Abbott's response to the Appraisal Consultation Document for sequential use of TNF inhibitors in Rheumatoid Arthritis

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) prepared by the Committee for the appraisal of adalimumab, etanercept and infliximab for sequential use of TNF inhibitors in case of inefficacy. Abbott's detailed comments from page 3 onwards are set out under section headings containing the questions NICE asks consultees to comment on for the ACD.

Executive Summary

Abbott considers that there is a strong rationale for the recommendation of sequential use of TNF inhibitors in case of inefficacy:

1. Estimates from the BSRBR modelling using categorical response according to the EULAR criteria indicate a cost per QALY estimate for sequential TNF inhibitors of under £30K applying discount rates of 6% and 1.5%. This estimate of cost effectiveness supports Abbott's contention that the higher cost per QALY estimates generated in the BRAM model should not be considered as realistic estimates, as they are based on unduly pessimistic assumptions of comparative effectiveness of TNF inhibitors when used sequentially.

2. In order to have a full understanding of the cost effectiveness estimates from the BRAM, Abbott would like to request an executable version of the model, with a list of the data inputs for key variables in this revised version of the BRAM modelling. It is unclear whether cost offsets are included in the latest analyses using the BRAM model. For consistency with the modelling conducted for the appraisals of rituximab and abatacept, it is appropriate that cost offsets due to lower non-drug resource utilisation are included in the current revised BRAM modelling. Abbott considers inclusion of cost offsets due to lower hospitalisation and surgery costs will further reduce the ICERs for sequential use of TNF inhibitors. It is also unclear whether the latest BRAM results reflect the use of lower starting HAQ scores from the NOAR database, or a more reflective distribution of HAQ scores for the sequential TNF inhibitor population. Given the greater effectiveness of TNF inhibitors compared to other treatment options in the latest version of BRAM model results, it is important to consider whether the results of the BRAM model are sensitive to the starting HAQ level. Abbott considers that use of a HAQ distribution for a population with higher mean HAQ than the NOAR cohort may further reduce the estimated ICERs for sequential use of TNF inhibitors.

3. It should be recognised that the HAQ improvements observed for patients in the BSRBR and ReACT studies partly reflect historical data for switch patients with long disease duration and a high number of failed prior DMARDs. In this population the HAQ levels are to a large degree driven by irreversible joint damage[1, 2]. Given the evolving trend to treat early in RA to avoid disability, it is likely that future patients failing their 1st TNF inhibitor for efficacy reasons would have a greater propensity to respond to a second TNF inhibitor. Abbott considers that future TNF inhibitor switch patients would therefore be able to achieve higher levels of mean HAQ improvement than were observed in the BSRBR and ReACT studies. Therefore, Abbott considers that the rationale for restricting sequential use of TNF inhibitors based on historical data is unnecessary on cost effectiveness grounds.

4. HAQ improvement data from cohorts that have recommended DMARD therapy after inefficacy of a TNF inhibitor are rare. Therefore, data from cohorts that start new DMARD therapy in established rather than early RA are important. It is unclear why the effectiveness of conventional DMARDs from the British Rheumatoid Outcomes Study Group (BROSG) study when used in established RA has not been taken into greater consideration in this appraisal. The initial HAQ improvements of the placebo arm in Genovese as used in the BRAM modelling are not supported by the available evidence on conventional DMARD effectiveness from the BROSG study. Abbott considers that use of a lower HAQ multiplier for conventional DMARDs than applied in the "new" values

BRAM analyses using the Genovese data would result in improved cost effectiveness for sequential use of TNF inhibitors versus conventional DMARDs. Abbott is unable to predict what the cost per QALY estimates would be without seeing any sensitivity analyses on this point using the BRAM model. However, it is also important to assess the uncertainty around the effectiveness of conventional DMARDs when the minimum effectiveness required for sequential use TNF inhibitors is analysed.

5. The committee noted that the incremental cost effectiveness of adalimumab, etanercept and infliximab after the failure of a TNF inhibitor would not be a cost effective use of NHS resources in comparison with the use of rituximab. Abbott considers that the mean retreatment interval for rituximab would be less than 9 months in UK clinical practice when patients would be retreated to maintain adequate DAS28 response. Alternatively, use of a 9 month mean retreatment interval should be associated with commensurately lower QALY gains for rituximab, as patients losing response would suffer a reduction in their quality of life until retreated. Therefore, the cost per QALY for sequential use of TNF inhibitors versus rituximab would be lower than estimated in the latest BRAM modelling and would likely fall within a range considered acceptable for the use of NHS resources.

