Abbott Laboratories comments on the Appraisal Consultation Document of golimumab (Simponi) for the treatment of rheumatoid arthritis

Abbott welcomes the opportunity to comment on the Appraisal Consultation Document (ACD) for the appraisal of golimumab for the treatment of rheumatoid arthritis in patients who have had an inadequate response to DMARD therapy. Abbott's comments are set out under section headings containing the questions NICE asks stakeholders to comment on for the ACD.

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

Abbott believes there is additional relevant evidence that needs to be taken into account when the Committee makes its final recommendations to the NHS regarding the use of golimumab for patients with rheumatoid arthritis (RA). Although golimumab has been shown to control the signs and symptoms of RA; it has not demonstrated that it inhibits structural joint damage in the same way the other anti-TNFs do. Therefore, Abbott asks that the Committee explores how these findings impact on the assumptions used in the economic modelling.

1.1 Lack of radiological progression data for golimumab

In section 3.27 of the ACD, it sates that, "*The ERG noted that the manufacturer's original submission did not include any evidence of the effect of golimumab on the radiological progression of rheumatoid arthritis. This outcome measure had been specified in the scope of this appraisal. Evidence on radiological progression was subsequently provided in the form of a research abstract but was marked commercial in confidence."*

This abstract was presented at the 2009 American College of Rheumatology Annual Congress in Philadelphia. Results from this abstract showed that there was no significant reduction in disease progression in patients with established RA who had an inadequate response to methotrexate receiving 50mg golimumab plus methotrexate. There was some discussion that the trial population in the GO-FORWARD study seemed to be at a lesser risk of radiographic progression as the baseline characteristics of these patients were less severe than have previously been reported for the other anti-TNF trials; however there was still no difference in the mean change from baseline in the vdH-S score between the 50mg golimumab + methotrexate group and the placebo + methotrexate group at 24 weeks, 0.55 and 0.6, respectively.[1]

Conversely, the 24 and 52 week radiographic data from the phase III trials of adalimumab, etanercept and infliximab resulted in the inclusion of specific wording in the licence to reflect this benefit. For example in the therapeutic indication section of the adalimumab SmPC it states: "…*Adalimumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate"*.[2] There is no such wording in the golimumab SmPC as the manufacturer did not include the radiographic data for golimumab in its regulatory application.

Indeed, on page 69 of the EPAR the European Medicines Agency discussed the risk: benefit profile of golimumab for the treatment of RA in DMARD-IR patients and stated that, "*The lack of x-ray data are considered acceptable for a second line indication, since there is sufficient indirect evidence for no deleterious effects on the joints (e.g. data from other anti-TNFα agents, support for a relationship between CRP, tender and swollen joints and radiologic progression)*." [3] Abbott considers that a class effect for anti-TNF agents to prevent structural joint damage cannot be assumed when the evidence for golimumab from the GO-FORWARD trial does not support this.

Furthermore, golimumab was not granted a licence for use in methotrexate naïve RA patients. On page 70 of the EPAR the EMA gave the following reasoning, "*Considering the risks with anti-TNF agents, it is not considered justified to add golimumab to MTX in the treatment of treatment naïve RA without evidence of beneficial effects on structural damage. Thus, the lack of x-ray data for golimumab is still considered a major shortcoming, particularly taking the somewhat unconvincing data for signs and symptoms with the dose applied for, both at week 24 and week 52, into account."*

This is in contrast to adalimumab, which has the following wording in the licence based on data from PREMIER[5]: *Humira in combination with methotrexate, is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate"*[2]

It is widely accepted that conventional DMARDs control the signs and symptoms of RA initially (i.e. tender and swollen and joints), but they do not prevent radiological progression.[4,5] For example Emery *et al* showed that even ACR20 non-responders receiving adalimumab + MTX had less radiographic progression than the ACR70 responders receiving MTX alone at 26 and 104 weeks.[4] Therefore, although it has been demonstrated that there is a relationship between CRP, tender and swollen joints and radiologic progression for adalimumab, etanercept and infliximab, this relationship hasn't been shown for conventional DMARDs or golimumab. Similarly, radiological progression data from the REFLEX study for rituximab showed no statistically significant difference in the Total Genant-modifed Sharp radiographic score between rituximab + MTX and placebo plus MTX at 24 weeks (p=0.169).[6] Abbott presumes this is why the manufacturer of golimumab assumed a 0.045 HAQ decrement annually for rituximab in the economic model.

