

**HEALTH TECHNOLOGY APPRAISAL: NICE Health Technology Appraisal -
Assessment Report**

**Adalimumab, etanercept, infliximab, rituximab and abatacept for
Rheumatoid Arthritis after the failure of a TNFa inhibitor**

TO: NICE

**FROM: NHS Quality Improvement
Scotland
12 January 2010**

1. My comments on the WMHTAC Assessment report are as follows:
 - 1) Epidemiology – the data presented are representative of Scotland as well as the rest of the UK.
 - 2) Treatment pathways – the treatment pathways are no different in Scotland when compared to the rest of the UK. However, I would make the following points about the assumptions used in the HE model:
 - a. Number of prior DMARDs used – the models assume that patients will have tried and failed only MTX, sulfasalazine and hydroxychloroquine before embarking on anti-TNF therapy. Consequently, the treatment sequence used in the HE model includes the use of leflunomide, IM gold, ciclosporin and azathioprine after the failure of anti-TNF therapy. Data from the BSRBR (and locally in Scotland) indicates that on average patients have tried ~5 DMARDs before moving on to anti-TNF therapy. I would suggest that a scenario analysis should be performed in which patients receive only 2 conventional DMARDs before they move onto palliative therapy.
 - b. This emphasises that patients who fail anti-TNF represent a growing area of unmet medical need, and the restriction of use of biologic drugs in these patients is likely to represent substantial hardship.
 - c. p37 – patients with RA are described as ‘risk averse’. This is an unhelpful generalisation; some patients are risk-averse but others, particularly with severe, active disease put a high premium on current quality of life even at the expense of potentially severe toxicity.
 - 3) Response criteria – it is particularly important that the Appraisal Committee appreciates the significance of a good/excellent response to a patient with severe RA who has failed anti-TNF therapy. Such patients have severe disability, impaired quality of life and increased mortality. Whilst a fall in DAS of >1.2 is meaningful, a reduction of DAS/DAS28 to <2.4/3.2 (‘low disease activity’) or <1.6/2.6 (‘remission’) represents a very substantial improvement in quality of life. A significant minority of patients achieve such high grade responses in all the clinical trials. If the committee is minded to reject the use of one or more biologic drugs on the grounds of cost-effectiveness based on a stopping rule of failure to achieve a DAS response, I would hope the committee would consider the cost effectiveness of these therapies in patients who achieve a higher grade of response. Patients achieving low disease activity or remission will have a larger QALY gain at the same cost which will significantly alter the estimated ICER.

4) BRAM model

- a. HAQ improvement – the model assumes a proportionate improvement in HAQ such that a patient starting with a HAQ score of 2 improves by twice as much as a patient starting with a HAQ score of 1. There is no justification provided for this assumption and there is some evidence to the contrary from the BSRBR (namely, that baseline HAQ is not a good predictor of HAQ improvement). What impact this has on the ICERs should be explored through a scenario analysis.
- b. Magnitude of HAQ improvement – the model estimates that the HAQ multiplier for conventional DMARDs should be half of that calculated from early RA trials. No justification for this decision is given, **and the results are not credible** – for example, the HAQ multiplier derived for leflunomide is greater than that for etanercept, infliximab and rituximab. A scenario that models the HAQ improvement with conventional DMARDs to be much lower (equivalent to that seen with azathioprine) should be performed.
- c. Early quitting/drug survival – if I interpret the model correctly, those patients who quit early because of inefficacy are modelled as those with least improvement in HAQ (quite appropriately). Consequently, from a cost-effectiveness viewpoint, this model will favour those therapies that have a high early quit rate (weeding out the lowest HAQ responders) with long drug survival thereafter (maximising the QALY gain in good responders). If I am correct, it would appear that the model favours the conventional DMARDs:
 - i. Early quitting on biologic therapy – the BSR/NICE guidelines indicate that patients with no response to biologic therapy (defined by an improvement in DAS28<1.2) should have their treatment withdrawn. Data from the BSRBR indicate that 22% of patients fail to respond to anti-TNF therapy (2008 data) after 6 months. The early withdrawal rates for adalimumab and etanercept, therefore, in the model are too low and the model over-represents patients with minimal improvement in HAQ yet continue on therapy; in turn this will dilute the average QALY benefit seen in those staying on therapy. Is it possible to perform a scenario analysis in which the early quit rate is increased because of inefficacy?
 - ii. Duration on conventional DMARD therapy – table 77 details the ‘Times to quitting treatment’ for different treatments. Again, if I understand this table correctly, the model uses times on treatment for azathioprine, ciclosporin and leflunomide that exceed that for anti-TNF therapy. These assumptions - in particular, the longevity of azathioprine and ciclosporin therapy - are not credible. The figures are derived from Edwards et al (Rheumatology, 2005; 44:1394-8) and there are good reasons to question the legitimacy of using these figures:
 - this study covered all RA patients in the GP database irrespective of disease duration and number of prior DMARDs. It is recognised that the response to therapy is lower in patients with more severe disease and the more prior DMARDs that have been tried unsuccessfully.
 - the number of patients included in the database on leflunomide and ciclosporin would have been very small.
- d. combining an over-estimate of the benefit of conventional DMARDs with an over-estimate of the longevity of conventional DMARD therapy and under-estimate of

