Immunosuppressive agents in adult kidney transplantation in the NHS: a model-based economic evaluation

Tristan Snowsill[1], Jason Moore[2], Ruben Mujica Mota[1], Jaime Peters[1], Tracey Jones-Hughes[1], Nicola Huxley[1], Helen Coelho[1], Marcela Haasova[1], Chris Cooper[1], Jenny Lowe[1], Jo Varley-Campbell[1], Louise Crathorne[1], Matt Allwood[1], Rob Anderson[1]

Corresponding author:

Tristan Snowsill

South Cloisters, St Luke's Campus, Heavitree Road, Exeter EX1 2LU

Tel: 0 (+44) 1392 726092

Email: t.m.snowsill@exeter.ac.uk

[1] Peninsula Technology Assessment Group (PenTAG), University of Exeter, UK
[2] Exeter Kidney Unit, Royal Devon & Exeter NHS Foundation Trust, Exeter, UK

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Abstract

Background

Immunosuppression is required in kidney transplantation to prevent rejection and prolong graft survival. We conducted an economic evaluation to support the National Institute for Health and Care Excellence in developing updated guidance on the use of immunosuppression, incorporating new immunosuppressive agents, and addressing changes in pricing and the evidence base.

Methods

A discrete-time state transition model was developed to simulate adult kidney transplant patients over their lifetime. Sixteen different regimens were modelled to assess the cost-effectiveness of basiliximab and rabbit anti-thymocyte globulin (rabbit ATG) as induction agents (with no antibody induction as a comparator), and immediate-release tacrolimus, prolonged-release tacrolimus, mycophenolate mofetil, mycophenolate sodium, sirolimus, everolimus and belatacept as maintenance agents (with ciclosporin and azathioprine as comparators). Graft survival was extrapolated from acute rejection rates, graft function and post-transplant diabetes rates, all estimated at 12 months post-transplantation. NHS and personal social services costs were included. Cost-effectiveness thresholds of £20,000 and £30,000 per quality-adjusted life year (QALY) were used.

Results

Basiliximab was predicted to be more effective and less costly than rabbit ATG and induction without antibodies. Immediate-release tacrolimus and mycophenolate mofetil were cost-effective as maintenance therapies. Other therapies were either more expensive and less effective, or would only be cost-effective if a threshold in excess of £100,000 per QALY were used.

Conclusions

A regimen comprising induction with basiliximab, followed by maintenance therapy with immediate-release tacrolimus and mycophenolate mofetil, is likely to be effective for uncomplicated adult kidney transplant patients and a cost-effective use of NHS resources.

Keywords

Adults; Cost-effectiveness; Cost–utility; Economic model; Immunosuppression; Kidney transplantation; Renal transplantation

Key points

- An economic model was developed to determine the cost-effectiveness of agents for induction and maintenance immunosuppression in adult kidney transplantation.
- At conventional cost-effectiveness thresholds, induction therapy with basiliximab, and maintenance therapy with immediate-release tacrolimus and mycophenolate mofetil were found to be cost-effective.

Introduction

Kidney transplantation is the preferred form of renal replacement therapy for most patients who have end stage renal disease, with clinical and economic benefits over dialysis [1]. Kidney transplant recipients (KTRs) take immunosuppressive drugs to prevent their immune system from rejecting or damaging the graft [2]; a number of such drugs have received European marketing authorisation recently. The costs of older drugs have also fallen following patent expiry.

Patients can vary significantly in their needs, and a patient-centred approach is needed to prolong graft survival and manage comorbidities. Nevertheless, it is important to establish which immunosuppressive drugs are likely to be cost-effective in the majority of patients, so that limited healthcare resources can be targeted towards more complex KTRs and patients elsewhere in the health system.

The National Institute for Health and Care Excellence (NICE) technology appraisal processes seek evidence on the clinical and cost-effectiveness of treatments for use in the NHS in England [3] to produce guidance with statutory reimbursement requirements. This economic evaluation was conducted to support the technology appraisal of immunosuppressive drugs in adult KTRs [4]. A systematic review of the clinical effectiveness of immunosuppressive therapy in adult KTRs was conducted [5]; our analysis is informed by the results of the systematic review.

This economic evaluation sought to identify cost-effective induction and maintenance immunosuppressive regimens for adult KTRs. It is a cost–utility study in which health benefits are expressed in quality-adjusted life years (QALYs), which encapsulate both quantity and quality of life [6]. Cost-effectiveness thresholds of £20,000 and £30,000 per QALY were used. It is a model-based economic evaluation, allowing for extrapolation from clinical trial endpoints, synthesis of data from multiple sources, and exploration of the impact of different assumptions on results.

Methods

Target population

The target population was adult patients undergoing kidney transplantation. Multi-organ transplant recipients were not included. The treatment of acute rejection was also not within the scope of the economic evaluation.

In the base case analysis, a cohort of 50-year-old patients was modelled (the median age at transplantation was 50.5 years in the UK in 2012 [7]). 62% were men (based on data from 2007–2012) [8]. The body weight of KTRs was assumed to be 70.2 kg (standard deviation 1.2 kg), estimated from reported body weights in RCTs [5].

Setting and location

Patients in the NHS are transplanted as inpatients in hospital-based transplant units. After being discharged they are managed through outpatient clinics with a transplant surgeon or nephrologist. Shared management arrangements may be put in place with primary care physicians, but hospital nephrologists retain responsibility for prescribing.