On page 17 of the Assessment Report, the ERG notes: "*Of particular interest would be the impact of golimumab vs. comparator drugs in terms of radiological progression and the potential impact this may have on the cost-effectiveness estimates were this outcome to be incorporated in the model."* Abbott considers that the impact of radiological progression on the cost-effectiveness estimates can be incorporated in to the model to some extent. Given that physical functioning and disability (as measured by the HAQ) are highly correlated with structural joint damage (section 1.3), it can be argued that the assumption of zero HAQ progression for patients receiving 50mg golimumab + MTX doesn't hold true based on the GO-FORWARD radiological progression data. However, an assumption of zero HAQ progression for adalimumab, etanercept and infliximab is supported by radiographic progression data. Therefore, Abbott suggests it would be appropriate for the economic analyses to be re-run assuming an annual HAQ decrement for golimumab equivalent to that of conventional DMARDs or rituximab, i.e. 0.045.

Given that one of the primary drivers for the cost-effectiveness of adalimumab, etanercept and infliximab is their ability to attenuate radiologic progression, resulting in substantial improvement in physical functioning and a reduction in disability in the long-term, it is highly unlikely based on the radiological progression data that golimumab will be cost-effective vs. other anti-TNFs. Furthermore, without this benefit and given its higher cost, it is also unlikely that golimumab will be cost-effective vs. conventional DMARDs.

1.2 Possible rationale as to why golimumab has not been shown to prevent joint damage

The European Medicines Agency discussed the rationale for the chosen doses of golimumab in the phase III clinical trial programme, 50 mg and 100mg every 4th week. The Agency concluded that the rationale for the choice was "*not fully obvious*" (Page 63 of the EPAR).[3] Abbott suggests that a monthly interval between doses of golimumab is probably too great to maintain tight disease control. This is evidenced by data in the EPAR discussion on serum trough levels of golimumab (outlined below) and data presented to the FDA showing variability of dosing intervals for administration of golimumab.[7] As a consequence patients are not achieving adequate control of their underlying disease, which may explain the lack of data showing that golimumab inhibits radiographic progression in RA.

The posology for golimumab states that it should be given once monthly and not once every 4 weeks. This is because although dosing was scheduled at 4-week intervals, a dose window of ± 3 to 7 days was specified in the clinical trial protocol allowing for 30 to 31 day intervals if necessary (EPAR). Data are available from the application to the FDA detailing the proportion of doses of golimumab that were administered every 4 weeks or less (0-28 days). These data indicate that 72% of doses were administered at intervals of 0-28 days, in other words, more frequently than monthly dosing. It is surprising that only 16% of doses were administered between 29-31 days which is the interval which corresponds with monthly dosing as per the licensed dosing regimen. The data are only available for the combined golimumab 50mg and 100mg doses, so it is not possible to assess whether there were any differences between the two doses. What isn't clear from the FDA application is the proportion of patients who had for example 22 or 25 day dose intervals, as this suggests there is considerable

uncertainty in the 'correct' dosing interval. Even if a small proportion of patients require a 22 day dose interval before re-treatment, based on the unit price per dose, golimumab will never be a cost-effective option vs. adalimumab or etanercept.

On page 19 of the EPAR it discusses the pharmacokinetic data for golimumab. In most golimumab studies, serum concentrations of golimumab were measured using the sandwich ECLIA assay. The lower limit of quantification (LLOQ) of this assay was 200 ng/ml with an MRD (minimum required dilution) of 10, however, the EPAR notes that this limit was not low enough to estimate trough concentrations in all subjects following the administration of 50 mg every 4 weeks (q4w). In other words, even with a very low level of quantification to detect serum concentrations of golimumab, following the administration of 40mg every 4 weeks it was still not possible to detect trough concentrations in some patients.