6. Abbott considers that the recommendation that no patients should be allowed to use TNF inhibitors sequentially is unnecessarily restrictive given the cost effective estimates of £31K to £39K per QALY applying mean HAQ improvements of –0.51 from the ReACT study. Abbott considers that the cost per QALY would be lower than these estimates for the reasons outlined above. Abbott is concerned that due consideration has not been given to the cost effectiveness of subgroups of switching patients. In particular, studies that have considered the issue have consistently found a greater propensity to respond among those patients who have lost response to a previous TNF inhibitor. This subgroup is therefore likely to be associated with a lower cost per QALY versus conventional DMARDs and versus rituximab.

7. Emerging data suggest that successful therapy with TNF inhibitors may have an impact on secondary outcomes including work disability, mortality and cardiovascular outcomes in RA, in addition to the core outcomes of disease activity, function and radiographic progression. Although it is accepted that survival benefits of TNF inhibitors have not been proven in randomised controlled trials, the benefits observed in observational studies suggest an important benefit for TNF inhibitors that has not been captured in the current cost effectiveness modelling. Furthermore, inclusion of the societal benefits of maintaining patients in work and reducing reliance on state disability benefits would substantially reduce the cost per QALY for sequential use of TNF inhibitors.

8. Abbott is concerned that the provisional recommendations not to allow switching to an alternative TNF inhibitor in case of inefficacy do not appear to have taken account of potential safety issues around sequencing of treatments including rituximab or patient preferences for home treatment with adalimumab or etanercept.

9. Given the cost per QALY estimates presented in the ACD and the uncertainty around these results, Abbott considers that the low quality of life of the patient population, patient preferences for home treatment, potential mortality benefits of TNF inhibitors, the societal costs associated with RA and uncertainty around safety with sequences of treatment involving rituximab should also weigh in favour of patients having the option to receive sequential TNF inhibitors in case of inefficacy.

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

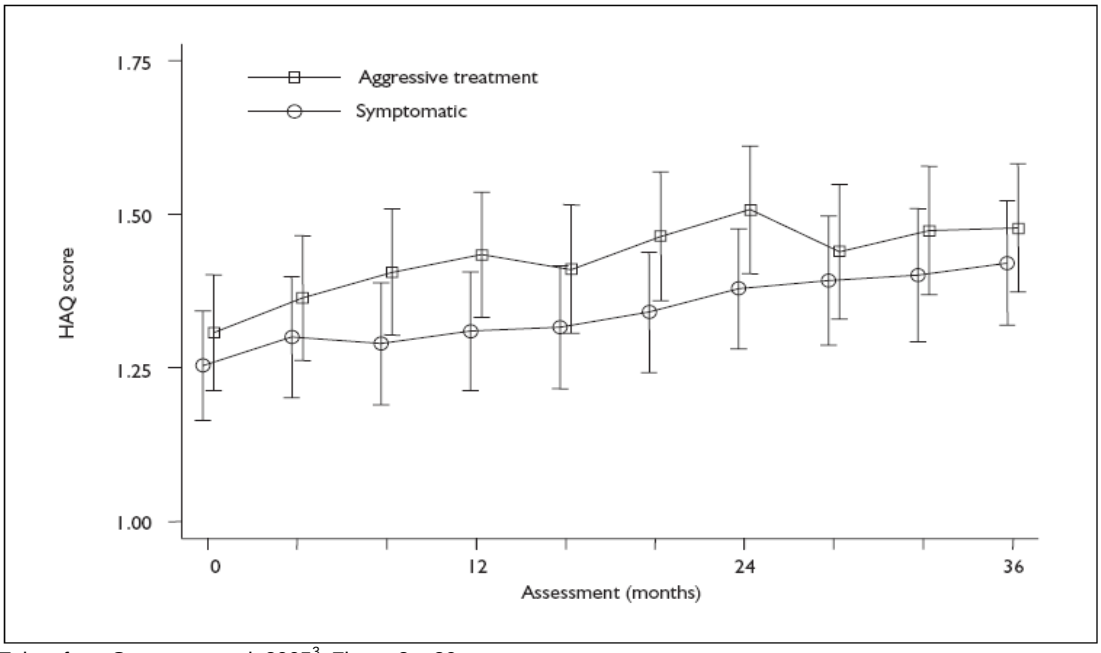
In general, Abbott considers that the majority of published evidence has been identified regarding the effectiveness of TNF inhibitors when used sequentially. However, Abbott considers that a number of relevant aspects of the evidence have not been taken into account.

