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Dear Dr Helliwell

Re: Final Appraisal Determination – Immunosuppressive therapy for kidney transplant in children and young people (review of technology appraisal guidance 99)

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.

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 4.54 of the FAD states, 'People have different preferences for dosing regimens and side-effect profiles, so it is important to tailor treatment to each person. The Committee concluded that patients and clinicians prefer to have a choice of immunosuppressive treatments.'

The summary of section 4.56 of the FAD states 'There were insufficient data to permit analyses of subgroups.

Section 4.77 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 concerns arise for those patients who are intolerant or unsuitable for these medications. 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 available for clinical use in 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). It is accepted that most clinical experience in tailoring individuals' immunosuppression to minimise side effects and maximise efficacy has been gained in adult transplant units. However clinicians in adult and paediatric transplant units work closely together, and this clinical experience is transferable. 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 1.4 the Committee have chosen 'to make no recommendation' rather than 'not to recommend' in two specific scenarios.

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 ≥10% (defined as very common) for these four adverse events, with diarrhoea being more common in children and young people than adults. In comparison the SPC for mycophenolate sodium in adults quotes ≥10% for diarrhoea and ≥1/100 to <1/10 (common) for vomiting, abdominal pain and nausea. There is limited data on the use in children and young people, although the pharmacokinetic profile is similar to adults. Overall 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 in adults 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

There are no trials or observational studies in children or young people with mycophenolate sodium. Section 4.25 of the FAD states that the AG did meta-analyses of adverse events in RCTs in adults with a follow-up of 1 year, but gastro-intestinal adverse events were not included within this analysis. Section 4.38 of the FAD states, 'The model included 4 adverse events: anaemia, new-onset diabetes, cytomegalovirus infection and dyslipidaemia.' It is also noted in section 4.39 that 'The network meta-analysis did not include mycophenolate sodium.' Section 4:23 also states 'The network meta-analysis assumed that mycophenolate mofetil and mycophenolate sodium were the same drug' although the SPC suggests the side effect profile is different.

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 ≥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 adults there is non-randomised evidence that shows prolonged release tacrolimus results in lower within-patient variability. There is also 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. Most experience has been gained in adults, but there is a growing use in adolescents who are known to be more susceptible to non-adherence. In adults where adherence is an issue, moving to a once daily immunosuppressive regimen of prolonged release tacrolimus, azathioprine and prednisolone has been of benefit. We note the comment in section 4.63 of the FAD that 'that switching from immediate-release to prolonged-release tacrolimus would remove only 1 tablet a day.' This is only the case if the patient is on 1mg or 5mg bd; but because of available tablet size it could be four fewer tablets if they are on a 4mg bd dosage. We acknowledge that there isn't published evidence to support this current clinical practice and experience.

We consider it unfair that this subgroup of adolescents is 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 two 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
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 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 two ways that sirolimus is currently used in children and young people 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 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%.

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%. There are fewer highly sensitised paediatric transplant recipients than adults, with panel reactive antibodies greater than 80%. Nevertheless 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 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.

There is limited evidence in children and young people and the FAD describes only 3 RCTs found and that although these were generalizable to the NHS they were quite old. There were 10 non-randomised studies which were of poor quality and not generalizable to the NHS. There was a lack of evidence from children and young people, and as a consequence estimates of effectiveness from a network meta-analysis of 86 RCTs in adults were used.
Within section 4 of the FAD for *Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)* 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 only 3 in children and young people and the following points are made:

- 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 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

Section 4.16 of the FAD states, 'The review did not find any studies (either randomised or non-randomised) of prolonged-release tacrolimus or mycophenolate sodium in children and young people.' As a consequence adult data has been extrapolated into the clinical and cost-effectiveness data for children and young people.

Within the clinical effectiveness section of the FAD *Immunosuppressive therapy for kidney transplant in adults (review of technology appraisal guidance 85)* 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 assumed to be equivalent in children and young people as it is in adults. This is not surprising as mycophenolate sodium, prolonged release tacrolimus and sirolimus are not yet available in generic formulation, unlike their comparator immunosuppressive agents.

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 (up to £100k per year for haemodialysis in children and young people) 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 2.2 – 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 25-37 paediatric transplants 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 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, and would seem more appropriate when there is no evidence for or against.

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.

Clinical Director Specialised Services