ORIGINAL ARTICLE

Induction therapy with rabbit antithymocyte globulin versus basiliximab after kidney transplantation: a health economic analysis from a German perspective

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SUMMARY

A health economic analysis was undertaken based on the 1-year database from a randomized study of rabbit anti-human thymocyte immunoglobulin (rATG) versus basiliximab, in kidney transplantation using resource utilization data and cost estimates from three German hospitals. A three-state Markov model was applied to estimate cost-effectiveness to 10 years post-transplant. Total mean treatment cost per patient to year 1 post-transplant was €62 075 vs. €59 767 for rATG versus basiliximab ($P < 0.01$). rATG therapy was associated with similar treatment costs to basiliximab by year 2, and a predicted cumulative treatment cost saving of €4 259 under rATG versus basiliximab by year 10 post-transplant. The mean number of quality-adjusted life years (QALYs) per patient by year 1 was 0.809 vs. 0.802 in the rATG and basiliximab cohorts, respectively ($P = 0.38$), with cumulative QALYs of 6.161 and 6.065 per patient by year 10. By year 2, the cumulative cost per QALY was slightly lower under rATG (€35 378) than basiliximab (€35 885), progressing to a saving of €1 041 under rATG for the cumulative cost per QALY by year 10. In conclusion, this model indicates that rATG induction provides a modest increase in QALYs with lower long-term costs than basiliximab in deceased-donor high-risk kidney transplant patients.

Introduction

Induction therapy is widely used in kidney transplant recipients. The two most frequently prescribed agents are rabbit anti-human thymocyte immunoglobulin (rATG, Thymoglobulin®), a lymphocyte-depleting agent, and basiliximab, a monoclonal anti-interleukin 2 (IL2) receptor antibody [1]. The efficacy of rATG [2] and basiliximab [3,4] in reducing acute rejection after kidney transplantation is well-established. In patients at low immunological risk, both agents showed similar efficacy in terms of preventing biopsy-confirmed acute

rejection (BPAR) in two randomized trials, although in both cases the studies were underpowered to detect superiority for either regimen, and the start of calcineurin inhibitor therapy was delayed in the rATG arm [5,6]. For patients at higher immunological risk, such as sensitized individuals, those with HLA antigen mismatching or receiving a repeat transplant, rATG appears to offer more potent immunosuppression. A large randomized trial of at-risk patients by Brennan *et al.* [7] found that rATG induction achieved significantly lower incidences of acute rejection and steroid-resistant acute rejection than basiliximab. Similar results were reported by Noël and colleagues when rATG induction was compared to the anti-IL2 receptor antagonist daclizumab in a high-risk cohort of kidney transplant recipients [8]. Accordingly, the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines recommend that an anti-IL2 receptor antagonist be first-line induction therapy, with a lymphocyte-depleting agent reserved for higher-risk cases [9].

Clinical prescribing decisions should also be informed by economic assessments. Solid organ transplantation is an expensive intervention in which economic evaluation is particularly relevant [10], but publications in this area are infrequent [11]. Cost-effectiveness analyses of induction agents must take into account not only the direct drug regimen costs but possible clinical sequelae such as effects on risk for acute rejection, delayed graft function (DGF), infection, graft failure with return to dialysis, and mortality. A meaningful assessment requires detailed data collection and examination of costs beyond the first year post-transplant to reflect long-term costs to the payer, for example, due to late graft failure. Such data, however, are often lacking. Health economic analyses of basiliximab up to year 1 after kidney transplantation, based on data from randomized trials, have shown cost neutrality versus placebo [12,13], or a cost benefit for basiliximab due primarily to reduced acute rejection [14–16]. Cost-effectiveness analyses of rATG induction versus no induction in kidney transplantation are rare, either comparing rATG versus no induction in a nonrandomized setting [17,18] or comparing the direct costs of different rATG dosing strategies [19–21]. One recent evaluation based on US patient databases concluded that rATG was cost-effective given a threshold of US$50 000 per quality-adjusted life year (QALY) for both high- and low-risk kidney transplant recipients [18]. Only one comparison of basiliximab versus rATG (Thymoglobulin®) has been published. This was a single-center cost minimization analysis [22] based on a randomized trial of the two induction agents in which

patients at high immunological risk were excluded by protocol [5]. As might be expected, in this low-risk cohort, no efficacy benefit was observed with rATG, and there was small saving in overall treatment costs for basiliximab versus rATG during the first year post-transplant [22].

