A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children

G Yao,[1] E Albon,[2] Y Adi,[2] D Milford,[3] S Bayliss,[2] A Ready,[4] J Raftery[5] and RS Taylor[2*]

[1] Health Economics Facility, Health Services Management Centre, University of Birmingham, UK
[2] Department of Public Health and Epidemiology, University of Birmingham, UK
[3] Department of Nephrology, Birmingham Children's Hospital, UK
[4] Department of Nephrology, Queen Elizabeth Hospital, Birmingham, UK
[5] National Coordinating Centre for Health Technology Assessment, University of Southampton, UK

* Corresponding author

Executive summary

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Executive summary

Background

The prevalence of end-stage renal failure in the UK paediatric population varies from 13.6 per million in the under 4-year-old population to 53.4 per million in the under 18-year-old population. Renal transplantation has established itself as the optimum treatment for end-stage renal failure. The goal of immunosuppression is to maintain graft and patient survival without exposing the patient to the risks of excessive immunosuppression or nephrotoxicity related to the use of immunosuppressant drugs. The current mainstay of therapy in children in the UK is a triple immunosuppression consisting of a calcineurin inhibitor (ciclosporin or tacrolimus), a DNA proliferation inhibitor (usually azathioprine) and steroids.

Objective

The objective was to review the clinical and cost-effectiveness of basiliximab, daclizumab, tacrolimus, mycophenolate mofetil (MMF), mycophenolate sodium (MPS) and sirolimus as possible immunosuppressive therapies for renal transplantation in children.

Methods

We searched for systematic reviews of randomised controlled trials (RCTs) undertaken in adults, children or both, systematic reviews of non-randomised comparative studies undertaken in children and RCTs undertaken in adults, children or both. A variety of bibliographic sources were used and database searches were undertaken up to November 2004. Studies were assessed for inclusion according to predefined criteria. Data extraction and quality assessment were also undertaken.

An economic model [Birmingham Sensitivity Analysis paediatrics (BSAp)] was developed based on an adaptation of a model previously developed for assessment of the cost-effectiveness of immunosuppressants in adults following renal transplant.

Number and quality of studies and direction of evidence

Clinical effectiveness

Addition of basiliximab

One unpublished paediatric RCT, four adult RCTs and six non-randomised comparative studies were included. The paediatric RCT reported that the addition of basiliximab to tacrolimus-based triple therapy (BTAS) failed to significantly improve 6-month biopsy-proven acute rejection (BPAR) [relative risk (RR) 0.93, 95% CI: 0.53 to 1.65], graft function, graft loss and all-cause mortality. No significant difference between groups was seen in 6-month or 1-year or longer graft loss, all-cause mortality and side-effects. In a meta-analysis of adult RCTs, the addition of basiliximab to a ciclosporin, azathioprine and steroid regimen (CAS) significantly reduced short-term BPAR (RR 0.61, 95% CI: 0.46 to 0.80). There was no significant difference in short- or long-term graft loss, all-cause mortality or side-effects.

Addition of daclizumab

One adult RCT was included. The addition of daclizumab to CAS reduced 1-year BPAR (RR 0.63, 95% CI: 0.42 to 0.94). No difference between groups was seen in either 1- or 3-year graft loss, all-cause mortality and side-effects.

Tacrolimus versus ciclosporin

One unpublished paediatric RCT, nine adult RCTs and two paediatric non-randomised comparative studies were included. The paediatric RCT found that a regimen of tacrolimus, azathioprine and a steroid (TAS) reduced 6-month BPAR (RR 0.42. 95% CI: 0.26 to 0.69) and improved graft function [glomerular filtration rate (GFR)] compared with CAS. This improvement in BPAR with tacrolimus was as shown in the meta-analysis of adult RCTs. There was evidence, particularly in children, that in comparison with ciclosporin, tacrolimus may reduce long-term graft loss, although there is no benefit on total mortality. The total level of withdrawal in children was reduced in children receiving tacrolimus. Adult RCTs showed an increase in post-transplant diabetes mellitus with tacrolimus.