early biologic quitters runs the risk of compounding errors and substantially over-estimating the QALY benefit associated with conventional DMARD therapy compared to biologic therapy. It is notable that none of the assumptions made about the efficacy of conventional DMARDs are tested in the scenario analyses. In conclusion, the basis of the models assumptions should be questioned and scenario analyses run in which the time to quitting azathioprine, ciclosporin and leflunomide should be reduced, the HAQ multiplier used for conventional DMARDs should be reduced and the early quit rate for biologic therapy increased.

- e. HAQ scores on biologic therapy – the model assumes stable HAQ whilst on therapy (but a scenario analysis is performed with HAQ deterioration of 0.03/year) which is a reasonable assumption for anti-TNF and abatacept therapy. However, the model does not capture the ‘flare and treat’ nature of repeated rituximab therapy - in clinical practice, patients who respond to rituximab are not re-treated unless/until their disease flares again. This involves a period of increased disability and reduced QOL before control is re-established. For subsequent cycles the re-treatment period is stable and so flare can to some extent be predicted and pre-empted. Alternatively, clinicians might attempt to avoid ‘flare and treat’ by increasing the frequency of rituximab administration which is shown to have a large impact on the ICER of rituximab in the scenario analyses. The overall impact of this may be very difficult to model, but it should be acknowledged that the ICER for rituximab is probably an under-estimate as a result.

I would like to finish with some general comments. From the perspective of a clinical rheumatologist, it is apparent that some patients respond very well to their third or fourth biologic drug. Firstly, the positive impact this has on the patients’ quality of life, employment prospects and societal productivity should not be under-estimated. Health Economic evaluations that continue to be restricted to an NHS (rather than a societal) perspective remain, in my opinion, fundamentally flawed. Secondly, the negative impact of potentially effective drugs being restricted for use should also not be under-estimated. An increasing number of patients have tried and failed their first anti-TNF drug and there will be enormous unmet need if other biologic drugs are not recommended for use.



2.

1. Overall the epidemiology and clinical presentation of RA is not significantly different in Scotland compared to England and Wales. The recent NAO report for England and Wales, which is referred to in the “Background” section, is noted which has suggested a higher incidence and prevalence than previously believed and this is likely to be true of Scotland also.
2. The patterns of service provision are similar whilst recognising the different NHS structures in Scotland. Numerically, however, provision of specialist services may be poorer. It is estimated that there are 0.65 WTE Consultants/100 000 population (Scottish Society for Rheumatology figures, predating recent appointments) compared to the figures of 1/100 000 for England and 1/106 000 for Wales quoted in the report. In addition, whilst no formal data exist on provision of specialist nurses, it is likely that the role of specialist nurses in delivering care for RA patients is less well developed in Scotland. This may have an effect on the extent that NICE clinical guideline on RA is implemented in Scotland compared to England and Wales, although as the report notes, practice will vary across centres in all nations of UK.
3. Regulatory approval for some of the technologies assessed may be different in Scotland. For example, the NICE STAs for Abatacept and Rituximab currently have no status in Scotland, although SMC advice has been similar. The newer technologies (Tocilizumab, Certilizumab Pegol etc) are currently undergoing appraisal by SMC and NICE (under the STA programme) and it is possible that different advice may be issued in Scotland than in England and Wales which could lead to subsequent differences in sequencing of biologic agents.
4. It is noted that the conclusions of this report have been limited by the relative lack of “head to head” RCTs between currently available biologic agents and rely to a large extent on observational studies. A forthcoming study, supported by Arthritis Research Campaign and based in Scotland, will compare anti TNF therapy with Rituximab in biologic naïve patients. Ultimately data from this study may influence the future sequencing of biologic agents, but in the short term, there may be Scottish patients who will have received Rituximab prior to anti TNF therapy, which otherwise would be outwith its current licensed indication. For these individuals, again the treatment pathway may be different to the scenario described in this report

Overall, I would consider that these differences in the disease epidemiology and presentation, clinical practice and service provision would have fairly marginal overall effect on the extent that the conclusions of this assessment report would be applied differently in Scotland.

