UNIVERSITY OF CAMBRIDGE

Department of Surgery

Christopher J E Watson
MA MD BChir FRCS
Professor of Transplantation
& Honorary Consultant Surgeon

7th May 2015

Dear Sir or Madam

Re: Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85) [ID456]

I attach my comments on the PenTAG Assessment Report for the above technology appraisal.

With best wishes

Yours faithfully

C. J. E. Watson

[redacted]

Direct Line: [redacted]
Personal Assistant:
E-mail:
www.cam.ac.uk

This is the second technology appraisal in the field of Kidney Transplantation that has been produced by the PenTAG group, the first being related to machine perfusion for preservation of kidneys before transplantation. In reviewing this assessment of immunosuppression I have concentrated on the areas I am qualified to comment on, and will not comment on the detail of the individual analyses. PenTAG have clearly done a lot of work on this report and are to be commended on that.

The assessment assumes all drugs are dosed identically in all trials, yet this will not be the case. Immunosuppression can be increased, and consequently rejection reduced, by increasing the therapeutic drug level. There does not appear to have been consideration of this in the assessment.

The report considers death and graft survival as distinct entities, censoring death from its graft survival data. The immunosuppressive regimen may contribute to the likelihood of death, and therefore it is inappropriate to analyse the drugs in terms of graft survival data censored for death. NHS Blood and Transplant use the term Transplant Survival to denote the survival of a patient with a functioning graft and it would be helpful to see an analysis using this as an endpoint; being alive with a functioning graft is the endpoint in kidney transplantation that both patient and clinician aim to achieve.

The Assessment Report supports a regimen involving basiliximab, mycophenolate and tacrolimus. This immunosuppressive regimen is in wide use in the UK at the moment in spite of the de novo use of mycophenolate not being supported in the previous NICE appraisal of this technology (TA085, September 2004).

The Assessment Report also supports the use of rabbit ATG as induction. Although this was available at the time of the last appraisal in 2004 it was excluded from consideration, yet it has now been shown to be clinically and cost effective. It is regrettable, therefore, that alemtuzumab, another induction agent widely used in the UK at the moment, has not been evaluated even though it falls into the same category as rATG did last time.

Given that the PenTAG group have previously worked in the field of kidney transplantation, and have had the opportunity of enlisting the help of clinicians with expertise in kidney transplantation, I would have expected the background information to be sound, which it is not in parts. There follow a list of comments, some referring simply to typographical errors or inaccuracies of background, but some referring to potentially more fundamental issues (e.g. the use, or not, of the MeSH term "Kidney Transplantation" as a search term).

MAJOR CONCERNS

Page 32. Identification of studies.

The National Library of Medicine Medical Subject Heading (MeSH term) is "kidney transplantation", not kidney transplant, renal transplant, or any of the other terms listed in the executive summary or body of the document. Could PenTAG confirm that they did use the MeSH term "kidney transplantation" as one of their search terms for this assessment.

Page 35. Study selection.

"Only economic evaluations from UK, USA, Canada, Australia, and western Europe were included as these settings may include data generalizable to the UK.

I would question how generalizable data for cost effectiveness are for some of these countries. For example, until the advent of the Affordable Care Act in the US the patient did not pay for his/her immunosuppression for the first 12 months, but had to thereafter. Consequently graft survival in the US was poorer beyond the first year, compared to other healthcare systems like the UK and Australia.

P36. Economic model.

PenTAG have developed their own economic model, and estimated graft survival independently from UK Transplant Registry data presumably supplied by NHS Blood and Transplant (NHSBT). PenTAG do not appear to have consulted NHSBT with the graft survival aspects of the model – NHSBT have a transplant statistical unit that has an international reputation for its expertise and data collection, and has established models for predicting graft life. They are also familiar with the limitations of their own data.

P92. 4.2.2.6 "… In all except one of these trials this was primarily due to the fact that patients, donors or organ characteristics were not representative of the current NHS in England (e.g. >90% deceased donors, or 'suboptimal transplants', or 'high risk of rejection population)."

I am not sure what is being said here. The donor demographics in the UK comprise 64% deceased donors of which 37% fulfil the UNOS expanded criteria definition and 41% are donors following circulatory death. None of the trials has studied the same population of donor kidneys that are currently being transplanted in the UK *and* included recipients at high-risk of rejection. Nevertheless only 11 studies were considered admissible, while most were not. I would like to see a better justification as to why each of the trials in Appendix 4 were ruled adequate or inadequate in terms of applicability to the NHS.

OTHER CONCERNS

Page 25. Definitions.

Cadaveric transplant.