1.1 Data on conventional DMARD effectiveness from BROSG study

It is unclear why the evidence on the effectiveness of conventional DMARDs from the British Rheumatoid Outcomes Study Group (BROSG) study when used in established RA has been consistently overlooked in this appraisal. It is acknowledged that HAQ improvement data from cohorts that have recommenced DMARD therapy after inefficacy of a TNF inhibitor are rare. Therefore, data from cohorts that start new DMARD therapy in established rather than early RA are important.

Data from the BROSG Study, a randomised trial of symptomatic versus aggressive use of DMARD therapy, have been published as a HTA monograph in September 2005 and provide estimates of the effectiveness of a sequence of conventional DMARDs used as part of either a symptomatic or aggressive treatment strategy[3]. For all time points and in both treatment arms, regardless of symptomatic or aggressive treatment with a sequence of conventional DMARDs, the HAQ score actually worsened rather than improved (see Figure 1 below).

Figure 1. HAQ change over time in an RCT of symptomatic control of RA using conventional DMARDs or aggressive control of RA using conventional DMARDs



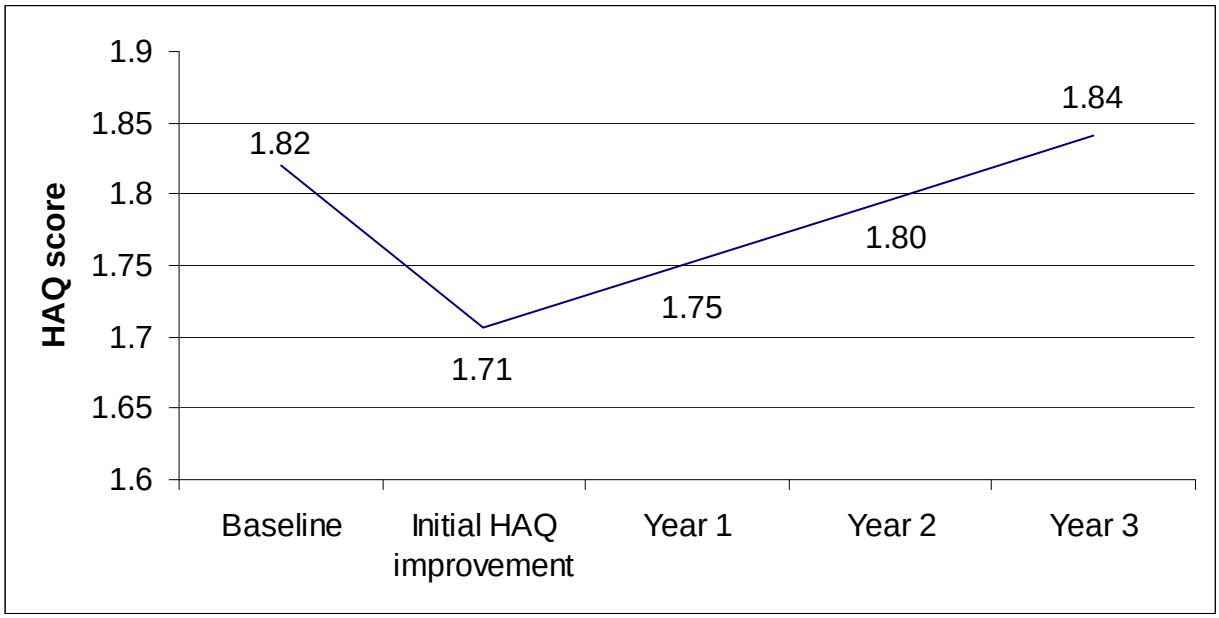
Taken from Symmons et al. 2005[3], Figure 3, p39.