Perspective

Costs were included from an NHS and personal social services perspective, meaning that societal costs (e.g., lost productivity) and other public sector costs (e.g., lost tax revenue) were not included. The perspective on outcomes was direct health effects on patients. Costs and QALYs were discounted at 3.5% per year. These are the preferred perspectives for NICE technology appraisals [6].

Interventions and comparators

For induction therapy, the evaluation compared basiliximab, rabbit anti-thymocyte globulin (rabbit ATG) and induction without mono- or polyclonal antibodies. For maintenance therapy, the model compared immediate-release tacrolimus (IR-Tacrolimus), prolonged-release tacrolimus (PR-Tacrolimus), mycophenolate mofetil (MMF), mycophenolate sodium (MPS), sirolimus, everolimus, belatacept and maintenance with a calcineurin inhibitor with or without an antiproliferative agent. Alemtuzumab was excluded from the NICE scope since it does not have European marketing authorisation.

Sixteen regimens were identified as being appropriate for evaluating the cost-effectiveness of all the interventions (**Table 1**). These were identified as being current or potential future practice in the NHS and having a significant amount of RCT evaluation. Steroid avoidance was not within scope of the appraisal, so all regimens also include low dose corticosteroids.

Health outcomes

The main health outcome of the economic evaluation was QALYs. Other outcomes included overall survival (life expectancy) and graft survival.

Model structure

KTRs were assumed to be in one of three health states: FUNCTIONING GRAFT, GRAFT LOSS or DEATH (**Figure 1**).

Up to two retransplantations were modelled, which could take place from the GRAFT LOSS state. For the initial graft only, pre-emptive retransplantation from the FUNCTIONING GRAFT state was also modelled. The rate of retransplantations (104 per 1,000 patient years [8]) was assumed to be constant below age 65, then decrease linearly, reaching zero by age 80.

A cycle length of three months was used, and transitions were modelled as occurring midway through each cycle. A time horizon of 50 years was used for the economic evaluation, when surviving KTRs would be aged 100.

Short-term graft survival (first year post-transplantation) was estimated using a proportional odds statistical model. Baseline graft survival was estimated from the UK Transplant Registry standard national organ transplant dataset [8]. A regimen of basiliximab induction with IR-Tacrolimus and MMF maintenance was assumed to represent the baseline as it is believed to be the most commonly used regimen. The odds ratios for graft survival at 12 months (**Table 2**) were used to estimate survival for the other arms within the first year.

Subsequent graft survival was estimated using a proportional hazards statistical model. Baseline graft survival was extrapolated from the UK Transplant Registry standard national organ transplant dataset, using a Weibull model. The Weibull model fit was assessed using the Akaike information criterion (AIC) and visual inspection of the survival curves and Cox–Snell residuals. Other parametric

models were assessed and the Weibull performed best on AIC, with the exception of the generalised gamma model, which produced almost identical long-term survival curves to the Weibull model. Proportional hazards were applied on the basis of estimated graft function (estimated glomerular filtration rate; eGFR) [9], acute rejection and post-transplantation diabetes mellitus (PTDM) [10] (all measured at 12 months post-transplantation).

Effectiveness

As part of the technology appraisal process a systematic review of the clinical effectiveness of immunosuppressive therapy in adult KTRs was performed [5].

A total of 86 RCTs were included, 11 evaluating induction agents, 73 evaluating maintenance agents and two evaluating both.

Four outcomes (biopsy-proven acute rejection, BPAR; graft loss; mortality; graft function) at one year were synthesised using fixed effects network meta-analyses (separately for induction agents and maintenance regimens). The results of these network meta-analyses are given in **Table 2**.

Further network meta-analyses of these studies were conducted for the rate of PTDM, dyslipidaemia and cytomegalovirus (CMV) infection to support the economic modelling (**Table 3** and **Table 4**). These analyses were conducted on individual immunosuppressive agents rather than regimens.

Utilities

An age-dependent utility function was used in the calculation of QALYs, estimated from the Health Survey for England [11, 12]. From this baseline, utility decrements were applied to patients with functioning grafts and patients receiving dialysis. These were derived from a systematic review and meta-analysis [13]. A utility decrement was also applied for patients with PTDM [14].

Equation 1 describes the utility function, where *Age* is measured in years (since birth).

$$\begin{aligned} U = {} & 0.967981 - 0.001807 \times Age - 0.000010 \times Age^2 + 0.023289 \times \mathrm{I}(Male) \\ & - 0.053 \times \mathrm{I}(Functioning\ graft) \\ & - 0.277 \times \mathrm{I}(Haemodialysis) \\ & - 0.264 \times \mathrm{I}(Peritoneal\ dialysis) \\ & - 0.060 \times \mathrm{I}(PTDM) \end{aligned} \quad (1)$$

Estimating resources and costs

Drug acquisition

Drug acquisition costs were drawn from the CMU eMit database [15] for immunosuppressive agents available as generics and from the British National Formulary [16] otherwise (**Table 5**).

Immunosuppressant dosages were estimated based on the RCTs included in the systematic review [5] or from the summary of product characteristics (**Table 6**).

Wastage was included for belatacept since vial sharing is not permitted, but not for other maintenance immunosuppressants, where it was assumed that there would be minimal wastage since these are tablets or capsules with a long shelf life which are taken over a long period of time. Wastage was not included for basiliximab as the dose is fixed. Wastage was also not included for rabbit ATG, although it is a possibility.

KTRs at high risk of CMV infection received 200 days of prophylaxis with valganciclovir. KTRs at intermediate risk receiving rabbit ATG received 4½ months prophylaxis.

