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Dear Dr Helliwell

Re: Final Appraisal Determination – Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)

NHS England would like to appeal against the Final Appraisal Determination for the above mentioned technology appraisal on the following grounds:

Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE; and specifically

2.1 Recommendation 1.4 would be at variance with much of current clinical practice in the absence of sufficient trial data for or against the recommendations, thereby reducing effective options for future patients who are intolerant of, or unsuitable for, the interventions recommended in section 1.1-1.3 of the FAD.

2.2 Recommendation 1.4 reduces effective options for future patients who are intolerant of mycophenolate mofetil by not recommending mycophenolate sodium (section 1.3). Gastrointestinal side effects were not considered in the analysis and are less for mycophenolate sodium in the published SPC.

2.3 Recommendation 1.4 reduces effective options for the subgroup of future patients who have poor adherence or marked variability of drug levels with immediate release tacrolimus (1.2) by not recommending prolonged release tacrolimus. This is despite there being evidence that non-adherence and high within-patient variability are associated with worse outcomes, generally graft loss.

2.4 Recommendation 1.4 reduces effective options for future patients who would benefit from sirolimus treatment. The Committee has not taken into consideration the current ways in which sirolimus is used.

2.5 Recommendation 1.4 reduces effective options for future patients who are not suitable for basiliximab induction therapy (section 1.1) by not recommending rabbit ATG.

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No compelling evidence has been presented showing the safety and effectiveness of using Basiliximab outside the marketing authorisation.

2.6 The Appraisal Committee acknowledge that there are limitations in the available evidence and of the consequent clinical and cost-effectiveness analysis which raises concerns about the robustness of the recommendations.

2.7 The recommendations are based on the wrong comparator used in the economic analysis

2.1 Recommendation 1.4 would be at variance with much of current clinical practice in the absence of sufficient trial data for or against the recommendations, thereby reducing effective options for future patients who are intolerant of, or unsuitable for, the interventions recommended in section 1.1-1.3 of the FAD.

The summary of section 4.58 of the FAD states, 'The Committee heard that the choice between immunosuppressive therapies is affected by a number of factors, including the characteristics and preferences of the person having treatment. The Committee understood the value of having a choice of immunosuppressive therapies.'

The summary of section 4.64 of the FAD states 'The Committee noted that there were very little subgroup data for any of the interventions. It considered that there are likely to be some subgroups of people for whom individual treatment options may be particularly beneficial, but it had not seen sufficient evidence of clinical or cost effectiveness in specific subgroups'.

The summary of section 4.75-4.76 of the FAD states, 'The Committee understood that some treatments are associated with complications and so must be avoided or withdrawn for some people. The Committee was aware that it had not seen evidence supporting the clinical or cost effectiveness of alternative treatments in these situations.'

The concerns arise for those patients who are intolerant or unsuitable for these medications and examples are covered in paragraphs 2.2-2.5 of this appeal. Section 1.4 does not recommend the use of mycophenolate sodium, prolonged release tacrolimus, sirolimus and rabbit ATG for induction therapy. These are all interventions that have been in routine clinical use for those patients who are intolerant or unsuitable for the recommended interventions, and which are

currently funded through specialised commissioning in NHS England. Mycophenolate sodium was launched in the UK in 2004, prolonged release tacrolimus in 2007, sirolimus in 2001 and rabbit ATG has been in use for at least 30 years for this indication (although a marketing authorisation was not gained until 2008). These agents are well embedded into the transplant guidelines of each unit and there is a wealth of clinical experience in tailoring individuals' immunosuppression to minimise side effects and maximise efficacy. It is acknowledged that there is not published evidence to support this clinical experience.

We are unclear that if the Committee has not seen the evidence because it does not exist, as to why they have chosen 'not to recommend' these agents, as opposed to making 'no recommendations.' In section 4 the Committee have chosen 'to make no recommendation' rather than 'not to recommend' in two specific scenarios where again there is no evidence for or against.

2.2 Recommendation 1.4 reduces effective options for future patients who are intolerant of mycophenolate mofetil by not recommending mycophenolate sodium (section 1.3). Gastrointestinal side effects were not considered in the analysis and are less for mycophenolate sodium in the published SPC.

