Immunosuppressive therapy for kidney transplantation in adults: a systematic review and economic model

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Scientific summary

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Scientific summary

Background

End-stage renal disease is a long-term irreversible decline in kidney function requiring renal replacement therapy (RRT): kidney transplantation, haemodialysis or peritoneal dialysis. Kidney transplantation is preferred because of the improved duration and quality of life.

Kidney transplantation is the 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 (DBD) or donation after circulatory death (DCD).

In 2013–14, 2464 adult kidney transplant operations were performed in England, 97 in Northern Ireland, 112 in Wales and 242 in Scotland. The number of adult transplants from DCDs has been increasing over time, reaching 779 in the last financial year. Similarly, the number of adult transplants from DBDs increased to 1101 and the number of adult living kidney transplants performed increased to 1049. Patient survival following a kidney transplant, over 5 years, for deceased and living donors is 89% [95% confidence interval (CI) 88% to 90%] and 95% (95% CI 95% to 96%), respectively.

Following kidney transplantation, the immune response of the host may attempt to destroy the graft (acute kidney rejection). Therefore, immunosuppressive therapy is implemented. However, side effects include possible skin cancer, crumbling bones, fatigue, body hair growth, swollen gums and weight gain.

Immunosuppression comprises induction and maintenance therapy. Induction involves powerful antirejection drugs taken at the time of transplantation, when the risk of rejection is highest. 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 UK Ltd) and rabbit anti-human thymocyte immunoglobulin (rATG) (Thymoglobulin®, Sanofi) as induction immunosuppressive therapy, and immediate-release tacrolimus (TAC) (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 (Accord Healthcare, Actavis, Arrow Pharmaceuticals, Dr Reddy's Laboratories, Mylan, Sandoz and Wockhardt); mycophenolate sodium (MPS) (Myfortic®, Novartis); sirolimus (SRL) (Rapamune®; Pfizer); and everolimus (EVL) (Certican®, Novartis) as maintenance immunosuppressive therapy in adult renal transplant.

Methods

Clinical effectiveness systematic review

Searching was conducted on 14 April 2014 and updated on 18 November 2014, using the terms kidney or renal transplant, or kidney or renal graft AND the interventions under review AND a study design limit to randomised controlled trials (RCTs) or controlled trials. The search was date limited to 2002–current, in line with the previous assessment. The databases searched were MEDLINE (via Ovid), EMBASE (via Ovid), Cochrane Central Register of Controlled Trials (via Wiley Online Library) and Web of Science (via ISI).

Systematic reviews were identified using the terms above AND a limit to systematic reviews. The search was run from database inception in MEDLINE (via Ovid), EMBASE (via Ovid), Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and Health Technology Assessment (via The Cochrane Library via Wiley Online Library) and the Health Management Information Consortium (via Ovid).

Records were screened for inclusion independently by two researchers, with disagreements resolved with a third reviewer. Included full papers were split between five reviewers for data extraction, with disagreements resolved by consensus. Quality assessment was based on Centre for Reviews and Dissemination guidance.

Estimates of overall treatment effect and assessment of heterogeneity were performed using a random-effects model. For binary data, odds ratio (OR) was used and, for continuous data, mean differences (MDs) were calculated. A narrative synthesis accompanies all included study data.

Network meta-analyses (NMAs) were undertaken within a Bayesian framework. Fixed- and random-effects NMAs were compared using the deviance information criteria. Outcomes analysed were graft loss, mortality, biopsy-proven acute rejection (BPAR) and graft function (GRF).

Cost-effectiveness systematic review

Searching was conducted on 8 April 2014 and updated on 18 November 2014, using the terms kidney or renal transplant, or kidney or renal graft and the interventions under review and a costs or economic literature search filter. The search was date limited to 2002–current in line with the previous assessment. The following databases were searched: MEDLINE (Ovid), EMBASE (Ovid), NHS Economic Evaluation Database (Wiley), Web of Science (ISI), Health Economic Evaluations Database (Wiley) and EconLit (EBSCO*host*).

Records were screened by two reviewers, with disagreements resolved by discussion. Studies meeting the criteria for inclusion were assessed by one reviewer using the checklist developed by Evers *et al.* (Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: consensus on health economic criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5). Studies based on decision models were quality assessed using the checklist developed by Philips *et al.* (Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al.* Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36); Philips Z, Bojke L, Sculpher M, Claxton K, Golder S. Good practice guidelines for decision-analytic modelling in health technology assessment: a review and consolidation of quality assessment. *Pharmacoeconomics* 2006;**24**:355–71).

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

Peninsula Technology Assessment Group economic model

A new economic model was developed, utilising a discrete time–state transition model (semi-Markov), with transition probabilities that are dependent on age and time since initial transplantation. A cycle length of a 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 UK NHS and Personal Social Services perspective. Health effects were measured in quality-adjusted life-years (QALYs) and were calculated by assuming health state-specific utility decrements from a baseline utility, which was age dependent and derived from the Health Survey for England 2012 (Craig R, Mindell J, editors. *Health Survey for England 2012: Health, Social Care and Lifestyles*. Leeds: Health and Social Care Information Centre; 2013). The utility decrements were based on a published systematic review and meta-analysis of preference-based quality-of-life studies in patients who were undergoing RRT, with the EQ-5D [European Quality of Life-5 Dimensions, three-level version (EQ-5D-3L) used for measurement. Costs and QALYs were discounted at 3.5% per annum, and costs were inflated as necessary to 2014–15 prices. A total of 16 regimens were modelled.