Drug administration

Most immunosuppressants are administered orally, incurring no drug administration cost. Basiliximab, rabbit ATG and belatacept are administered parenterally. Basiliximab and rabbit ATG were assumed to be delivered by intravenous infusion [17] with estimated costs of £229 and £326 for the first and subsequent infusions respectively [18]. Belatacept is also delivered by intravenous infusion at a cost of £168 per infusion [18].

Renal replacement therapy

All patients without a functioning graft were assumed to be receiving haemodialysis or peritoneal dialysis, with the proportion receiving each dependent on age [19]. Haemodialysis patients were assumed to require one temporary access procedure (£823 [18]) and one permanent access procedure (arteriovenous fistula; £1,946 [18]). Peritoneal dialysis patients were assumed to require one permanent access procedure (£1,101 [18]).

Haemodialysis was estimated to cost on average £24,400 per year, and peritoneal dialysis £24,000 per year [18].

The total average cost of retransplantation was estimated to be £27,000, of which £16,000 is the cost of transplant surgery [18]. For living donor kidney transplantation (34.9%) there were estimated costs of £8,900 for screening, pre-transplantation work up of the donor and the explant procedure [18]. For deceased donor kidney transplantation (65.1%) there were estimated costs of staffing, consumables and transport for retrievals [20].

Clinical events

Acute rejection episodes were estimated to cost £3,557 on average based on an unpublished microcosting study submitted by the pharmaceutical company Bristol–Myers Squibb in their submission to NICE [21]. Patients are susceptible to multiple acute rejection episodes, and an average of 1.19 episodes was assumed for patients experiencing at least one episode [22].

CMV infection was estimated to cost £3,009 based on the same microcosting study [21]. It was assumed that patients would experience at most one CMV infection.

Patients with PTDM incurred costs of anti-diabetic treatment (metformin) and complications (average annual costs of £2,084 [23]).

Patients experiencing graft loss were assumed to commence dialysis, and a certain proportion were assumed to have their graft removed (explant surgery £4,966 [18]); this proportion was small for patients whose grafts had functioned for over a year before graft loss.

KTRs with dyslipidaemia were assumed to have annual visits to dietetics outpatients clinics (£63 [18]) and their primary physician (£51 [24]) in relation to dyslipidaemia. The cost of medication with statins was also included.

It was assumed that anaemia requiring treatment with erythropoiesis stimulating agents would occur in 5.2% of patients and these would require a mean weekly dose of 5,832 IU [25].

Monitoring

KTRs receive monitoring on a frequent basis, which is gradually tapered for KTRs with stable grafts. In the model KTRs attended clinics and received the following monitoring: full blood count; renal profile; liver function tests; therapeutic drug monitoring; and, on separate schedules, viral quantitative PCR (CMV, Epstein–Barr virus, BK virus). The frequency of clinic visits and routine monitoring tests was based on an unpublished retrospective observational study submitted by Bristol–Myers Squibb in their submission to NICE [26].

Currency and price date

All costs are presented in 2014/15 pounds sterling (GBP; £). No prices required currency conversion. Prices were inflated to 2014/15 prices where necessary using the Hospital and Community Health Services pay and prices index to 2013/14 and then by a further year using average inflation over the previous three years [24].

Analysis

Cost–utility analyses were conducted at:

1. The level of individual agents by comparing regimens which differed only by one agent;
2. The level of regimens in a fully incremental analysis.

Deterministic and probabilistic sensitivity analyses were conducted.

Results

Effectiveness

An immunosuppressive regimen comprising induction with basiliximab and maintenance with belatacept and MMF was predicted to give the longest graft survival (18.0 years) and greatest overall survival (23.2 years), and most discounted QALYs (11.29). A regimen comprising induction without mono- or polyclonal antibodies and maintenance with ciclosporin and azathioprine was predicted to give the shortest graft survival (15.0 years), while a regimen with IR-Tacrolimus and sirolimus maintenance was predicted to give the lowest overall survival (22.1 years) and least discounted QALYs (10.6).

Figure 2 demonstrates that graft survival was usually associated with overall survival, although regimens with elevated rates of PTDM have reduced overall survival due to the increased risk of death with a functioning graft.

Cost-effectiveness

The total costs and QALYs for each regimen are shown in **Table 7**.

Induction agents

Basiliximab and rabbit ATG were compared alongside induction without mono- or polyclonal antibodies (“no induction”) in three comparisons (with different maintenance regimens). Across the comparisons, rabbit ATG was more effective (more QALYs) than no induction and basiliximab was more effective than rabbit ATG. Rabbit ATG was the most costly, followed by no induction, with

basiliximab induction being least costly. Basiliximab was less costly and more effective than the other treatment options and was therefore *dominant*.

These results were confirmed in probabilistic analyses, with basiliximab predicted to be cost-effective in 93–95% of simulations.

Maintenance agents

IR-Tacrolimus was compared to ciclosporin in four comparisons and was predicted to be less costly in all four. When used with no induction and with azathioprine, IR-Tacrolimus was predicted to be more effective and was therefore dominant. In the other three comparisons, IR-Tacrolimus was predicted to be marginally less effective (longer graft survival but reduced QALYs due to increased incidence of PTDM), but with the ICER for ciclosporin versus IR-Tacrolimus over £100,000/QALY.

IR-Tacrolimus was compared to PR-Tacrolimus in one comparison and was predicted to be dominant. In another comparison IR-Tacrolimus was compared to sirolimus and belatacept, and was predicted to dominate sirolimus and be cost-effective versus belatacept (ICER of belatacept >£400,000/QALY).

