Royal College of Physicians statement on the appraisal of use of tumour necrosis factor alpha (TNF-α) inhibitors (adalimumab, certolizumab pegol and infliximab) and natalizumab for Crohn's disease

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Relevant Clinical Experience: [redacted] has a large IBD practice, personal experience in prescribing and managing patients on infliximab and adalimumab, knowledge of the published literature on certolizumab and natalizumab (but no personal experience of their use). He is a [redacted] in National IBD Audit, clinical trial experience with inflixiamb and adalimumab.

Conflict of interest: [redacted] has no current conflict of interest and is 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 [redacted] 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.

Comments on TAR report

1. Minor comments on page 2 paragraph 4 'Medications that are effective in the short term may not result in sustained remission, and in contrast, drugs used for maintenance may have minimal effects of active disease' Although the first statement is certainly true for corticosteroids and antibiotics (but not for azathioprine/mercaptopurine and methotrexate and anti-TNF-α), We are not aware of the latter statement being true for any currently used drug for CD i.e. all drugs that are effective in maintaining remission (azathioprine/mercaptopurine, methotrexate and anti-TNF) have been shown to be effective in active disease.
2. '4.6 Key factors to be addressed' Prolonged survival is stated as a clinical effectiveness factor. Mortality is rare in CD and it is arguable whether the standardized mortality ratio is increased in adults diagnosed with IBD (it is probably slightly increased) However there are no data to suggest that 'biological' therapy reduces mortality. The question is in fact the opposite. Do these therapies increase mortality by increasing serious infections and malignancies?

TNF-α inhibitors and natalizumab in moderate to severe Crohn's disease.
General Comments

- Currently available therapies do not cure Crohn's disease therefore treatments need to be evaluated on the improvement of quality of life.
- None of the available treatment modalities to date have been demonstrated to alter the natural history of Crohn's disease.
- Evaluation of current and proposed therapies needs to carefully balance risk/benefit.

- A further goal of therapy (not mentioned in the TAR) is maintenance of steroid-free remission. Corticosteroids are ineffective at maintaining remission and are the biggest risk factor for infection and post-operative complications (Agrawal 2004, Aberra 2003)

Anti-TNF-α therapies in Crohn's disease

- Anti-TNF-α therapies are a significant advance in the treatment of moderate to severe Crohn's disease unresponsive to conventional therapy (steroids, antibiotics, dietary therapy, thiopurines or methotrexate). They are effective in inducing and maintaining short to medium term remission in luminal disease.
- Infliximab is effective in inducing and maintaining closure of fistulas. Although the effect is modest, it is one of the few effective medical therapies available. It is used in conjunction with surgical drainage.
- With all anti-TNF-α therapies, there appears to be a long-term diminution in response/remission rates. However data is lacking at present for long-term remission rates.
- The maintenance trials of anti-TNF-α are nearly all drug withdrawal trials in patients who have initially responded to anti-TNF-α. Thus overall 'real world' remission rates are difficult to ascertain accurately. The only genuinely placebo-controlled maintenance trial which includes all patients with resistant Crohn's is PRECISE 1 (Sandborn 2007) of certolizumab. This showed a 23% response at for both week 6 and 26 versus 16% placebo.
- Although there are no head-to-head trials as yet, it is likely that infliximab and adalimumab have similar efficacy and side effects in moderate to severely active luminal CD. There seems to be a more modest effect for cetolizumab but this requires cautious interpretation of the evidence in the absence of directly comparable trials or head-to-head trials.
- The only trial which has specifically looked at the effect on patients who have failed infliximab is the GAIN trial (Sanborn 2007). This trial supports the use of adalimumab in patients with active CD who have either initially responded then become non-responsive to infliximab or intolerant of infliximab. The remission rates are probably less than that of primary anti-TNF-α naïve patients. There is also the caveat that in this study the reasons for infliximab failure are not well documented.
- Current evidence suggests that regular therapy is more effective and has fewer side effects than 'as required' therapy. From personal experiences in managing patients with CD, it seems illogical and unfair for patients to have to wait until their symptoms are sufficiently severe before they can be eligible for a therapy. From discussion with a large number of patients treated with infliximab they much prefer scheduled infusions.
- Patients receiving anti-TNF-α should be on a thiopuirine or methotrexate (unless previously intolerant). It is not known whether lower doses than that required for therapeutic response are needed to reduce adverse events from anti-TNF-α therapy.

