NICE guidance for anti-tumour necrosis factor therapy in Crohn's disease: what does it mean for the inflammatory bowel disease community?

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The publication of the new National Institute for Clinical Excellence (NICE) guidance on the use of infliximab and adalimumab in Crohn's disease on 19 May (TA187) marked the completion of a lengthy and long overdue process. The advice it superseded dated back to 2002 (TA40) and restricted use of infliximab to episodic use for severe active Crohn's disease which was unresponsive to treatment with corticosteroids and an immune suppressant. The publication of ACCENT 1 and subsequent trials demonstrated the clear superiority of scheduled maintenance therapy over episodic therapy in the treatment of Crohn's disease¹ but it was not until the middle of 2006 that NICE began its review, including adalimumab usage in the remit. Since then there have been extensive discussions and the publication of three appraisal consultation documents before the advice was finalised this year. In this case, the guidance was worth the wait, in that the new guidance appears to have taken account of the representations made and the available evidence, and may lead to some major changes in practice and the availability of these drugs.

The 2002 guidance (summarised in figure 1) was very restrictive, allowing the use of infliximab in patients with severe active Crohn's disease (equating to a Crohn's Disease Activity Index of >300) but not in patients with fistulising disease alone. Despite the large number of studies suggesting more effective ways of using infliximab in the interim, some primary care trusts in the UK have interpreted this guidance very strictly and have continued to restrict the use of infliximab to the

2002 guidance and have refused to fund adalimumab at all.

Since 2002, we have learnt much about the best ways to use infliximab: the ACCENT 1 trial clearly demonstrated that scheduled treatment was more effective than episodic treatment in maintaining remission¹ and that antibodies to infliximab were minimised by this approach.² The correct time in the disease natural history to use infliximab has also been addressed by the 'Step Up–Top Down' trial and more recently by SONIC. The 'Step Up–Top Down' trial compared initiating treatment with infliximab and azathioprine with the traditional model of starting with corticosteroid therapy and moving through immune suppressants to biologic therapy. Patients in this trial were, on average, started on treatment within 2 weeks of diagnosis. After 2 years there was no statistically significant difference in the number of people in clinical remission in the two arms but those in the infliximab arm had required much less steroid therapy and a higher proportion had been in remission at 6 months and 1 year.³ However, in this study, there was no assessment of mucosal healing. SONIC addressed a different group of patients—those who had relapsed after a single course of corticosteroid therapy. Patients were randomised to receive azathioprine, infliximab or both. The trial demonstrated that for both remission and mucosal healing the combination was most effective, and monotherapy with infliximab was more effective than azathioprine. These effects were noted out to 1 year.⁴ These trials have clearly

- 1.1 Infliximab is recommended for the treatment of patients with severe Crohn's disease who fulfil all three of the following criteria:
 - ▶ Patients who have severe active Crohn's disease. These patients will already be in very poor general health with weight loss and sometimes fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. They may or may not be developing new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more and a Harvey-Bradshaw Index of 8/9 or above (see Appendix D)
 - ▶ Patients whose condition has proved to be refractory to treatment with immunomodulating drugs (eg, azathioprine or 6-mercaptopurine, methotrexate) and corticosteroids, or who have been intolerant of, or experienced toxicity from, these treatments.
 - ▶ Patients for whom surgery is inappropriate (eg, because of diffuse disease and/or a risk of short bowel syndrome).
- 1.2 Treatment can be repeated for those patients who match the above criteria and have responded to the initial treatment course, but then relapsed. A decision about whether or not to re-administer infliximab after the first course or subsequently should be made only after discussion with the patient who has been fully informed of the potential risks and benefits of repeated therapy (episodic treatment).

Figure 1 Summary of the NICE 2002 guidance.

demonstrated that maintenance therapy with infliximab is effective but there remain many circumstances within the disease natural history where there is no direct trial evidence to guide treatment and drug usage depends on clinical judgement in combination with patient preference.