Sirolimus was also compared to azathioprine and MMF, and was predicted to be dominated by both. Everolimus was compared to azathioprine and MMF, and was predicted to be more costly and more effective (ICER >£1m/QALY).

MMF was compared to azathioprine in four comparisons and was predicted to be dominant in all four. MPS was compared to azathioprine and MMF, and was predicted to be more costly and more effective (ICER £144,000/QALY).

Deterministic analyses demonstrated that only IR-Tacrolimus and MMF are cost-effective at thresholds of £20,000 and £30,000 per QALY.

Regimens

The only cost-effective regimen when all regimens were compared simultaneously comprised basiliximab induction and IR-Tacrolimus and MMF maintenance (**Table 8**). Three other regimens were on the cost-effectiveness frontier, but with ICERs in excess of £100,000/QALY.

Analyses of uncertainty

Probabilistic sensitivity analyses were conducted, which confirmed that at cost-effectiveness thresholds of £20,000 and £30,000 per QALY, IR-Tacrolimus and MMF were expected to give the highest net health benefit (once additional costs have been exchanged for health forgone by patients elsewhere in the health system) and were most likely to be cost-effective.

To determine the importance of the impact of PTDM on cost-effectiveness, a scenario analysis was conducted in which no disutility was applied to patients with PTDM. Basiliximab, IR-Tacrolimus and MMF remained the only cost-effective agents, and IR-Tacrolimus dominated ciclosporin in all comparisons.

The importance of the surrogate relationship from graft function, acute rejection and PTDM to graft survival was investigated by varying the duration for which these outcomes affected graft survival through proportional hazards. As the surrogate relationship was weakened, ciclosporin became

optimal (instead of IR-Tacrolimus), then induction without mono- or polyclonal antibodies became optimal (instead of basiliximab).

Discussion

We found that basiliximab, immediate-release tacrolimus and mycophenolate mofetil are likely to be optimal immunosuppressants (in terms of cost-effectiveness) for the majority of adult KTRs in the NHS.

These results should be considered alongside the need to tailor therapy to an individual patient's needs. For some patients there may be a different balance of potential benefits and harms from different immunosuppression regimes compared to "the average patient" [27]. It was not possible to perform subgroup analyses of effectiveness for this economic evaluation because subgroup analyses of effectiveness were not conducted in the systematic review [5], since these were not reported by the included trials.

Tacrolimus, although an effective immunosuppressant, is also diabetogenic [28]. For patients at risk of diabetes or at risk of complications from diabetes, it may be more effective and cost-effective to use ciclosporin instead, since diabetes is associated with adverse events and increased mortality. Ciclosporin offered the second-best net health benefit after immediate-release tacrolimus.

Tacrolimus (along with ciclosporin) is also associated with nephrotoxicity. If dose reduction is not able to halt chronic allograft injury due to nephrotoxicity then clinicians may consider withdrawal of tacrolimus in low immunological risk patients, or switching to an alternative therapy, such as sirolimus, everolimus or belatacept [28]. Our economic evaluation suggests that for such patients, sirolimus would be most cost-effective.

Mycophenolate mofetil has been associated with gastrointestinal side effects, including diarrhoea, nausea and vomiting [28] – these can lead to impaired absorption and decreased adherence, which could cause graft loss. In such circumstances our economic evaluation suggests that azathioprine should first be considered as a replacement (mycophenolate sodium is estimated to cost over £50,000 per QALY gained compared to azathioprine), although this is not based on evidence in patients with mycophenolate mofetil intolerance.

Rabbit ATG has been recommended in guidelines (e.g., KDIGO [28]) for induction therapy in kidney transplant recipients at high immunological risk. We were not able to separately assess cost-effectiveness in such patients in this evaluation, because there were no studies comparing rabbit ATG to basiliximab or placebo in patients with high immunological risk identified in the review of clinical effectiveness [5]. The review did not include daclizumab as an intervention or comparator (since its marketing authorisation was withdrawn), but some other reviews (e.g., Webster et al. 2010 [29]) have included daclizumab and assumed a class effect of interleukin-2 receptor antagonists (IL2Ra; basiliximab and daclizumab). A study by Noël et al. [30] compared daclizumab to rabbit ATG in patients with high immunological risk. It found that patients inducted with rabbit ATG had a significantly lower risk of biopsy-proven acute rejection (odds ratio 0.47, 95% CI 0.25 to 0.91). In the daclizumab group 27% of patients experienced biopsy-proven acute rejection. We conducted a scenario analysis in which we incorporated this data (assuming a class effect), and found that basiliximab continued to be less costly and more effective (in terms of QALYs) and this finding was robust to changes in baseline graft survival. It is possible that further studies comparing ATG to IL2Ra

in patients at high immunological risk, with longer follow-up, could demonstrate sufficient effectiveness to make rabbit ATG cost-effective.

Our results contrast with those in a recently published cost–utility study by Muduma et al., which found that sirolimus as part of a calcineurin inhibitor minimisation strategy would be cost-effective compared to immediate-release tacrolimus, prolonged-release tacrolimus, ciclosporin and belatacept [31]. Muduma et al. used a 25-year time horizon, compared to the 50-year time horizon in this evaluation (although the results of this evaluation are not significantly altered by adopting a 25-year time horizon). Muduma et al. also did not account for the effect of short-term graft function on long-term graft survival, and they have not reported the sources or values of effectiveness estimates.