We undertook a health economic analysis to quantify the long-term economic consequences of induction with rATG (Thymoglobulin®) versus basiliximab during the first year after kidney transplantation in patients at increased immunological risk, the population in which rATG is recommended by KDIGO [9]. The analysis was designed to assess treatment costs in a "real-world" environment, taking into account the expected short-term and long-term sequelae of either induction agent. The study quantified healthcare resources, costs, and health outcomes based on the 1-year clinical database from the randomized study by Brennan *et al.* [7].

Methods

Clinical data set

Clinical outcomes data were obtained from the original SAS® database of the 1-year prospective, randomized, international study by Brennan and colleagues [7]. The study enrolled patients aged 18 years or older who were at protocol-defined risk for acute rejection or DGF who received a kidney graft from a deceased donor. Patients were required to have one or more of the following risk factors: cold ischemia <16 h (or ≤30 h with any machine perfusion) and a heart-beating donor aged >50 years, donor serum creatinine >220 μmol/l or donation after cardiac death; or cold ischemia 16–24 h with one donor or recipient risk factor (donor factors: donation after cardiac death, acute tubular necrosis, high-dose inotropic support; recipient factors: retransplant, pre-transplant panel reactive antibodies [PRA] >20%, black race, ≥1 HLA mismatch); or cold ischemia time >24 h. Patients were randomized to either rATG (Thymoglobulin®) at a dose of 1.5 mg/kg, started intra-operatively and continued until day 4 ($n = 141$) for a maximum total dose of 7.5 mg/kg (with pre-specified adjustments based on platelet and neutrophil counts), or to basiliximab at a dose of 20 mg on days 0 and 4 ($n = 137$). The mean (SD) dose of rATG was 6.5 (1.5) mg/kg.

Treatment costs

Analyses were based on the cost of treatment to the institutions. Data on resource utilization and cost

estimates were obtained for patients who underwent deceased-donor kidney transplantation and received either rATG or basiliximab induction at German hospitals to calculate a health economic perspective for the German setting. Internal hospital costs were obtained and pooled from three German centers (Universitätsklinik Erlangen-Nürnberg, Erlangen; Universitätsklinik Eppendorf UKE, Hamburg; and Universitätsklinik Köln, Cologne), with mean values applied to the analysis. Costs were obtained through interviews with financial managers at each center with access to German national hospital financial databases. Tariffs from 2014 were applied based on data collected from one site and validated at the other two sites, so as to represent the most recent and comprehensive costs at the three centers.

The cost evaluation of the clinical database included the system costs related to organ procurement, the transplant hospital stay, cost of the induction regimen, management of DGF, graft rejection (BPAR, antibody-treated BPAR, suspected rejection episodes) and infections, costs related to routine graft maintenance (including immunosuppression), management of graft failure (with or without nephrectomy), and return to dialysis after graft failure, all during the first year post-transplant. An initial list of relevant healthcare goods and services to be analyzed was developed based on the literature, which was reviewed by clinical consultants at site levels prior to development of the final data collection instrument. The final list of infections, adverse events and serious adverse events comprised mild, moderate and severe cellulitis, urinary tract infection, sepsis, upper respiratory infection, pneumonia, nephritis, oral cavity, and intra-abdominal infection. The system costs of organ procurement and routine post-transplant hospital stay were assumed to be identical for both induction therapies. Assumptions regarding length of post-transplant hospital stay were based on 2015 data from University Hospital Cologne, Cologne, Germany, which showed no difference between patients given rATG or basiliximab induction.

Treatment costs under rATG or basiliximab were compared using the Wilcoxon rank sum test.

Markov modeling

Health economic modeling to determine cost-effectiveness was conducted using a 10-year three-state Markov model with the following two cohorts: transplant patients receiving rATG induction and transplant patients receiving basiliximab induction (Figure S1). In the model, patients were predicted to transition between three health states: (i) alive with functioning graft, (ii) alive following graft failure, and (iii) deceased. The model made several simplifying assumptions, including that patients with graft failure never receive a second transplant, and that only one health state transition (functioning graft to failed graft, functioning graft to death, graft failure to death) may occur each year. The model's transition probabilities (i.e., the risks of death and nonfatal graft failure) remained constant from year to year.