Abbott considers that the study design of the BROSG is able to answer the question required for the economic modelling, namely what is the effectiveness of conventional DMARDs used sequentially in patients with established RA. It could be argued that the BROSG study does not provide evidence of the effectiveness of individual conventional DMARDs. However, given the use of the Genovese placebo + methotrexate arm HAQ improvement from the abatacept study as a proxy for the effectiveness of all conventional DMARDs, this argument is considered not applicable.

Furthermore, the BROSG data highlight that the short term HAQ improvement observed in the Genovese study[4] and used in the economic modelling does not necessarily represent the lower bound of HAQ improvement of conventional DMARDs after failed TNF inhibitor therapy.

Figure 2 illustrates the HAQ profile over time for a patient on conventional DMARDs using the Genovese data in the BRAM model.

Figure 2. HAQ change over time for conventional DMARDs applying data from Genovese et al (-0.11 initial HAQ improvement and 0.045 annual worsening)



These data highlight that a short term HAQ improvement of –0.11 leads to a sustained reduction in the mean HAQ score over 2.5 years. Abbott believes it is therefore misleading to characterise the use of the Genovese placebo data as "*no active treatment effect of conventional DMARDs*". The initial HAQ improvements of the placebo arm in Genovese are not supported by the available evidence on conventional DMARD effectiveness from the BROSG study or the US National Databank for rheumatic diseases. Abbott considers that use of a lower HAQ multiplier for conventional DMARDs than applied in the "new" values using the Genovese data would result in improved cost effectiveness for sequential use of TNF inhibitors versus conventional DMARDs. Abbott is unable to predict what the cost per QALY estimates would be without seeing any sensitivity analyses on this point using the BRAM model. However, it is also important to assess the uncertainty around the effectiveness of conventional DMARDs when the minimum effectiveness required for sequential use TNF inhibitors is analysed.

1.2 Modelling of cost offsets and HAQ improvement

In order to have a full understanding of the cost effectiveness estimates from the BRAM, Abbott would like to request an executable version of the model, with a list of the data inputs for key variables in this revised version of the BRAM modelling.

It is unclear whether cost offsets are included in the latest analyses using the BRAM model. Section 4.2.2 of the ACD indicates that joint replacement and associated costs were included in sensitivity analyses, however it is unclear where the results of these analyses are presented. For consistency with the modelling conducted for the appraisals of rituximab and abatacept, it is appropriate that cost offsets due to lower non-drug resource utilisation are included in the current revised BRAM modelling.

In the BRAM, as in the model submitted by Abbott, cost offsets due to hospitalisation/ surgery are modelled as a function of the HAQ improvement *i.e.* each HAQ point improvement was associated with a £860 reduction in medical costs. Sensitivity analyses in the Technology Assessment Report indicated that the cost offsets have a negligible impact on the overall model results of the BRAM. However, these analyses were run on the previous base-case model where TNF inhibitors were considered to be broadly similar in effectiveness to conventional DMARDs in terms of the HAQ multipliers used for short-term improvement.

Given the greater effectiveness of TNF inhibitors compared to other treatment options in the latest version of BRAM model results, it is important to assess whether the latest results of the BRAM model are sensitive to the absolute value of cost offsets attributable to a one-unit HAQ improvement. Abbott considers inclusion of cost offsets due to lower hospitalisation and surgery costs will further reduce the ICERs for sequential use of TNF inhibitors.

Similarly, changing the baseline HAQ level had a negligible effect on the original base-case BRAM results. It is unclear whether the latest BRAM results reflect the use of lower starting HAQ scores from the NOAR database, or a more reflective distribution of HAQ scores for the sequential TNF inhibitor population. Given the greater effectiveness of TNF inhibitors compared to other treatment options in the latest version of BRAM model results, it is important to consider whether the results of the BRAM model are sensitive to the starting HAQ level. Abbott considers that use of a HAQ distribution for a population with higher mean HAQ than the NOAR cohort may further reduce the estimated ICERs for sequential use of TNF inhibitors.