A limitation of our evaluation is the poor quality of the underpinning clinical effectiveness literature. RCTs of immunosuppression in kidney transplantation are plentiful, but are often underpowered for key clinical outcomes (graft loss and mortality) and have limited follow-up [5]. Baseline graft survival in this evaluation was extrapolated from mature registry data [8], but treatment effects were assessed at one year post-transplantation. For regimens where progressive loss of graft function is not typically observed (those not including calcineurin inhibitors), this may have led to an underestimation of long-term graft survival.

Comparative effectiveness analyses of kidney transplant registries could overcome issues of statistical power and limited follow-up, and include patient groups who are typically excluded from RCTs (such as the elderly and the multi-morbid). It is possible that adjusted treatment effects may be estimated for some agents (those which are widely prescribed) through the use of advanced statistical techniques [32]. Analyses of these registries may also give greater insight into the prognostic value of graft function in patients receiving different immunosuppressive regimens.

A number of factors will limit the generalisability of these results to other settings (e.g., other countries) [33, 34], due to differences in costs, service designs, valuation of health outcomes and willingness-to-pay. To facilitate economic evaluation of immunosuppressive agents for kidney transplantation in other settings, we have made the underlying economic model free to download under a Creative Commons license [35].

Future assessments of immunosuppressive agents may consider the effectiveness and cost-effectiveness of immunosuppressive agents in subgroups (potentially including non-RCT and individual patient data). Most RCTs did not report subgroups, or reported them poorly, but clinicians and healthcare providers would likely benefit from high-quality evidence of the effectiveness and cost-effectiveness of immunosuppressive agents in certain subgroups, e.g., those at high immunological risk.

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Transparency declarations

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Tables

Table 1: Regimens considered in the economic evaluation

With induction without mono- or polyclonal antibodies	With basiliximab induction	With rabbit ATG induction
• Ciclosporin + mycophenolate mofetil • Ciclosporin + azathioprine • Immediate-release tacrolimus + mycophenolate mofetil • Immediate-release tacrolimus + azathioprine • Ciclosporin + everolimus • Immediate-release tacrolimus + sirolimus • Prolonged-release tacrolimus + mycophenolate mofetil	• Ciclosporin + mycophenolate mofetil • Ciclosporin + azathioprine • Immediate-release tacrolimus + mycophenolate mofetil • Sirolimus + mycophenolate mofetil • Belatacept + mycophenolate mofetil • Ciclosporin + mycophenolate sodium	• Ciclosporin + mycophenolate mofetil • Ciclosporin + azathioprine • Immediate-release tacrolimus + mycophenolate mofetil

Table 2: Median treatment effects used in the economic model from fixed effects network meta-analyses

Treatment (regimen)	Odds ratio[a] (95% CrI)			Mean difference[b] (95% CrI)
	Biopsy-proven acute rejection	Graft loss	Patient death	Graft function (eGFR, ml/min/1.73 m²)
Induction agent (versus placebo/no induction)				
Basiliximab	**0.52 (0.41, 0.65)**	0.82 (0.56, 1.18)	0.99 (0.53, 1.85)	2.11 (−0.45, 4.68)
Rabbit ATG	**0.36 (0.24, 0.54)**	0.77 (0.39, 1.47)	0.84 (0.33, 2.07)	−3.95 (−11.80, 3.94)
Maintenance regimen (versus ciclosporin and azathioprine)				
IR-Tacrolimus and azathioprine	**0.58 (0.36, 0.93)**	1.13 (0.67, 2.15)	1.38 (0.74, 2.60)	**9.31 (4.32, 14.28)**
Ciclosporin and mycophenolate[c]	**0.47 (0.25, 0.88)**	0.76 (0.35, 1.44)	0.94 (0.45, 1.95)	1.61 (−4.16, 7.41)
IR-Tacrolimus and mycophenolate[c]	**0.40 (0.19, 0.79)**	0.69 (0.28, 1.55)	1.53 (0.63, 3.71)	**6.53 (0.38, 12.68)**
Belatacept and mycophenolate[c]	0.81 (0.34, 1.94)	0.62 (0.20, 1.78)	0.47 (0.15, 1.38)	**10.54 (2.47, 18.66)**
Ciclosporin and everolimus	**0.46 (0.21, 0.99)**	0.63 (0.20, 1.58)	1.40 (0.52, 3.65)	4.85 (−2.84, 12.58)
IR-Tacrolimus and sirolimus	**0.38 (0.16, 0.93)**	1.19 (0.38, 3.35)	1.38 (0.49, 3.88)	−0.34 (−8.53, 7.85)
Sirolimus and mycophenolate[c]	**0.43 (0.22, 0.92)**	1.06 (0.38, 2.43)	1.72 (0.68, 4.31)	3.84 (−2.72, 10.43)

Key: (Rabbit) ATG, rabbit anti-thymocyte globulin; CrI, credible interval; eGFR, estimated glomerular filtration rate; IR-Tacrolimus, immediate-release tacrolimus

Notes: a, Odds ratio below one favours intervention; b, Mean difference above zero favours intervention; c, Mycophenolate mofetil or mycophenolate sodium; **Bold face** indicates 95% CrI does not contain one (for odds ratio) or zero (for mean difference)

Source: Jones-Hughes et al. 2016 [5]

Table 3: Impact of maintenance agents on incidence of post-transplant diabetes used in the economic model

Maintenance agent	Odds ratio of PTDM incidence [Median (95% CrI)]
IR-tacrolimus	(Baseline)

