparison of dose escalation rates. The study sample included 701 patients initiated on adalimumab and 873 patients initiated on infliximab. Based on 1-year follow-up using a Kaplan-Meier analysis, patients treated with adalimumab had a significantly lower rate of dosage escalation compared with patients treated with infliximab (24.3% vs. 55.1%; p<0.01). Cox regression analysis also demonstrated that adalimumab was associated with a significantly smaller risk of dose escalation (HR=0.57;p<0.01) compared with infliximab. One of the key

strengths of this analysis is that it compares dose escalation rates in similar patient populations over a similar length of follow-up. However, the authors provide the caveat that payer restriction might be a reason for lesser dosage adjustment with adalimumab, because the opportunity to adjust is specified only in the label for infliximab in the US.

In conclusion, taking into consideration the similar dose escalation rates observed in the CHARM and ACCENT studies despite the inclusion of a potentially more refractory disease population for patients receiving adalimumab, as well as the greater dose escalation rates observed in US clinical practice for infliximab, Abbott considers that the available evidence indicates that adalimumab is likely to be associated with lower rates of dose escalation than infliximab.

1.2 Data on use of adalimumab for greater than 1 year in CD

During the 5th Appraisal Committee meeting on 22 October 2009, members of the Committee raised concerns around the risk: benefit profile of the anti-TNFs, particularly around the long-term safety and efficacy of these drugs. In Abbott's response to the WMHTAC in July 2008, Abbott provided evidence showing sustained efficacy of adalimumab for up to 2 years, as well as 2,374 patient years worth of safety data.

Since these data were outlined, longer-term data have become available which show that patients with moderately to severely active Crohn's disease treated with adalimumab have sustained clinical remission for up to three years. Panaccione *et al* presented data from the ADHERE study (Additional Long-Term Dosing With HUMIRA to Evaluate Sustained Remission and Efficacy in CD), at the 2009 ECCO meeting⁵. ADHERE is the long-term extension study to the one year randomised study CHARM. A total of 467 patients enrolled in the open-label extension trial. Remission results for the 145 patients initially randomised to adalimumab who were in remission (CDAI < 150) at the end of CHARM are shown in Table 1.2.1. As can be seen from the table, 83% (120 of 145) of patients were in remission 3 years after enrolment in CHARM (Week 108 of the open-label extension) in the post-hoc LOCF analysis.

Table 1.2.1: Remission rates for adalimumab treated patients at 3 years of therapy in those patients in remission at the end of the randomised CHARM trial

Week of OL extension trial following CHARM	Remission, Non Responder Imputation N=145 n (%)	Remission, LOCF N=145 n (%)
Week 24 ADHERE	113 (78)	118 (81)
Week 48 ADHERE	111 (77)	123 (85)
Week 60 ADHERE*	105 (72)	122 (84)
Week 108 ADHERE*	93 (64)	120 (83)

* 2 years and 3 years from CHARM baseline, respectively

Furthermore, no new safety signals were identified through the three years of adalimumab exposure in patients with Crohn's disease. In a recent review of the safety of adalimumab in the global clinical trials of Crohn's Disease, over 50% (1652/3160) of the patients had been followed for more than one year⁶. The authors concluded that the rate of adverse events observed in Crohn's disease patients were comparable to other approved indications for adalimumab spanning greater than 10 years of clinical observation.

Another concern raised was the perception that concurrent steroids were a requirement for continued adalimumab treatment which is not the case. Indeed, there are also 3 year data showing continued steroid free remission in patients with moderate to severely active Crohn's disease⁷. This *post-hoc* sub-analysis evaluated data from the intention-to-treat population of patients receiving steroids at baseline who were randomised to adalimumab and assessed for steroid-free remission at 3 years from CHARM baseline. Remission rates were calculated using non-responder imputation (NRI) analysis. Results showed that at 2 and 3 years after CHARM

baseline, respectively, 27% and 28% of these patients were in steroid-free remission (Table 1.2.2).

Table 1.2.2: Steroid-free remission rates for adalimumab treated patients following up to 3 years of therapy in those patients receiving steroids at CHARM baseline randomised to adalimumab (NRI)

Week of OL extension trial following CHARM	Adalimumab N=206 n (%)
End of CHARM	44 (21)
Week 24 ADHERE	52 (25)
Week 48 ADHERE	63 (31)
Week 60 ADHERE*	55 (27)
Week 108 ADHERE*	57 (28)

* 2 years and 3 years from CHARM baseline, respectively

Therefore, there is a considerable evidence base (newly documented in this response and previously supplied to the Institute) that demonstrates the safety and efficacy of adalimumab beyond one year of treatment in patients with Crohn's disease that should help alleviate the Committee's concerns on long term safety and efficacy.