The other major change since 2002 is the launch of adalimumab for the treatment of Crohn's disease. This is a fully humanised monoclonal antibody to tumour necrosis factor (whereas infliximab is a chimeric antibody) and has the potential advantage of subcutaneous administration. Efficacy for induction of remission was demonstrated in the CLASSIC-1 trial, with 160 mg followed by 80 mg 2 weeks later being the optimal dosing regimen.⁵ Fortnightly dosing was demonstrated to maintain remission in the CLASSIC-II study⁶ and then in the CHARM study and its open label extension.⁷ There have been no head to head trials of adalimumab and infliximab but clinical trials suggest that the efficacy of adalimumab is similar to that of infliximab.

The new NICE guidance has taken account of the new evidence, and the 2010 guidance (figure 2) suggests a scheduled course of treatment of 1 year with the most cost effective therapy, after which a full reassessment of disease activity is required, possibly involving endoscopy. This is important because there is emerging evidence that mucosal healing is linked with better long term outcomes and a reduction in the requirement for major abdominal surgery.⁸ The guidance also allows for the use of infliximab for fistulising disease and in paediatric populations.

The other major change is in the wording, and is more subtle. The new guidance refers to the licensed indications which involve failure of steroids and/or

- 1.1 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 (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as 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 should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate.
- 1.2 Treatment should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.
- 1.3 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.
- 1.4 Treatment with infliximab or adalimumab should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.

Figure 2 Summary of the 2010 NICE guidance TA187 'Infliximab (review) and adalimumab for the treatment of Crohn's disease'. For full guidance see <http://www.nice.org.uk/guidance/TA187>.

immune suppressants, rather than steroids and immune suppressants, raising the option of using biologics earlier in the disease course than possible hitherto. This potentially widens the scope for the use of these drugs in Crohn's disease.

Currently the UK uses less biologic therapy than its European neighbours but the effect of the new guidance remains to be seen. It seems certain that the use of biologic therapy in the UK will increase: maintenance therapy up to 1 year is now officially sanctioned and it is possible to use the drugs earlier in the disease course, and this will help clinicians to tailor therapy to individual patients more effectively. We know that some patients have a significantly more severe disease course than others and there are factors which can help to predict this, including young age of onset, fistulising disease and extraintestinal manifestations.⁹ Although these factors are not fool proof, the new guidance will allow clinicians to take these sorts of factor into consideration in personalising care for patients with Crohn's disease. However, it is unlikely that the UK will wholeheartedly embrace a 'top down' approach—there are currently no long term outcome data to suggest that this is the most effective way to use biological therapy and there remain significant safety concerns about long term use of these drugs, particularly in relation to

malignancy and infection. This concern is particularly acute in patients who are on combination therapy with an immune suppressant—the treatment recommended by SONIC. Furthermore, there are currently few data on when it is appropriate to stop biologic therapy: The STORI trial (currently only available in abstract form)¹⁰ has identified that a group of patients in ‘deep remission’ with a haemoglobin estimation of greater than 14.5 g/dl, a normal highly sensitive C reactive protein and totally normal endoscopy may be able to stop infliximab with a low likelihood of relapse but this is a small group. Many authorities in Europe suggest that the safety concerns have been overplayed and that there is no reason not to continue biologic therapy in the long term, but the results of such treatment, particularly in combination with immune suppression, will need continued vigilance.

The final issue with the new NICE guidance is whether it will end the variability of availability of biologic therapy or the ‘postcode lottery’. Each primary care trust in the UK will have to make its own interpretation of the guidance and may come to different conclusions about matters such as the most cost effective firstline biologic and sequential use of biologics. Thus the clear guidance on a scheduled course of therapy will remove the current inequalities in access to initial maintenance but there could continue to be variability over whether a choice of biologic is offered, how efficacy is assessed, loss of response and dose escalation. Although there is good evidence for dose escalation and switching from infliximab to adalimumab, this is not covered explicitly in the guidance.¹¹ The issue of how to reassess after a year and decide on treatment continuation is also an important issue where there may be some variability. The decision should rest with the treating clinician and patient, and where there are any biological or clinical parameters of activity the treatment will need to continue.

Thus the 2010 NICE guidance will increase the availability of biologic therapy and make its use much more uniform across the country, and it has, at last, caught up with clinical practice. However, the clinical complexity of Crohn’s disease, and the requirement for individual clinical judgment, may mean that there

may still be significant variation from area to area in its use.

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