ESPRIT

Efficacy and Safety of PRescribing In Transplantation

January 18th 2016

Dr Margaret Helliwell
Vice Chair
National Institute for Health and Care Excellence
10 Spring Gardens
London SW1A 2BU

Dear Dr Helliwell

Re: Final Appraisal Determination – Immunosuppressive therapy for kidney transplant in adults ID 456 (review of technology appraisal guidance 85)

The Efficacy and Safety of PRescribing in Transplantation (ESPRIT) Group 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

2.1 The blanket 'not recommended' in section 1.4 of the FAD is contrary to current best clinical practice, based on hands-on experience of transplant specialists over many years of managing individual patients' immunosuppression. Experience in practice has shown that some patients just cannot tolerate, or are clinically unsuitable for, other therapies recommended in the FAD. For these patients, despite an acknowledged lack of formal published clinical trial data, medications listed in section 1.4 have provided undoubtedly effective options to help prevent organ rejection.

Examples of problems encountered in a proportion of patients, which have mandated current use of agents cited in section 1.4, include poor adherence and variability of blood levels with immediate-release tacrolimus (which are proven predictors of poor outcomes), intractable gastrointestinal side effects with mycophenolate mofetil and pre-existing and post-transplant malignancies. Enabling effective immunosuppression in these patients is key in terms of helping preserve precious donated kidneys.

2.2 We question how the Assessment Committee arrived at the active 'not recommended' statement in section 1.4 of the FAD given that:

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.'*

Section 2.6 of the FAD states, *'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'.*

Arguably, in the acknowledged absence of formal clinical trial data on the agents cited in section 1.4 of the FAD, the more logical statement might have been '*unable to make a recommendation for use of these agents [where the*

recommended agents cannot be used]' rather than the definitive '*not recommended'*.

Indeed, in section 4 of the FAD the Assessment Committee have specifically chosen '*to make no recommendation*' rather than '*not to recommend'* in two specific situations where there is currently lack of formal clinical trial evidence.

2.3 The economic analysis has apparently neglected a pivotal comparator, namely the cost of graft failure as a consequence of inadequate immunosuppression, and the resulting return to costly dialysis. This should be the main comparator when assessing the cost-effectiveness of immunosuppressant agents, especially as the cost *per se* of immunosuppression following transplantation is minimal in comparison with the overall cost of managing a transplant patient.

The prime objective of immunosuppression following transplantation is to prevent organ rejection. Many patients undergoing a transplant will have been on haemodialysis for some time before transplantation – at a direct cost of over £30,000 per annum. Effective immunosuppression to preserve function of their donated graft may ultimately depend on the use of one of the 'not recommended' agents. The incremental drug cost for this compared to a 'recommended agent' is irrelevant if the latter is not a clinical option, and is minimal anyway compared with the cost of a return to dialysis.

Conclusion

The blanket 'not recommended' in section 1.4 of the FAD is contrary to current best clinical practice, based on hands-on experience of transplant specialists, over many years, of managing individual patients' immunosuppression.

For a significant proportion of patients, despite an acknowledged lack of formal published clinical trial data, medications listed in section 1.4 have provided undoubtedly effective options to help prevent organ rejection. The flexibility to prescribe these agents is therefore of key importance in helping maintain and

develop the transplant programme and optimise the use of precious organ resources.

In the acknowledged absence of formal clinical trial data on the agents cited in section 1.4 of the FAD, a more logical statement in this section might have been '*unable to make a recommendation for use of these agents [where the recommended agents cannot be used]'* rather than the definitive '*not recommended'*.

Any cost-effectiveness analysis in transplantation should be in the context of the overall cost of immunosuppression, which is minimal compared to the overall costs of managing transplant patients. Plus, most importantly, effective immunosuppression is key to preventing rejection of transplanted kidneys, and the consequent return in most cases to costly dialysis.

We sincerely urge NICE to reconsider their recommendations on the basis of our appeal.

ESPRIT wishes this appeal to proceed at an oral appeal.

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