- There is no compelling evidence for a 'step down' approach i.e. starting on anti-TNF-α therapy initially and then introducing other therapy rather than the current 'step up' approach. Ongoing trials may clarify which approach (if any) is more effective. Unlike rheumatoid arthritis we do not have a measurable index of equivalent to joint erosions, therefore we do not have a concept of 'early Crohn's disease'.
- Adverse events for active treatment or placebo occur at similar rates in most trials. Recently, however, there have been several worrying reports of a very rare but almost uniformly fatal hepatosplenic T-cell lymphoma in young patients with CD receiving both infliximab and thiopurines. Meta-analysis of trials of infliximab and adalimumab show an increased risk of serious infection (OR 2.0, 95% CI 1.3-3.1) and malignancy (RR 3.3, 95% CI 1.2-9.1) (Bongartz, 2006). There needs to be rigorous monitoring of the long term side effects of anti-TNF-α therapy.

Natalizumab in Crohn's disease

- Clinical experience is much more limited and there are more concerns about safety.
- The initial randomized controlled trial failed to show a significant difference at the primary end-point but secondary end points suggested a positive effect.
- Subsequent large maintenance trials of drug withdrawal in responding patients showed significant effects in maintaining remission- sustained response of 39% natalizumab vs 22% placebo (Targan, 2007). This suggests an efficacy similar magnitude to anti-TNF-α therapy.
- There have been 3 patients treated with natalizumab in combination with interferon beta or azathioprine in other studies who developed progressive multifocal leucoencephalopathy. The estimated incidence is 1:1000 patients treated (95% confidence interval, 1:200 –1:2800)

Recommendation for use of tumour necrosis factor alpha (TNF-α) inhibitors (adalimumab, certolizumab pegol and infliximab) and natalizumab for Crohn's disease

- Infliximab and adalimumab are effective in inducing remission in moderate to severe Crohn's disease (CDAI >220 or HBI >8) unresponsive to conventional therapy (steroids, antibiotics, dietary therapy, thiopurines and methotrexate).
- If initial response is seen after 2 or 3 doses then regular maintenance therapy should be initiated at a dose or 5mg/kg every 8 weeks for infliximab and 40mg every other week for adalimumab. If relapse occurs then dose intervals can be shortened.
- Patients who initially respond to infliximab but later become non-responders or develop infusion reactions should be given adalimumab
- Adalimumab may be preferred by some patients as it can be self-administered.
- Patients receiving anti-TNF-α should be on a thiopurine or methotrexate (unless previously intolerant).

- There are no data on when to stop therapy. A reasonable approach is to continue maintenance therapy for 6 months and then discuss the pros and cons of stopping therapy (prolonged remission off anti-TNF-α against risk of relapse).
- Regular scheduled treatment is more effective than 'as required' and importantly avoids the patient enduring relapse of disease before 'earning' further therapy.
- The evidence for certolizimab suggests there is slightly less efficacy and at present there is insufficient evidence to justify widespread use out-with further trials.
- Natalizumab may have similar efficacy to anti-TNF-α in maintaining remission (though probably less efficacy in inducing remission). However there are concerns about the side effect profile and I would not recommend therapy out-with clinical trials.
- There is a need for head-to-head trials to look at comparative efficacy and relative cost effectiveness/health economics of different anti-TNF-α therapies.
- A biological registry in the UK would be a positive advance to both gaining useful long term data on efficacy and side effects as well as epidemiological data. This should be run independent of the pharmaceutical industry and allow rigorous follow up of complications such as death, serious infection or malignancy. It would be worth of seriously considering make these registries compulsory.

Appendix

Personal review of literature by Dr Keith Leiper. The RCP endorse this response.

Infliximab

Infliximab is effective in inducing remission in patients refractory to other medical therapies (81% response versus 17% placebo at week 4) (Targan 1997). This response rate has been replicated in 'real world' settings. There is consensus that infliximab is effective in inducing remission in corticosteroid dependence, corticosteroid refractoriness or corticosteroid intolerance, and that it be considered after failure of either azathiorine/ mercaptopurine or methotrexate (ECCO guidelines, 2006). I would advocate that the definition of treatment refractoriness be widened to include all those who fail a non-steroid therapy for CD (specifically antibiotics and dietary therapy) and either azathiorine/ mercaptopurine or methotrexate.

Two trials have assessed maintenance infliximab in patients who responded to initial infusions. In the first (Rutgeerts 1999), after 54 weeks, remission rates were 53% in the infliximab group *v* 20% in the placebo group ($p = 0.013$); response rates were 63% and 38% ($p = 0.16$), respectively. In the second larger trial (Hanuer 2002), 573 patients were randomised to 5mg/Kg, 10mg/Kg or placebo every 8 weeks with loss of response as primary end point. The rates of response and remission after 54 weeks were 17% and 14% (for placebo); 43% and 28% (for 5 mg/kg); and 53% and 38% (for 10 mg/kg). Rutgeerts et al (2004) using this dataset suggested that regular treatment was superior to episodic treatment and associated with fewer admissions and operations. Episodic infusions associated with increased antibodies to infliximab which correlates with reduced efficacy, in particular more infusion reactions and shortened duration of response (Baert 2003, Hanauer 2004).

