Rituximab in combination with glucocorticoids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis

Further ERG analysis – CYC intolerant group

Nicholas Latimer

22nd November 2013

The economic analysis presented by the manufacturer for the subgroup of patients who could not have CYC treatment was inadequate. Key issues were:

- Uncertainty about the relevance of MMF/MTX as relevant comparators – although it is acknowledged that these may be used in this patient group as a last resort – where nothing else is available
- MMF and MTX are likely to be associated with higher glucocorticoid use (clinical opinion), yet the costs and utility decrement associated with this are not included in the model
- Assumed equal effectiveness in terms of remission rates for MMF and MTX compared to CYC (though relapse rates were assumed to be 20% higher). Evidence on this is highly uncertain, particularly in "severe" patients. MYCYC suggests induction of remission may be similar, but no final results as yet, and patient population is not exactly the same. No indirect comparisons have been undertaken.

Below we report some arbitrary analyses to show the sensitivity of the ICER to these parameters.

1. Base case from ERG post ACD report, quoted in second ACD

Table 1: ERG preferred analyses cost-effectiveness results – CYC-ineligible patients with RTX retreatment for responders

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
MMF/MTX → BSC	£14,560.57	8.35	-	-	-
RTX → RTX → BSC	£22,905.99	8.49	0.14	8,345.42	**£60,569.08**

Table 1 demonstrates that treating people who are ineligible for CYC treatment with RTX (with retreatment for responders) rather than MMF or MTX is associated with an ICER of £60,569.08 per QALY gained.

2. Utilities

It is acknowledged that MMF and MTX do not represent "ideal" induction treatments, rather they are viewed as a last resort for people who cannot take CYC. Although there is not good evidence on their effectiveness compared to RTX, it seems reasonable to assume that for patients who "respond", the benefit is not as great as for people who respond to RTX. In the previous version of the manufacturer's model no distinction was made between the health state utility of responders in the RTX group and the utility of responders in the MMF/MTX group. If we reduce the utility of response in the MMF/MTX group by 5%, the utilities in the different response categories by treatment group are:

Table 2: Health state utilities sensitivity analysis

Health state utilities (equal for all treatments)	*RTX group*	*MMF/MTX group*
Remission	0.84	0.79
Non-remission	0.75	0.75
Uncontrolled disease	0.67	0.67

This leads to the following probabilistic results:

Table 3: ERG cost-effectiveness results – CYC-ineligible patients health state utilities sensitivity analysis

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
MMF/MTX → BSC	£14,560.57	8.25	-	-	-
RTX → RTX → BSC	£22,905.99	8.49	0.24	8,345.42	**£34,090.18**

3. Glucocorticoid use

Clinical expert opinion received by the ERG suggests that glucocorticoid use is likely to be higher under an MMF or MTX treatment regimen than under a CYC treatment regimen. As an illustrative analysis, increasing the glucocorticoid costs by 50% while in the "remission" health state (from £292.71 per 6-month treatment cycle to £439.06 per 6-month treatment cycle), leads to the following probabilistic results:

Table 4: ERG cost-effectiveness results – CYC-ineligible patients health state utilities and glucocorticoid use sensitivity analysis

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
MMF/MTX → BSC	£14,705.67	8.25	-	-	-
RTX → RTX → BSC	£22,905.99	8.49	0.24	8,200.32	**£33,497.44**

4. MTX/MMF efficacy

Data on the relative efficacy of MMF/MTX compared to CYC is sparse. Early results from the MYCYC trial suggest similar induction of remission rates for CYC and MMF (though the point

estimate is lower for MMF – 66% Vs 69%), but final results are not available. Evidence seems to suggest that relapse rates are higher after MMF or MTX than after CYC (Faurschou 2012), and thus the manufacturer modelled a 20% increased relapse rate. It is feasible that there could be a similar reduction in the remission induction rate associated with MMF/MTX in the severe patient group. As an illustrative analysis, increasing the remission induction rate by 20% in the MMF/MTX group (mean 0.52 for patients with new disease, compared to 0.65 for CYC and 0.60 for RTX) leads to the following probabilistic results:

Table 5: ERG cost-effectiveness results – CYC-ineligible patients health state utilities, glucocorticoid use and remission rate sensitivity analysis

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
MMF/MTX → BSC	£14,855.55	8.19	-	-	-
RTX → RTX → BSC	£22,905.99	8.49	0.30	8,050.44	**£26,599.79**