PR-tacrolimus	1.18 (0.63, 2.23)
Ciclosporin	**0.44 (0.26, 0.66)**
Belatacept	**0.19 (0.09, 0.39)**
Sirolimus	0.79 (0.51, 1.22)
Mycophenolate mofetil	(Baseline)
Mycophenolate sodium	0.94 (0.27, 3.08)
Sirolimus	1.60 (0.84, 3.10)
Everolimus	0.95 (0.51, 1.78)

Key: CrI, credible interval; IR-Tacrolimus, immediate-release tacrolimus; PR-tacrolimus, prolonged-release tacrolimus; PTDM, post-transplant diabetes
Notes: Results from fixed effects models; **Bold face** indicates 95% CrI does not contain one

Table 4: Impact of mTOR-I (sirolimus or everolimus) use on incidence of dyslipidaemia and cytomegalovirus infection in the economic model

mTOR-I use	Odds ratio of dyslipidaemia incidence[a] [Median (95% CrI)]	Odds ratio of CMV incidence[b] [Median (95% CrI)]
None	(Baseline)	(Baseline)
Sirolimus or everolimus	**1.74 (1.43, 2.12)**	
Sirolimus (with MMF)		0.45 (0.21, 1.01)
Sirolimus (with IR-tacrolimus) or everolimus (with MPS)		**0.31 (0.12, 0.89)**

Key: CMV, cytomegalovirus; CrI, credible interval; IR-tacrolimus, immediate-release tacrolimus; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; mTOR-I, mechanistic target of rapamycin inhibitor
Notes: a, Fixed effects model; b, Random effects model; **Bold face** indicates 95% CrI does not contain one

Table 5: Unit costs of drug acquisition

Agent	Pack size	Pack price	Unit	Price per unit
Immunosuppressants				
Basiliximab (Simulect®, Novartis)	1× 20-mg vial	£842.38	20 mg	£842.38
Rabbit ATG (Thymoglobuline®, Sanofi)	1× 25-mg vial	£158.77	1 mg	£6.35
IR-tacrolimus (generic)			1 mg	£0.5201
PR-tacrolimus (Advagraf®, Astellas)	50× 5-mg capsule	£266.92	1 mg	£1.068
Ciclosporin (generic)			1 mg	£0.0165
Mycophenolate mofetil (generic)			1 g	£0.3774
Mycophenolate sodium (Myfortic®, Novartis)	120× 180-mg tablet	£96.72	1 mg	£0.0045
Azathioprine (generic)			1 mg	£0.0011

Sirolimus (Rapamune®, Pfizer)	30× 2-mg tablet	£172.98	1 mg	£2.883
Everolimus (Certican®, Novartis)	60× 0.25-mg tablet	£148.50	1 mg	£9.90
Belatacept (Nulojix®, Bristol-Myers Squibb)	1× 250-mg vial	£354.52	250 mg	£354.52
Prednisolone (generic)			1 mg	£0.0033
Infection prophylaxis				
Co-trimoxazole (Septrin®, Aspen)	100× 480-mg tablet	£15.52	480 mg	£0.1552
Valganciclovir (Valcyte®, Roche)	60× 450-mg tablet	£1,081.46	450 mg	£18.02
Anti-diabetics				
Metformin (generic)			500 mg	£0.0054
Statins				
Fluvastatin (generic)			1 mg	£0.0022
Pravastatin (generic)			1 mg	£0.0026
Simvastatin (generic)			1 mg	£0.0003

Key: IR-tacrolimus, immediate-release tacrolimus; PR-tacrolimus, prolonged-release tacrolimus

Table 6: Immunosuppressant resource use

Agent	**Concomitant treatment**	**Mean daily dose[a]**		
		First year	**Second year**	**Thereafter[b]**
AZA	CSA	102 mg	85 mg	85 mg
AZA	TAC	95 mg	84 mg	84 mg
BEL	MMF	9.0 vials **per month**	6.2 vials **per month**	6.2 vials **per month**
CSA	AZA	275 mg	206 mg	200 mg
CSA	EVL	274 mg	147 mg	147 mg
CSA	MMF/MPS	232 mg	198 mg	198 mg
EVL	CSA	2.7 mg	2.6 mg	2.0 mg
MMF	BEL	2.0 g	2.0 g	2.0 g
MMF	CSA	1.9 g	1.7 g	1.7 g
MMF	SRL	1.8 g	1.5 g	1.5 g
MMF	TAC/TAC-PR	1.8 g	1.5 g	1.5 g
MPS	CSA	1242 mg	1107 mg	1107 mg
SRL	MMF	4.1 mg	2.9 mg	2.7 mg
SRL	TAC	3.7 mg	2.8 mg	2.2 mg
TAC	AZA	9.6 mg	6.3 mg	5.7 mg

TAC	MMF	7.3 mg	5.6 mg	5.6 mg
TAC	SRL	6.9 mg	4.9 mg	4.9 mg
TAC-PR	MMF	10.6 mg	6.3 mg	5.7 mg

Key: AZA, azathioprine; BEL, belatacept; CSA, ciclosporin; EVL, everolimus; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; SRL, sirolimus; TAC, immediate-release tacrolimus; TAC-PR, prolonged-release tacrolimus