1.3 Uncertainty over retreatment period for rituximab

In the ACD (section 4.3.13) the committee noted that the incremental cost effectiveness of adalimumab, etanercept and infliximab after the failure of a TNF inhibitor would not be a cost effective use of NHS resources in comparison with the use of rituximab. If the cost effective use of NHS resources for sequential use of TNF inhibitors vs. rituximab is to be made, it is critical to ensure that the comparison is appropriate.

In TA 130 (for the use of adalimumab, etanercept and infliximab in RA) it is recommended that treatment should only be continued if there is an adequate response at 6 months, such response being defined as a reduction in DAS28 of at least 1.2 from baseline.

In TA 126 (for the use of rituximab for the treatment of RA) it is recommended that the treatment should only be continued if there is an adequate response following initiation of therapy (without regard to timeframe). Such adequate response is defined as an improvement in DAS28 of 1.2 or greater. Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months. In order for continued treatment of TNFs, the maintenance of DAS28 reduction of 1.2 is required, such requirement does not appear to be in place for rituximab.

The latest BRAM analyses of the cost effectiveness of sequential use of TNF inhibitors versus rituximab are based on a mean cost of £6,848 for rituximab. This cost was taken from NICE TA 126 for rituximab and was based on a mean retreatment period of 9 months (307 days). As noted in TA 126, the cost effectiveness of rituximab is sensitive to the mean retreatment interval applied in the modelling.

It should be noted that the timing of retreatment with rituximab was at the investigator's discretion in clinical studies[5]. Abbott considers that the optimal interval for retreatment with rituximab remains to be determined for UK clinical practice. In this respect, it should be noted that according to the NICE criteria for response to rituximab, an adequate response would be defined as a 1.2 point improvement in DAS28 score. At the time of loss of this response the patient should be retreated with rituximab. It can therefore be observed that the mean time to retreatment in the clinical studies of rituximab does not necessarily equate to the mean retreatment interval if a maintenance rule requiring a 1.2 point DAS28 improvement for rituximab therapy in clinical practice were to be applied. It should also be noted that the modelling of rituximab costs should not be independent of treatment effect, that is to say, the modelling of QALY gains achievable with rituximab should take account of lower quality of life improvements when patients have lost response, as defined by maintenance of a 1.2 point DAS28 improvement.

In Keystone et al. the DAS28 of patients prior to re-treatment is assessed[5]. The mean time between treatments for course 1 to course 2 was 33.2 weeks (232 days). This figure of 33.2 weeks is substantially less than the 307 days between re-treatment as cited by the

manufacturer in TA 126. The mean DAS28 for the Keystone study population just prior to course 1 was 7.01 and just prior to course 2 re-treatment was 6.17 or a reduction of 0.84. The mean DAS28 just prior to course 3 of re-treatment was 6.01 (with a mean re-treatment interval of 32.2 weeks between courses 2 and 3) resulting in a reduction of –1.00 from baseline. In neither case (between course 1 and course 2 or between course 1 and course 3) does the mean decrease in DAS28 meet the NICE defined level of "adequate response" of >-1.2 from baseline. This is in spite of the fact that the time between re-treatment intervals were in both cases substantially less than the 307 days cited in TA 126. It should also be noted that the manufacturer of rituximab has been asked by the FDA for a post approval commitment of a safety and efficacy trial with respect to the re-treatment of rituximab (NCT00422383). In this trial patients will be dosed at day 0 and day 180. This dosing schedule therefore suggests a 9-month retreatment interval may not be optimal to maintain response with rituximab.

In summary, Abbott considers that the mean retreatment interval for rituximab would be less than 9 months in UK clinical practice when patients would be retreated to maintain adequate DAS28 response. Alternatively, use of a 9 month mean retreatment interval should be associated with commensurately lower QALY gains for rituximab, as patients losing response would suffer a reduction in their quality of life until retreated. Therefore, the cost per QALY for sequential use of TNF inhibitors versus rituximab would be lower than estimated in the latest BRAM modelling and would likely fall within a range considered acceptable for the use of NHS resources.

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?

2.1 Minimum effectiveness required for sequential use of TNF inhibitors to be cost effective according to the BRAM model estimates

Consideration should be given to the limited evidence base for RA treatments that is available using HAQ as an outcome measure. Of the 21 studies considered eligible for full review in evaluating the sequential use of TNF inhibitors, 21 reported improvements in DAS, DAS 28, ACR and/ or EULAR criteria compared to only 4 reporting HAQ outcomes. Furthermore, the majority of conventional DMARDs have limited HAQ outcome data available.