Infliximab is the only therapy to be shown to significantly improve the closure of perineal fustualas (although there is convincing non-RCT evidence for the effect of antibiotics and thiopurines). ACCENT II (Sands 2004) showed an initial response of 69% for a 0,2 and 6 week induction regime and randomised responders to 8-weekly infusions. Complete closure at week 54 was achieved in 36% infliximab versus 19% placebo. Adverse effects are well documented. TREAT registry of 3179 patients receiving infliximab and 3111 receiving other therapies reported a mean length of follow up of 1.9 years. The registry is sponsored by the manufacturers of infliximab. Although the infliximab group had more severe disease, more hospital admissions and more were on prednisolone and immunosuppressives, there was no difference in mortality. Age, duration of disease and use of prednisolone were independent predictors of death. The unadjusted risk of infection was higher with infliximab but not when adjusted for other variables. Variables associated with infection were duration of CD, moderate to severe disease, steroid use and narcotic use. Criticism of this registry is that it is i) sponsored by the manufacturer, ii) not rigorously monitored and iii) 21% of the patients were withdrawn for a variety of reasons. Other retrospective studies have suggested an infliximab related death rate of 1% (Mayo clinic, Colombel, 2004) and 2.8% (Stockhom, Ljung 2004) but without a non-infliximab comparitor.

Recently there have been several reports of a rare T cell lymphoma (hepatosplenic T cell lymphoma) in young people with CD treated with infliximab and concomitant immunosuppression with thiopurines. The occurrence seems to be very rare but these lymphomas have been almost uniformly fatal.

Adalimumab

Adalimumab is a fully humanised anti-TNF antibody which may elicit less antibody response than infliximab. The CLASSIC 1 (Hanauer 2006) was the initial dose-ranging trial of two doses (week 0 and 2) of adalimumab (40 mg/20 mg, 80 mg/40 mg, or 160 mg/80 mg or placebo 160mg week 0, 80mg week 2) in 299 patients with moderate to severely active CD who were infliximab-naive. The primary endpoint was remission at week 4 (CDAI <150). Remission rates at week 12 were 18%, 24%, 36% and 12% respectively (p=0.04 for 80mg or 160mg versus placebo). Adverse events were similar except for an increased incidence of site injection pain in the adalimumab groups.

CLASSIC II (Sandborn, 2007) enrolled 276 of the 299 patients in CLASSIC 1 and gave further open-label adalimumab 40 mg at Weeks 0 (Week 4 of CLASSIC I) and 2. Fifty five (20%) of these patients were in remission at week 0 and 4 and were then re-randomised to adalimumab 40 mg every other week , 40 mg weekly, or placebo for 56 weeks. Primary endpoint was maintenance of remission (CDAI<150) in randomised patients through Week 56 and this was achieved in 79% who received adalimumab 40 mg e.o.w., 83% who received 40 mg e.w. versus 44% for placebo (p<0.05). Of the 204 patients entered the open label arm of the study 46% were in clinical remission at Week 56. The higher remission rate is likely to be due to the selection bias of choosing the 20% who had a very good response to continue in the blinded maintenance arm. The open label arm is in keeping with other trials on maintenance therapy with adalimumab.

CHARM (Colombel, 2007) used a lower dose induction regime of 80mg week 0 then 40mg week 2 and then responders (CDAI fall >70) were randomised to either 40mg e.o.w, 40mg e.w. or placebo up to week 56. Primary end points were remission at week 26 (40%, 47% and 17% respectively) and week 56 (36%, 41% and 12%). These data are for those who responded at week 4. It has to be borne in mind that this is 58% of the cohort studied, i.e. 42% did not gain response at week 4. Curiously steroid-free remission rates were fairly low (6% placebo, 29% 40mg every other week, 23% 40mg every week) at week 56. There were no differences in frequency of side effects between the adalimumab groups and placebo.