Notes: a, For patient weighing 70.2 kg; b, Based on 24 months to 10 years

Table 7: Total lifetime discounted costs and QALYs for all regimens

Regimen	Total discounted costs	Total discounted QALYs
Ciclosporin and MMF	£97,400	10.91
IR-tacrolimus and MMF	£92,200	10.89
Ciclosporin and azathioprine	£101,600	10.77
IR-tacrolimus and azathioprine	£93,300	10.87
Ciclosporin and everolimus	£176,200	10.97
IR-tacrolimus and sirolimus	£125,500	10.60
PR-tacrolimus and MMF	£106,500	10.79
Basiliximab, ciclosporin and MMF	£95,200	11.02
Basiliximab, IR-tacrolimus and MMF	£90,400	10.99
Basiliximab, ciclosporin and azathioprine	£98,200	10.90
Basiliximab, sirolimus and MMF	£114,500	10.90
Basiliximab, belatacept and MMF	£209,400	11.29
Basiliximab, ciclosporin and MPS	£111,500	11.14
Rabbit ATG, ciclosporin and MMF	£101,900	10.93
Rabbit ATG, IR-tacrolimus and MMF	£97,100	10.90
Rabbit ATG, ciclosporin and azathioprine	£104,600	10.82

Key: IR-tacrolimus, immediate-release tacrolimus; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; QALY, quality-adjusted life year

Notes: Total discounted costs rounded to nearest £100; Total discounted QALYs rounded to 2 decimal places

Table 8: Cost-effectiveness results for regimens on the cost-effectiveness frontier (deterministic; base case)

Regimen	Total discounted costs	Total discounted QALYs	ICER (cost per QALY)

Basiliximab, IR-tacrolimus and MMF	£90,400	10.99	—
Basiliximab, ciclosporin and MMF	£95,200	11.02	£131,000
Basiliximab, ciclosporin and MPS	£111,500	11.14	£144,000
Basiliximab, belatacept and MMF	£209,400	11.29	£626,000

Key: ICER, incremental cost-effectiveness ratio (the cost per additional QALY); IR-tacrolimus, immediate-release tacrolimus; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; QALY, quality-adjusted life year

Notes: Total discounted costs rounded to nearest £100; Total discounted QALYs rounded to 2 decimal places; ICERs rounded to nearest £1,000 per QALY

Figures

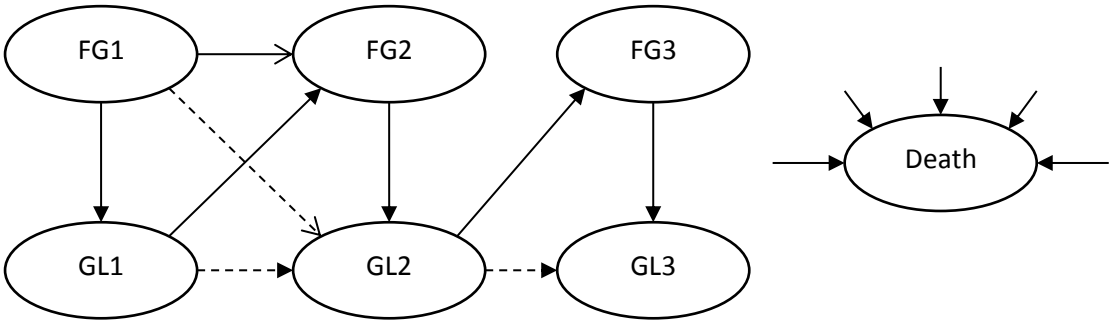

Figure 1: Decision model diagram

Key: FG, FUNCTIONING GRAFT; GL, GRAFT LOSS

Notes: Dashed arrows indicate primary non-function; Arrows with unfilled heads indicate pre-emptive retransplantation; Self-links omitted for clarity