Section 3.23 of the FAD states that adverse reactions occur in at least 10% of adults having mycophenolate mofetil and this includes the gastrointestinal ones of vomiting, abdominal pain, diarrhoea and nausea. The SPC for mycophenolate mofetil quotes $\geq 10\%$ (defined as very common) for these four adverse events. In comparison the SPC for mycophenolate sodium quotes $\geq 10\%$ for diarrhoea and $\geq 1/100$ to $< 1/10$ (common) for vomiting, abdominal pain and nausea. This suggests that gastrointestinal side effects are less frequent with mycophenolate sodium than mycophenolate mofetil.

In routine clinical practice these gastrointestinal adverse reactions can be disabling despite dose reductions or split dosing. Over the last decade widespread clinical experience in these situations has demonstrated that changing a patient to mycophenolate sodium can fully relieve the symptoms in a proportion of patients, and if not successful, a switch to sirolimus can instead be

effective. The only other option is to switch to azathioprine, but that comes with an increased risk of rejection as azathioprine is a less potent immunosuppressive.

- Other observational studies have shown that dose reduction and dose splitting is less common in mycophenolate sodium treated patients compared with mycophenolate mofetil treated patients and was associated with less biopsy proven acute rejection.
- Ref: Sollinger HW, Sundberg AK et al. *Mycophenolate mofetil versus enteric-coated mycophenolate sodium: a large, single-center comparison of dose adjustments and outcomes in kidney transplant recipients*. *Transplantation* 2010; 89(4):446-51
- Section 4.16 of the FAD states, 'The Assessment Group (AG) summarised adverse event data focusing on 6 groups of adverse events: new-onset diabetes, malignancy, post-transplant lymphoproliferative disorders, infections, cytomegalovirus (CMV) infections and dyslipidaemia.'

Gastrointestinal adverse events were not considered in the analysis and recommendation 1.4 will deprive patients of effective options to manage unwelcome side effects that affect $\geq 10\%$ of patients.

2.3 Recommendation 1.4 reduces effective options for the sub-group future patients who have poor adherence or marked variability of drug levels with immediate release tacrolimus (1.2) by not recommending prolonged release tacrolimus. This is despite there being evidence that non-adherence and high within-patient variability are associated with worse outcomes, generally graft loss.

In section 4.55- 4.56 of the FAD the discussion around the available evidence and potential benefits of prolonged release tacrolimus is summarised. It states, 'The AG agreed that the non-randomised evidence presented showed that prolonged release tacrolimus resulted in lower within-patient variability. The AG also agreed that there was evidence that non-adherence and high within-patient variability are associated with worse outcomes, generally graft loss.'

There is evidence to show that:

1. Where patients take medication in divided doses it is the evening dose that tends to be forgotten
2. Adolescents and young adults are an 'at risk' group for non-adherence; and in transplant patients there are increased rates of late rejection and graft failure
3. Transplant recipients have their tacrolimus blood levels measured on a regular basis and it is usually clear from those if there is a problem with non-adherence or high within-patient variability. Sub-therapeutic levels are associated with development of donor specific antibodies and earlier graft loss

Clinical experience gained over the last seven years within the UK has shown that for those patients who are susceptible to either non-adherence or high within-patient variability then the use of prolonged released tacrolimus has been a valuable therapeutic alternative.

We consider it unfair that these subgroups are being discriminated against by denying access to the options of tailoring their immunosuppressive regime, and point to the special consideration given to other groups who require changes to the formulation of the standard drugs (e.g. those who cannot readily swallow tablet formulations)

2.4 Recommendation 1.4 reduces effective options for future patients who would benefit from sirolimus treatment. The Committee has not taken into consideration the current ways in which sirolimus is used.

Section 3.28 of the FAD describes the marketing authorisation for sirolimus in the UK as being used immediately post transplantation as part of maintenance immunosuppression. However sirolimus is not used immediately post-transplantation in the UK because of the problems of delayed wound healing and greatly increased rate of lymphocele formation, and any use delayed until at least three months post-transplant.