The following estimates based on US Renal Data System (USRDS) data for patients aged 50–59 years were used to model health state transitions: Patients with a functioning kidney graft face a 2.1% annual risk of death; and patients with a failed graft face a 12.3% annual risk of death [23]. Patients with a functioning graft were assumed to face a 1.1% annual risk of nonfatal graft failure based on extrapolation of long-term follow-up data from the study by Brennan et al. [24].

The following estimates were assigned as treatment costs based on hospital tariffs and utilization estimates obtained from the three study centers: patients awaiting transplant and those with graft failure incur annual dialysis costs of €54 777. Patients with functioning grafts were assigned annual graft maintenance costs of €6 468 and patients experiencing nonfatal graft failure were assigned costs of €7 239.

Quality-adjusted life years

Utility scores were obtained from the literature to calculate the cost per QALY. Utility values range from 0 to 1, with 1 representing a year in perfect health, and 0 representing death. A utility score of 0.84 was assumed for patients with functioning grafts, and a utility score of 0.68 was assumed for patients with a failed graft who returned to dialysis [25].

Cost analyses

Costs and costs per QALY were estimated for the year of transplant and over the 10-year time horizon of the Markov model. A 5% annual discount rate for both costs and cost per QALY was assumed, consistent with German guidelines.

Statistical analyses

Demographic characteristics of the two treatment groups were compared using chi-square and Student's

t-tests. The incidences of DGF, graft failure, and death within year 1 post-transplant were compared using the chi-square test. As the number of rejection episodes and infections per patient was found to be not normally distributed, comparisons were made using the Wilcoxon rank sum test. The duration of graft and patient survival during year 1, and the number of QALYs to year 1, was compared between groups using the Wilcoxon rank sum test. All costs are shown in Euros (€).

Results

Observed outcomes in the clinical data set

As per the study eligibility criteria, the analysis population of the study by Brennan *et al.* [7] included a high proportion of black recipients and retransplants, with high rates of extended cold ischemia time and sensitized patients (Table 1).

At the end of the 12-month study, the incidence of DGF was similar in both treatment arms but rates of BPAR and antibody-treated BPAR were significantly lower in the rATG cohort (Table 1). Graft and patient survival did not differ significantly between groups. The mean duration of graft survival during the first year

post-transplant was 344 days in the rATG cohort and 331 days in the basiliximab cohort (P = 0.34). The incidence of adverse events, and serious adverse events, was also similar using either rATG or basiliximab induction. There was a higher incidence of infection with rATG induction versus basiliximab (85.3% vs. 75.2%, P = 0.02). Table 2 summarizes the frequency of infection categories in each group.

Treatment costs during year 1 post-transplant

The mean cost of induction therapy was €7 792 per patient when rATG was used, compared to €2 141 per patient when basiliximab was used (P < 0.01), a difference of €5 378 per patient in favor of basiliximab. This was partly offset by a mean reduction of €1 044 for management of rejection during the first year post-transplant (mean [SD] €471 [1 428] with rATG versus €1 151 [3 006] with basiliximab; P = 0.02). Costs associated with DGF, graft failure, and dialysis after graft failure were numerically lower among rATG-treated patients, while graft maintenance costs were correspondingly slightly higher, but no between-group difference was significant (Fig. 1). Infection treatment costs were nearly identical in the two groups. In total, the

Table 1. (a) Key characteristics relating to eligibility criteria and (b) clinical events during year 1 (Brennan *et al.* [7]).

