Assessment of Biologic Treatments for Moderate and Severe Rheumatoid Arthritis

Comments from UCB on the ScHARR Technology Assessment Report

UCB welcomes the opportunity to respond to the ScHARR report on the use of biologics in rheumatoid arthritis. Following a review of the report we would like to provide a number of comments and observations for the NICE committee which we believe have significance for the discussion at ACD1. We also welcome the opportunity to provide additional data that was highlighted in the report and will provide this ahead of the committee meeting.

Summary of UCB comments on key findings from the report

1. Access to the ScHARR economic model

UCB would like to ask for access to the economic model created by the assessment group and for reconciliation between the newly created ScHARR model and the BRAM model used in previous NICE reviews to highlight where differences in model assumptions are driving the outcome.

2. Exclusion of UCB trials from the base case analysis

UCB would like to understand further the decision to exclude the main, relevant certolizumab pegol clinical trials, (RAPID 1 and RAPID 2) from the base cases analysis. We request that this decision is reversed and that all the submitted trials are considered in the base case analysis.

3. Calculation of the costs of certolizumab pegol in the ScHARR economic model

UCB would like to understand further the calculation of the annual costs in the first and subsequent years, for those interventions requiring a loading dose upon treatment initiation as per their approved license. More specifically, the report did not provide clarifications on how the year 1 and future year costs for certolizumab pegol have been estimated and the generated costs differ from the UCB submitted evaluations. UCB ask that the assessment group provides more information on how these costs have been estimated and also on how the certolizumab pegol patient access scheme approved by NHS has been accounted for in the calculations.

4. Deviation from the scope in merging populations 2 and 3 in the analysis

The assessment group has combined populations 2 and 3 to form one group in the network meta-analysis (NMA), which is a significant deviation from the scope which clearly states that each population should be investigated separately. It is also unusual as the submitted UCB certolizumab pegol trials cover each population distinctly; the RAPID trials reflect population 2 (severe DMARD inadequate responder [IR]) and CERTAIN represents population 3 (moderate to severe DMARD IR). UCB would like to understand from the assessment group and the DSU why this fundamental deviation from the scope was undertaken when evidence exists to allow independent evaluation of these two populations.

5. Use of ERAS and NMD databases to drive HAQ assumptions in the ScHARR economic model

UCB would like to understand further the use of the ERAS and NMD databases in the economic model. From the group analyses, it seems that the use of these two sources is the major driver of the cost-effectiveness results and the HAQ assumption differs from previous models. UCB would like to ask what alternatives for this assumption were considered and how the choice was validated as it is one key driver of the significant difference between this appraisal and previous biologic cost-effectiveness results.

Detailed explanation of UCB comments on key findings from the report

1. Access to the ScHARR economic model

During previous Single Technology Appraisals the manufacturers have developed economic models, that have been reviewed for accuracy and interpretation by the assessment groups. In previous Multiple Technology Appraisals, the BRAM model has been used and has been established as a standard in these reviews. Previously (and in other MTA reviews) the manufacturers have been allowed access to the assessment group models to validate the assumptions and understand the impact of non-treatment elements as the drivers of the cost effectiveness results.

Since the initial release of the assessment report UCB has received communication to suggest that access will be given to the model after the first ACD meeting. It will be impossible to understand the reasoning behind the ERG findings before the ACD meeting without an opportunity to test the model. UCB would like to understand what confidential material within the model is currently precluding its release.

In addition, there are significant differences between the evidence base, the cost structures and the outcomes of each biologic therapy that are best reflected within their own models and this critique of each manufacturer model in the assessment report has been carried out at a very high level (and is factually incorrect in several instances for the UCB model submitted).

Furthermore, the variations between each treatment are not adequately addressed in the model.
UCB asks that the model, the data assumptions driving the model and a reconciliation between the ScHARR model and the BRAM model is developed so that the committee can understand the difference between this assessment and previous reviews (TA130 and various published STA reviews) (e.g. whether it is largely driven by difference between the sources of evidence (such as ERAS) rather than the clinical and cost effectiveness consideration of each treatment).