GAIN (Sanborn 2007) examined 311 patients who initially responded to infliximab but later either lost response or developed adverse effects related to infliximab. These were randomised to either adalimumab (160mg week 0, 80mg week 2) or placebo. Response rates (>70-point decrease in the CDAI) were 52% versus 34%, whilst remission rates (CDAI <150) were 21% versus 7% (absolute difference 14.2%, 95% CI 6.7-21.6%). There were no differences in the response for those patients with fistulas between

adalimumab and placebo. However this study has been difficult to interpret because of data lacking on the reasons for stopping infliximab and previous duration of infliximab therapy (Mannon Ed AnnInt Med 2007). GAIN however supports the use of adalimumab in people with CD who are secondarily refractory to or intolerant of infliximab, although the remission rates are probably less than that of primary anti-TNF-α naïve patients.

Certolizumab

Certolizumab is a pegylated humanised Fab' fragment of an anti-TNF-α monocloncal antibody. It does not contain a Fc domain and therefore does not activate complaceboement, induce apoptosis or antibody dependent cytotoxicity. The initial phase II trial in 292 patients with active CD compared 100mg, 200mg and 400mg certolizumab or placebo. At the primary end point (clinical response, CDAI>100 at week 12) there was no difference between certolizumab and placebo, though the numerical response was highest for certolizumab 400mg. Post hoc analysis should a significantly different response between those with a CRP- ≥10mg/l versus <10- 53% certolizumab 400mg versus 18% placebo (p=0.005).

Two recent large trials examined the effect of maintenance certolizumab in Crohn's (PRECISE 1 and PRECISE 2). Both were trials of moderate to severe Crohn's in multiple centres, used CDAI as end point, up to week 26 and stratified for CRP (at least 10 or less than 10). The major difference is that PRECISE 1 were randomised to certolizumab or placebo at the start of the trial whilst in PRECISE 2 (as with several other trials) only examined those who responded to 3 doses who were then randomised to certolizumab or placebo.

PRECISE 1 (Sandborn 2007) studied cohort of 662 patients with a CDAI 220-450 and who had not received an anti-TNF-α agent for 3 months. Patients were randomised to 400mg certolizumab or placebo at week 0, 2, 4 and then every 4 weeks to week 26. Stratification was for CRP- ≥10mg/l or <10, use of corticosteroids and use of concurrent immunosuppressives. Corticosteroids could be reduced at the discretion of the investigator. For PRECISE 1 the primary end points were a fall in CDAI of >100 points at week 6 and at both week 6 and 26 in those with a baseline CRP ≥10mg/l - this was achieved in 37% certolizumab and 26% placebo (p=0.04) at week 6 and at both time points by 22% and 12% respectively (p=0.05). For all patients (including those with a CRP lower than 10) response rates were 35% for certolizumab and 27% placebo (p=0.02) at week 6 and 23% and 12 % respectively for both week 6 and 26. Remission rates were not different at week 6 for those with a CRP ≥10 (22% versus 17%, p=0.17) nor at week 6 and 26 (13% and 8%, p=0.24) but were at both week 6 and 26 (14% versus 10% p=0.07). Similarly there was no difference in either time point when all patients were analysed. There was no difference in the magnitude of response at either primary end point with respect to immunosuppressives, corticosteroids, previous treatment with infliximab or smoking status. Adverse events were similar between groups (any adverse event 79% placebo and 81% certolizumab), however nasopharyngitis (8% placebo and 13% certolizumab). One death occurred in a 22 year old due to MI and metastatic lung cancer who had 3 doses of certolizumab. Serious adverse events occurred in 10% certolizumab and 7% placebo and adverse events

leading to withdrawal in 12% and 1% respectively. Injection site reactions were more common in the placebo group (14% versus 3%), the reason for this is not clear.

PRECISE 2 (Screiber 2007) was a medication withdrawal study similar to other anti-TNF-α studies. Entry criteria were the same as PRECISE 1. Patients received open-label induction therapy of 400mg at week 0, 2 and 4, if the CDAI had fallen by 100 points these patients were randomised to 400mg certolizumab or placebo every 4 weeks and followed up to week 26. Stratification was for CRP- ≥10mg/l or <10, use of corticosteroids and use of concurrent immunosuppressives. Primary end point was response at week 26 in those with a CRP ≥10mg/l. Open label induction response was 64% (428/668 patients) and remission 43%. Fifty percent of those who responded had a CRP ≥10mg/l. Of these, at week 26 62% had response to certolizumab compared to 34% placebo ($p<0.001$). Overall response rates were 63% certolizumab compared to 36% placebo ($p<0.001$). Remission rates at week 26 were 48% cer and 29% placebo ($p<0.001$). For those with a CRP ≥10mg/l, remission rates were 42% certolizumab and 26% placebo ($p=0.01$). There was no difference in response rates for patients receiving immunosuppressants or with a raised CRP but there was a significant difference in those who had previously received infliximab. Serious adverse events occurred in 6% cer and 7% placebo. Serious infections 3% certolizumab and <1% placebo. One patient developed pulmonary tuberculosis. Combined induction and maintenance rates were 40% (though this will include a placebo response to the induction phase)
Interestingly there was a difference in the initial response rates between PRECISE 1 (35%) and PRECISE2 (45%) and open label arm of PRECISE 2 (64%). Likewise the rates of decrease of 100 points and remission at week 6 were substantially different between trials – PRECISE 1 35% and 22%, PRECISE 2 64% and 43%.
In summary certolizumab has a modest benefit in active CD- improves CDAI but no significant difference in remission rates. Although initial evidence had suggested efficacy in those CD patients with an elevated CRP, subsequent large trials have not supported this.

