Abatacept, etanercept, infliximab, rituximab and abatacept for the
treatment of rheumatoid arthritis after the failure of a TNF inhibitor.

Personal Statement
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1. Introduction

I have 20 years experience of working as a single handed rheumatologist in a district general hospital and have had a prolonged interest in clinical pharmacology. I have participated in clinical trials of most of the biologic drugs used for rheumatoid arthritis. Until the appointment of a colleague 3 months ago I had sole responsibility of 2000 patients with rheumatoid arthritis on my database, with 800 patients currently receiving DMARDs or biologic drugs.

I am a member of the BSR Standards, Audit and Guidelines Working Group. I was involved in the NICE appraisal for TA130 and involved in the development of the subsequent appeal document.

I was appointed an NHS member of the NICE appeal panel in September 2008.

2. Current Guidance

TA130 published in 2007, concluded that although clinically effective, patients who have failed on their first anti-TNF agent due to lack or loss of response should not be allowed to have access to a second anti-TNF agent because this was not considered to be a cost-effective use of NHS resources. This conclusion is similar in TA36 with regard to switching to a second anti-TNF drug, and leaves NHS patients who fail on their first anti-TNF agent with only the choice of either rituximab, or standard therapy.

3. Management of rheumatoid arthritis

Rheumatoid arthritis is an unpleasant disease. In addition to inflammation of the joints (synovitis) causing pain, stiffness and disability, there is a risk of irreversible joint damage leading to further disability. The object of treatment is to improve symptoms and reduce the risk of the joints becoming damaged. Many patients will respond to standard DMARD therapy but for those who fail these treatments, many will respond to one or other biologic drug. For those who fail to respond to the first anti-tnt treatment NICE guidance allows treatment with rituximab. However, this drug is largely ineffective in those who have a negative rheumatoid factor and in view of recent reports of the risk of progressive multifocal leukoencephalopathy following rituximab for rheumatoid arthritis, in my opinion it should not be prescribed in sero-negative rheumatoid arthritis. In addition rituximab is less effective in patients who are not co-prescribed methotrexate. Therefore for those who are intolerant of methotrexate, and for sero-negative patients, treatment options are limited if a second anti-TNF treatment cannot be considered. Standard therapy with other DMARDs and DMARD combinations have usually failed and patients are often managed with high doses of steroids leading to significant co-morbidity from side effects. This is confirmed by published data. The BeSt trial has demonstrated that patients who fail on methotrexate are unlikely to respond to other conventional DMARDs. All NHS patients will have been exposed to methotrexate prior to going onto anti-TNF, therefore returning to conventional DMARDs following the failure of anti-TNF is very unlikely to be helpful. Data from the British Rheumatoid Arthritis Outcomes Study Group shows that patients on either symptomatic or aggressive treatment strategies show progressive deterioration in HAQ over three years of follow up.

4. Evaluation of response to treatment

Disease activity and clinical improvement is usually measured in a composite score of disease activity (DAS). In addition disability is usually measured using a self administered health assessment questionnaire of activities of daily living (HAQ). When a patient has a high DAS score, it is likely that they will have a high HAQ score. The converse however is not necessarily true as patients could be in full clinical remission but because of previous joint destruction may remain significantly disabled. Both measures are relevant to
the determination of utility and quality of life. A patient with severe disability from previous joint damage who also has persistent synovitis will have a better quality of life if the pain and stiffness from the synovitis is resolved even if this does not have a measurable effect on disability. The longer the disease duration, the greater the likelihood of joint damage and the less likely that HAQ scores will reflect the clinical benefits from treatment of inflammation.

5. Observational data

Data from the British Society for Rheumatology Biologics Register (BSRBR) has shown that patients who switch anti-TNF therapy following the failure of their first anti-TNF therapy show a significantly better improvement in Health Assessment Questionnaire (HAQ (0.15)) than those who stay on their first anti-TNF therapy (in spite of inadequate response) or stop the anti-TNF therapy. These data hold true despite the fact that patients have had disease for 14 years, failed on a mean of 4 DMARDs, and concurrent methotrexate was only being used in 47% of patients. Other observational studies show greater HAQ improvements on switching from a failing first anti-TNF agent to a second (0.33 to 0.52 in the ReAct study).

There is therefore clear evidence of a clinical response with a 2nd anti-TNF treatment after failure of primary treatment. Some patients may not respond as well as others and recent data suggests this may be related to the development of auto-antibodies to the biologic drugs. Nevertheless, the difficulty is in measuring the clinical benefits for economic modelling.

6. Instruments for economic modelling

Currently, there is not an accepted single measure for evaluating health utility in rheumatoid arthritis. Direct and indirect measures have been evaluated and the HAQ has been used most widely in modelling. This approach was criticised by Scott and colleagues who found a poor correlation between HAQ scores and the indirect utility measure EuroQol (EQ-5D) in 321 patients with rheumatoid arthritis (RA). In contrast, Ariza-Ariza and colleagues found a close correlation between HAQ and EQ-5D in 260 RA patients. They found a poor correlation between EQ-5D and DAS 28 but a similar correlation between both HAQ and DAS28 and the Time Trade-Off (TTO) instrument of utility. Interestingly however, there was only a moderate correlation between the mean change in EQ-5D and HAQ. Witney and colleagues also found a stronger correlation between HAQ and EQ-5D and only a moderate correlation between HAQ and the direct utility measures TTO and Standard Gamble (SG). One reason for the disparity in these measurements suggested by the researchers is that patients with established RA report a higher health utility on the EQ-5D indicating that such patients have a higher acceptance of their illness and less depression.