2. Exclusion of UCB trials from the base case analysis

UCB has submitted a range of evidence covering moderate to severe populations (RAPID 1 and RAPID 2) showing significant efficacy when compared with MTX treatment. The Phase III RAPID 1 and RAPID 2 trials demonstrated that treatment with CZP plus MTX was more efficacious than placebo plus MTX, resulting in a rapid and sustained reduction in RA signs and symptoms, inhibition of the progression of structural joint damage, and improved physical function.[1, 2] Between them these two trials had over 1,275 patients in the active arms, making them amongst the largest trials in RA. In addition, other studies with a similar design have been conducted in Japanese and Korean patients, and have been included in UCB submission.

UCB subsequent clinical trial programme has looked at the operation of the TNF blockers in a moderate population (CERTAIN) and a real life setting (REALISTIC). We believe that the range of evidence supplied by UCB covers the main populations that represent our licensed population – which has been acknowledged and accepted in previous assessments (NICE TA 186).

Despite the range of trials and evidence provided, the Phase III studies RAPID 1, RAPID 2 and J-RAPID have all been excluded from the group evaluation due to the inclusion of patients with previous exposure to biologic therapy (4%, 1.6%, and 16% respectively). Whilst UCB accept there is a risk of confounding

due to the inclusion of patients with previous biologic exposure, this small proportion of patients with previous exposure to biologics will have no or marginal effect on the efficacy results.

It is particularly surprising that the Assessment Group have separated out trials with a small percentage of biologic experienced patients, while including studies with unclear explanation on the prior treatment and also ignored other significant confounding risks. The main example of this is the pooling moderate and severe patient populations, which is of key importance and is covered further in point 4 below. Another example is the inclusion of trials that report DAS28(CRP) and DAS28(ESR) in the same analysis. UCB ask for further clarification on the assumption stating that DAS28(CRP) and DAS28(ESR) are interchangeable where only one is reported (pg 65). This assumption appears flawed as a number of articles state that DAS28(ESR) and DAS28(CRP) are not interchangeable.[5-7] This is particularly important considering that DAS28(ESR) can result in a higher proportion of patients being defined as high disease activity, especially women, compared to DAS28(CRP), which can have important implications in the comparative analyses. UCB would like to see separate sensitivity analyses performed on studies reporting DAS28(CRP) and DAS28(ESR).

In summary, UCB requests that the RAPID 1, RAPID 2 and J-RAPID trials are included in the base case analysis of the assessment group. The sensitivity analysis conducted by the assessment group including certolizumab pegol trials, indicated that certolizumab pegol has the highest probability of achieving a moderate or good EULAR response. In addition, the inclusion of the RAPID trials substantially reduces the level of overall uncertainty in the analysis as was acknowledged in the report..

3. Calculation of the costs of certolizumab pegol in the ScHARR economic model

The calculation of the annual costs in the first and subsequent years, for those interventions requiring a loading dose upon treatment initiation as per their approved license is not clear in the assessment group report. Moreover, the assessment group calculation of the cost structure of certolizumab pegol is not clear in Table 3 of the report. The annual cost of certolizumab pegol (without administration cost) is stated as £9830.86. The first year cost (without the inclusion of the patient access scheme) is £10,367.50 and the second year cost is £9295. It appears that the assessment group has calculated an average of year 1 and year 2 costs in order to arrive at an annual cost for certolizumab pegol. It is likely that the patient will on average be treated for 3 – 5 years,[8] and so the cost structure in Table 3 overestimates the annual cost of certolizumab pegol by £321.75 each year of treatment (the average of 2 years compared with 5 years on therapy). Furthermore, the cost calculations of other therapies, particularly infliximab, were similarly unclear which may indicate a challenge around the treatment of loading doses in the cost structures.

The inclusion of the certolizumab pegol patient access scheme (PAS) in cost calculations is unclear. The Table 3 footnote acknowledges that the PAS removes the cost of 10 vials in year 1 of treatment and has been treated as a negative year 1 cost. However the calculation (£2628.50/£357.50) suggests that only 7.35 vials are removed from the cost. This understates the savings delivered by the PAS by £946.50.