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MMF versus azathioprine

Seven adult RCTs and three paediatric non-randomised comparative studies were included. A meta-analysis of adult RCTs showed MMF [regimen of ciclosporin, MMF and a steroid (CMS)] to reduce 1-year BPAR (RR 0.60, 95% CI: 0.47 to 0.76) compared with azathioprine (CAS). There was evidence, particularly in children, that in comparison with azathioprine, tacrolimus may reduce long-term graft loss, although there is no benefit on total mortality. There was an increase in the level of cytomegalovirus infection with MMF, although the overall level of withdrawal due to adverse events was not different to that of azathioprine-treated adults.

MPS versus azathioprine

No study comparing MPS with azathioprine (CAS) was identified. In an adult RCT comparing MMF with MPS, there was no significant difference between groups in 1-year efficacy or side-effects.

Sirolimus

One unpublished paediatric RCT and three adult RCTs were included. The paediatric RCT assessed the addition of sirolimus to CAS. BPAR, graft loss and all-cause mortality were not reported. Two adult RCTs compared sirolimus with azathioprine. Compared with azathioprine, sirolimus reduced 1-year BPAR (pooled RR 0.60, 95% CI: 0.45 to 0.80), reduced graft function (as assessed by an increased serum creatinine) and increased the level of hyperlipidaemia. No significant differences were seen in other efficacy and side-effect outcomes. One adult RCT compared sirolimus with ciclosporin. There were no significant differences between groups in 1-year efficacy or side-effects with the exception of an increased level of hyperlipidaemia with sirolimus substitution.

Cost-effectiveness

Both the assessment group and drug companies assessed the cost-effectiveness of the newer renal immunosuppressants currently licensed in children using an adaptation (BSAp) of the Birmingham Sensitivity Analysis (BSA) model initially developed by the assessment group to inform the National Institute for Health and Clinical Excellence (NICE) guidance on the use of the newer renal immunosuppressive drugs for adult renal transplant recipients. This model is based on a 10-year extrapolation of 1-year BPAR results sourced from paediatric RCTs or adult RCTs (where paediatric RCTs were not available).

Both the addition of basiliximab and that of daclizumab to CAS were found to increase quality-adjusted life-years (QALYs) and decreased overall costs, a finding that was robust to sensitivity analyses. The incremental cost-effectiveness ratio (ICER) of replacing ciclosporin with tacrolimus was highly sensitive to the selection of the hazard ratio for graft loss from acute rejection, dialysis costs and the incorporation (or not) of side-effects. The ICERs for tacrolimus versus ciclosporin ranged from about £46,000/QALY to about £146,000/QALY. Although sensitive to varying the hazard ratio for graft loss with acute rejection, the ICER for replacing azathioprine with MMF remained in excess of £55,000/QALY.

Limitations of the calculations

There are substantive differences in the incremental costs per QALY results in this report compared with industry submissions for MMF. These differences reflect, principally, variations in parameter values for BPAR and drug doses/costs.

Conclusions

We found limited RCT evidence of the benefits and harms of the use of newer immunosuppressive agents (basiliximab, daclizumab, mycophenolate mofetil/sodium, tacrolimus and sirolimus) in children with kidney transplants, although, in some cases, there was instead evidence from non-randomised comparative studies in children and RCTs in adults. In general, compared with a regimen of ciclosporin, azathioprine and steroid, the newer immunosuppressive agents consistently reduced the incidence of short-term biopsy-proven acute rejection. However, evidence of the impact on side-effects, long-term graft loss, compliance and overall health-related quality of life is limited. Cost-effectiveness was estimated based on the relationship between short-term acute rejection levels from RCTs and long-term graft loss. Both the addition of daclizumab and that of basiliximab were found to be dominant strategies, that is, regarding cost savings and increased QALYs. The incremental cost-effectiveness of tacrolimus relative to ciclosporin was highly sensitive to key model parameter values and therefore may well be a cost-effective strategy. The incremental cost-effectiveness of MMF compared with azathioprine, although also sensitive to model parameter, was unattractive.

Need for further research

There is a particular need for RCTs to assess the use of MMF, MPS and daclizumab for renal ▶

transplantation in children where no such evidence currently exists. Future comparative studies need to report not only on the impact of the newer immunosuppressants on short- and long-term clinical outcomes but also on side-effects, compliance, healthcare resource, costs and health-related quality of life.

Publication

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Research suggestions are carefully considered by panels of independent experts (including service users) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or conducting a trial to produce new evidence where none currently exists.

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