	rATG (n = 141)	Basiliximab (n = 137)	P value
(a) Characteristics			
Black recipient, n (%)	41 (29.1)	39 (28.5)	–
Cold ischemia time >24 h, n (%)	73 (51.8)	84 (61.3)	0.26
Retransplant, n (%)	16 (11.3)	13 (9.5)	0.83
Donation after cardiac death, n (%)	7 (5.0)	6 (4.4)	1.00
Donor >50 years, n (%)	75 (53.2)	74 (54.0)	0.90
Pretransplant PRA, %	6.3 (19.0)	5.7 (17.1)	–
(b) Clinical events			
Delayed graft function, n (%)	57 (40.4)	61 (44.5)	0.54
BPAR, n (%)	22 (15.6)	35 (25.5)	0.02
Antibody-treated BPAR, n (%)	2 (1.4)	11 (8.0)	**0.01**
Graft loss at year 1			
n (%)	13 (9.2)	14 (10.2)	0.68
Graft survival time, days, mean (SD)	344 (72)	331 (99)	0.34
Death at year 1			
n (%)	6 (4.3)	6 (4.4)	0.90
Patient survival time, days, mean (SD)	353 (58)	353 (62)	0.94
Any adverse event, n (%)	140 (99.3)	135 (98.5)	0.62
Any serious adverse event, n (%)	103 (73.0)	99 (72.3)	0.89
Infection, n (%)	121 (85.3)	103 (75.2)	**0.03**

PRA, panel reactive antibody; BPAR, biopsy-proven acute rejection.

Significant P values are shown in bold.

Table 2. Mean (SD) number of infections to month 12.

	rATG (*n* = 141)	Basiliximab (*n* = 137)	*P* value*
Cellulitis	0.23 (0.49)	0.20 (0.71)	0.05
Urinary tract infection	0.55 (0.97)	0.36 (0.74)	0.09
Sepsis	0.14 (0.44)	0.16 (0.46)	0.76
Upper respiratory tract infection	0.11 (0.33)	0.09 (0.40)	0.34
Pneumonia	0.11 (0.33)	0.07 (0.25)	0.30
Nephritis	0.04 (0.35)	0.01 (0.09)	0.58
Oral cavity	0.12 (0.39)	0.13 (0.42)	0.92
Intraabdominal	0.05 (0.22)	0.07 (0.25)	0.57

*Wilcoxon rank sum test.

mean (SD) treatment cost during the first year post-transplant was €62 075 (11 236) with rATG and €59 767 (18 823) with basiliximab, a difference of €2 308 in favor of basiliximab (*P* < 0.01).

### Predicted long-term treatment costs

Figure 2 illustrates predicted patient health status after completion of the first year post-transplant. Ten-year graft survival was predicted to be 65.9% in the rATG group versus 63.6% with basiliximab induction.

Mortality by 10 years was predicted to be 27.8% with rATG versus 29.4% with basiliximab.

