

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

The British Transplant Society, Renal Association, British Association for Paediatric Nephrology and British Renal Society would like to appeal against the Final Appraisal Determination for the above mentioned technology appraisal, in particular with regard to recommendation 1.4 on '**Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE**' on the grounds that we believe it to be unreasonable in light of current clinical practice.

1.4 Rabbit anti-human thymocyte immunoglobulin, prolonged-release tacrolimus, mycophenolate sodium, sirolimus, everolimus and belatacept are not recommended to prevent organ rejection in children and young people having a kidney transplant

After reviewing the final appraisal document we believe that recommendation 1.4, as currently written, is unreasonable in light of the evidence presented to NICE, or lack thereof. Other than Everolimus and Belatacept which are currently not in routine clinical practice, we are of the opinion that a lack of availability of the remaining agents could have a detrimental effect on the outcome of kidney transplantation in UK paediatric recipients who are currently receiving some form of tailored immunosuppression.

Most of the medications listed in recommendation 1.4 have been in routine clinical use for patients who are unsuitable for the recommended interventions in sections 1.1-1.3 and are currently funded through specialised commissioning. Mycophenolate sodium, prolonged release tacrolimus and sirolimus have been in use for the past 10 years and rabbit ATG has been in use for at least 30 years. These agents are well embedded in the immunosuppressive protocols of most renal transplant units. Although there may not be robust published evidence to support their use, there is a wealth of clinical experience attesting to their benefit for individuals by minimising side effects and maximising efficacy. The evidence considered by NICE fails to cover a substantial spectrum of routine clinical practice in the care of patients following renal transplantation in which the choice of immunosuppression is determined by the only reasonable therapeutic option, application of acquired expert clinical experience, national consensus and established practice. This is simply ignored by NICE as the evidence is not represented in randomised controlled clinical trials. In order to act reasonably NICE should have made a 'no recommendations' as opposed to a 'not to recommend' decision.

NICE accept that a substantial number of renal transplant recipients are intolerant of first line therapy or suffer a variety of significant adverse outcomes. This requires institution of alternative immunosuppression, including prompt conversion to an agent identified within recommendation 1.4. There is at present no NHS England process which is 'fit for purpose' to assess and approve funding of an application such as an alternative suitable drug. It is consequently unreasonable to propose recommendation 1.4 in this guidance without ensuring a suitable mechanism to process the substantial numbers of applications for funding. Failure to do so is likely to lead to unnecessary graft loss or other adverse outcome.

Recommendation 1.4 – disadvantages patients who are intolerant of MMF and experience GI disturbances.

Gastrointestinal adverse reactions to MMF are common and disabling despite dose modification. Clinical experience in these situations has demonstrated that changing a patient to mycophenolate sodium or even sirolimus can relieve the symptoms in a significant proportion of patients. The only other option is to switch back to azathioprine, a less potent immunosuppressive agent. For those patients who have already experienced a rejection episode this poses the risk of further rejection and inferior outcomes.

Recommendation 1.4 – does not account for drug variability and non adherence

With regards to the prolonged release tacrolimus preparation, clinical evidence has shown that for patients who are susceptible to either non-adherence or who have significant dose variability the use of prolonged released tacrolimus has been a valuable therapeutic alternative. The current recommendations remove this option completely despite a specific request by patient representatives for inclusion of this preparation.

Recommendation 1.4 – prevents the use of r-ATG in 'high immunological risk' patients

We note an acknowledgment by the committee that rabbit ATG may provide additional benefit to recipients with high immunological risk. Even though there is no compelling published evidence for its use in the highly sensitised kidney transplant recipients (PRA >80%) there is considerable clinical experience in both Europe and North America to consider using r-ATG for this subgroup of patients. Furthermore there is no good published evidence that Basiliximab is effective in this high risk group of patients. The continued availability of this therapy is essential to allow successful transplantation in this group of patients who might otherwise remain on dialysis, accruing morbidity and cost to the NHS.





Recommendation 1.4 – prevents the use of Sirolimus as a CNI sparing agent or in patients with MMF intolerability and those with malignancy

Sirolimus has been used as a nephron sparing agent to minimize CNI toxicity; it is also useful in patients with GI disturbance related to MMF in whom Mycophenolate Sodium has been ineffective, and in patients at risk of malignancy especially those with a history of recurrent skin cancer.

Conclusion:

As transplant professionals representing the combined experience of those in the British Transplantation Society, Renal Association, British Association for Paediatric Nephrology and British Renal Society managing renal transplant recipients we are unified in our opinion that the excluded agents in recommendation 1.4 (other than everolimus and belatacept) are essential to ensuring good clinical outcome and it is unreasonable to ‘not recommend’ rather than conclude with ‘no recommendation can be given’. In addition it is unreasonable to propose such guidance without first ensuring that an appropriate mechanism is identified which is fit for purpose to allow an immunosuppressive drug switch that is considered necessary to improve long term graft outcome. Failure to allow such a drug switch is likely to lead to higher rates of graft loss with the associated high monetary cost of dialysis and accrual of cardiovascular and psychosocial morbidity.

Electronic approval given

			
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