Immunosuppressive therapy for kidney transplantation in children and adolescents: systematic review and economic evaluation

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Scientific summary

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Scientific summary

Background

Chronic kidney disease in childhood leads to lifelong health complications. A long-term progression of irreversible decline in kidney function to end-stage renal disease will require renal replacement therapy (kidney transplant, haemodialysis or peritoneal dialysis) for a child or adolescent to survive. The preferred option is kidney transplantation (transfer of a healthy kidney from a donor to a recipient). Kidneys for transplantation may be obtained via living donation (related or unrelated), donation after brain death or donation after circulatory death. Between April 2013 and March 2014, 125 kidney transplant operations were performed on children and adolescents in the UK.

Following kidney transplantation in children and adolescents, major clinical concerns are acute kidney rejection, graft loss and growth. Acute kidney rejection occurs when the immune system attempts to destroy the graft. Immunosuppressive therapy is then implemented to reduce the risk of kidney rejection and prolong graft survival. Immunosuppression comprises induction and maintenance therapy; induction involves powerful antirejection drugs taken at the time of transplantation, when the risk of rejection is highest, and maintenance drugs are less powerful and are used as both initial and long-term therapy.

Objectives

To review and update the evidence for the clinical effectiveness and cost-effectiveness of basiliximab (BAS) (Simulect,® Novartis Pharmaceuticals) and rabbit antihuman thymocyte immunoglobulin (r-ATG) (Thymoglobuline,® Sanofi) as induction immunosuppressive therapy and immediate-release tacrolimus (TAC-IR) [Adoport® (Sandoz); Capexion® (Mylan); Modigraf® (Astellas Pharma); Perixis® (Accord Healthcare); Prograf® (Astellas Pharma); Tacni® (Teva); Vivadex® (Dexcel Pharma)]; prolonged-release tacrolimus (TAC-PR) (Advagraf,® Astellas Pharma); belatacept (BEL) (Nulojix,® Bristol-Myers Squibb); mycophenolate mofetil (MMF) [Arzip® (Zentiva), CellCept® (Roche Products), Myfenax® (Teva), generic MMF is manufactured by Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt], mycophenolate sodium (MPS) (Myfortic,® Novartis Pharmaceuticals), sirolimus (SRL) (Rapamune,® Pfizer), everolimus (EVL) Certican,® Novartis Pharmaceuticals) as maintenance immunosuppressive therapy in children and adolescents undergoing renal transplantation.

Methods

Clinical effectiveness systematic review

Bibliographic literature searching was conducted on 14 April 2014 (updated 7 January 2015). The searches for individual studies [randomised controlled trials (RCTs) and controlled clinical trials] took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a study design limited to RCTs or controlled trials). Literature searches were not restricted to child or young adult populations, primarily to preserve the sensitivity of the searches. In order to update the previous assessment by Yao *et al.* [Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al.* A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children. *Health Technol Assess* 2006;**10**(49)] the searches were date limited (2002–current). The following databases were searched: MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials (via Wiley Online Library) and Web of Science [via Institute for Scientific Information (ISI) – including conference proceedings]. In addition, the following trials registries were hand-searched in January 2015:

Current Controlled Trials, ClinicalTrials.gov, Food and Drug Administration website, European Medicines Agency website (European Public Assessment Reports).

Separate searches were undertaken to identify systematic reviews of RCTs and non-randomised controlled studies, run from database inception in MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations (via Ovid), EMBASE (via Ovid), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) (The Cochrane Library via Wiley Online Library) and Health Management Information Consortium (via Ovid). These searches took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a pragmatic limit to systematic reviews).

Records and subsequent full papers were dual screened for inclusion independently by two researchers. Disagreements were resolved by discussion, with involvement of a third reviewer. Data were extracted if appropriate and quality appraisal conducted based on Centre for Reviews and Dissemination (CRD) guidance.