Natalizumab
Natalizumab is humanised immunoglobulin G4 monoclonal antibody against α4 integrins. Ghosh (2003) reported 248 adult patients with moderate to severe CD (CDAI 220-450) in a 12 week induction trial. Patients who received methotrexate and current use of more than 25 mg per day of oral prednisolone were excluded. Patients were randomized to one of four treatment groups: two infusions of placebo (n=63), one infusion of natalizumab (3 mg/kg) and one infusion of placebo (n=68), two infusions of natalizumab (3 mg/kg; n=66), and two infusions of natalizumab (6 mg/kg; n=51). The primary outcome was remission at week 6. Although the primary end-point was not significantly different from placebo, there were significant differences in response rates.

In the ENACT-1 study (Sandborn 2005), 905 adult patients (CDAI 220- 450) were studied. Concomitant medication for Crohn's disease, including stable doses of prednisone (< 25 mg/day), azathioprine,6-mercaptopurine, methotrexate, and antibiotics were permitted. Enrolment of patients who were nonresponders to anti-TNF treatment was limited to a maximum of 30% of total study enrolment. Patients were

randomized in a 4 to 1 ratio to receive an infusion of either 300 mg of natalizumab (n=724) or placebo (n=181) for a total of three infusions given at weeks zero, four and eight. The primary end point was defined as a reduction of > 70 points in the CDAI score from baseline. Primary and secondary outcomes were measured at week 10. The primary outcome was clinical response (> or = 70 point reduction in CDAI from baseline). Natalizumab and placebo groups had similar rates of response (56% and 49%, respectively (P=0.05)) and remission (37% and 30%, respectively; P=0.12) at 10 weeks. Continuing natalizumab in the second trial resulted in higher rates of sustained response (61% percent vs. 28% percent, P<0.001) and remission (44% vs. 26 percent, P=0.003) through week 36 than did switching to placebo.

ENCORE trial of natalizumab enrolled 509 patients (from 832 screened) with active CD (CDAI 220-450 and CRP >2.87 mg/l) to 300mg natalizumab or placebo at weeks 0, 4 and 8. Primary end-point was response defined at CDAI decrease of ≥ 70 points at week 8 and sustained to week 12. Patients were excluded if they had previously received anti-TNF-α medications. Recuitment was only allowed if the dose of prednisolone was ≤20mg or budesonide ≤6mg. Primary end point was achieved in 48% natalizumab and 32% placebo (p<0.001). Remission occurred in 26% natalizumab and 16% placebo (p<0.001). At Week 12, 60% of patients receiving natalizumab vs 44% placebo were in response (*P* <0 .001) and 38% vs 25%, respectively, were in remission (*P* < .001). The proportion of patients with a 100-point response at Week 8 and sustained through Week 12 was higher for patients in the natalizumab group compared with those in the placebo group (39% [102 of 259] for natalizumab vs 22% [56 of 250] for placebo; *P* <0.001). Adverse events were similar between the two groups-serious AE 20% placebo and 5% natalizumab. Nasopharyngitis was significantly more common in the natalizumab group (11% vs 6% placebo) as were hypersensitivity type reactions (4% vs <1% placebo). The presence of anti-natalizumab antibodies increased the incidence of hypersensitivity type reaction (17% with antibodies vs 3% without antibodies), however there was no diminution of response to therapy in those with antibodies.

However, 3 patients treated with natalizumab in combination with interferon beta or azathioprine in other studies have developed PML with an estimated incidence of 1:1000 patients treated (95% confidence interval, 1:200 –1:2800), and other opportunistic infections have been observed during therapy with natalizumab

Meta-analysis of the induction trials (McDonald 2007) has been performed. Pooled data suggest that natalizumab is effective for induction of clinical response and remission in some patients with moderately to severely active Crohn's disease.

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