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

Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, Raftery J, Taylor R S

CRD summary
This review assessed the clinical effectiveness and cost-effectiveness of newer immunosuppressive agents for renal transplantation in children. The authors’ conclusion, that there was limited evidence from randomised controlled trials for the benefit or harms of the newer immunosuppressive agents in children with kidney transplants, is appropriate.

Authors’ objectives
To determine the clinical effectiveness and cost-effectiveness of immunosuppressive therapy using basiliximab, daclizumab, tacrolimus, mycophenolate mofetil (MMF), mycophenolate sodium (MPS) and sirolimus for renal transplantation in children.

Searching
The Cochrane Library (Issue 4, 2004), DARE, MEDLINE (1996 to 2004), MEDLINE In-Process and Other Non-Indexed Citations (December 2004), EMBASE (1980 to 2004) and CINAHL (1982 to 2004) were searched; the search terms were reported. The National Research Register (Issue 4) and Current Controlled Trials Register were also searched for ongoing trials. The bibliographic references of all included RCTs and submissions from industry were checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and non-randomised controlled trials (NRCTs) were eligible for inclusion. Studies that had not finished recruiting were excluded. RCTs, and NRCTs cited from company submissions to the National Institute for Health and Clinical Excellence (NICE), were included.

Specific interventions included in the review
Studies that compared initial treatment with daclizumab or basiliximab with placebo or no therapy were eligible for inclusion. Studies comparing maintenance therapy (tacrolimus, MMF, MPS or sirolimus) with triple therapy (ciclosporin, azathioprine and steroids) were also eligible for inclusion. Studies were excluded if they included an intervention drug in the comparator arm, examined a strategy of drug tapering or switching, or only compared different doses of the same drug.

Participants included in the review
Studies of adults and/or children who had been recipients of first or subsequent kidney transplant (either live donor or cadaver donor) were eligible for inclusion. Studies that involved multiple organ transplants, or recruited patients with failed or failing renal transplants such as allograft nephropathy, were excluded.

Outcomes assessed in the review
Studies reporting all-cause mortality, graft loss, graft function, incidence of biopsy-proven acute rejection, growth in children, drug switching, side-effects, withdrawal due to adverse events, total withdrawals and health-related quality of life were eligible for inclusion. Studies that only reported baseline or follow-up outcomes for less than 50% of the sample were excluded.

How were decisions on the relevance of primary studies made?
Three reviewers independently selected papers for inclusion in the review.

Assessment of study quality
The quality of the RCTs was evaluated according to the following criteria: the method of randomisation, allocation
concealment, blinding, loss to follow-up and intention-to-treat analysis. The quality of the NRCTs was assessed according to the primary forms of bias (i.e., selection, assessment, performance and attrition). Studies were also awarded a score according to the Jadad scale. The authors did not state how many reviewers evaluated the primary studies.

Data extraction
One reviewer extracted the data using a standardised form and a second checked the extraction; any disagreements were resolved by discussion or by the involvement of a third reviewer. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for dichotomous data and mean differences for continuous data.

Methods of synthesis
How were the studies combined?
Where possible, the studies were combined in a meta-analysis using a fixed-effect model; a random-effects model was used where significant statistical heterogeneity was found. Binary and continuous outcomes were reported as pooled RRs with 95% CIs and weighted mean differences with 95% CIs, respectively.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic or Cochran's Q test. Differences between the studies were also highlighted in the tables and in the body of the text.

Results of the review
Twenty-eight RCTs (n at least 4,653), three of which were paediatric trials, were included in the review. Eleven NRCTs (company submissions to NICE) were also included (number of participants unclear).

In terms of quality, the Jadad scores ranged from 0 to 4, with half of the studies scoring 2 or less.