Furthermore, the EPAR notes on page 20 that, "*median serum trough concentrations obtained over longer time periods indicate a tendency toward a decrease over time [up to 52 weeks], which may be related to increased formation of antibodies toward golimumab and possibly an increased risk of inefficacy."*[3]

Interestingly, as the LLOQ of the detection assay was not low enough to estimate trough concentrations in all subjects the observed median values may also be upward biased (EPAR, page 20). This coupled with a tendency toward a decrease over time suggests that serum levels of golimumab are too low when it is administered once every 4 weeks. If in some subjects serum trough levels of golimumab were not detectable following the administration of 50 mg every 4 weeks, it is a concern that an increased interval between doses will have serious implications for disease control.

Therefore, if a more frequent dosing regimen was implemented for golimumab, it is possible that the underlying disease would be better controlled, which would be supported by evidence of inhibition of radiological progression. However, such a dosing regimen would have a substantial effect on the cost-effectiveness estimates.

1.3 Correlation between joint damage measured by X-ray and HAQ

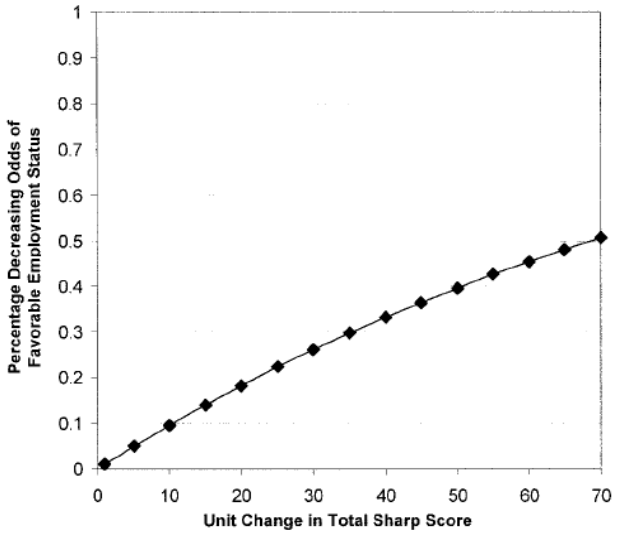
The prevention of radiographic progression has become an important clinical outcome for patients with rheumatoid arthritis in recent years. This is because there is an increasing amount of literature providing evidence for the links between joint damage and disability in RA. Furthermore, studies have demonstrated that inhibition of radiographic progression has a meaningful impact on patients' lives in terms of both HAQ scores and employment status.

Scott *et al* conducted a systematic review to evaluate the relationship between joint damage and functional disability in patients with rheumatoid arthritis. Unsurprisingly, the authors found that joint damage and disability both increase throughout the duration of RA. Although disability (as measured by the HAQ score) was correlated with disease duration (correlation coefficients between 0.27 and 0.30), the link between X-ray damage and disability was stronger (correlation coefficients between 0.30 and 0.70). Scott *et al* concluded that joint damage progresses constantly over the first 20 yeas of RA, and it accounts for approximately 25% of disability in established RA. Furthermore, the link between damage and disability is strongest in established (>8 years) RA. However, avoiding or reducing joint damage in both early and established RA is likely to maintain function.[8]

Oedegard *et al* investigated the longitudinal relationship between physical disability, disease activity and radiographic damage over 10 years in patients with rheumatoid arthritis. The authors found that the HAQ score and grip strength were longitudinally associated with the momentary modified Sharp/van der Heijde score as well as with progression in this score, independent of the ESR. [9] Using data from an RCT of etanercept + methotrexate in patients with rheumatoid arthritis, van der Heijde *et al.* found that after adjusting for age, sex and disease activity, both the absolute level of joint damage and the radiographic progression significant determinants of the HAQ score.[10] The authors concluded that patients with greater radiographic damage, and those with recent radiographic progression, have a higher degree of disability.