Current terminology refers to transplants from someone who as died as deceased donor transplants, not "cadaveric transplants"

Calcineurin inhibitor

Ciclosporin is variously referred to throughout the document as ciclosporin (the UK accepted spelling), cyclosporine, and cylsoporine (page 374). It should be standardised.

Regimen

An immunosuppressive protocol involving a number of drugs is usually referred to as a regimen. In this document the words regimen, regime, and regiment are used interchangeably.

1-Haplotype identical

I am not clear why this term is included. It is poorly defined in this list of terms, and is not used anywhere else in the document.

List of abbreviations.

KM: kaplan-meier

Should read "Kaplan-Meier"

Page 28. Three main service provision steps for the management of a transplant. May I suggest that there are 4, and that the second is preservation of the kidney (see TA165).

Page 28. Interventions.

Ciclosporin and azathioprine are not mentioned here but should be since they are frequently used as comparators in the studies described in the assessment report.

Page 29. "mycophenolate sodium is an enteric-coated formulation of mycophenolate mofetil (MPS)"

Incorrect. Mycophenolate sodium is the sodium salt of mycophenolic acid; mycophenolate mofetil is the mofetil salt of mycophenolic acid.

Page 29. "**sirolimus** (Rapamune® [Pfizer]) which is a non-calcineurin inhibiting immunosuppressant and acts as an antiproliferative; **everolimus** (Certican ® [Novartis Pharmaceuticals]) which is a proliferation signal inhibitor and is an analogue of sirolimus."

Sirolimus and everolimus have identical actions on proliferation through exactly the same pathway (inhibition of TORC1). I am not clear why there actions are described differently here.

Page 31. Outcome measures.

"Graft function – (estimated) glomerular filtration rate (eGFR), which is an estimate of actual glomerula [sic] filtration rate, using a formula involving age, weight, gender, and serum creatinine."

The data you analysed include other measures of graft function, such as creatinine clearance.

GFR stands for glomerul**ar** filtration rate. There are a number of equations that can be used to estimate it. The most common is the MDRD equation which does not involve weight (Levey et al. Ann Intern Med 1999;130(6):461.)

Weight is used by the Cockcroft Gault formula which gives an estimate of Creatinine Clearance, not GFR, although the two are similar (Cockcroft & Gault. Nephron 1976;16(1):31)

Page 38. The rate of mortality following graft loss.

This is a subject of much current interest in the transplant community. Did PenTAG use the

UK Transplant Registry data to supply the NHS numbers of the recipients to the Renal Registry, or indeed to the Office of National Statistics, in order to ensure an accurate picture of the rate of death before and after graft loss? Or did they assume that the Renal Registry captured all the transplant patient data?

Page 40. "Infection prophylaxis costs were estimated based on the kidney transplant protocol of a UK hospital".

The UK hospital quoted was the Royal Devon and Exeter Hospital, which is not a transplant unit but rather it follows up patients transplanted elsewhere. Prophylaxis associated with particular induction regimens may be missed. In addition the prophylaxis and monitoring of CMV is very variable and may differ where rATG is used routinely.

Page 44. "Since the previous NICE appraisal, the main development in economic evaluation modelling of immunosuppressive regimens is the use of renal function as a surrogate outcome in addition to acute rejection for extrapolating trial efficacy outcomes to long term graft and patient survival"

The use of renal function as a surrogate of graft survival was suggested during the previous appraisal. The main economic difference relevant to this appraisal is the widespread availability of generic formulations of most of the immunosuppressants and consequent reduction in their cost.

Page 48. 1.6.1. Limitations

Key Strengths.

Donor kidney quality has not been looked at. In the UK now the average age of a DBD donor is 52, and a DCD donor is 54. Donor age is a strong predictor of graft quality in all studies where donor factors affecting long term graft survival have been studied, including those by Port et al, Rao et al, and the UKKDRI published in conjunction with NHSBT.

Page 49. 1.6.2.1 Limitations: Anaemia

The assessment assumed that anaemia would not vary between regimens. Anaemia, and the requirement for exogenous erythropoietin, is much more common in patients on sirolimus (and probably everolimus), and in patients with failing grafts. It is uncommon in patients who are not on mTOR inhibitors and who have good graft function.

2. Background.

Page 56. "However, it should be noted that the total number of transplants for the year 2013/14 given in Figure 2 as 2,929 appears to be 14 transplants more than the total number of tranplants[sic] performed around the UK given (2,464 for England, 91 for NI, 112 for Wales and 242 for Scotland) from the same resource.[11]"

This criticism of the NHSBT report is unnecessary. The explanation is simple. PenTAG have arrived at their figure by adding up activity in the NHS hospitals in figure 5.2 of the NHSBT 2013/14 annual kidney report (http://www.odt.nhs.uk/pdf/organ_specific_report_kidney_2014.pdf), and assumed this to

be the total UK adult kidney transplant activity. In addition to this 14 live donor kidney transplants were carried out in private hospitals, 5 at the London Clinic, 5 at the London Cromwell, and 4 at London Bridge. The comment directed at NHSBT should be removed. I would have expected that the Assessment Group would have made every effort to ensure that data queries were resolved rather than accept data that they presume to be incorrect, or to infer criticism of another organisation without first checking with them.