The lower rate of graft failure and return to dialysis resulted in a lower predicted cost under rATG versus basiliximab induction over time. By the end of year 2, the cumulative treatment cost per patient was projected to be virtually identical with rATG induction (€79 429) or basiliximab (€79 797) per patient. By the final year of the 10-year model, the cumulative treatment cost was predicted to be €131 674 and €135 933 per patient, respectively, in patients receiving rATG or basiliximab
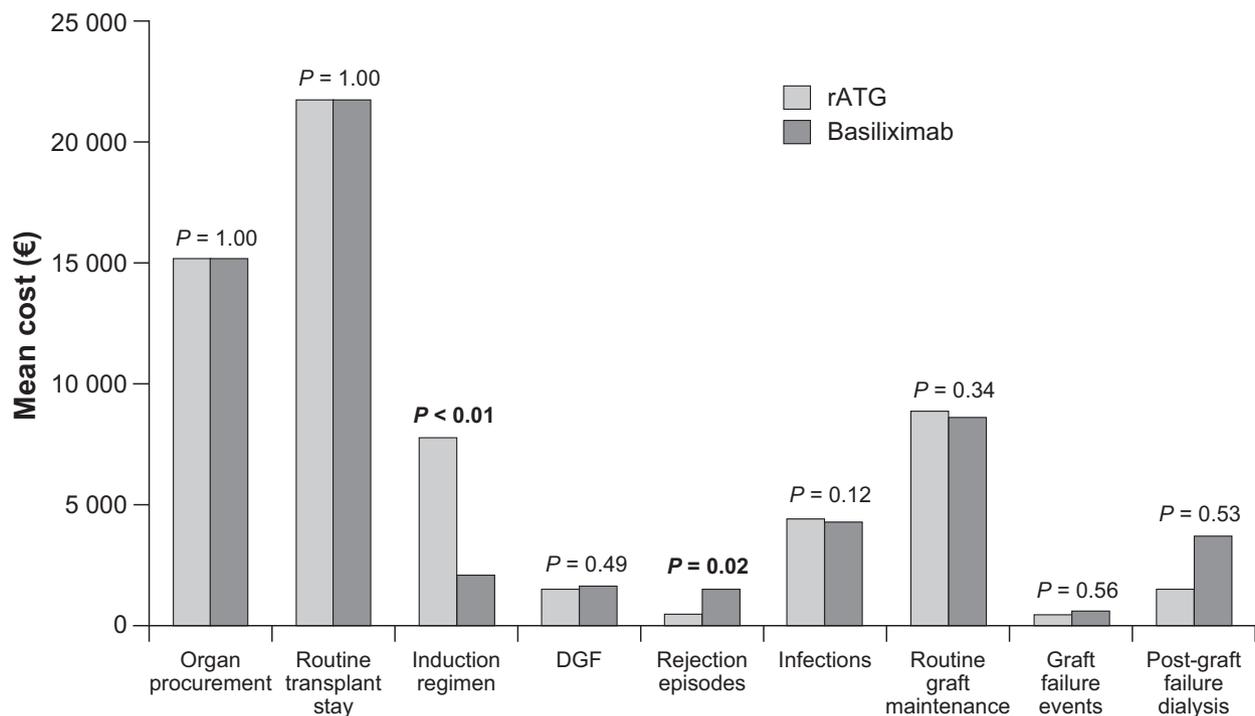
Figure 1 Healthcare costs within year 1 after kidney transplantation according to type of induction therapy. Mean values are shown.
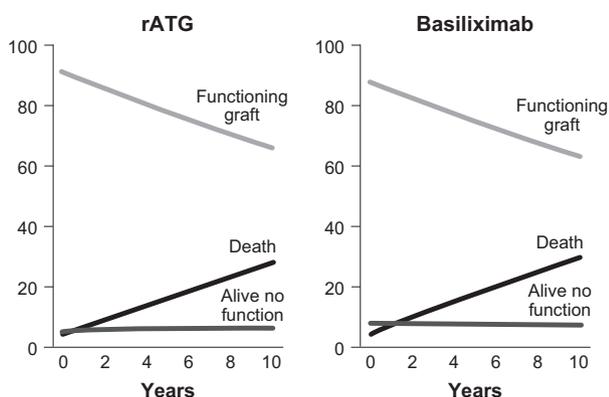
Figure 2 Predicted patient health status to year 10 according to kidney transplantation with rATG induction or basiliximab induction. Year 0 represents the first year post-transplant.

induction (€4 259 lower per patient in favor of rATG) (Fig. 3).

Quality-adjusted life years

The mean (SD) number of QALYs experienced in the first year post-transplant was 0.809 (0.135) vs. 0.802 (0.144) per patient in the rATG and basiliximab cohorts, respectively ($P = 0.38$), a utility difference of 0.007 QALYs per patient. This modest difference was projected to increase slightly over the 10-year model time horizon, with cumulative QALYs of 6.161 and 6.065 per patient in the rATG and basiliximab groups, respectively, by year 10. This represents total QALY gain of 0.096 per patient under rATG induction (Fig. 4a).

By year 2, the cumulative cost per QALY was slightly lower under rATG (€35 378) than basiliximab (€35 885), a difference that increased to a saving of €1 041 under rATG for the cumulative cost per QALY by year 10 (€21 372 vs. €22 413) (Fig. 4b).
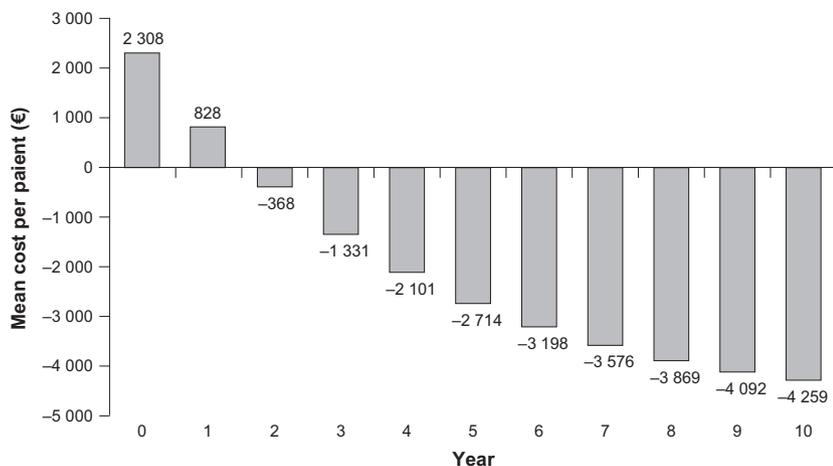
Discussion