Given the weaknesses of the evidence base specifically for HAQ improvements, Abbott considers that the ACD recommendations place undue focus on those aspects of the evidence that indicate small HAQ improvements with sequential TNF inhibitor use. It is important that HAQ data are not considered in isolation from the patient population and clinical setting in which the improvements were derived.

The two largest available data sources for HAQ improvement with sequential TNF inhibitor use are the BSRBR and the ReACT study (Bombardieri et al[6]). The BSRBR indicates a mean HAQ improvement of 0.21 when adjusted for confounders. The BSRBR data does not distinguish between types of switch patients. The ReACT study indicates mean HAQ improvements of 0.33 to 0.52 for switches due to inefficacy depending on whether switchers were primary non-responders or those who had experienced a loss of response. This is compared to a mean HAQ improvement of 0.55 for patients receiving their 1st TNF inhibitor. It should be borne in mind that the standard deviation for HAQ improvement is greater than 0.50 for all subgroups, therefore a substantial proportion of switch patients will have a response equal to that achieved on their 1st TNF inhibitor, particularly those patients experiencing loss of response rather than those who were primary non-responders to their 1st TNF inhibitor. The minority of studies that have stratified primary non-responders versus loss of response have consistently found a greater propensity to respond among those who have lost response to a TNF inhibitor[6,7,8]. Furthermore, forthcoming data to be presented at the EULAR conference 2008 supports a greater response rate among patients who have lost response to a TNF inhibitor[9]. This subgroup is therefore likely to be associated with a lower cost per QALY versus conventional DMARDs and versus rituximab.

2.2 Effectiveness of a second TNF inhibitor based on US National Databank for Rheumatic Diseases data.

Abbott considers that it is misleading to use the mean HAQ improvement observed in the US National Databank for Rheumatic diseases as justification that the treatment effect of a 2nd TNF inhibitor could be very small. It is unclear why the HAQ improvement in absolute terms is only around 1/3 of that observed for the placebo + methotrexate arm in the Genovese study as used for the modelling of the effectiveness of conventional DMARDs post TNF inhibitor failure. These HAQ changes highlight the dangers of utilising HAQ changes from different studies without detailed consideration of differences in the patient populations. Abbott considers the absolute HAQ improvements in the US dataset are unlikely to be representative of the effectiveness of sequential TNF inhibitor use in the UK.

2.3 Evolving trend for early aggressive treatment of Rheumatoid Arthritis and implications for HAQ improvements attainable by switching patients

As the committee has recognised, one of the weaknesses of the HAQ measure is that it encompasses aspects of disease activity and functional impairment. In this context it should be recognised that the HAQ improvements observed for patients in the BSRBR and ReACT studies partly reflect historical data for switch patients with long disease duration and a high number of failed prior DMARDs. Given the evolving trend to treat early in RA to avoid disability, it is likely that future patients failing their 1st TNF inhibitor for efficacy reasons would have a greater propensity to respond to a second TNF inhibitor due to having sustained lower levels of irreversible joint destruction.

Abbott considers that future TNF inhibitor switch patients would therefore be able to achieve higher levels of mean HAQ improvement than were observed in the BSRBR and ReACT studies. Therefore, Abbott considers that the rationale for restricting sequential use of TNF inhibitors based on historical data is unnecessary on cost effectiveness grounds.

2.4 Excessive focus on the BRAM model results compared to the results from the model developed by the BSRBR.

Abbott is concerned that the results of the modelling of sequential use of TNF inhibitors as submitted in the appeal by the BSR, utilising BSRBR data appear to have been dismissed without due consideration. An assertion has been made that the difference in cost per QALY estimates for the BSR modelling compared to the BRAM is largely attributable to the use of different discount rates in the latest version of the BRAM modelling:

"The committee noted that the BRAM and BSRBR analyses had used different discount rates, and considered that had the same discount rates been applied to both analyses then the estimates of cost effectiveness would have been similar." Section 4.3.7 ACD, page 24 of 37.