In relation to the health economic analyses of sequential anti-TNF therapy, the previous appraisal committee were concerned that the Birmingham Rheumatoid Arthritis Model (BRAM), modelled predominantly on HAQ changes in the BSRBR, found very high incremental cost-effectiveness ratios (ICERs) and failed to approve the use of a second anti-TNF. In my view the HAQ response in these patients significantly underestimates the clinical response, for the reasons described in section 3. above.

In patients with a HAQ in the upper part of the range, the relationship between utility and HAQ appears to be less well defined. Kobelt and colleagues found that the EQ-5D was able to discriminate between patients with different HAQ scores but only in ACR functional class II. Witney and colleagues found a greater variability in SG, TTO and EQ-5D utility scores in those with higher HAQ scores. Bansback and colleagues also found the difference between actual and predicted EQ-5D utility was greater in those with a HAQ score ≥ 2.5 and concluded that the HAQ is a suboptimal measurement compared with a direct measurement of health utility.

In the BSRBR the duration of disease is greater and the mean HAQ scores are higher than in published clinical trials of anti-TNF therapy. For example in the ReACT trial the mean disease duration prior to first anti-TNF was 11 years with a mean HAQ score of 1.6; HAQ scores improved by approximately −0.5 and DAS scores by approximately −2.0. In the DREAM study disease duration was between 6 and 7.7 years and baseline HAQ scores between 1.3 and 1.4. The HAQ scores improved by approximately −0.4 and DAS
scores by approximately –1.8. In the BSRBR data of second anti-TNF response, the mean duration of disease is greater than 14 years with a base line HAQ of 2.1. The clinically significant fall in DAS scores is not reflected in the reduction in HAQ score of only –0.15.

7. **Failure of HAQ score to reflect utility**

These data indicate that the clinical response and improved utility following anti-TNF therapy in those with significant disability is not reflected in the HAQ scores. Patients with established longstanding disease often have irreversible damage and deformity in their joints. However, treating active synovitis – reflected in high DAS scores – in this group of patients will have a significant benefit in utility with little effect in HAQ score.

The importance of including clinical response, as well as disability, is reflected in the study by Brennan and colleagues. They modelled the clinical response to the disability/utility improvement rather than using average improvement in HAQ scores. They also differed from the BRAM in modelling the concept of withdrawal unless an adequate clinical response was achieved. The result of this study indicated that using a second anti-TNF after failure of the first drug was cost effective using the current parameters accepted by NICE.

8. **Conclusions of switching anti-tnf**

It is my opinion from the published data that switching to a second anti-tnf drug after failure of response to the first drug is a cost effective form of treatment as defined by NICE. The problem is that the modelling of the utility benefit is difficult in those with permanent disability. In clinical practice, all rheumatologists have seen a patient respond to one anti-tnf drug having failed to have any response with another. The possibility of response is slightly less than the response rate to the first anti-tnf drug. Nevertheless, if a patient has an inadequate response to treatment, it should be withdrawn and it is essential that this is incorporated into any health economic model. If the model includes data from the BSRBR then it is also important to correct for the anticipated smaller reduction in HAQ in those patients with established disability in the upper part of the range. The reliance on the BRAM model by the appraisal committee in TA130 was inappropriate: by not taking account of disease activity scores (in comparison with the Brennan model) there was an underestimate of the utility benefits of treatment.

9. **Rituximab**

Rituximab is an effective option for treatment in sero-positive rheumatoid arthritis particularly when co-prescribed with methotrexate. In my opinion the guidance in TA126 is appropriate and should be incorporated into the new guidance.

10. **Abatacept**

The guidance in TA 141 denied patients with refractory rheumatoid arthritis the opportunity of treatment with a clinically effective drug with proven efficacy in patients who had failed anti-tnf treatment. As discussed in Section 3. above, this group of patients have few therapeutic options.

I have concerns with the economic modelling in the guidance in two areas. The first concern is the same as that described in section 7. above, that reliance on improvement in HAQ fails to reflect the full utility benefit of treatment. The other concern relates to estimations of underlying HAQ progression. For TA130, the committee decided to examine the estimates of cost effectiveness with an assumption of no HAQ progression on treatment.

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*Therefore, the Committee considered it appropriate to primarily examine the estimates of cost effectiveness based on the assumption of no HAQ progression while on TNF-α inhibitor therapy, while acknowledging the effects on the estimates of incorporating different assumptions of HAQ progression.*
In contrast the committee for TA141 assumed a HAQ progression of 0.03 with consequent increase in ICER. The assessment of abatacept was therefore subject to a significant disadvantage from a health economic perspective and would appear to be a failure of the principle of a ‘level playing field’ for assessment of these compounds. In my view the health economic assessments for these compounds should use the same assumptions throughout as was concluded in TA130.

11. **Overall Conclusions**

It is counter intuitive to consider that treatment with a second anti-tnf inhibitor or with abatacept is significantly less cost effective than first treatment with an anti-tnf inhibitor. I consider that reliance on HAQ improvement has led to underestimation of utility improvement particularly in patients with established disease and irreversible joint damage. I consider this currently to be the greatest challenge facing patients with rheumatoid arthritis in the UK.

**References**

8. Witney AG et al. The relationship of medical, demographic and psychosocial factors to direct and indirect health utility instruments in rheumatoid arthritis. Rheumatology (Oxford) 2006; 45:975-981