When these two calculation aspect listed above are taken together - overstatement of the annual cost by £321.75 and understatement of the PAS saving by £946.50 - the year 1 costs of certolizumab pegol seem to have been overestimated by £1268.25.

UCB asks that the assessment group provides a clearer explanation of the year 1 and subsequent year costs calculation for certolizumab pegol and the inclusion of the Patient Access Scheme.

4. Deviation from the scope in merging populations 2 and 3 in the analysis

The primary purpose of this assessment was to understand the clinical and cost effectiveness of biologic therapy in both the moderate and severe populations who have shown an inadequate response to DMARD treatment. Despite this clarity in the scoping stage and the clear desire of the clinicians at the scoping discussion to both widen the access to biologic therapy and clarify the role of intensive DMARD therapy, the assessment group has merged these two populations in the NMA - defined as populations 2 and 3 in the assessment report – rather than assessing these two populations independently. No adequate explanation is offered for this significant deviation from the scope.

The current treatment paradigm in the UK accepts the positioning of biologic therapy in patients who have failed 2 DMARDs and have a DAS score greater than 5.1. However, the UK is virtually unique in denying access to biologics for patients who are DMARD inadequate responders but have a DAS score between 3.2 and 5.1. It is difficult to understand how the NICE committee will be in a position to make a decision on these distinct populations when the ScHARR report have merged the effectiveness data from these two distinct patient groups.

Furthermore, it is unclear how the effectiveness inputs into the economic model differ between ScHARR's severe and moderate models, given that they have been treated as one population in the NMA. UCB would like to understand further the different inputs and assumptions between the moderate and severe economic model and the decision making rationale behind this approach.

In addition, the report casts a level of doubt on the cost effectiveness of biologic therapy in the existing, approved, patient group. The report conclusion states that the most likely ICER for MTX experience patients is £50,000 which is markedly above the current NICE approval threshold of £20-30k. If the analysis had been completed with evidence base for each distinct population considered, it is likely that the severe population would remain cost effective.

UCB would like to see a clearer explanation of the reasons behind this departure from the scope and a re-analysis of the efficacy data based on separate moderate and severe populations.

5. Use of ERAS and NMD databases to drive HAQ assumptions in the ScHARR economic model

Previous NICE reviews have been sensitive to the HAQ assumptions that have frequently been the driver of result variability in the main economic models. Particularly critical has been the assumption of the HAQ progression of patients who remain on conventional treatment. Typically, manufacturers assume that patients on biologic therapy will experience no worsening of HAQ, i.e. that progression is 0 whilst on treatment. This assumption is supported by the BSR biologics register and by the manufacturers' clinical trials that were used to support the Abbvie, MSD, Pfizer and Roche models.[9, 10] The progression of patients on conventional therapy is less well characterised and is defined by manufacturers as between 0.045 and 0.06 a year, ultimately reaching a maximum HAQ score of 3. As the gap between progression whilst on the two therapies is the major driver of utility, and therefore cost effectiveness, even minor variations on this figures will have significant impact on the model results.

The assessment group has selected a specific database (ERAS) that seems unusual as a contemporary source of evidence on HAQ progression whilst on DMARD treatment. The ERAS database (Early Rheumatoid Arthritis Study) was recruited between 1986 and 1998 and whilst is shows a different level of HAQ progression to the assumptions in the manufacturers models (and the evidence used in previous ERG models) it is unclear how applicable this patient group will be to patients in each of the decision populations. The assessment report is unclear on how confounding issues have been explored and addressed and also whether a moderate longitudinal population from a time before intensive DMARD use is truly a relevant comparator for current patients. Additionally, moderate patients will likely show a lower level of HAQ progression over time than patients who are severe enough to justify treatment with a biologic therapy.

UCB asks for a fuller explanation of the reasons behind the choice of the ERAS and NMD databases as sources of evidence for HAQ progression. In addition reconciliation between the evidence sources used in previous assessments such as the BRAM and ScHARR models outlining the impact of these different assumptions would be valuable in understanding the different findings of each model.

References

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