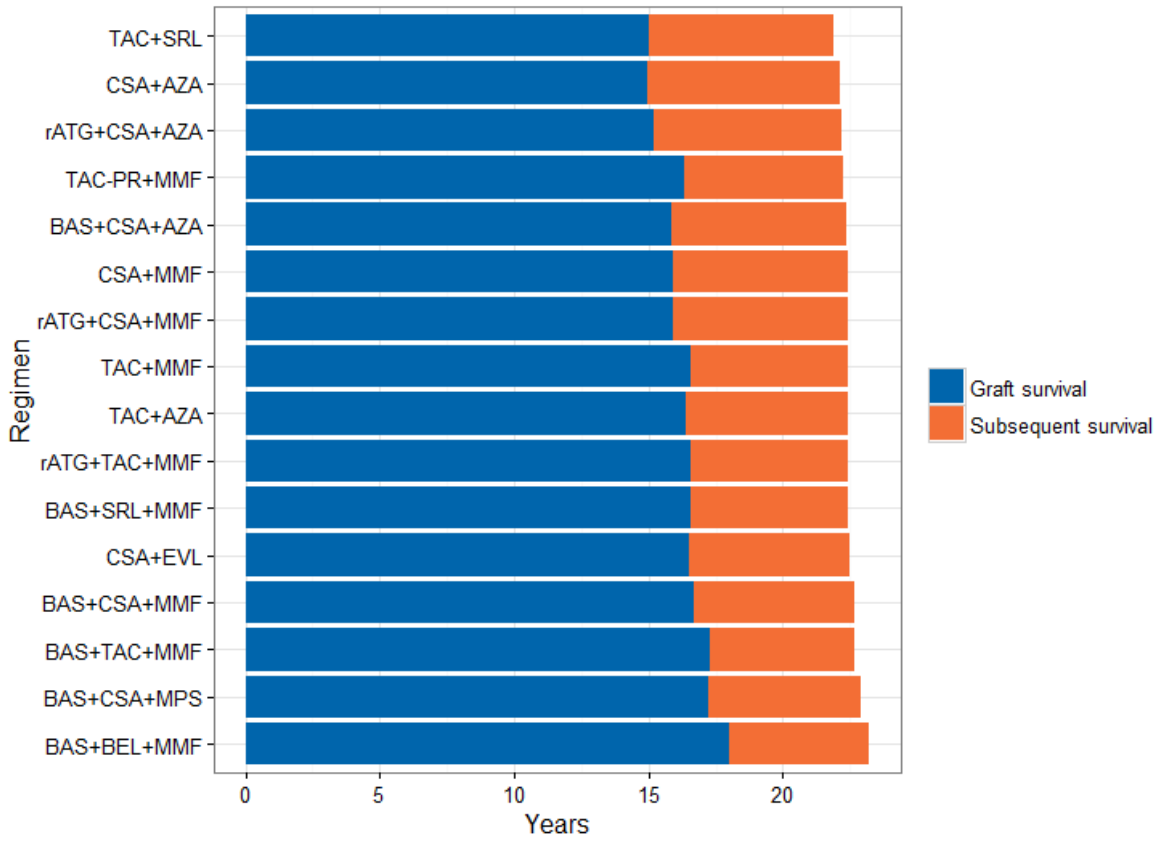

Figure 2: Mean graft survival and overall survival for regimens modelled in the economic evaluation

Key: AZA, azathioprine; BAS, basiliximab; BEL, belatacept; CSA, ciclosporin; EVL, everolimus; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; rATG, rabbit anti-thymocyte globulin; SRL, sirolimus; TAC, immediate-release tacrolimus; TAC-PR, prolonged-release tacrolimus

Notes: Regimens are ordered by increasing overall survival from top to bottom.

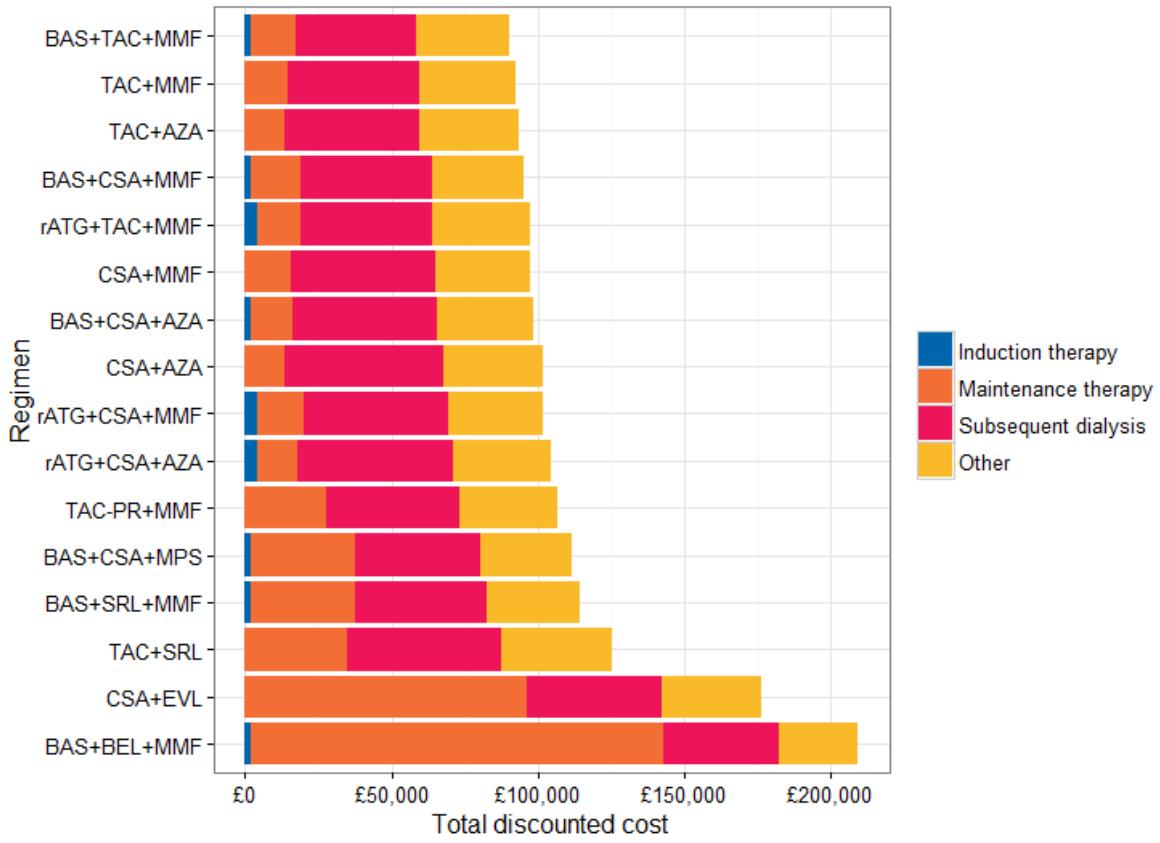

Figure 3: Total discounted costs for regimens modelled in the economic evaluation

Key: AZA, azathioprine; BAS, basiliximab; BEL, belatacept; CSA, ciclosporin; EVL, everolimus; MMF, mycophenolate mofetil; MPS, mycophenolate sodium; rATG, rabbit anti-thymocyte globulin; SRL, sirolimus; TAC, immediate-release tacrolimus; TAC-PR, prolonged-release tacrolimus

Notes: Regimens are ordered by increasing total discounted costs from top to bottom.