Addition of basiliximab (5 RCTs, 6 NRCTs): no statistically significant between-group difference was found for biopsy-proven acute rejection (BPAR) at the 6-month follow-up, and graft function, graft loss or all-cause mortality at the 6-month and 1-year follow-up, in a paediatric RCT comparing the addition of basiliximab with tacrolimus-based triple therapy. The addition of basiliximab to a ciclosporin, azathioprine and steroid regimen (CAS) significantly reduced short-term BPAR (RR 0.61, 95% CI: 0.46, 0.80) in adults, based on 3 RCTs; there was no evidence of statistical heterogeneity. No statistically significant between-group differences were found for short- or long-term graft loss, all-cause mortality or side-effects. Overall, no difference was found between groups for BPAR or graft loss at 1 year in NRCTs.

Addition of daclizumab (1 RCT): the addition of daclizumab to CAS was found to reduce BPAR at the 6-month follow-up (RR 0.63, 95% CI: 0.42, 0.94) in adult patients compared with placebo. No statistically significant between-group differences were found for 1- or 3-year graft loss, all-cause mortality or side-effects.

Tacrolimus versus ciclosporin (10 RCTs, 2 NRCTs): 1 paediatric RCT found a reduction in BPAR at 6 months (RR 0.42, 95% CI: 0.26, 0.69) and improved graft function in favour of tacrolimus. A significant reduction in BPAR was also found for tacrolimus in adults (RR 0.61, 95% CI: 0.53, 0.71), based on 6 RCTs; there was no evidence of statistical heterogeneity. The 2 paediatric NRCTs did not find a statistically significant difference between the intervention groups for acute rejection or graft survival. One study found a small improvement in graft function at the end of the 1- and 2-year follow-up.

MMF versus azathioprine (7 RCTs, 3 NRCTs): MMF (within a ciclosporin, MMF and steroid regimen) reduced BPAR at 1 year (RR 0.60, 95% CI: 0.47, 0.76) in adults, based on 3 RCTs; there was no evidence of statistical heterogeneity. Overall, in the 3 paediatric NRCTs, BPAR levels were lower with MMF than azathioprine at 6 months and at 1 year.

MPS versus azathioprine: no studies were identified.

Sirolimus (4 RCTs): no statistically significant between-group differences were found when sirolimus was compared with azathioprine or ciclosporin in adults. One paediatric RCT was found but BPAR, graft loss and all-cause mortality
were not reported. No NRCTs were identified.

Cost information
The addition of basiliximab and daclizumab to CAS was found to increase quality-adjusted life-years (QALYs) and decrease overall costs. The incremental cost-effectiveness ratio (ICER) of replacing ciclosporin with tacrolimus was sensitive to the selection of the hazard ratio for graft loss from acute rejection, dialysis costs and the incorporation of side-effects. The ICER for tacrolimus compared with ciclosporin ranged from approximately £46,000 to £146,000 per QALY, while that for replacing azathioprine with MMF was in excess of £55,000 per QALY.

Authors' conclusions
There was limited evidence from RCTs for the benefit or harms of the newer immunosuppressive agents in children with kidney transplants. Non-randomised comparative studies in children and RCTs in adults indicated some evidence of a beneficial effect. Compared with ciclosporin, azathioprine and steroid, the newer immunosuppressive agents reduced the incidence of short-term biopsy-proven acute rejection. Evidence for the impact on side-effects, long-term graft loss, compliance and overall health-related quality of life was limited.

CRD commentary
The review question was supported by clear inclusion and exclusion criteria. Several electronic databases were searched without restrictions and efforts were made to check grey literature, thereby reducing the likelihood of publication bias. The methods adopted for the study selection, data extraction and quality assessment processes were likely to have minimised reviewer error and bias. The analysis was appropriate and the authors assessed differences between the studies. The authors’ conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated the need for RCTs assessing the use of MMF and daclizumab for renal transplantation in children. Future comparative studies should report on side-effects, compliance, health care resource, costs and health-related quality of life, as well as the effect of immunosuppressive agents on short- and long-term clinical outcomes.

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