This analysis sought to evaluate real-world costs associated with rATG versus basiliximab induction in deceased-donor kidney transplant donors at high immunological risk. In this setting, the higher purchase price of rATG compared to basiliximab induction is partly offset during the first year post-transplant by reduced costs related to management of DGF, acute rejection, and graft failure with return to dialysis. Over the 10-year time horizon of the model, rATG-treated patients are projected to enjoy a modest gain in total QALYs compared to basiliximab, and total healthcare costs are estimated to be €4 259 lower. According to this model, the cost per QALY gained is slightly lower with rATG versus basiliximab induction, and rATG can be considered dominant to basiliximab as it accrues greater clinical benefit (QALY gain) at lower cost.

The small, nonsignificant difference between groups in 1-year graft survival was reflected by a slight numerically higher cost for dialysis after graft loss in the basiliximab cohort. The small graft survival advantage predicted in the rATG cohort by year 10 (approximately 2%) generated an estimated reduction in long-term dialysis costs, partly counterbalanced by the higher mortality observed in dialysis recipients compared to patients with a functioning graft [23]. Overall, the cumulative saving in healthcare costs increases over time post-transplant under rATG induction in this model.

As kidney transplantation potentially affects all future medical care, the most comprehensive approach would consider lifetime medical costs. Predicting all effects to the point of death is, of course, impractical. Here, we focused on adverse events with a possible relation to choice of induction, and modeled major outcomes


Figure 3 Cumulative incremental costs per patient to year 10 after kidney post-transplantation for rATG versus basiliximab induction. Year 0 represents the first year post-transplant.
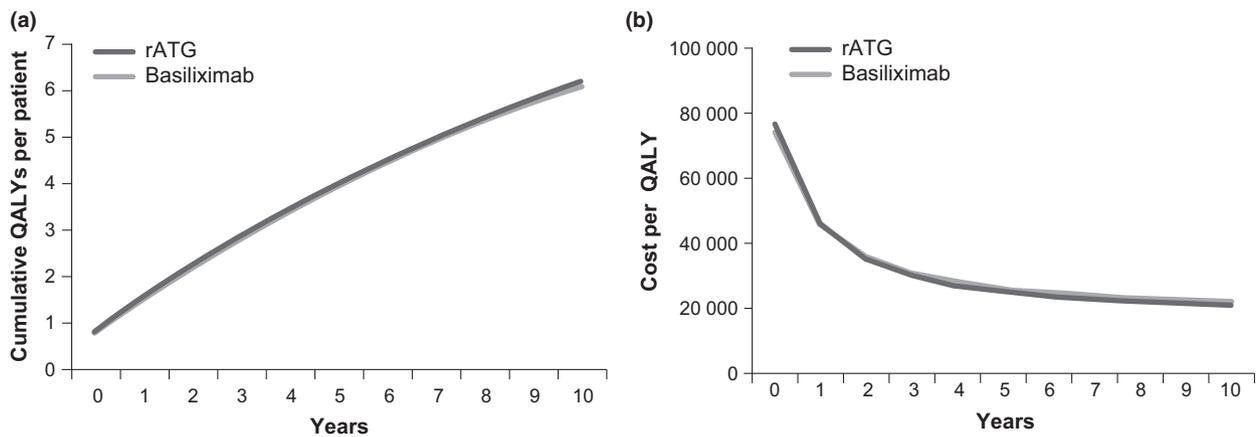
Figure 4 (a) Cumulative quality-adjusted life years (QALYs) per patient and (b) cost per QALY to 10 years according to kidney transplantation with rATG induction or basiliximab induction. Year 0 represents the first year post-transplant.

