NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal (MTA)

Immunosuppressive therapy for kidney transplantation in adults (review of technology appraisal guidance 85)

Submisssion on behalf of the British Transplantation Society

Prepared by [redacted], October 2014

Introduction

We very much welcome the current MTA as a number of new immunosuppressive drugs have become available since the publication of TA85 and the evidence base for immunosuppression in renal transplantation has evolved substantially. We have concerns over the scope of this MTA which does not cover the full range of immunosuppressive drugs currently being used in the UK. There is a risk of this being misinterpreted and applied as a guideline by healthcare funders and a clear statement that this document is not intended to be a guideline for immunosuppression for renal transplantation would be welcome. Indeed, a NICE guideline in this area would be useful.

Appropriate follow-up period

Most of the randomised controlled trials of immunosuppressive drugs are based on a short follow-up period with transplant survival at one year as the commonest hard endpoint. While these short-term data may predict long-term outcomes, patient and graft survival with a horizon of 10-30 years is essential. Clinical trials rarely provide these data but registries do, although there are some limitations of the quality of immunosuppression prescribing data. UK specific follow-up data are available through NHS Blood and Transplant. International Registry data are available through the International transplant Study, UNOS and ANZDATA.

Current practice in the UK

There is a general feeling amongst the transplant community that TA85 was obsolete at the time of publication and very few transplant centres in the UK follow the guidance. The most widely based regimen, based on the findings of the SYMPHONY study (1), comprises tacrolimus with mycophenolate mofetil, usually with Basiliximab induction and prednisolone with many centres adopting early steroid withdrawal. Almost no patients in the UK are now transplanted using the reference regimen of ciclosporin, azathioprine and steroids to be used for this appraisal.

Induction therapy

The planned analysis of induction therapy will look only at Basiliximab and Anti-Thymocyte Globulin (Thymoglobulin). The analysis will not be readily applicable to clinical practice if Alemtuzumab which is now widely used in the UK, with data from two large randomised controlled trials published (2,3) is excluded. Other induction agents, specifically Rituximab and Eculizumab have been adopted for use in antibody incompatible transplantation and their omission from this appraisal is disappointing.

Generic preparations
The calcineurin inhibitors have a narrow therapeutic index. It is particularly important that generic calcineurin inhibitors meet the more stringent bioequivalence criteria (90-111%) and, ideally have pharmacokinetic data in renal transplant recipients. The European Society for Organ Transplantation has published guidelines on the appropriate use of generic immunosuppressive drugs (4).

Points on specific drugs

Tacrolimus
The target therapeutic range employed in current practice is well below the range stated in the licencing documents and has gradually decreased over time. The SYMPHONY study used a target of 3-7 µg/L although actually achieved a target closer to 5-10 µg/L. It is important that cost calculations for tacrolimus take into account actual drug usage in contemporary practice.

Mycophenolate
Although the manufacturers would not support this view, there is a substantial body of evidence supporting the use of lower doses of mycophenolate in patients not on treatment with ciclosporin which inhibits enterohepatic recirculation reducing drug exposure (5). The optimal daily dose in patients treated with tacrolimus is probably 1g twice daily for mycophenolate mofetil (or equivalent as mycophenolate sodium) for the first month and subsequently is lower between 500 mg and 750 mg twice daily. This should be taken into consideration in recommendations and costing.

Adherence
Evidence that non-adherence is a major factor in long-term renal allograft failure due to chronic antibody-mediated rejection is accumulating (6). Adherence will be specifically studied in the children and adolescents but is not planned for adults. We would be strongly in favour of inclusion of adherence as a key factor in the adult appraisal.

Assessment of costs
Competitive tendering processes have resulted in most immunosuppressive drugs being purchased at well below list price. It is important that financial assessments are made on actual acquisition cost rather than the relatively meaningless list prices.

References

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4. van Gelder T. European Society for Organ Transplantation Advisory Committee recommendations on generic substitution of immunosuppressive drugs. Transpl Int 2011;24: 1135-1141.

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