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Re: Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (including review of TA35) [ID783]

Dear Meindert

Thank you for your invitation to comment on the assessment report of the ongoing NICE MTA for Juvenile Idiopathic Arthritis. We have a number of points within the report that we would like to respond to and have detailed these below.

The Assessment Group (AG) estimate the incremental cost-effectiveness ratio (ICER) for adalimumab, etanercept and tocilizumab versus methotrexate is between £30,000 to £40,000 per QALY. They note a number of limitations that could result in underestimation of the cost-effectiveness. BMS also identified limitations in the model and approach adopted by the AG that may impact the cost-effectiveness results. These are addressed in the following sections.

1. Disease flare risk

Each of the four included randomized controlled trials (RCTs) comparing the biologic DMARDS to placebo reports a statistically significant reduction in the relative risk of disease flare. However, the CIs (presumably 95%) reported Table 1 below, taken from Appendix 11 (page 229) of the assessment report imply that it is possible for the risk of disease flare for placebo (lower CI 0.16) to be less than the risk of disease flare for the biologics (whose higher CIs are greater than or equal to 0.16) when varying with 95% CIs. This should not be possible because the relative risks are statistically significant at the 95% significance level. This error would increase the probability that methotrexate is cost-effective in the probabilistic analysis.

TABLE 1: ASSESSMENT GROUP MODEL PARAMETERS

Parameter	Mean	Higher CI	Lower CI	Standard error	distribution
Disease Flare					
Placebo	0.25	0.34	0.16	0.046	Beta
Abatacept	0.09	0.16	0.05	0.021	Beta
Adalimumab	0.14	0.23	0.04	0.028	Beta
Etanercept	0.09	0.17	0.04	0.021	Beta
Tocilizumab	0.14	0.20	0.09	0.025	Beta

2. Treatment Discontinuation

It is unclear if the states in the model are “on treatment” and “off treatment” as in the model diagram (Figure 8, page 121) or “on biologic DMARD” and “off biologic DMARD” as in the results (Table 56, page 131).

The AG reports that “Following withdrawal from these biologic DMARDs, patients continue on a standard treatment regimen that does not contain a biologic DMARD” (Section 5.6, page 120) but no detail is provided as to what treatments this regimen entails. We would expect patients who discontinued biologic DMARDs would receive methotrexate alone, with the associated efficacy, cost and utility data. Patients treated with methotrexate only are also able to discontinue treatment, but it is unclear if they can discontinue in cycle 1 or if this only applies to later cycles. Again it is unclear what happens to patients who discontinue methotrexate as no cost, efficacy or utility data is provided for untreated patients.

The AG assumes that 9.47% of abatacept patient discontinue due to lack of efficacy in the first cycle. In the RCT (Ruperto 2008), 8.95% (17 of 190) patients discontinued due to lack of efficacy. The AG model is overestimating the proportion of patients discontinuing abatacept.

3. Variation of health state costs in sensitivity analysis

The health state costs appear to be applied as one sum cost which is varied, rather than the more accurate approach of varying each cost and resource use individually (Appendix 11). The health state costs appear to be arbitrarily assumed to have CIs ±30% of the mean which is likely to be an overestimation of the uncertainty and is not

accurate. If the resource use is assumed to be the same for patients who are on and off biologic DMARDs then these costs should not be varied independently.

4. Comparison of first line and second line treatments

To estimate the cost-effectiveness of second line biologic DMARDs, the AG compare a sequence of etanercept followed by another biologic DMARD to methotrexate alone (page 132). It is not clear why other biologic DMARDs are not considered as the first line treatment in this scenario, and it is not intuitive that a patient would receive etanercept as both a first line and second line treatment. We suggest the more appropriate analysis to estimate the incremental cost-effectiveness of second line biologics would be to compare one biologic DMARD to a sequence of two biologic DMARDs. In this situation it is imperative that the efficacy of the treatment following the first line biologic is accurate.

5. Utility values

The utility values from Prince et al are applied at the end of the period at which they were observed. It may be reasonable to assume patients treated with a biologic experience a gain in utility before the 3 month period, and that the long-term improvement seen at month 15 occurred before this point. Given that the model is sensitive to utility values, we would expect to see sensitivity analysis using data shown in Table 2.

TABLE 2: UTILITIES - PROPOSED SENSITIVITY ANALYSES

HRQoL utility values	**Used in AG model**	**Proposed scenario analysis 1**	**Proposed scenario analysis 2**
No treatment	0.53	0.53	0.53
Treatment with first line biologic, 0-3 months	0.53	0.69	0.61
Treatment with first line biologic, 3-15 months	0.69	0.74	0.715
Treatment with first line biologic, 15-27 months	0.74	0.78	0.76
Treatment with first line biologic, 27+ months	0.78	0.78	0.78

We would also suggest performing sensitivity analyses to use alternative utility values for second/third line biologics would be informative.

6. Abatacept dosing

The report states the dosing schedule for abatacept is “Infusions given at week 0, 2, 4 8, 12, 16” (table 52, page 126). It is unclear how this dosing schedule has been applied in the model – it should be every 4 weeks, with an additional dose at week 2 (the additional dose is not required every 3 month cycle).

In summary, JIA is a chronic disease that can continue into adulthood and can have a significant impact on patients’, parents’ and carers’ quality of life including impact on children’s education. Biologic DMARDs have been shown to significantly improve patient’s outcome compared with methotrexate when treatment to methotrexate is inadequate. Additionally, abatacept offers an option to those that have inadequate response to anti-TNF biologics.

We agree with the assessment group that it is unlikely that any positive NICE recommendations for the use of these biologic DMARDs will significantly increase the number of patients requesting treatment, and thus affecting budget impact. Additionally, given that biologic DMARDs are currently used in the management of patients with JIA in the NHS it is unlikely that substantial modifications will be needed to services, such as infrastructure development or increased staff training. Continued access to these treatment options is important to support the care of patients with this long-term condition.

Yours sincerely,

[redacted]
[redacted]
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References

1. National Institute for Health and Care Excellence, (NICE). Arthritis (juvenile idiopathic) - abatacept, adalimumab, etanercept and tocilizumab (inc review TA35) [ID738] Final protocol. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-tag465/documents Accessed: 29 January 2015.

2. National Institute for Health and Care Excellence, (NICE). Guide to the methods of technology appraisal 2013. Available at: http://www.nice.org.uk/article/pmg9/chapter/1-introduction Accessed: 12 December 2014.

3. Ruperto N, Lovell DJ, Li T, et al. Abatacept improves health-related quality of life, pain, sleep quality, and daily participation in subjects with juvenile idiopathic arthritis. Arthritis Car Res. 2010; 62(11):1542-51.

4. Prince FH, de Bekker-Grob EW, Twilt M, van Rossum MA, Hoppenreijs EP, ten Cate R *et al*. An analysis of the costs and treatment success of etanercept in juvenile idiopathic arthritis: results from the Dutch Arthritis and Biologicals in Children register. *Rheumatology (Oxford, England)* 2011;50:1131-6.