Although the NICE methods Guide to technology Appraisals asks that an NHS perspective is adopted, work or employment status is an important and meaningful outcome which impacts on a patient's quality of life. Analysis of data from an RCT of adalimumab + methotrexate in patients with RA found that radiographic progression was significantly correlated with employment status, indicating that this measure of disease has a direct impact on the patient.[11] Figure 1.3 from the van Vollenhoven study shows the relationship between increasing joint damage measured by the Sharp score and the percentage of decreasing odds of gaining/maintaining favourable employment.

Figure 1.3: Relationship between worsening joint damage and the odds of being in employment



Therefore, given that there is increasing evidence that radiological progression is associated with worsening physical function, disability, and other meaningful outcome measures such as employment status, Abbott concludes that the assumption of zero HAQ progression for golimumab + MTX used in the economic modelling cannot be supported by the available evidence.

1.4 Exclusion of ACR70 response rates in the economic modelling

Section 3.39 of the ACD states that, "*The ERG considered that it would have been appropriate to include ACR70 response data in the model so that all the available clinical evidence is used to evaluate golimumab. The manufacturer justified the exclusion of these data by stating that there was not a statistically significant difference between golimumab and the comparators and that incorporating this outcome would only add an element of uncertainty to the model inputs. The ERG noted that this reason was not justified because there was no statistically significant difference in the ACR20 and ACR50 response data for golimumab and the comparators.*"

Abbott is in complete agreement with the ERG and the Committee, and welcomes the Appraisal Committee's recommendation in section 1.4 of the ACD that the economic model be revised to include ACR70 data. Given that an ACR20, ACR50 and ACR70 response equates to a 20%, 50% or 70% improvement in the American College of Rheumatology criteria; omitting data relating to the largest improvement of the signs and symptoms of RA underestimates the benefits of the interventions. This is particularly important in the modelling because a patient achieving an ACR70 response will have a greater improvement in their quality of life, and therefore have a higher utility, than those patients achieving only a 50% improvement.

The ERG recognised the implications of not including ACR70 response data in the modelling, "*Not including ACR70 responses is likely to have biased the results in favour of golimumab, as golimumab has a lower relative risk estimate than all but one comparator drug [infliximab] although the confidence intervals are wide and overlapping for all interventions*." The confidence intervals for the ACR70 response rates are wide because the likelihood of being an ACR70 responder is relatively low compared to that for an ACR20 and ACR50 responder, and therefore there is less precision in the

estimate. However, the relative treatment effect for the ACR70 response rates in the MTC for the 50mg golimumab + MTX was still one of the lowest.

Furthermore, although there were no statistically significant differences in the ACR20 and ACR50 response rates between golimumab and the comparator anti-TNF agents, response rates for patients receiving 50mg golimumab + MTX were lower than they are for the other anti-TNFs. Abbott suggests that the reason there weren't any statistically significant differences between golimumab and the other interventions is because patient numbers in the golimumab trials are small. Small n numbers in the arms will obviously result in wide confidence intervals for all the golimumab estimates, which in turn will increase the likelihood of them overlapping with the other interventions resulting in non-significant differences. In total, 124 patients (89 patients receiving 50mg golimumab + MTX from GO-FORWARD and 35 receiving 50mg golimumab + MTX from Kay et al) contributed to the estimates of relative treatment effect for golimumab in the MTC. This is in comparison to the 896 RA patients who received 40mg adalimumab either as monotherapy or in combination with a DMARD(s). Therefore, as the ERG noted, excluding ACR70 data for all the interventions because there isn't a statistically significant difference between golimumab and the comparators is not a valid reason.

1.5 Importance of fatigue, pain, extra-articular disease manifestations, and health related quality of life as outcome measures in RA

In section 3.24 and 3.27 of the ACD it states that, "*The ERG noted that health-related quality of life and fatigue were not adequately addressed in the clinical evidence section of the submission*" and "*The ERG also noted that SF-36 data were not provided in the manufacturer's submission or following a clarification request*", respectively.

Fatigue and pain are important characteristics contributing towards the symptoms of rheumatoid arthritis. Data are widely available showing the benefits of adalimumab, etanercept and infliximab to improve all the symptoms of RA, such as pain and fatigue. Given that there is a lack of data showing that golimumab inhibits structural joint damage (discussed in section 1.1), which suggests that a class effect for the efficacy of the anti-TNFs cannot be assumed, then data ought to be provided showing the benefit of golimumab on these outcomes as they are important.