2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence and that the preliminary views on the resource impact and implications for the NHS are appropriate?

In paragraph 1.1 of the ACD3, the recommendations around treatment duration have changed from the wording that the Committee stated in the ACD2. In the ACD2, based on the available evidence, NICE recommended that *"maintenance treatment with adalimumab or infliximab (as indicated in 1.1 or 1.2) should continue until treatment failure (which includes the need for surgery), or until 12 months after the start of treatment, whichever is shorter. The person's disease should then be reassessed. Maintenance treatment should only then be continued if there is clear evidence of ongoing active disease, as determined by clinical symptoms and investigation, including endoscopy if necessary. People whose disease relapses after maintenance treatment is stopped should have the option to resume treatment for a further 12 months. They should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate."*

In the ACD3 the wording is as follows: *"Treatment with infliximab or adalimumab may be a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People whose disease relapses after the planned course of infliximab or adalimumab is stopped should have the option to resume treatment for a further 12 months."*

However, the summaries of clinical- and cost-effectiveness providing the evidence base for these recommendations have not changed in the move from the ACD2 to ACD3. Therefore, Abbott does not understand why this change has been made, particularly as comments received from consultees and commentators, especially patients and clinicians, fully supported the recommendations in the ACD2 around treatment duration. This may be important given that when the discussions around treatment duration were raised again at the 5th Committee Meeting, there were no clinicians or patient experts in attendance to give their expert opinion, as had been sought previously for this issue at the 4th Committee Meeting in August 2009.

Sections 4.1 in both ACD documents do not differ in their content. This section summarises data from the induction trials of adalimumab and infliximab, and also data from either 52 weeks (infliximab) or 56 weeks (adalimumab) maintenance treatment, all of which were provided in the original submission. Abbott would like to draw attention to the fact that considerable additional

evidence has been submitted since the original evidence submission on 30 July 2007. As there was a delay to this appraisal, a significant amount of time elapsed before the release of the first and subsequent ACDs, in which a substantial amount of additional data from open-label extension trials have been presented and published. These data include information on fistula healing, mucosal healing, reduction in the risk of all-cause hospitalisation, sustained long-term remission data (up to 3 years), and long-term steroid free remission (up to 3 years) (see Abbott response to WMHTAC July 2008 and Section 1.2 above).

Therefore, given the fact that the evidence base supporting the safety and efficacy of treatment with adalimumab beyond one year has increased, and that there is no documented new evidence in the ACD3 that supports the arbitrary change in the wording around treatment duration, Abbott considers that the recommendations should revert to the original wording in the ACD2 and allow the clinician discretion to stop treatment when they consider it appropriate.

3. Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?

Abbott considers that two aspects of the provisional recommendations do not constitute a suitable basis for the preparation of guidance to the NHS. Section 3.1 highlights the concern that the recommendations in ACD3 are not in line with the licensed indication for adalimumab for the treatment of severe active CD. Section 3.2 outlines critical concerns regarding an inflexible 12-month stopping rule for all patients.

3.1 The recommendation that adalimumab is only for non-fistulising disease is not in line with the licensed indication.

Both adalimumab and infliximab are licensed for the treatment of severe, active Crohn's disease, in patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. According to the ACD3, patients fulfil the criteria for severe disease if they have a CDAI score > 300. The CDAI is a composite score comprising 8 categories describing the signs and symptoms of Crohn's disease. One of the eight categories of the CDAI index includes the following items: 'anal fissure, fistula or abscess; other fistula'. In order to obtain a CDAI score > 300 to qualify for anti-TNF treatment, it is highly likely that a proportion of patients will have fistulising disease forming a part of their total disease severity index measure. This is supported by the fact that 15.2% of patients in CHARM had fistulising disease both at screening and at baseline. Therefore, the definition of severe Crohn's disease stipulated within adalimumab and infliximab licences includes a proportion of severe patients who have fistulising disease as part of their severe CD symptoms.

There are also a proportion of CD patients who have predominantly fistulising Crohn's disease. Indeed, the literature shows that a patient can have fistulae years prior to the onset of luminal Crohn's disease itself⁸. These patients with fistulising disease often do not obtain CDAI scores > 300 because they do not manifest all the other symptoms related to the other 7 domains of the CDAI necessary to attain severe CDAI scores⁹. It is in these patients with fistula but not severe luminal disease as determined by the CDAI score that the wording in the infliximab licence around fistulising disease refers to: "Infliximab is licensed for use in active fistulising Crohn's disease". The median CDAI score in patients in the infliximab ACCENT II fistulising trial (forming the evidence base for the licence) was 180 and 41% of patients had a CDAI < 150 at baseline¹⁰. The infliximab licence therefore includes patients with severe Crohn's disease (some of whom will have fistulas), and also patients who do not have severe disease but do have the presence of fistulas and are therefore able to use infliximab.

