2nd April 2015

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Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, abatacept and tocilizumab for the treatment of rheumatoid arthritis (review of TA guidance 130, 186, 224, 234 and part review of TA guidance 225 and 247) [ID537] – Comments on Decision Support Unit Report.

Dear Lori,

Thank you for your invitation to comment on the Decision Support Unit (DSU) report for the ongoing NICE MTA for Rheumatoid Arthritis.

While we are unable to validate the analysis ourselves without access to the dataset, we have some concerns about the suitability of the dataset in this population and the analyses performed. We would like to highlight the ongoing uncertainty regarding the Health Assessment Questionnaire (HAQ) trajectories of patients who would be eligible for biologic drug therapy.

Suitability of datasets used in the analysis
The Early Rheumatoid Arthritis Study (ERAS) dataset is an inception cohort study and patients at baseline had an average disease duration of only eight months. Although the DSU has attempted to adjust for differences between the ERAS patients and those eligible for biologic drug therapy under NICE guidance, they were unable to validate their results by producing analyses for the population who had failed two disease modifying antirheumatic drugs (DMARDs) and had a disease activity score (DAS) >5.1.

The analysis for the population who had failed two DMARDs showed a greater annual HAQ change than the whole population, but the impact of this analysis has not been tested in the Assessment Group (AG) model.

Fitting of latent class growth models

The ERAS dataset indicates that the mean change in HAQ score between year two and the end of study is greater than the 0.045 value considered by the manufacturers (table 7, page 33 of DSU report). However the rate of change from the cubic and quadratic latent class growth analysis (LCGA) of the ERAS dataset is less than 0.045, for the British Society for Rheumatology Biologics Register (BSRBR), High DAS, and Moderate DAS. We understand the probabilities of class membership for these subgroups differ from the full ERAS dataset, but the rate of change for the full ERAS dataset using these models is not presented for validation.

We question whether it is appropriate to use the full ERAS study duration to fit the models, as the predictions based on the later time-points rely on fewer observations and so are more uncertain. We suggest fitting models to data up until year eight could provide an interesting analysis and may find different results. The cubic model for ERAS (figure 8, page 42 of DSU report) shows HAQ to be decreasing beyond year 12 for all classes, and we query whether this improvement would be expected in clinical practice. The quadratic model shows HAQ to continue to increase for three of the classes. While the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) do indicate that the cubic model is a better fit to the data, we suggest clinical validation would be helpful to determine whether the extrapolated HAQ trajectory is appropriate.

We suggest that the DSU could have considered using some additional modelling approaches to produce curves that fit both the initial J-shape, and the later HAQ trajectory. Such approaches could include the use of piecewise curves.

Assumption that HAQ is flat beyond 15 years

The Assessment Group has assumed that HAQ would be flat beyond 15 years for all latent classes (page 4 of AG report impact of DSU report), as they state that Class 1 and 2 do not show a trend for HAQ increasing between 10 and 15 years. We suggest that the modelling we proposed above could have shown a trend for HAQ increasing for Class 1 and 2 and that this should be explored in sensitivity analyses. Furthermore, Class 3 and 4 could potentially differ from Class 1 and 2, so we suggest sensitivity analyses be explored allowing their trajectories beyond 15 years to increase.

The ICERs differ substantially in the AG model when the linear HAQ trajectory of ERAS analysis is used, but the actual annual HAQ change from the ERAS dataset is not dissimilar to the linear assumption of 0.045, so we suggest it is likely the difference is driven by the assumption that HAQ ceases to increase beyond 15 years. Given that the long-term extrapolation may be based on models fitted to a dataset with a high attrition rate (40.70% at year 8 to 97.55% at year 15, page 35 of DSU report) we believe this analysis is subject to considerable uncertainty.

We would be grateful if you would consider the points that we make in this response prior to the meeting of the Appraisal Committee on Thursday 21st May.

If you have any questions please do not hesitate to contact me.

Yours sincerely,

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