██████████, ██████████

3. This submission is based on the evidence contained within the above document and interpreted with special reference to NHS Scotland.

With respect to this, the following are noted:

- 1) Rheumatologists in Scotland are not restricted currently in their ability to switch patients to a second TNF inhibitor or Rituximab after failure of a first TNF blocker.
- 2) There is no guidance in Scotland as to which is the most cost-effective or preferred second agent or patient pathway after the first TNF failure.
- 3) Abatacept is not recommended by the SMC for use in patients with Rheumatoid Arthritis (RA).
- 4) Tocilizumab has recently been recommended by the SMC as either a first biologic agent after traditional DMARD failure or for use subsequent to one or more TNF failures.
- 5) Certilizumab pegol is currently under assessment by the SMC (due Jan 2010). This product has a 'Patient Access Scheme' attached to it which allows an initial 3 months of free treatment. If this is approved in Scotland then the ability to try a TNF blocking agent for a 3 months free trial may well influence the decision of rheumatologists in Scotland about the order in which they wish to try different therapies.
- 6) Scotland has a largely rural population and this affects decisions by both patients and Consultants on which treatment to select as patients may be reluctant to travel to major hospitals for regular infusions.

Other factors that may have an impact on which treatments should be recommended in Scotland are:

- 1) Scotland has a lower rate of Rheumatologists per population than in England and there is therefore even greater restriction on outpatient space. Consequently, the ability of consultants to closely monitor their patients, as recommended by NICE 2009 and which results in good response with traditional DMARDs (Grigor et al., 2004), is impaired.
- 2) The availability and capacity of Day Case Units is critical to any treatment pathway that is recommended by the SMC. Infliximab, Rituximab, Abatacept and Tocilizumab all require regular infusions. In the absence of data regarding sufficient access to such facilities in Scotland, the SMC must ensure that any pathway accounts for the possibility that patients are either unable to travel to a suitable unit or that there is insufficient capacity within these units to accommodate RA patients.

Comments on the MTA report.

- 1) The conclusions made on the various therapies are accepted but it is felt that there is data available that would have been helpful to the process. This data may have been published after the literature review had taken place:
 - a. A Finnish Uncontrolled Retrospective study on Rituximab after 1 or more TNF failures (Valleala et al, 2009)

- 2) There is strong data to show that there is a link between smoking and RA, in particular in the citrullination of peptides. There are recent reviews (e.g Baka Z et al., 2009) and evidence from longitudinal cohort studies (Costenbader et al, 2008, Morgan AW et al., 2009). There is also gradually accumulating evidence that continued smoking blunts the response to therapy and with particular relevance to this report, anti-TNF therapy (van der Woude et al., 2009). It is therefore recommended that the report reflects this.

Evolving Data that is relevant

- 1) Data shown to Rheumatologists in Scotland by Dr. Will Dixon and Prof Deborah Symmonds from the BSRBR in 2008 showed that patients with interstitial fibrosis had a poorer outcome on TNF blocking agents than those without interstitial fibrosis and have double the mortality rate. As yet this data is only available in abstract form, I believe. Rheumatologists in Scotland are wary of prescribing anti-TNF agents to those with interstitial disease. In our Unit in Fife (and rheumatologists in Tayside) we screen all patients for fibrosis prior to initiating a TNF blocker and do not commence treatment if there is evidence of this. There is therefore a need for other treatments in these patients and this is likely to be either Rituximab or Tocilizumab.
- 2) At Eular 2009, Isaacs et al presented data from the Biomarkers study, a pooled post-hoc analysis from 2 Phase III Rituximab studies. The analysis determined the serological status of patients (RF or CCP positive) and compared the clinical outcomes at weeks 24 and 48 of those who were seropositive or negative. Measures included ACR and EULAR responses as well as DAS28 scores. 554 seropositive and 116 seronegative patients were included. At week 24 seropositive patients were more than twice as likely to achieve an ACR20 or 50 than those who were seronegative. At week 48 seropositive patients were more than 3 times more likely to achieve an ACR70 (20.9% vs 6.9% for seronegatives).

