Response to Evidence Review Group assessment report

Immunosuppressive therapy for kidney transplantation in children and adolescents (review of TA99)

Comments from Astellas Pharma Ltd.

Thank you for the opportunity to comment on the Evidence Review Group assessment report. Having reviewed the document, we have identified similar factual inaccuracies and concerns with TA99 as those expressed in our response to TA85.

Summary of concerns

- The ERG assessment uses drug cost data from heterogeneous sources that favour tac-IR over tac-PR by capturing the manufacturer discount for tac-IR while including only the undiscounted British National Formulary (BNF) list price for tac-PR.
- In modeling patient death and graft loss, the ERG assessment comparing tac-PR with tac-IR differentiated between the formulations based on non-significant findings from a meta-analysis of a single RCT that was designed and powered to establish non-inferiority with respect to biopsy-confirmed acute rejection at 24 weeks. Furthermore, the meta-analysis made use of data reported at 12 months post-transplant despite the trial having been unblinded at 24 weeks.
- Given that the benefits of tac-PR (relative to tac-IR) in routine clinical practice would be anticipated to arise primarily from improved adherence (possibly in concert with differences in pharmacokinetics), the ERG assessment is likely to underestimate the effectiveness of tac-PR relative to tac-IR. This is of concern to Astellas, especially in light of the recent publication of documentation from the NICE Decision Support Unit advocating the use of applicable data from routine clinical practice.
- Modigraf and special formulations of tacrolimus suspensions, which have a license for use in children and adolescents, have not been considered as options in the ERG model; hence the patient groups that these products cater for have been overlooked.

Drug acquisition costs

Drug acquisition costs as reported in the base case analysis are based on heterogeneous data sources that unfairly inflate the cost of tac-PR relative to tac-IR. Namely, the tac-PR costs are taken directly on the BNF 68 list price (£1.07/mg), which doesn't accurately reflect the true cost borne by the NHS. Meanwhile, tac-IR costs have been based on data from CMU eMit (£0.52/mg), thereby reflecting a manufacturer discount in the tac-IR arm but not the tac-PR arm.

Efficacy data

In differentiating tac-PR from tac-IR, the ERG assessment utilized data from the 2010 Kramer and 2013 Tsuchiya randomized controlled trials,[1,2] in addition to fixed effects meta-analysis (for BPAR) and random effects meta-analysis (for death, graft loss and renal function) of the two studies. In the case of death with a functioning graft, and graft loss, Astellas would like to

register a concern that the comparative efficacy of tac-PR and tac-IR have been misrepresented and would object to the use of these meta-analysis data on the following grounds:

- The 2013 Tsuchiya *et al.* study contributed no data to the meta-analyses of death or graft loss, leaving only data from Kramer *et al.* 2010 to inform the analyses.
- The per-protocol analysis in the Kramer *et al.* study was only powered to demonstrate non-inferiority with regard to biopsy-confirmed acute rejection at 24 weeks.
- The findings of differences in graft loss and patient mortality at 12 months were not statistically significant.
- The data used in the model includes follow-up from the open-label extension of the study (i.e. data at 12 months post-transplantation after 28 weeks of unblinded follow-up).

The inequitable impact of the inclusion of these non-significant findings is compounded by the ERG assessment's *exclusion* of significant (and costly) differences between the treatments, such as the incidence of bacterial infections (22.6% versus 16.0% with tac-IR and tac-PR respectively; p=0.032) and malignancy (2.4% versus 1.8% with tac-IR and tac-PR respectively; significance not reported).

In cases in which the meta-analysis was able to make use of data from both studies, non-significant results of the meta-analysis were still incorporated into the model. For instance, differences between tac-IR and tac-PR in NODAT incidence were captured in the model, despite the parallel TA85 ERG assessment reporting that "no difference in NODATs and CMV infection were found between TAC and TAC-PR regimens at 1–year -follow-up".

Finally, with regard to efficacy estimates, the ERG assessment made no use of data from routine clinical practice. Given that tac-PR and tac-IR deliver the same active ingredient, differences in routine clinical practice could only arise as a result of improved patient adherence to maintenance immunosuppression or from different pharmacokinetic profiles. Improvements in adherence in renal transplant patients have already been demonstrated in a 2013 RCT[3] and reduced intrapatient variability of tacrolimus exposure has been demonstrated in prospective conversion studies.[4,5] Given this, in concert with evidence that improved adherence and reduced variability improve graft survival, and the emerging techniques by which observational data can be incorporated into network meta-analyses, the ERG assessment may substantially underestimate the efficacy of tac-PR relative to tac-IR.[6,7] We appreciate that this limitation was acknowledged in the report, but are concerned that it was not explored quantitatively in the ERG assessment.

Exclusion of Modigraf and special tacrolimus formulations

A final concern for Astellas is that Modigraf and special formulations of tacrolimus suspensions, both of which have a license for use in children and adolescents, have not been considered as options in the ERG assessment of the patient group to which they are tailored and licensed.

Concluding remarks

Astellas would appreciate the opportunity to debate these issues at the appropriate point in the NICE process.

For reference, we include a table, below, summarising what Astellas considers to be the key drivers of the differences between the cost-utility analyses in the Astellas submission and the ERG assessment.

Key model data source differences between Astellas and PenTAG analyses for Prograf versus Advagraf in TA99

	Astellas		**PenTAG**	
Mortality	No direct mortality difference modelled		**IR OR:** 0.78292683	Kramer 20101
			PR: Reference	
GFR	No difference in GFR modelled		**IR MD:** +0.211 ml/min/1.73m^2	Kramer 2010 and Tsuchiya 20131[,2]
			PR: Reference	
Acute rejection incidence	**IR:** 12.6%	Kramer 2010, Silva 2007 and Albano 20131[,8,9]	**IR OR:** 1	Kramer 2010 and Tsuchiya 20131[,2]
	PR: 14.6%		**PR OR:** 1.025	
Dosing	**IR:** 0.09 mg/kg/day	Silva *et al.* 2007	**IR:** 0.08–0.18 mg/kg/day	Grenda 2010[10]
	PR: 0.095 mg/kg/day		**PR:** 0.095–0.195 mg/kg/day	Kramer 2010. Wlodarczyk 2009, Tsuchiya 2013, Oh 20141[,2,11,12]
Drug costs	**IR:** £1.62	BNF 68	**IR:** £0.5201/mg	CMU eMit
	PR: £1.24	BNF 68	**PR:** £1.0677/mg	BNF 68
Hemodialysis cost	£42,543	Baboolal 2008[13]	£81,112	HRG4
PD cost	£19,452	Baboolal 2008	£42,060	HRG4
Acute rejection cost	£1,838	NHS tariff information	£3,557	TA85
Annual NODAT cost	£17.38	BNF 68 (metformin only)	£2,084	Alva 2015[14]
Quality of life utilities	Lee *et al.* 2005[15]		Liem *at al.* 2008[16]	
Bodyweight to surface area mapping	Children's Cancer And Leukaemia Group: Chemotherapy Standardisation Group		BNF for Children 68	

GFR, glomerular filtration rate; HRG4, healthcare resources group revision 4; IR, immediate-release; MD, mean difference; NODAT, new-onset diabetes after transplantation; OR odds ratio; PD, peritoneal dialysis; PR prolonged-release; TA, technology appraisal

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