Data were tabulated and discussed in a narrative review and, when data permitted, meta-analysis was conducted. Estimates of overall treatment effect and assessment of heterogeneity were performed using a random-effects model. Odds ratios (ORs) and mean differences were calculated (for binary and continuous data, respectively).

Cost-effectiveness systematic review

Bibliographic literature searching was conducted on 8 April 2014 (updated 15 January 2015) in MEDLINE (via Ovid), EMBASE (via Ovid), NHS Economic Evaluation Database (via Wiley Online Library), Web of Science (via ISI – including conference proceedings), Health Economic Evaluations Database (HEED) (via Wiley Online Library) and EconLit (EBSCO*host*). The searches took the following form: (terms for kidney or renal transplant or kidney or renal graft) AND (terms for the interventions under review) AND (a costs or economic literature search filter). The search was date limited 2002–current in line with the previous assessment, but was not limited by language or to human-only studies.

Records were dual screened by two reviewers (disagreements resolved by discussion). Studies meeting the criteria for inclusion were assessed by one reviewer using the Evers checklist. Studies were based on decision models were quality assessed using the Philips checklist.

Economic studies were extracted, summarised and synthesised using tabulated data and narrative synthesis.

Appraisal of company submissions

The appraisal of company submissions focused on their model-based economic analyses. Their systematic reviews were primarily assessed to establish whether or not any includable RCTs were missed by our searches. None were found.

Assessment group economic model

A new economic model was developed to address the decision problem in a cost–utility analysis. A discrete time state transition model (semi-Markov) was employed in which transition probabilities were dependent on age and time since initial transplantation. A cycle length of one-quarter year was used and transitions were assumed to occur mid-cycle. A time horizon of 50 years was adopted. Costs were included from a NHS and Personal Social Services perspective. Health effects were measured in quality-adjusted life-years (QALYs) and calculated by assuming health state-specific utility decrements from a baseline utility, which was age-dependent and derived from the Health Survey for England (Health and Social Care Information Centre. *Health Survey for England – 2012*. London: Health and Social Care Information Centre; 2013). Costs and QALYs were discounted at 3.5% per annum and costs were inflated as necessary to 2014/15 prices.

Model structure

Kidney transplant recipients were assumed to be in one of three health states at any time: *functioning graft* (not dependent on dialysis), *graft loss* (dialysis dependent) or *death*. In addition to these health states, for each regimen the incidence of acute rejection (AR), cytomegalovirus (CMV) infection, dyslipidaemia and new-onset diabetes mellitus after transplantation (NODAT) were estimated, with corresponding costs (one-off for AR and CMV infection; ongoing for dyslipidaemia and NODAT). NODAT was also associated with a utility decrement. The incidences of AR and NODAT (and graft function after 12 months) were used as surrogate determinants of graft survival and the rate of death with functioning graft (DWFG) (NODAT only).

Up to three retransplantations were modelled, which could take place from the *graft loss* state. Pre-emptive retransplantation was also modelled for the initial graft, allowing retransplantation from the first *functioning graft* state. Kidney transplant recipients would transition to the next *functioning graft* state if retransplantation was successful or to the next *graft loss* state if it was unsuccessful.

Results

Clinical effectiveness systematic review

Three RCTs are included in the clinical effectiveness systematic review: one new RCT and two RCTs from the previous assessment.

Four non-RCTs are included in our review, all of which were also included in the previous assessment by Yao *et al.* (2006).

Induction therapy

Two RCTs of induction therapy evaluating BAS in children and adolescents were identified in the review. No RCTs were identified that evaluated r-ATG in children and adolescents. No non-RCTs in the child and adolescent population evaluated induction therapies.

We found no significant difference in survival, graft loss, graft function and incidences of biopsy-proven acute rejection (BPAR) and time to BPAR between BAS and placebo (PBO)/no induction.

The results of the current review are similar to the previous HTA (Yao *et al.* 2006).