(surviving graft, return to dialysis or death) over the subsequent 10 years, a period considered reasonable to anticipate based on data from the large-scale USRDS database. We recognize the difficult of undertaking long-term health economic studies, but consider USRDS data to be an adequately robust indicator of likely outcomes to 10 years. While not as ideal as observed rates of events, this 10-year time span can be regarded as informative as an analysis restricted to only the first year post-transplant would not offer the reader a relevant picture of the likely long-term economic implications of choice of induction. It should also be noted that the utility scores were selected from a single study, rather than from a range identified from a comprehensive literature review. A fixed cost per year was assigned to each state regardless of type of induction. The analysis did not attempt to include the cost of retransplantation, but assumed that patients with a failed graft would remain on dialysis indefinitely. In terms of the ongoing cost of maintenance immunosuppression, it was assumed that the immunosuppressive therapy from the clinical database did not change during the long-term follow-up. The cost of biopsies was not included, and no direct or indirect costs incurred by patients were incorporated.

The three German hospitals from which costings were obtained represent a small sampling frame and may not be representative of all transplant centers. No analysis was done to determine whether the costs from the three centers are representative of other German hospitals, but the relatively small variation between them suggests a larger sample of centers would provide little benefit. The patient records in the selected sample may not reflect the deceased-donor kidney transplant population elsewhere, and it is possible that patient records were incomplete. Notably, however, the total mean treatment cost calculated for the first year post-transplant (€48 412 under rATG induction, €45 977 under basiliximab induction) is close to that calculated for deceased-donor kidney transplants in a detailed cost-effectiveness analysis reported recently by Haller et al. [26] based on data from Austria (€51 000), indicating that the data collection for the current analysis was reliable.

These results were derived from the clinical data set in the randomized 1-year trial by Brennan et al. [7], which specifically selected deceased-door patients at protocol-defined risk for DGF or acute rejection. Although patients could be included if they were at high risk for DGF but without risk factors for rejection (e.g., cold ischemia <16 h but with donation after cardiovascular death), in practice the cohort was at high risk for rejection. Almost 30% of patients were African American, approximately 10% received a retransplant, more than half had an extended cold ischemia time (>24 h) and mean PRA was approximately 6% [7]. The cumulative dose of rATG was at least 6.0 mg/kg in 87% of patients, with 69% receiving 7.5 mg/kg. Reduced dosing strategies for rATG in lower-risk patients inevitably lowers purchase costs [19,27], but the regimen applied by Brennan et al. [2] appears typical of current practice for at-risk patients. If, for example, an rATG dose of 4.5 mg was used and the same clinical outcomes achieved, the resulting 40% reduction in the purchase cost for rATG would mean the current estimate suggesting that treatment costs during year 1 are €2308 higher with rATG than basiliximab would change to show a slightly lower treatment cost with rATG versus basiliximab in year 1. Basiliximab is universally given as a fixed regimen of two doses of 20 mg each.

It should also be noted that maintenance therapy in the study by Brennan *et al.* [7] comprised cyclosporine, started in both groups according to renal recovery but no later than day 4, with mycophenolate mofetil (MMF) and steroids. Tacrolimus is now more widely used *de novo* than cyclosporine but no randomized study of rATG (Thymoglobulin®) versus basiliximab has been carried out in a high-risk kidney transplant population receiving tacrolimus. However, Noël and colleagues compared rATG versus the anti-IL2 receptor antagonist daclizumab in 227 patients with current PRA >30%, peak PRA >50%, previous graft loss to rejection, or receipt of two or three previous grafts [8]. Both treatment groups received tacrolimus with MMF and steroids. The relative immunosuppressive efficacy of the two induction therapies was remarkably similar to that described by Brennan *et al.*, with significantly lower rates of BPAR and steroid-resistant BPAR using rATG versus daclizumab in this tacrolimus-treated population. Conceivably, earlier start of calcineurin therapy or early steroid withdrawal could also affect relative outcomes for rATG versus basiliximab, and the current results do not necessarily apply to different early immunosuppressive regimens.

In conclusion, this model indicates that rATG provides a modest increase in the number of QALYs with lower long-term costs than basiliximab when used as induction therapy in deceased-donor kidney transplant patients at high immunological risk. The cumulative treatment cost was higher with rATG versus basiliximab during the first year post-transplant, but was projected to become increasingly lower thereafter, driven by a reduced rate of graft failure and return to dialysis.

Authorship

LC, RV, TB, MW, NZ, and FT: Provided data and/or medical input to the analysis. GM and TP: Undertook the economic analyses. MG: Assisted with protocol development and with analysis and interpretation of findings.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article:

Figure S1. Overview of the Markov model.

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