Page 57. The legend on the figure should read DCD: "donation after *circulatory* death", not "donation after *cardiac* death".

Page 58. Figure 3.

The figure title should read "Number of donors, transplants and people on the active transplant list from **1 April** 2004 to 31 March 2014".

Page 59. Last paragraph. "This, in effect, means that people are back to where they started with their treatment, …"

This is not the case. Patients with failed transplants are commonly sensitized to the mismatched HLA on the failed donor kidney, such that they cannot have a future transplant bearing the same HLA. Moreover this sensitization is often to a wider spectrum of HLA. The end result is a much longer wait on dialysis for a second transplant than for a first, and when they get that transplant they may have a poorer outcome on account of the sensitization.

Page 64. "The cross-matching for donor-recipient compatibility will include an assessment on HLA matching"

The cross-match is a test to detect antibodies in the recipient serum directed to donor HLA as a consequence of which hyperacute rejection would occur were the transplant to proceed.

HLA matching aims to find a donor kidney with a minimal number of HLA that are not present on the recipient. It is not cross-matching.

The sentence is meaningless as written.

Page 65. "The immunosuppression regime[sic] can then be tapered and withdrawn whilst the patient returns to dialysis and waits for a new kidney to become available."

In fact the immunosuppression may be continued after the patient returns to dialysis. This is done in patients who have not already formed antibodies to the donor HLA and aims to prevent the formation of said antibodies, and thus give the patient access to a wider pool of potential donors (and hence a shorter wait) for their next kidney graft. It is generally practised if there is a live donor being worked up, when stopping the immunosuppression with resultant HLA antibody formation may make the retransplant impossible.

This highlights the importance of maximizing the life of the first transplant, particularly in young patients if they are to have a long life which will usually be achieved with a number of kidney transplants.

Page 67. "Clinician estimations of average frequency of outpatient visits have been reported as 34.3, 6.3 and 4.7 visits respectively for the first, second and third years posttransplant, with UK database figures suggesting 39.7, 11.0 and 9.2 visits respectively for the first, second and third years posttransplant.

This gives the false impression that the data are derived from a large database when in fact the "UK database" is the database at the Cardiff transplant unit.

Page 70. "**Mycophenolate sodium.** MMF is also available as an enteric-coated formulation mycophenolate sodium (MPS)"

MMF is a different drug to MPS, as mentioned previously. They are different salts of mycophenolic acid.

Page 71. "Donor type"

ECD is variously used to mean extended or expanded criteria donors. This category is a definition of the United Network for Organ Sharing (UNOS) in the USA and follows work by Port et al (Transplantation 2002;74:1281) showing that donors 60 years or older, or those between 50 and 59 who have two of death from a stroke, creatinine over 1.5mg/dl, and a history of hypertension, have a relative risk of graft loss at least 1.7 fold that of an ideal donor (aged 10 to 39, no hypertension, normal creatinine, not dying from a stroke). It does not include donors who may pass on malignancy or infection (which may kill the recipient but are not otherwise associated with poor graft function). The term marginal is often used to cover these different donor-associated risks, but it is probably best to adopt the phrase "less than ideal". Age is the most important factor influencing graft function and survival, but there are other factors, the most important of which is probably the cold ischaemic time.

Both DBD and DCD kidneys can be ECD kidneys – ECD are a subset of deceased kidney donors.

Page 73. Table 6.

"Immunosuppression" in the table title is spelt incorrectly.

"'Symphony study' regimen using triple therapy irrespective of immunological risk or delayed graft function risk with: tacrolimus; mycophenolate mofetil or mycopehnolate[sic] sodium and a reducing course of prednisolone"

The Symphony Study regimen also included daclizumab; does this unit use basiliximab instead, and can this be stated?

Note *mycophenolate* is spelt incorrectly.

Page 80. "In addition, the following websites were searched for background information…"

Given this is an assessment of kidney transplantation I am surprised to note that **no** transplant website has been accessed, including the British Transplantation Society, the European Society for Organ Transplantation, or the American Society for Transplantation.

Page 93. "The majority of trials report outcomes up to one year, with the period of induction therapy generally continued for up to 14 days, however, this was occasionally unclear since length of treatment varied according to participant trough levels."

Neither of the two induction agents under study, basiliximab or rabbit ATG, are dosed by participant trough levels. This paragraph does not make sense.