The ACD3 currently states: "*Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active non-fistulising Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*" The perception of this recommendation as it currently reads is not in line with adalimumab licence or the available evidence. The licence does not specify a sub-group of severe patients with non-fistulising disease; it instead encompasses all patients with severe disease, a proportion of whom will have fistulising disease.

Therefore Abbott requests that when the Committee prepares the Final Appraisal Determination, that the wording in paragraph 1.1 is amended to: "*Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe, active Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*" Furthermore, the recommendation in 1.3 for infliximab should be amended to "*Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulising Crohn's disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy.*" This would then be in line with both anti-TNF licences and the evidence supporting these.

3.2 Need for individual consideration of risks and benefits of continuation of therapy beyond 1 year

Abbott considers that the recommendation that all patients should stop therapy at 1 year is not an appropriate recommendation for the treatment of severe patients with Crohn's disease. The previous recommendation in ACD2 allowing the flexibility of clinicians and patients to discuss the need to continue therapy is pragmatic and appropriate as this would allow patients at high risk of relapse and hospitalisation or surgery to continue therapy based on a full consideration of the risks and benefits of treatment continuation.

It is unclear why the ACD3 has settled on a maximum of 1 year maintenance therapy for patients receiving anti-TNF therapy. In this respect it should be noted that the Bodger *et al* modelling study indicated that maintenance therapy with adalimumab and infliximab would reach a cost per QALY of £30,000 at 34 years continuous therapy and 4 years respectively. Despite being based on the Olmsted County cohort of mixed severity patients discussed extensively in previous correspondence, the results of this analysis indicate that maintenance therapy beyond 1 year would be cost effective. Therefore, Abbott considers that on cost effectiveness grounds restricting treatment to 1 year of maintenance therapy is unwarranted and overly restrictive.

Abbott acknowledges that there is uncertainty regarding the long term effectiveness and safety of anti-TNF agents for the treatment of Crohn's. However, as outlined in section 1 there are data for periods greater than 1 year to indicate that adalimumab remains an appropriate therapy option from a risk/benefit perspective. Further, the long term safety of adalimumab has been studied in patients with a variety of immune-mediated inflammatory diseases¹¹. Conversely, there are no data available to indicate that all patients with Crohn's disease can be safely stopped at 1 year of anti-TNF therapy. Data from Louis *et al*. indicate that some anti-TNF patients on long term steroid-free remission can have their therapy discontinued and not relapse in the short term¹². However, it is important to note that data for patients in long-term steroid-free remission cannot be extrapolated to indicate that all patients can have their anti-TNF therapy stopped at 1-year without suffering relapse. As noted in the ACD2 response by Schering Plough, no consideration has been made of prognostic factors that could help predict whether a patient is likely to relapse. The long term risk-benefit of continuing anti-TNF therapy will be best agreed between gastroenterologists and patients taking a pragmatic approach based on a consideration of prognostic factors for relapse and the personal circumstances of the patient. For example, consider a patient who has received 1 year of anti-TNF therapy about to start a 3-year university course. If this patient were not in long term steroid-free remission without signs of active disease,

rigid application of a 1-year stopping rule as per the ACD3 recommendations would mean this patient should stop anti-TNF therapy before starting his or her university course. This patient would then be at risk of being hospitalised or requiring surgery during this period. If the guidance allowed the gastroenterologist and patient to agree a treatment period for greater than 1 year it may be that the patient would decide to remain on anti-TNF therapy during this period. Given the uncertainty of relapse and patients' fear of relapse and surgery weighed against considerations of long term safety of anti-TNF agents, Abbott considers it is appropriate that clinicians and patients should discuss the need for long term anti-TNF therapy based on a pragmatic consideration of risks and benefits rather than having an arbitrary stopping rule at 1-year.

In conclusion, Abbott considers that the previous ACD2 recommendations that anti-TNF therapy could be continued if appropriate beyond 1 year is a more pragmatic recommendation that balances the needs for consideration of clinician and patient preferences with assessments of long term safety and cost-effectiveness. Given that gastroenterologists and patients were strongly in favour of the need for appropriate maintenance therapy Abbott considers that the recommendations in this appraisal should allow anti-TNF therapy for greater than 1-year when this is considered appropriate by clinicians and patients.

4. Are there any equality related issues that may need special consideration?

None that Abbott is aware of.

References

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