Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation

Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study

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Executive summary

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Executive summary

Background

Kidney transplantation is the treatment of choice for end-stage renal disease because, if successful, it achieves better quality and duration of life than with long-term dialysis. Approximately 1400 renal transplants are performed in England and Wales each year (1700 in the UK). A variety of immunosuppressive drugs is used in the management of renal transplants in the UK.

Objective

The aim of this study was to examine the clinical effectiveness and cost-effectiveness of the newer immunosuppressive drugs for renal transplantation: basiliximab, daclizumab, tacrolimus, mycophenolate (mofetil and sodium) and sirolimus.

Methods

The clinical effectiveness review followed the explicit Quality Standards agreed by InterTASC. A search for reviews and primary studies was undertaken using a variety of sources. Studies were assessed for inclusion according to predefined criteria. Data extraction and quality assessment were also undertaken.

Each of the five company submissions to the National Institute for Clinical Excellence (NICE) contained cost-effectiveness models. Given both the breadth of this review and details of these submitted models, rather than develop a *de novo* model, a three-stage critique of the company models was undertaken. This included (1) model checking (technical checking and quality assessment), (2) a detailed model description (assumptions, model parameters, sources and values) and (3) model rerunning.

Number and quality of studies, and direction of evidence

Induction therapy

Daclizumab: three randomised controlled trials (RCTs) were found comparing daclizumab to either placebo or another induction agent (OKT3). Daclizumab significantly reduced the incidence of biopsy-confirmed acute rejection and patient survival at 6 months/1 year compared with placebo, but not compared with OKT3. There was no significant gain in patient survival or graft loss at 3 years. The incidence of side-effects with daclizumab reduced compared to OKT3. No RCTs in children were found.

Basiliximab: eight RCTs compared basiliximab to placebo/no therapy or other induction agents (either ATG or OKT3). Basiliximab significantly improved 6-month/1-year biopsy-confirmed acute rejection compared to placebo, but not compared to either ATG or OKT3. There was no significant gain in either 1-year patient survival or graft loss. The incidence of side-effects with basiliximab was similar compared to OKT3/ATG. Although one RCT included children, results in this group were not reported.

Initial/maintenance therapy

Tacrolimus: 13 RCTs compared tacrolimus to ciclosporin (either Sandimmun® or Neoral®). Tacrolimus reduced the 6-month/1-year incidence of biopsy-proven acute rejection compared to ciclosporin. There was no significant improvement in either 1-year or long-term (up to 5 years) graft loss or patient survival. The magnitude of the acute rejection benefit of tacrolimus over ciclosporin appeared to be equivalent for Sandimmun and Neoral. There were important differences in the side-effect profile of tacrolimus and ciclosporin. One paediatric RCT reported a reduction in rejection rate and improvement in graft survival with tacrolimus compared to ciclosporin at 1 year.

Mycophenolate mofetil (MMF): seven RCTs compared MMF to azathioprine (AZA). MMF reduced the incidence of acute rejection. There was no significant difference in patient survival or graft loss at 1-year or 3-year follow-up. There appeared to be differences in the side-effect profiles of MMF and AZA. No RCTs comparing MMF with azathioprine were identified.

Mycophenolate sodium (MPS): one RCT compared MPS to MMF and reported no difference between the two drugs in 1-year ▶

acute rejection rate, graft survival, patient survival or side-effect profile. No RCTs in children were found.

Sirolimus: two RCTs were included. The results suggest, first, that the addition of sirolimus to a ciclosporin-based initial/maintenance therapy reduces 1-year acute rejections in comparison to a ciclosporin (Neoral) dual therapy alone and, second, that substituting azathioprine with sirolimus in initial/maintenance therapy reduces the incidence of acute rejection. Graft and patient survival were not significantly different with either sirolimus regimen. The addition of sirolimus increases the incidence of side-effects. The side-effect profiles of AZA and sirolimus appear to be different. A small subgroup analysis of one RCT indicated the benefits of sirolimus in children to be similar to those in adults.

Treatment of acute rejection

Three RCTs were found that assessed the use of either tacrolimus or MMF in the treatment of acute rejection. Tacrolimus was compared to ciclosporin and MMF compared to either AZA or high-dose steroids. The results suggested that both tacrolimus and MMF reduce the incidence of subsequent acute rejection and the need for additional drug therapy.

