

Dr Tomkins-Nezter and colleagues challenge the robustness of our economic evaluation of adalimumab for juvenile idiopathic arthritis associate uveitis (JIA-U) based on the findings of the SYCAMORE trial. They correctly note that our lack of consideration of severe visual impairment or blindness was a limitation which we acknowledged. The impact of visual impairment on health-related quality of life and costs are significant, and any improvements in visual outcomes will have a favourable effect on cost-effectiveness. We estimated that an average of 1.0 (discounted) quality-adjusted life year (QALY) gained per patient would be necessary to bring the cost-effectiveness in line with the threshold of £30,000 per QALY. If loss of sight is associated with an annual QALY decrement of 0.4 [1], corresponding to 3.9 discounted QALYs over the 11.5 year time horizon of the analysis, then blindness would need to be prevented at a rate of 2.2 per 100 person years for adalimumab to be cost-effective. The efficacy of adalimumab in achieving this effect is unknown. Expected rates of blindness may be low in SYCAMORE participants as they had mild or moderate uveitis, with 91% having AC cell counts of 1+ or 2+ at baseline. Additionally, time has not accrued to see the incidence of glaucoma or cataract development that will influence future evaluation.

Health technology assessment relies on generic measures of health utility for comparability across interventions and diseases. HUI3 is the generic measure of choice in this context, as it has validity in paediatric populations [2], and is sensitive to change in visual disorders [3]. The HUI questionnaire was administered to participants or their parents (guardians) where appropriate for self-completion. The majority of respondents reported on the vision scale as being “Able to see well enough to read ordinary newsprint and recognise a friend on the other side of the street, without glasses or contact lenses”, and no differences were evident between groups (Figure).

We adopted the costing perspective of the National Health Service and Personal Social Services in the UK and, consistent with the methods of NICE [4], did not consider broader societal issues such as lost days at work for parents, potential sub-optimal educational achievement and economic output of children with visual impairment if not treated effectively. Had we done this, the £30,000 per QALY threshold would not be relevant to judge cost-effectiveness, and a lower threshold might apply.

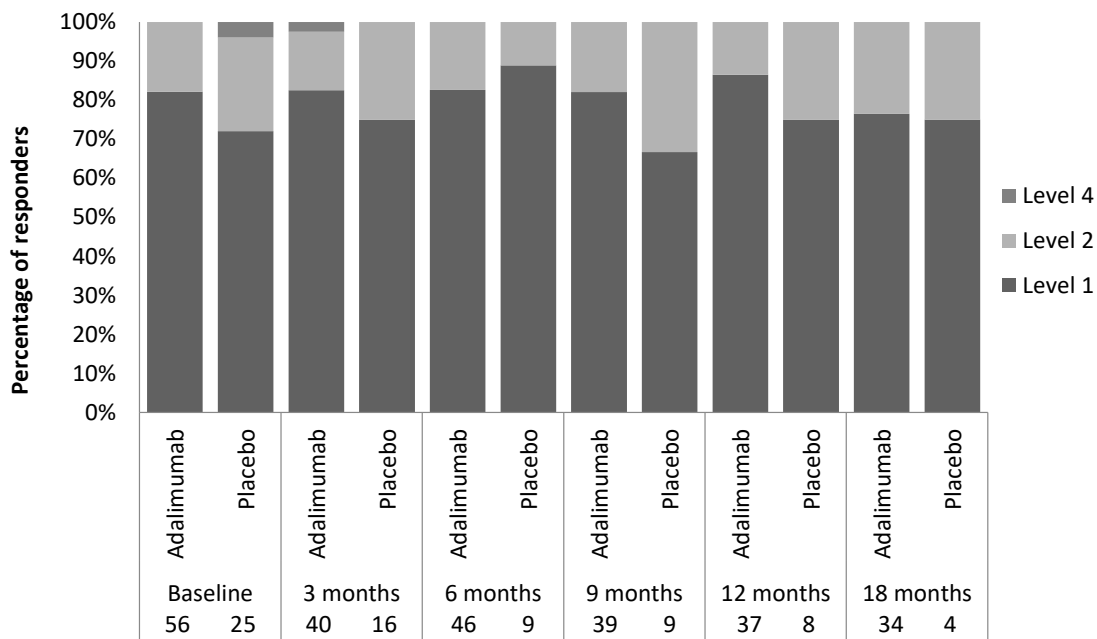
Our analysis made use of all available relevant data from SYCAMORE, but some data were missing, and others were unavailable due to censoring. A longer time horizon would be preferred, but making assumptions on long term treatment effects and costs without any supporting evidence on disease trajectory can also bias the findings. Reliance on the Bristol cohort may limit the generalisability of our findings, but maintained internal validity as this centre recruited the most patients into the SYCAMORE trial. Our use of data from patients with either JIA-U or idiopathic uveitis was justified on the basis of no significant differences in visual outcomes between cohorts [5].

We agree that there are many uncertainties and limitations surrounding the economic evaluation, but there are no available data or analyses to refute our conclusion that at present, adalimumab is does not meet the cost-effectiveness threshold in the UK. However, there is likely to be significant value in seeking further evidence of the effectiveness of adalimumab in preventing sight loss.

References

1. Multiplicative Multi-Attribute Utility Function for the Health Utilities Index Mark 3 (HUI3) System: A Technical Report. Hamilton, Ontario: McMaster University Centre for Health Economics and Policy Analysis; 1998. Working Paper 98-11.
2. Sung L, Petrou S, Ungar W. Measuring health utilities in children and their parents. In: Ungar W, ed. *Economic Evaluation in Child Health*. Oxford University Press. 2009
3. Tosh J, Brazier J, Evans P, Longworth L. A review of generic preference-based measures of health-related quality of life in visual disorders. *Value Health*. 2012;15(1):118-27
4. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal 2013. Process and methods [PMG9]*. 2013.
5. Cann M, Ramanan AV, Crawford A, Dick AD, Clarke SLN, Rashed F, Guly CM. Outcomes of non-infectious Paediatric uveitis in the era of biologic therapy. *Pediatr Rheumatol Online J*. 2018;16(1):51.

Figure. Responses to the vision attribute of the HUI3



HUI3 vision levels:

1. Able to see well enough to read ordinary newsprint and recognise a friend on the other side of the street, without glasses or contact lenses
2. Able to see well enough to read ordinary newsprint and recognise a friend on the other side of the street, but with glasses
3. Able to read ordinary newsprint with or without glasses but unable to recognise a friend on the other side of the street, even with glasses
4. Able to recognise a friend on the other side of the street with or without glasses but unable to read ordinary newsprint, even with glasses
5. Unable to read ordinary newsprint and unable to recognise a friend on the other side of the street, even with glasses
6. Unable to see at all