BRITISH SOCIETY OF GASTROENTEROLOGY

Royal College of Physicians
Setting higher medical standards

9 September 2009.

Dear Dr Longson,

Re: Health Technology Appraisal: Use of tumour necrosis factor alpha (TNFa) inhibitors (adalimumab, and infliximab [review[for Crohn's disease. Appraisal consultation document Sept 2009.

Many thanks for giving us the opportunity to respond to this new appraisal consultation document. Taking your questions in turn:

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

   Yes – with one possible exception - we are appending a published abstract of the study from the GETAID group that we referred to at your committee meeting on August 20th. You will see that the data to which we referred during the discussion about possible protocols for stopping anti-TNF were based on a cohort of patients who had been "in stable remission without steroids for at least 6 months".

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?

   Yes.

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?

   Yes with some qualification:

   (i) Evidence regarding likely course following cessation of anti-TNF after 12 months treatment currently comes only from the Louis et al, GETAID study (appended below and referred to in [1] above). This is based on a cohort of patients who have been "in stable remission without steroids for at least 6 months". We would recommend that para 1.3, sentence three, should have an insert (in italics): "Maintenance treatment should only then be continued if there is clear evidence of ongoing active disease, as determined by clinical symptoms *and/or need for corticosteroids within the previous 6 months* and investigation, including endoscopy if necessary"

(ii) The CDAI is cumbersome for use in clinical practice, requiring a one week patient diary and laboratory tests – we would recommend an insert (in italics) in para 1.4 last sentence: "This clinical definition normally but not exclusively corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more *(or to an equivalent Harvey-Bradshaw Score of 9 or more)*.

(iii) One of the indications for infliximab given in 1.2 : "there is clear evidence of primary intolerance to adalimumab" is ambiguous. Moreover patient preference with respect of 8weekly hospital (day-case) -delivered intravenous infusion (for infliximab) versus 2weekly self-administered subcutaneous injection (for adalimumab) should also be take into account, particularly since there is no evidence to suggest superior efficacy for either of these anti-TNF preparations compared with the other. We would therefore recommend that this section of 1.2 should read:

. there is clear evidence of intolerance to adalimumab
. the patient is unable to self-administer subcutaneous therapy
. the Crohn's disease is fistulising
. the patient is a child or adolescent

4. Are there any equality related issues that may need special consideration?
No

We are very grateful to the NICE Committee members for the attention that they have paid to the concerns about the previous inappropriate use of low relapse rates from the Silverstein cohort in economic modelling and to the scientific and medical concerns about the poor efficacy of episodic anti-TNF treatment. The latest version of the appraisal will allow clinicians to give their patients something that approximates much more closely to optimal care.

Many thanks,

Yours sincerely,
[redacted]
(on behalf of Royal College of Physicians)

[redacted]
(on behalf of British Society of Gastroenterology)

http://download.abstractcentral.com/DDW2009/myddw2009/961.html
(Presented American Gastroenterological Association annual meeting, Chicago May 2009).
961
Infliximab Discontinuation in Crohn'S Disease Patients in Stable Remission On Combined Therapy with Immunosuppressors: a Prospective Ongoing Cohort Study
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Infliximab (IFX) is an effective maintenance therapy in Crohn's disease (CD). The question of whether this treatment can be safely interrupted after a period of prolonged remission is of great interest to patients and physicians. Objectives: To asses the risk of relapse after IFX discontinuation in patients on combined maintenance therapy with immunosuppressors (IS) and to identify factors of relapse. A secondary objective was to assess response and tolerance to IFX re-treatment in relapsers. Methods: Luminal CD patients treated for at least one year with combined IFX + IS and in stable remission without steroids for at least 6 months were prospectively recruited. Data recorded at baseline were: blood cell counts, CDAI, ileocolonoscopy with CDEIS, centralized USCRP, fecal calprotectin, ATI and IFX through level. Patients were followed up every two months with IS kept at a stable dose. Relapse was defined by a CDAI >250 or a CDAI between 150 and 250 with a 70 pts increase during two consecutive weeks. Association between demographic, clinical and biological factors and time-to-relapse was assesed through log-rank method. Hazard ratio (HR) were estimated through Cox model. Relapsers were retreated with IFX and both efficacy and tolerance were evaluated. Results: 115 patients were recruited in 20 GETAID centres. Median duration of IFX and IS treatments were 2.2 years and 2.8 years. At inclusion, median CDAI and CDEIS were 37 and 0.7; median USCRP, fecal calprotectin and IFX trough levels were 2.0 mg/l, 51 microg/g and 3.8 microg/ml. After a median follow-up time of 12 months, 45 relapses have been observed. In univariate analysis, current smoking, previous steroid treatment, lower haemoglobin, higher CDAI, CDEIS, USCRP and fecal calprotectin were associated with the risk of relapse. In multivariate analysis, a model based on CDEIS (≥2, HR=3.0, P<0.001) USCRP (≥5 mg/l, HR=3.8, P<0.001), haemoglobin (≤14.5g/dl, HR=4.7, P=0.002) and IFX trough levels (≥2microg/ml, HR=2.9, P=0.006) identified 4 subgroups of patients with increasing risk of relapse. Thirty seven relapsers are currently evaluable 4 weeks after IFX re-infusion for response to IFX retreatment: 36/37 were in remission and none experienced acute or delayed reaction. Conclusion: after a stable remission under combined IFX + IS therapy for at least one year, more than half of patients have not relapsed one year after IFX discontinuation. In relapsers, IFX re-treatment was well tolerated and induced remission in the short term. A subgroup of patients with very low risk of relapse could be identified through a combination of biological and endoscopic markers.