Costs/cost-effectiveness

Induction therapy

Daclizumab: one cost-effectiveness study compared daclizumab to placebo. Combining costs and graft survival, the results of this US study suggested that daclizumab is cost-effective at 10 years, but not at 1 year.

Basiliximab: two cost-effectiveness analyses compared basiliximab to placebo. A US study reported basiliximab to have superior 1-year and 10-year graft survival cost-effectiveness to placebo. A Canadian study found basiliximab to have a similar gain in quality-adjusted life-years (QALY) to ATG at 1 year, but lower costs.

Initial/maintenance therapy

Tacrolimus: three cost-effectiveness analyses compared tacrolimus to ciclosporin (either Sandimmun or Neoral). Two modelling studies, undertaken from a UK perspective, demonstrated that the 1-year cost-effectiveness of tacrolimus relative to ciclosporin was unattractive (£120,000 vs £220,000/QALY or £30,000 per additional graft saved or patient death avoided). A more recent European-based retrospective cost-effectiveness analysis using 6-month RCT data concluded that, compared to ciclosporin, tacrolimus both improved clinical outcomes and reduced overall health service costs.

MMF: three cost-effectiveness analyses compared MMF to azathioprine. Results consistently demonstrated that at 1 year post-transplant, MMF may be a cost-effective substitute for azathioprine in initial and maintenance immunosuppressant renal transplant therapy (e.g. incremental cost of Can$14,268 per graft-year gained and incremental cost of Can$50,717 per QALY).

MPS: no cost-effectiveness studies for MPS were found.

Sirolimus: no cost-effectiveness studies for sirolimus were found.

Treatment of acute rejection

Only one cost-effectiveness analysis of the use of newer immunosupressants in acute rejection treatment was found. This study estimated a cost saving per graft of US$12,400 with MMF compared to muromonab CD3 in patients with intractable acute rejection.

Conclusions

The newer immunosuppressant drugs (basiliximab, daclizumab, tacrolimus and MMF) consistently reduced the incidence of short-term (1-year) acute rejection compared with conventional immunosuppressive therapy. The independent use of basiliximab, daclizumab, tacrolimus and MMF was associated with a similar absolute reduction in 1-year acute rejection rate (approximately 15%). However, the effects of these drugs did not appear to be additive (e.g. benefit of tacrolimus with adjuvant MMF was 5% reduction in acute rejection rate compared with 15% reduction with adjuvant AZA). Thus, the addition of one of these drugs to a baseline immunosuppressant regimen was likely to affect adversely the incremental cost-effectiveness of the addition of another.

The trials did not assess how the improvement in short-term outcomes (e.g. acute rejection rate or measures of graft function), together with the side-effect profile associated with each drug, translated into changes in patient-related quality of life. Moreover, given the relatively ▶

short duration of trials, the impact of the newer immunosuppressants on long-term graft loss and patient survival remains uncertain.

Five industry submissions included models assessing the cost-effectiveness of basiliximab and daclizumab as induction therapies and tacrolimus, MMF, MPS and sirolimus as initial/maintenance therapies. The differences in unit cost for the same drugs between models, along with wide variations in the ratios between the unit costs of drugs in the same regimen and differences in the range of other costs considered, mean that cost-effectiveness comparisons between the models must be treated with caution. The cost-effectiveness results of the meta-model analysis conducted in this report support this conclusion.

Limitations of the calculations

The absence of both long-term outcome and quality of life from trial data makes assessment of the clinical and cost-effectiveness on the newer immunosuppressants contingent on modelling based on extrapolations from short-term trial outcomes. The choice of the most appropriate short-term outcome (e.g. acute rejection rate or measures of graft function) for such modelling remains a matter of clinical and scientific debate. The decision to use acute rejection in the meta-model in this report was based on the findings of a systematic review of the literature of predictors of long-term graft outcome.

Recommendations for research

The majority of trials to date have been designed solely with drug licensing in mind and are powered to examine short-term changes in clinical outcome (e.g. acute rejection rate). Future trials need to include quality of life measures, examine effects in high-risk patients and children, and improve their reporting. It is recognised that a number of the issues in this area make RCTs potentially difficult to design and undertake (e.g. comparisons of multiple therapies, collection of long-term outcomes). Consideration should therefore also be given to the collection of prospective observational outcome data on immunosuppressant regimens and the potential to do this within the context of a national registry.

Publication

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