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?

Abbott considers that the summaries of clinical and cost-effectiveness are broadly reasonable interpretations of the evidence, however there are some issues that the Committee may want to consider when it makes its final recommendations.

2.1 Mixed Treatment Comparison (MTC)

There are some significant differences in the study characteristics of the studies included in the MTC that may have an impact on the probability of response. The MS states that a random effects model was used to account for these differences. However, there is a misconception that applying a random effects model is all that is required to take account of notable differences in baseline patient characteristics between trials included in the MTC. Sub-sections 2.1.1 to 2.1.3 highlight the differences between the adalimumab and golimumab RA trials as an example, and provide evidence showing the impact these differences have on a given patient's ability to respond. Abbott suggests that meta-regression techniques as documented by Nixon *et al*[12] ought to be used as standard in any evidence synthesis where there are such big differences in the trial populations of the included studies.

2.1.1 Selective inclusion of monotherapy data in the MTC

The mixed treatment comparison in the manufacturer's submission (MS) included monotherapy trial data for adalimumab and etanercept; however only data from patients receiving 50mg golimumab in combination with MTX were included in the evidence synthesis, although monotherapy data are available for golimumab. The MS did discuss the inclusion of the monotherapy studies and stated

that, "*To investigate the effect of the small group of monotherapy studies, and monotherapy treatment arms on the RR estimate additional fixed- and random-effects meta-analyses were performed. The RR of the monotherapy group versus the original group (all studies) was calculated*." The MS didn't quite present this, and instead presented the pooled RRs for the adalimumab and etanercept studies with and without the monotherapy studies included. Whilst not statistically significantly different, the overall RR when the monotherapy studies were included was lower than the pooled estimate when they were excluded. This is not surprising, given that it has been well documented that biologics + MTX have greater efficacy than biologics alone.

The manufacturer justified the inclusion of the monotherapy trials for adalimumab and etanercept because "*there was no statistical difference for all the other anti-TNF agents vs. golimumab*". This has been discussed in section 1.4, and is probably due to the small number of patients contributing towards the relative treatment effect for golimumab. If the monotherapy data for the other anti-TNFs are included in the evidence synthesis, then so should the monotherapy data for golimumab.

Furthermore, Korean and Japanese trials evaluating adalimumab in RA patients who have had an inadequate response to DMARDs were included in the MTC, but neither of the two Japanese RA trials evaluating golimumab were. It is not Abbott's intention to provide a set of different treatment effect estimates that should be used in preference to any other, but instead to highlight some inconsistencies. For example in this case, it seems that the application of inclusion criteria in the MTC has been inconsistent for golimumab vs. the other anti-TNFs.

2.1.2 Number of previous DMARDs

The average number of previous DMARDs used prior to study entry in the two golimumab trials is considerably lower than reported in trials of adalimumab. In the GO-FORWARD trial, around 70-78% patients had not received another DMARD other than methotrexate, meaning that approximately 25% patients had only ever had one DMARD prior to study entry[13]. This is compared to the adalimumab studies in which patients had received on average 2.4, 2.9 and 3.8 DMARDs prior to study entry[14,15,16]. It could be argued that patients in the adalimumab studies have more refractory disease as they have failed more DMARDs and are therefore a more difficult to treat patient population. [17]

2.1.3 Average disease duration and impact on magnitude of HAQ improvement

The average duration of disease differs markedly between the two golimumab RA trials and the adalimumab RCTs. Abbott considers that this difference has a considerable impact on the estimates of treatment effect for golimumab and adalimumab, particularly when comparing physical function between the interventions. In GO-FORWARD, the mean duration of RA in the 50mg golimumab + MTX arm was 4.5 (IQR = 2.1 to 9.7); whereas the mean disease duration in the 40mg adalimumab arms of the Keystone *et al*, Weinblatt *et al* and van de Putte *et al.* trials was 11.0 $\pm$ 9.4 years[14], 12.2 $\pm$ 11.1 years[15], and 10.6 $\pm$ 6.9 respectively.