These two issues should be pursued further before recommendations are made because they are fundamental to the choice of both an initial biologic agent and any subsequent biologic.

In Summary

This field is evolving very rapidly and new information is becoming available that will guide the rheumatologist towards the safest and most effective therapies. In addition, in Scotland, Tocilizumab (and possibly shortly Certilizumab pegol) is now available. These have not been considered by this MTA and there is therefore a strong likelihood that guidelines produced from this MTA will not be applicable to Scotland.

References

Grigor C, Capell H, Stirling A, McMahon AD, Lock P, Vallance R et al. Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study); a single blind randomized controlled trial. *Lancet* 2004; (364): 263-269

Valleala H, Korpela M, Mottonen T, Hienonen-Kampas T, Kauppi M, et al. *Scand J Rheumatol* Oct 2009, Vol. 38 Issue 5, p323-327
Rituximab therapy in patients with rheumatoid arthritis refractory or with contraindication to anti-tumour necrosis factor drugs: real-life experience in Finnish patients.

Baka Z. Buzas E. Nagy G
Rheumatoid arthritis and smoking: putting the pieces together. [Review] [96 refs] *Arthritis Research & Therapy*. 11(4):238, 2009.

Costenbader KH. Chang SC. De Vivo I. Plenge R. Karlson EW.
Arthritis Research & Therapy. 10(3):R52, 2008
Genetic polymorphisms in PTPN22, PADI-4, and CTLA-4 and risk for rheumatoid arthritis in two longitudinal cohort studies: evidence of gene-environment interactions with heavy cigarette smoking.

Morgan AW. Thomson W. Martin SG. Yorkshire Early Arthritis Register Consortium. Carter AM. UK Rheumatoid Arthritis Genetics Consortium. Erlich HA. Barton A. Hocking L. Reid DM. Harrison P. Wordsworth P. Steer S. Worthington J. Emery P. Wilson AG. Barrett JH.
Arthritis & Rheumatism. 60(9):2565-76, 2009 Sep.
Reevaluation of the interaction between HLA-DRB1 shared epitope alleles, PTPN22, and smoking in determining susceptibility to autoantibody-positive and autoantibody-negative rheumatoid arthritis in a large UK Caucasian population.

van der Woude D. Young A. Jayakumar K. Mertens BJ. Toes RE. van der Heijde D. Huizinga TW. van der Helm-van Mil AH.
Arthritis & Rheumatism. 60(8):2262-71, 2009 Aug.
Prevalence of and predictive factors for sustained disease-modifying antirheumatic drug-free remission in rheumatoid arthritis: results from two large early arthritis cohorts.

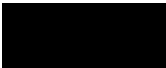
Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis.
Mattey DL. Brownfield A. Dawes PT.
Journal of Rheumatology. 36(6):1180-7, 2009 Jun.



4.

I have read the Executive Summary and some of the main body of the Report. You asked for my views regarding whether there are differences in epidemiology or current treatment pathways for RA in Scotland which would suggest that the evidence presented in the Report would differ in its applicability to the rest of the UK. I can comment as follows:

1. Regarding epidemiology, there is no reason to think that the epidemiology of RA in Scotland differs significantly from that in the rest of the UK.
2. The overall management of RA in Scotland does not differ from that in the rest of the UK in that a major therapeutic goal is the tight control of joint inflammation using the aggressive use of traditional DMARDs and biologic DMARDs.
3. Like other UK rheumatologists, rheumatologists in Scotland would normally follow British Society for Rheumatology guidelines for using biologic drugs.
4. There are significant differences in rheumatology manpower between Scotland and England (less in Scotland). This is likely to adversely impact service delivery including the administration of biologic drugs in that one agent may be chosen over another because of local manpower issues around administering the drug. This is particularly relevant for those drugs that require iv administration (infliximab, rituximab, abatacept and tocilizumab).
5. The recent approval of tocilizumab by SMC represents a potentially significant difference in the management of RA in Scotland compared to England and Wales.
6. There is local experience in Lothian of switching between anti-TNF drugs in patients with RA. Our experience would suggest that to do so results in a meaningful improvement in disease control in a significant proportion of cases.



End