It is used clinically in three scenarios

- i) As a substitute for tacrolimus or cyclosporine in situations of nephrotoxicity and the use of sirolimus or other agents appears to be covered by the following statement in section 1.4 of the FAD

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The Appraisal Committee was unable to make recommendations on these technologies to prevent organ rejection in adults having a kidney transplant who have:

- biopsy-proven nephrotoxicity associated with calcineurin inhibitors or
- biopsy-proven thrombotic microangiopathy.

ii) As a substitute for tacrolimus or mycophenolate when the recipient has a malignancy. Sirolimus has an in-vitro anti-tumour effect and results from a number of randomized controlled studies shows that it reduces the risk of recurrent skin squamous cell carcinoma, a problem that affects up to 50% of white renal transplant recipients

Refs:

Campbell SB, Walker R, Tai SS et al. *Randomised controlled trial of sirolimus for renal transplant recipients at high risk for non-melanoma skin cancer.* Am J Transplant 2012; 12: 1146-56

Euvrard S, Morelon E, Rostaing L et al. *Sirolimus and secondary skin cancer prevention in kidney transplantation.* N Eng J Med 2012;367:329-39

den Akker JMH-v, Harden PN, Hoitsma AJ. *Two-year randomized controlled prospective trial converting treatment of stable renal transplant recipients with cutaneous invasive squamous cell carcinomas to sirolimus.* J Clin Oncol 2013; 31: 1317-23

iii) As a substitute for mycophenolate mofetil or mycophenolate sodium when there are intractable gastrointestinal adverse events. This has already been described above in section 2.2

Within the clinical effectiveness and cost effectiveness sections of the FAD the analyses appear to have been done on the basis of the original marketing authorization, and not the three ways that sirolimus is currently used which would be considered as off label. It is considered that the recommendations on sirolimus have not been based on the ways in which the drug is actually used.

2.5 Recommendation 1.4 reduces effective options for future patients who are not suitable for basiliximab induction therapy (section 1.1) by not recommending rabbit ATG. No compelling evidence has been presented

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showing the safety and effectiveness of using Basiliximab outside the marketing authorisation.

The Marketing Authorisation for Basiliximab states that it should be used in patients with panel reactive antibodies (PRA) less than 80%.

Within the introduction to section 1 and 4 the FAD states, 'Under an exceptional directive from the Department of Health, the Appraisal Committee can consider making recommendations about the use of drugs outside the terms of their marketing authorisation when there is compelling evidence of their safety and effectiveness.'

From the available evidence looked at by the Committee, there appears to be no compelling evidence showing the safety and effectiveness of using Basiliximab in highly sensitised recipients where panel reactive antibodies are greater than 80%.

In section 4.67 of the FAD, 'The Committee acknowledged that there may be some subgroups of people, such as people with high immunological risk or delayed graft function, for whom r-ATG may provide additional benefits. The Committee noted comments received during consultation about evidence demonstrating r-ATG's efficacy in people with high immunological risk. The Committee noted the Brennan (2006) study in which the mean peak panel reactive antibody was approximately 14% in both groups, with a mean value of about 6% at the time of transplant. The Committee questioned whether the study had included a high immunological risk group and considered that there was not enough evidence to support recommendations in people with high immunological risk.'

It is acknowledged that there is no compelling published evidence for the use of Basiliximab or r-ATG in the highly sensitised kidney transplant recipient with panel reactive antibodies are greater than 80%. This group of patients wait longer for their transplant, have higher rates of acute rejection, have poorer long term graft survival – and consequently are considered more precious kidneys. It has been routine clinical experience over the last 20 years in both Europe and North America to consider using r-ATG for this subgroup of patients because of the desire to maximise graft and patient survival.

On the basis of the arguments above we would ask that the Committee consider

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changing a 'non-recommendation of r-ATG' to 'being unable to make a recommendation on r-ATG' for the prophylaxis of rejection in high risk patients.

2.6 The Appraisal Committee acknowledge that there are limitations in the available evidence and of the consequent clinical and cost-effectiveness analysis which raises concerns about the robustness of the recommendations.

Within section 4 of the FAD the AG cite the following limitations in the evidence and analysis.

- Section 4.1 'The AG highlighted that the identified clinical studies were of varying quality; all appeared to have limitations and most had reporting omissions.'
- Section 4.15 'The AG noted that there was substantial heterogeneity in all of the network meta-analyses. It stated that none of the maintenance regimens performed consistently well across all 4 outcomes assessed in the network meta-analysis (mortality, graft loss, acute rejection and graft function), although some differences between regimens were seen for some outcomes (see Table 2). The AG stated that because of wide confidence intervals, there was a great deal of uncertainty associated with the results and limited conclusions could be drawn.'
- Section 4.22 'The AG acknowledged the limitations in the evidence available.'
- Section 4.54, 'The AG acknowledged that there were limitations and uncertainties in its analysis....The AG also noted that there was not enough evidence to support subgroup analyses....The AG highlighted that there are a number of uncertainties remaining in its analysis, in particular the predicted survival differences between regimens (because there is limited long-term evidence from randomised controlled trials), the effects of immunosuppressive therapy on health-related quality of life, the costs associated with new-onset diabetes and the availability of discounts from the list price for immunosuppressive drugs.'