Therefore in the adalimumab trials, patients had RA for 6-7 years longer than patients in the golimumab trial. This is an important difference in the study populations, as patients who have had disease for longer are likely to have a greater proportion of irreversible joint destruction and therefore the magnitude of HAQ improvement is less for adalimumab than it is for golimumab.

This premise is supported by data from Aletaha *et al*[18]. Aletaha analysed data from clinical trials of RA to identify reversible and irreversible components of the HAQ. The authors found that the reversibility of HAQ scores decreased with duration of RA. In a separate analysis of 42 RCTs of interventions for RA, Aletaha and colleagues also found that discrimination of functional improvement between active drug groups and placebo is reduced in patients with a longer duration of RA (p=0.02 for the change in discrimination over time). The placebo-adjusted HAQ responses decreased on average by 0.37 per year of RA duration[19]. The authors concluded that responsiveness in HAQ scores is inversely associated with mean disease duration in RA, which impacts assessment of physical function and the ability to discriminate between active treatment and placebo. For this reason caution needs to be exercised when comparing trials with different study characteristics.

Given that patients in the adalimumab trials had RA three times longer and failed considerably more DMARDs than subjects in the golimumab trials before initiating a biologic, one would expect that patients receiving golimumab would demonstrate greater HAQ improvements than have been shown for adalimumab patients. However, even the absolute HAQ improvement in patients with extensive disease duration who have failed multiple DMARDs receiving adalimumab monotherapy are comparable to HAQ changes in the golimumab + MTX GO-FORWARD data. Although the MS only presents the median (IQR) absolute change from the GO-FORWARD trial, and data from the van de Putte adalimumab monotherapy study are presented in terms of the mean $\pm$ SD; the absolute HAQ improvement in patients receiving 50mg golimumab + MTX were -0.38 (-0.75—0.13) compared to -0.38 $\pm$ 0.60 in the 40mg adalimumab monotherapy group.

To conclude, Abbott believes that the most appropriate method for the MTC would have been to use meta-regression techniques in an attempt to explain the differences between the studies by regressing the effect sizes from each study onto the study level characteristics in a similar way to that reported by Nixon *et al*12.[12] Abbott believes that had this methodology been used, golimumab would not be cost-effective vs. adalimumab or the other anti-TNFs.

2.2 Estimation of nurse time required to teach subcutaneous administration

In the manufacturer's submission, the cost of an additional 4 hours of nurse time was added on top of the outpatient visit to train patients to self-administer an anti-TNF. This cost was applied to all the subcutaneous agents: adalimumab, etanercept and golimumab. Abbott contends that this is a gross overestimation of the time taken to train patients to self-administer. In NICE clinical guidelines and costing templates of subcutaneously administered agents, the cost of a one hour training session with a Band 6 nurse has been used routinely for the time taken to train patients to self-administer with an injectable pen.

Furthermore, for patients receiving adalimumab nurse training to teach self-injection is provided free of charge as part of the home delivery package.

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?

The Committee has not made any provisional recommendations for golimumab as a treatment for rheumatoid arthritis in people who have had therapy with conventional DMARDs only, as additional analyses were requested of the manufacturer.

However, should the Committee make a positive recommendation for golimumab, it is important that the recommendations are made in the context of the existing NICE guidance for other anti-TNF therapies. For example, TA186 recommends certolizumab pegol only if it "is used as described for other tumour necrosis factor (TNF) inhibitor treatments in 'Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis' (NICE technology appraisal guidance 130)"

Although Abbott appreciates that the scope for this appraisal states that: "if evidence allows, the appraisal will consider subgroups of people defined by the baseline severity of their RA", the existing NICE guidance for adalimumab, etanercept, infliximab and certolizumab pegol restricts their use to patients with a DAS score >5.1. Abbott feels that issues such as expanding the population eligible for anti-TNF therapy to include patients with moderate disease activity would be better dealt with as part of a multiple technology appraisal where all treatments are being assessed together. This approach seems to be particularly appropriate since NICE propose that the guidance on this technology is considered for review together with the review of NICE technology appraisal guidance 130 and 186 in 2011.

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

None that Abbott is aware of.

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