5. MMF comparator

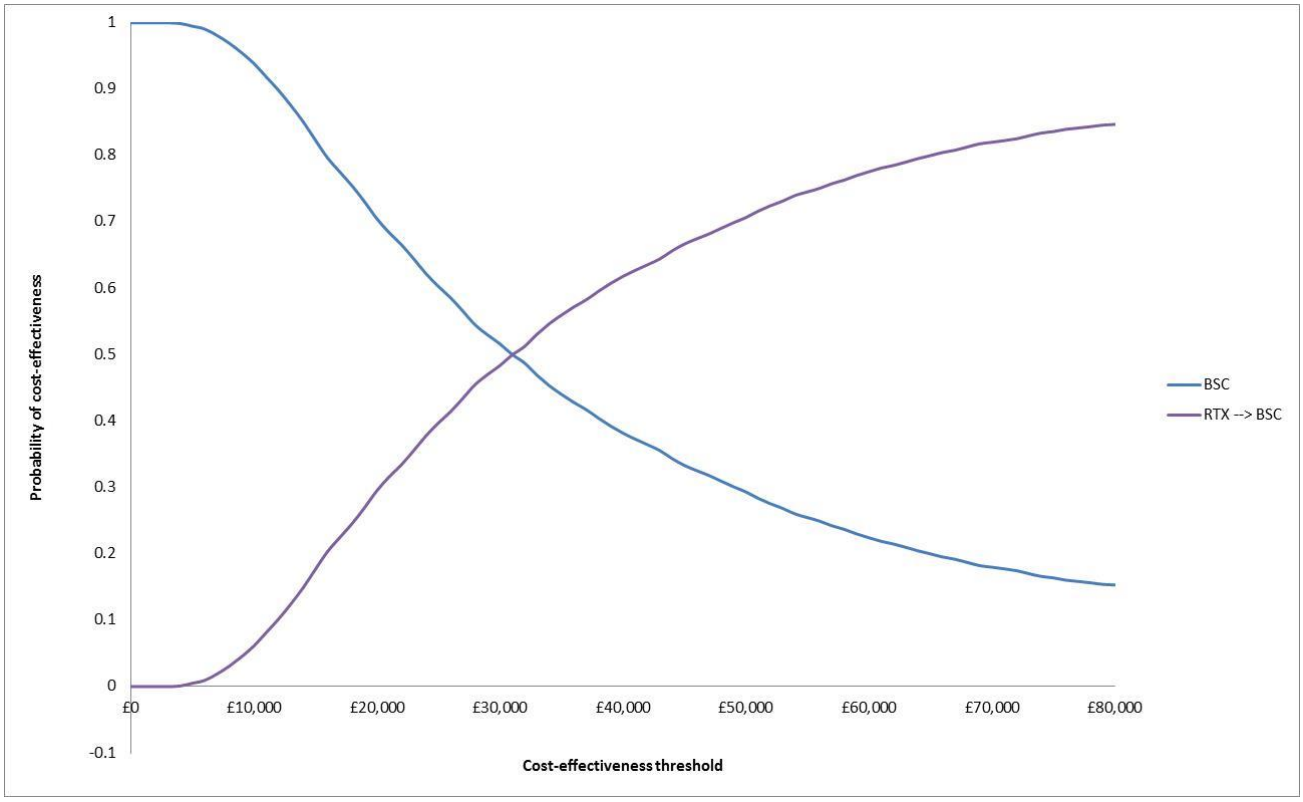
It may be argued that using "mixed" comparators is not useful for decision makers. The most relevant ongoing study of non-RTX treatments for the induction of remission in a patient group that includes severe ANCA vasculitis is the MYCYC study, which compares CYC to MMF. MMF is a more expensive treatment than MTX, but may be a more relevant comparator. Comparing to MMF, the following probabilistic results are obtained.

Table 6: ERG cost-effectiveness results – CYC-ineligible patients health state utilities, glucocorticoid, remission rate and MMF sensitivity analysis

Strategy	Total Cost	Total QALYs	Inc. QALYs	Inc. Costs	ICER
MMF/MTX → BSC	£14,914.19	8.19	-	-	-
RTX → RTX → BSC	£22,905.99	8.49	0.30	7,991.80	**£26,406.03**

The CEAC associated with this analysis is presented below. At a willingness-to-pay threshold of £30,000 per QALY gained, the probability that administering RTX (with retreatment for responders) is a cost-effective strategy is approximately 48.4%. At a willingness-to-pay threshold of £20,000 per QALY gained, the probability that administering RTX (with retreatment for responders) is a cost-effective strategy is approximately 29.5%.

Figure 1: Sensitivity analysis CEAC



Conclusions

It is relevant to note that these analyses are highly imperfect and arbitrary. However, they illustrate the uncertainty in the model results for the CYC intolerant patient group.