It was noted by the AG that of the 86 randomised controlled trials identified only 11 of these trials adequately matched the population and current practice in the NHS in England and the following points are made:

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- It is well known that most studies will invariably include transplant recipients with low-risk characteristics that are not representative of the general transplant recipient pool.
- Within the studies of maintenance agents there will be 20-30% patients withdrawn because of treatment failure or adverse events and it is not clear whether or how this group has been considered within the clinical or cost-effectiveness analyses.
- The economic model used was based on a discrete-time state transition structure, with a time horizon of 50 years and a cycle length of 3 months. However the majority of trials analysed looked predominantly at only medium term outcomes of up to 3 years, and with 10 year graft survival currently being 73% for deceased donor transplants (80% for living donor transplants), then this raises concerns about extrapolating medium term clinical studies into long term economic models. The comparator immunosuppressive regime used in the majority of these trials was ciclosporin, azathioprine and prednisolone which is certainly not standard treatment now for transplant patients.

We are concerned that recommendations are being made based on an evidence base that has limitations in terms of quality which means that the clinical and cost-effectiveness analyses also have major limitations.

2.7 The recommendations are based on the wrong comparator used in the economic analysis

Within the clinical effectiveness section of the FAD the following agents had been shown to have equivalent clinical effectiveness:

- Mycophenolate mofetil and mycophenolate sodium (section 4.11-4.12)
- Immediate and prolonged release tacrolimus (section 4.9)
- Combinations of recommended agents were broadly equivalent with Sirolimus when used in combination with other agents (section 4.13)
- Basiliximab and rabbit-ATG (section 4.5)

The recommendations in 1.4 therefore appear to have been made based purely on cost as clinical effectiveness is equivalent. This is not surprising as mycophenolate sodium, prolonged release tacrolimus and sirolimus are not yet

available in generic formulation, unlike their comparator immunosuppressive agents.

Most of the drugs under consideration are used at lower doses than that included within their marketing authorization. r-ATG is usually given based on the absolute lymphocyte count and so a 10-14 day course may actually require only 3 or 4 doses. It is not clear how this has been factored into the economic analysis and comparison with Basiliximab.

For the 20-30% of patients who do not tolerate or who are not suitable for the recommended intervention, the true comparator should be the cost of dialysis (around £35k per year for haemodialysis, although this does not include the non-cost comparison of the quality of life for patients) as graft failure is one of the potential outcomes of not being able to use one of the non-recommended alternatives. The specific details have been discussed in sections 2.2a – 2.5. Comparison with the generic immunosuppressive drug is not relevant if the patient is unable to tolerate it.

Conclusion

Recommendation 1.4 would be at variance with much of current clinical practice and appears to have been made in the absence of sufficient trial data for or against the recommendations.

NHS England is appealing because the proposed recommendations reduce effective options for the 20-30% future transplant patients who will be intolerant of, or unsuitable for Basiliximab, mycophenolate mofetil or immediate release tacrolimus – and where ciclosporin and azathioprine are not deemed effective options. This will equate to approximately 475-700 patients per year at current transplantation rates.

Mycophenolate sodium, prolonged release tacrolimus, sirolimus and rabbit-ATG are all established in routine clinical practice and are known to be effective alternatives where the recommended agents cannot be used. It is acknowledged that the AG noted that there was not enough evidence to support subgroup analyses. The Committee does state that these agents are all of equivalent clinical effectiveness to their comparator

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agents, and therefore the decision to not recommend them appears to be based entirely on cost. This comparator used in the analysis however is the immunosuppressive drug that cannot be tolerated, rather than the cost of potential graft failure.

NHS England would ask the Committee to reconsider their decision and rather than 'not recommending' mycophenolate sodium, prolonged release tacrolimus, sirolimus and rabbit-ATG, to say that they are 'unable to make a recommendation for their use where the recommended agents are unable to be used'. This approach has already been used in the two scenarios described in the second part of recommendation 1.4.

NHS England is not appealing the recommendations for everolimus and belatacept; and is supportive of recommendations 1.1 -1.3 for the 70-80% patients who are tolerant of, or suitable for these agents.

NHS England wishes this appeal to proceed at an oral appeal.

Yours sincerely



Clinical Director Specialised Services