Model structure

Kidney transplant recipients were assumed to be in one of three health states: functioning graft, graft loss or death. The incidence of acute rejection (AR), cytomegalovirus infection, dyslipidaemia and new-onset diabetes after transplantation (NODAT) was also estimated.

Up to two retransplantations were modelled, which could take place from the graft loss state or from the functioning graft state (for the initial graft only). The rate of retransplantations was assumed to reduce with age past 65 years, reaching zero by the age of 80 years.

Transitions out of the functioning graft state correspond to graft loss/survival, and are either death with functioning graft (DWFG) or graft loss excluding DWFG.

Uncertainty analyses

A probabilistic sensitivity analysis was conducted to estimate the joint effect of parameter estimation uncertainty on cost-effectiveness. Structural sensitivity analyses relating to graft survival were conducted. A scenario analysis – in which list prices were adopted for all drug acquisition costs – was performed and a two-way threshold analysis was conducted relating to the costs of BEL.

Clinical effectiveness results

The titles and abstracts of 5079 references were screened, with 750 papers retrieved for consideration. Eighty-nine RCTs matched the inclusion criteria, 14 of which investigated induction therapies, 73 investigated maintenance therapies and two investigated both. The RCTs were of variable quality, and reporting omissions was frequent.

Summary of benefits and risks

Following NMA for *induction therapy*:

- No evidence was found to suggest that BAS or rATG are more effective than placebo (PBO)/no induction or each other in reducing the *odds of graft loss or mortality*.
- For BPAR, rATG and BAS were both estimated to be more effective than PBO/no induction, with rATG being more effective than BAS.
- There was evidence to suggest that BAS is more effective than PBO/no induction at achieving better GRF. Head-to-head comparison for induction therapy also suggested that rATG and BAS are more effective than PBO or no induction at reducing BPAR (rATG at 1 year, OR 0.34, 95% CI 0.22 to 0.52; BAS at 1 year, OR 0.53, 95% CI 0.40 to 0.70).
- BAS was associated with lower odds of severe BPAR than rATG (1 year, OR 0.04, 95% CI 0.00 to 0.65).

For *maintenance therapy*, the analyses are as follows:

- No evidence was found to suggest that one treatment is more effective at reducing graft loss than any other. However, head-to-head analysis indicated that, at 0.5 years, there were reduced odds of graft loss for ciclosporin (CSA) + MMF compared with CSA + azathioprine (AZA) (OR 0.58, 95% CI 0.04 to 0.59) and, at 5 years, BEL + MMF may be more effective than CSA + MMF (OR 0.40, 95% CI 0.19 to 0.87).
- The NMA indicated that BEL + MMF may be more effective at reducing the odds of mortality than TAC + MMF and SRL + MMF. The head-to-head analysis found no evidence of greater effectiveness between treatments.
- MMF + CSA, TAC + MMF, SRL + TAC, TAC + AZA and EVL + CSA were estimated to be more effective than CSA + AZA and EVL + MPS at reducing BPAR. However, the 95% CIs were wide. Head-to-head analysis for MMF + CSA vs. CSA + AZA indicated a statistically significant difference in favour of MMF (0.5 years OR 0.50, 95% CI 0.35 to 0.72). TAC was shown to display lower odds of BPAR in the following comparisons:
  - TAC + AZA vs. CSA + AZA (at 1 year, OR 0.50, 95% CI 0.39 to 0.64; at 4 years, OR 0.38, 95% CI 0.25 to 0.57)
  - TAC + MMF vs. CSA + AZA (at 1 year, OR 0.35, 95% CI 0.15 to 0.82)
  - TAC + MMF vs. CSA + MMF (at 1 year, OR 0.59, 95% CI 0.37 to 0.94)
  - TAC + MMF vs. SRL + MMF (at 1 year, OR 0.32, 95% CI 0.12 to 0.87)
- For increasing GRF, SRL + AZA, TAC + AZA, TAC + MMF and BEL + MMF were estimated by the NMA to be more effective than CSA + AZA and MMF + CSA. However, direct evidence was limited and the 95% CIs were wide. The head-to-head analysis for MMF + TAC compared with MPS + TAC found MPS to be more effective [1 year, MD 1.9 ml/minute/1.73 m^2; $p < 0.0001$; 3 years, estimated glomerular filtration rate (eGFR) MD 0.5 ml/minute/1.73 m^2; $p = 0.0016$]. BEL appeared to be more effective for BEL + MMF than CSA + MMF [at 1 year, eGFR weighted mean difference (WMD) 7.83 ml/minute/1.73 m^2, 95% CI 1.57 to 14.10 ml/minute/1.73 m^2; at 3 years WMD 16.08 ml/minute/1.73 m^2, 95% CI 5.59 to 26.56 ml/minute/1.73 m^2]; however, heterogeneity across studies was substantial. TAC was associated with a higher level of GRF for the following comparisons:
  - TAC + MMF vs. CSA + MMF (at 3 years, eGFR WMD 4.60 ml/minute/1.73 m^2, 95% CI 1.35 to 7.85 ml/minute/1.73 m^2)
  - TAC + MMF vs. TAC-PR + MMF (at 0.5 years, eGFR WMD 1.90 ml/minute/1.73 m^2, 95% CI 1.70 to 2.10 ml/minute/1.73 m^2)
  - TAC + SRL vs. CSA + SRL (at 0.5 years, eGFR MD 6.35 ml/minute/1.73 m^2; $p < 0.0001$; at 1 year MD 5.25 ml/minute/1.73 m^2; $p = 0.0004$)
- Time to BPAR and severity of BPAR were generally poorly reported and with substantial heterogeneity.