However, it should be noted that discount rates of 3.5% in the BSRBR model have not been modelled in the sequential use analyses. To assess the potential impact of the different discount rates, the cost effectiveness results for the 1st use TNF inhibitor can be compared. Applying discount rates of 6% for costs and 1.5% for outcomes the base case ICER reported by Brennan et al. is £23,882 for a 1st TNF inhibitor. Applying discount rates of 3.5% for both costs and outcomes yields an ICER of £32,013 for the 1st TNF inhibitor (a 34% increase). Given the base case ICER for sequential TNF inhibitor use of £24,570 an estimated 34% increase in the ICER would yield a figure of £32,924. This is in the lower range of cost per QALY estimates from the BRAM model and further reinforces the point that the upper range of cost per QALY estimates from the BRAM model up to £164K should be viewed as outliers based on unduly pessimistic assumptions regarding the effectiveness of TNF inhibitors used sequentially.

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?

Abbott considers that the recommendation that no patients should be allowed to use TNF inhibitors sequentially in case of inefficacy is unnecessarily restrictive given the cost effective estimates of £31K to £39K per QALY applying mean HAQ improvements of –0.51 from the ReACT study. Abbott considers that the cost per QALY would be lower than these estimates for the reasons outlined above in sections 1 and 2. Given the magnitude of these cost effectiveness estimates Abbott believes it is important to also take into account a number of additional reasons why a sequential TNF inhibitor should be allowed as a treatment option in addition to the options of giving the patient rituximab or returning the patient to conventional DMARD therapy.

3.1 No consideration of safety issues with using rituximab rather than 2nd TNF inhibitor.

Abbott is concerned that the provisional recommendations not to allow switching to an alternative TNF inhibitor in case of inefficacy do not appear to have taken account of potential safety issues around sequencing of treatments including rituximab. Longer term data and more patient years of experience with rituximab are needed to allow better interpretation and characterisation of the changes seen in immunoglobulin levels and the long term effects of repeated B cell depletion. As yet there have been no full publications of safety data from independent national registries of patients with RA treated with rituximab, although collection of such data are underway. Furthermore, patients not responding to rituximab have severely limited treatment options as the safety of further biologic therapy in patients with low or no circulating peripheral B cells is largely unknown. Some physicians and patients may be concerned about risks of infusion reactions, which although decreased in frequency with increasing courses of rituximab, was significant at first dose in the REFLEX study (23%). Further discussion on these points is available in section 10 of our response to switching further analyses sent to NICE on 27th February 2008.

3.2 Insufficient consideration of non-HAQ benefits of TNF inhibitors

Emerging data from recent TNF inhibitor RCTs and registries suggest that successful therapy with TNF inhibitors may have an impact on secondary outcomes including work disability, mortality and cardiovascular outcomes in RA, in addition to the core outcomes of disease activity, function and radiographic progression. Further data on these points is available in Abbott's response to switching further analyses sent to NICE on 27th February 2008. Although it is accepted that survival benefits of TNF inhibitors have not been proven in randomised controlled trials, the benefits observed in observational studies suggest an important benefit for TNF inhibitors that has not been captured in the current cost effectiveness modelling. Furthermore, inclusion of the societal benefits of maintaining patients in work and reducing reliance on state disability benefits would substantially reduce the cost per QALY for sequential use of TNF inhibitors.

3.3 Rituximab is not suitable for all patients

A course of rituximab is given as two intravenous infusions two weeks apart. This requires admission to a day ward, which must be equipped with full resuscitation equipment. Further, the concomitant administration of intravenous prednisolone with rituximab and oral prednisolone throughout the two-week period is mandated.

Some patients may have significant difficulty to undertake this treatment regimen several times per year, including the journey to the hospital and back. Such patients may benefit from the option of therapy administered in the home, for instance with adalimumab and etanercept therapy. Further, many patients may prefer a subcutaneous route of administration afforded by adalimumab or etanercept as opposed to an intravenous route.

In addition, rituximab is less effective in Rheumatoid factor seronegative (RF-) RA patients which account for >20% of the RA population[10], whereas TNF inhibitors have shown comparable efficacy in both RF+ and RF- patients[6,11].

Given the above, the patient and his/her physician should be given the option to select the most appropriate therapy with careful benefit-risk assessment of the options driving the choice of sequential therapy in this situation.

4. Are there any equality related issues that may need special consideration?

No issues that Abbott is aware of.

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