Maintenance therapy

One RCT of maintenance therapy in children and adolescents was identified, evaluating tacrolimus (TAC) compared with ciclosporin (CSA). No RCTs were identified for the other maintenance treatments.

Three non-RCTs evaluating MMF [compared with azathioprine (AZA)] in children and adolescents were identified. One non-RCT compared TAC + AZA with CSA + MMF. No non-RCTs were identified for the other maintenance treatments.

From the RCTs, we found no significant difference in survival or graft loss between TAC and CSA. However, a significantly higher graft function [mean estimated glomerular filtration rate (eGFR) of 71.5 (standard deviation 22.9) ml/minute/1.73 m^2 in TAC vs. mean eGFR of 53.0 (21.6) ml/minute/1.73 m^2 in CSA, t-test = 4.03; $p < 0.01$ at 4-year follow-up] and less BPAR [OR 0.29, favours TAC, 95% confidence interval (CI) 0.15 to 0.57 at 6-month follow-up] was found in TAC compared with CSA.

The results of the current review for survival, graft function and BPAR are similar to the previous HTA. However, the child and adolescent RCT evidence identified in the previous HTA review concluded that TAC lowered graft loss at 2- and 4-year follow-up. The difference in these results is because we excluded graft loss due to death from all analyses to avoid double counting with another key outcome (mortality) and because death-censored graft survival is a well-established clinical outcome (to which DWFG is intrinsically related). After the removal of graft loss due to death from the analyses, the evidence from the RCT suggested statistically non-significant lower graft loss with TAC compared with CSA (OR 0.41, 95% CI 0.16 to 1.00, and OR 0.43, 95% CI 0.18 to 1.01 at 2 and 4 years' follow-up, respectively).

Adverse events

More infections were found in children treated with BAS than those treated with PBO (OR 2.23, favours PBO; 95% CI 1.03 to 4.68) and Grenda *et al.* (Grenda R, Watson A, Vondrak K, Webb NJ, Beattie J, Fitzpatrick M, *et al.* A prospective, randomized, multicenter trial of TAC-based therapy with or without basiliximab in pediatric renal transplantation. *Am J Transplant* 2006;**6**:1666–72) found that toxic nephropathy and abdominal pain was higher with BAS compared with no induction ($p = 0.03$ and $p = 0.02$, respectively). In one RCT, no statistically significant differences were found between TAC and CSA for a range of adverse events. In addition, there were no statistically significant differences identified between MMF and AZA, or between TAC + AZA and CSA + MMF, in the non-randomised evidence.

Cost-effectiveness systematic review

Only one previous cost-effectiveness study of immunosuppressive regimens in children and adolescents was identified. The study evaluated the cost-effectiveness of adding BAS induction to maintenance therapy with TAC or CSA combined with AZA and corticosteroids (CCSs). The study also compared CSA with TAC when given in combination with AZA and CCSs, and, separately, MMF versus AZA as part of the triple therapy containing CSA and CCSs.

The analysis was conducted using a Markov model of a cohort with starting age ranging between 3 and 13 years and a 10-year horizon, and found that BAS induction resulted in higher costs and more QALYs than no induction in both the TAC and CSA containing regimens. TAC was found to have a base-case incremental cost-effectiveness ratio (ICER) (incremental cost per QALY) of £145,000/QALY relative to CSA, while MMF had an ICER of £195,000/QALY relative to AZA when given as part of a CSA-containing triple therapy. The sensitivity analysis showed that these results were subject to a high degree of uncertainty.

Analyses based on randomised controlled trial evidence in children and adolescents

Base-case analysis

Compared with no induction, BAS was predicted to be cost-effective at £20,000–30,000 per QALY when used with TAC and AZA [based on Grenda *et al.* (2006), BAS was dominant], but not when used with CSA and MMF [based on Offner *et al.* (2008), BAS was dominated].