Cost-effectiveness results

Summary of cost-effectiveness evidence

Studies were typically economic evaluations of single-centre RCTs of ≤ 1 year, involving small samples with insufficient data to evaluate their generalisability.

- All studies of initial and maintenance immunosuppression are sponsored by the industry or conducted by a person affiliated to them.
- Studies of immunosuppression typically use a biomarker as a surrogate to extrapolate long-term outcomes.
- New evidence has emerged indicating that changes in renal function directly impact on health-related quality of life and costs.

Peninsula Technology Assessment Group economic model

Base-case analysis

In the base-case deterministic and probabilistic analyses, BAS, TAC and MMF were predicted to be cost-effective at £20,000 and £30,000 per QALY. Relevant incremental cost-effectiveness ratios (ICERs) do not exist for these agents because they dominated other agents or were less costly and less effective than other agents with ICERs that were significantly > £30,000 per QALY.

When all regimens were simultaneously compared, only BAS + TAC + MMF was predicted to be cost-effective at £20,000 and £30,000 per QALY.

Scenario analyses

Investigation of the impact of structural uncertainty in the surrogate effect of AR, NODAT and GRF at 12 months on graft survival found that if the surrogate effect was weakened then no induction and CSA became cost-effective at £20,000 and £30,000 per QALY, respectively, compared with BAS induction and immediate-release TAC. The duration of surrogate effect had to be limited to 1 year for no induction to be cost-effective compared with BAS at £20,000 per QALY and eliminated to be cost-effective at £30,000 per QALY. The duration of surrogate effect had to be limited to ≤ 3–8 years (depending on the comparison) for CSA to be cost-effective compared with immediate-release TAC at £20,000 or £30,000 per QALY.

A second structural uncertainty analysis considered that calcineurin inhibitor-free regimens could result in prolonged graft survival. The graft survival for BAS + SRL + MMF had to be markedly different from the base case for SRL to become cost-effective at £20,000 or £30,000 per QALY, and BAS + BEL + MMF was not cost-effective at £20,000 or £30,000 per QALY at any point in the analysis.

When list prices were adopted for drug acquisition costs, CSA and AZA became cost-effective at £20,000–30,000 per QALY in some combinations, with immediate-release TAC and MMF remaining cost-effective at £20,000–30,000 per QALY in other comparisons.

Belatacept was not found to be cost-effective at £20,000–30,000 per QALY, even at zero price, or at list price with zero administration cost.

Limitations of the systematic review of studies of effectiveness

- Owing to level of reporting detail, subgroup analysis was not performed.
- Substantial heterogeneity across studies owing to varying study design and participant characteristics.
- Reporting omissions for most of the trials hampered quality assessment.
- Very few trials reported long-term follow-up.

Limitations of the analyses and uncertainties of Peninsula Technology Assessment Group economic model

- Inconsistent reporting of adverse events (AEs) in identified RCTs meant that only a minority of AEs were modelled.
- The severity of ARs was assumed to be the same across regimens.
- Treatment discontinuation and switching were not modelled.
- Long-term outcomes from RCTs are seldom reported, so it has not been possible to externally validate the predicted survival differences between regimens.
- RCTs identified in the systematic review have not provided sufficient evidence to support subgroup analyses.
- The costs for diabetes mellitus are highly uncertain, especially as the costs relate to the general diabetic population rather than transplant recipients with NODAT.
- NHS hospitals might secure discounts from list prices when these are assumed in the model.

Conclusions

The clinical effectiveness review of the two induction agents found that both ATG and BAS were more effective than PBO/no induction at reducing BPAR, with ATG being more effective than BAS. However, no evidence was found to suggest either BAS or ATG were more effective than PBO/no induction, or each other, in reducing the odds of graft loss or mortality.

For the maintenance agents, none of the regimens was consistently better on mortality, graft loss, GRF or BPAR. For a number of pairwise comparisons, the arm containing TAC had lower odds of BPAR and reduced loss of GRF.

The cost-effectiveness analyses suggest that only a regimen of BAS induction followed by maintenance with immediate-release TAC and MMF would be cost-effective at £20,000–30,000 per QALY.

Study registration

This study is registered as PROSPERO CRD42014013189.

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