National Institute for Health and Clinical Excellence

Rheumatoid Arthritis – drugs for treatment after failure of a TNF inhibitor

Comments on the Assessment Report - Wyeth Pharmaceuticals

Points to Highlight	Section / page number	Consultee comment
Data source for etanercept efficacy	Section 5.3.2.4 Page 72 Figure 13	A comparison of baseline HAQ values in the studies included in this report reveals that across all biological agents HAQ values ranged from 1.29 to 2.07. This contrasts sharply with the range of baseline values seen in Iannone et al (2007), ranging from 0.09 to 2.16 (mean 0.9). The majority of patients in this study had achieved a satisfactory response to infliximab and switched due to adverse events. Whilst the majority of data referenced in this report refers to HAQ changes from the point of switch (i.e. after loss of efficacy), the study by Iannone et al (2007) does not measure the true incremental HAQ change from baseline, resulting in apparent lower changes (between 0.15 and 0.45 at 3 month and 0.00 at 6 month). Whilst the study supports the effectiveness of etanercept in maintaining clinical efficacy after switch due to adverse events, this data is not representative of the actual efficacy of etanercept, resulting in an overall underestimation of efficacy. Its inclusion in the model introduces bias and the exclusion of this data would lead to a more homogeneous dataset and robust outcome.
Data source for etanercept efficacy	Section 5.3.2.2 Page 67 Table 10	Similarly the study by Laas et al (2008) includes a high number of DMARDS (6-7), compared to the other biologics included in the analysis (maximum of 5). This observation points to the problem of comparing studies from different time periods as treatment paradigms have changed and earlier studies were generally performed in more severe patients (with a lower likelihood of responding to therapy), thus disadvantaging the evaluation of those agents that were first to the market (infliximab and etanercept). Any model needs to take account of this source of bias and weight these baseline characteristics as demonstrated by Nixon et al 2007 (Statistics in Medicine, 1237-1254).
Rituximab efficacy data	Section 5.3.5.1 Page 98 -113	As discussed earlier, a growing understanding of the pathology behind RA led to changes in treatment paradigms with earlier, "aggressive" treatment resulting in overall better outcomes for patients. These changes in clinical practice, in particular the emphasis on achieving remission through intensive DMARD therapy and earlier use of biological agents, may favour studies of agents that came more recently to the market and penalises those agents like etanercept and infliximab that were used in the infancy of clinical experience with biologics. In particular the data included in the analysis for etanercept shows a range of previous DMARD use between 4.1 and 7, whereas data for rituximab shows a DMARD range between 2.4 and 4.2. These differences will need to be weighted in the model.

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<tr><th>Points to Highlight</th><th>Section / page number</th><th>Consultee comment</th></tr>
<tr><td></td><td></td><td>Patient with longer disease history who have already failed multiple treatments have a reduced capacity to benefit from treatment, again there is no evidence that this has been taken into account in the evaluation of the individual groups or treatment groups as a whole.</td></tr>
<tr><td>Rituximab dosing frequency</td><td>Section 6.3.1.2
Page 213
Table 79</td><td>The dosing frequency has been modelled using a 8.7 month interval however data on repeat dosing indicates that the interval is 7.0 months:

• ‘Response to Rituximab in patients with Rheumatoid arthritis is maintained by Repeat Therapy: results from a Open label trail. Annals Rheumatic Diseases 2006, 65 (suppl II) :510 R.F.van Vollenhoven’ –

<table>
<tr><td colspan="3">Median Time to repeat treatment (weeks)</td></tr>
<tr><td></td><td>Prior TNF (n=82)</td><td>No Prior TNF (n=50)</td></tr>
<tr><td>Second Course</td><td>30.9</td><td>36.7</td></tr>
<tr><td>Third Course</td><td>30.1</td><td>43.0</td></tr>
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• Rituximab therapy in Rheumatoid Arthritis in Daily Practice. Assous et al, Journal of Rheumatology: January 2008. - This observational, retrospective analysis showed that of the fifty patients included in the review nine (18%) had no clinical response to rituximab. Of the responders, eleven (22%) relapsed during the first six months after initial treatment and were retreated with rituximab at six months. The paper does not give the mean or median time to relapse of these nine patients. All of the thirty remaining responders (60%) had a documented relapse. Neither the mean nor median times from initial treatment to relapse are reported for these patients. The paper highlights only the median time to initiation of a second treatment with rituximab for this group (9 months, range 6-24 months) and includes the 22% of early relapses in this analysis thus distorting the true reflection of time to relapse after an initial course of rituximab.</td></tr>
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Rituximab administration costs	Section 6.3.1.2 Page 212	Administration costs for infliximab, rituximab and abatacept are given as £141.83 within this MTA, where as the administration costs for rituximab within the single technology appraisal costing template are £1586 (£793x2) (H98). Patients are given an infusion of steroids prior to their first 2 infusions of rituximab and may require additional time and resources however this is not reflected in a different cost when compared to other IV administered regimens.
Modelling of initial HAQ improvement	Section 6.3.1.2 Page 209	The independent economic assessment model estimates the initial HAQ change using a randomly generated 'multiplier'. However, insufficient evidence is provided to justify this approach as opposed to a 'fixed' decrease (improvement) in HAQ upon commencing treatment. It would be of use to reviewers to be able to view the outputs from the model and to produce a 'mean HAQ change' for each treatment, which could then very validated against the source data.
Etanercept start-up costs	Section 6.3.1.2 Page 214 Table 81	Given the same drug costs and monitoring requirements for etanercept and adalimumab it is not clear why the start-up costs included in the BRAM model are higher for etanercept than adalimumab.
Modelling quality of life outcomes – credible results?	Section 6.3.2.1 Page 217	In the reference case model, the 95% credible range for costs (for etanercept) is £68,700 to £81,200. This range is relatively tight (varying within 10% of the mean), reflecting the relative certainty around key cost drivers (i.e. drug costs). However, the 95% credible range for QALY outcomes is -2.29 to +7.75. This range would appear to be very wide. It is not clear what proportion of results lead to an overall negative outcome in QALYs. It is thought that such findings are the results of patients quickly reaching a HAQ threshold where QoL becomes negative (i.e. around 2.5 HAQ) and, thereafter, continue to live with QoL for their remaining years. If patients quickly reach a HAQ ceiling (either through reaching a value of 3.000 or by reaching the negative QoL threshold in the 'non-negative' scenario analysis), then this will disadvantage those therapies that are producing QoL gains by successfully managing patients' HAQ levels. Furthermore, the quicker that patients reach that 'ceiling', the lower the potential scope for QoL benefits associated with the more effective treatments. It would be useful for the model to generate outputs showing the time until the ceiling is reached

		in order that this can be validated against long-term real world evidence. This is likely to be a key driver of the QALY outcomes and, as such, should be further investigated.
Costs associated with the treatment of adverse events	Section 6.3.2.2 Page 220 Table 86	It is not clear why the impact of including the costs of treating adverse events has a greater impact on the ICER for etanercept than on the other TNF inhibitors. None of the data selected for evaluation of adalimumab had reported adverse events (Section 5.3.1.5 Page 63). Data from the BSRBR demonstrates parity with respect to adverse events between the different TNF inhibitors. In a recent Cochrane review* etanercept had the least withdrawals due to adverse events compared with the other TNF inhibitors and the author judged etanercept to be safer than adalimumab, anakinra and infliximab. *Biologics for Rheumatoid arthritis: Singh et al, Canadian Medical Association Journal. 2009 DOI:10.1503/cmaj.091391.