Based on Trompeter *et al.* (Trompeter R, Filler G, Webb NJA, Watson AR, Milford DV, Tyden G, *et al.* Randomized trial of tracolimus versus cyclosporin microemulsion in renal transplantation. *Pediatric Nephrology* 2002;**17**:141–9), TAC (when used with AZA) was predicted to be cost-effective at £20,000–30,000 per QALY versus CSA (TAC was dominant).

Scenario analyses

Results were robust to removal of the surrogate relationship between AR and graft survival and/or to assuming weight would follow the ninth centile for age instead of the median.

Analyses based on randomised controlled trial evidence in adults

Base case

In the base-case deterministic and probabilistic analyses, BAS, TAC, MMF (only when used with CSA) and AZA (only when used with TAC) were predicted to be cost-effective at £20,000–30,000 per QALY. When all regimens were simultaneously compared, only BAS + TAC + AZA was cost-effective at £20,000–30,000 per QALY.

Scenario analyses

Results were robust to removal of the surrogate relationship between AR and graft survival. When it was assumed that weight would follow the ninth centile for age instead of the median, BAS and TAC were still predicted to be cost-effective at £20,000–30,000 per QALY. However, when used with BAS, MPS was predicted to be cost-effective at £30,000 per QALY (ICER £27,000 per QALY) and MMF was predicted to be cost-effective at £20,000 per QALY.

Limitations

The number of included randomised trials is low (also comparative non-RCTs may have been missed); only RCT evidence evaluating BAS and TAC and non-RCT evidence on the use of TAC and MMF was identified. In addition, no studies reporting on quality of life, adherence, growth or supporting the subgroup analyses specified in the review protocol were identified. Significantly, cost-effectiveness analyses comparing all interventions rely on effectiveness estimates from the adult RCTs (which may or may not generalise to children and adolescents). Finally, some of the newer immunosuppressive drugs, such as EVL and SRL, would normally be given to children and adolescents after an initial maintenance therapy that consists of more conventional drugs. This makes it challenging to compare the clinical effectiveness of such regimens because only children and adolescents who are well maintained on their initial maintenance therapy would be given such drugs.

Conclusions

There is limited high-quality evidence for the effectiveness of immunosuppressive agents in children and adolescents. A RCT comparing TAC with CSA demonstrated that TAC resulted in statistically significant improvements in graft function and AR. No other outcomes in that RCT or the other two included RCTs were statistically significant.

Based on effectiveness estimates from the adult population, BAS and TAC are cost-effective at a threshold of £20,000–30,000 per QALY in all considered combinations, while MMF is cost-effective only if used with CSA. Effectiveness estimates in children and adolescents are only available for BAS and TAC. Based on these, TAC (used with AZA and compared with CSA) is cost-effective at £20,000–30,000 per QALY, whereas cost-effectiveness results for BAS are mixed.

Implications for health care

BAS, TAC, MMF and AZA are all used regularly in the NHS. It is not clear whether or not changes to induction agents used in the NHS would significantly affect costs. However, replacing TAC with TAC-PR, SRL, BEL or CSA would likely result in increased costs.

It is possible that replacing MMF with AZA (when used with TAC) will result in reduced costs, while it is likely that replacing these with SRL, EVL or MPS would increase costs.

Recommendations for research

High-quality primary effectiveness research in children and adolescents is needed. Potentially, the UK Renal Registry could form the basis for a prospective study. This may require collection of some information not currently held, but could include health-related quality of life and growth measurements. In addition, given the perceived importance of adherence to immunosuppression in this population, an objective and practical measure of adherence is needed. Furthermore, a systematic review of non-RCTs is recommended.

Study registration

The protocol for the HTA is available on National Institute for Health and Care Excellence (NICE) website [NICE. PROTOCOL: Immunosuppressive therapy for kidney transplantation in children and adolescents (review of technology appraisal guidance TA99). London: NICE, 2014]. This study is also registered as PROSPERO CRD42014013544.

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