Health Economic Analysis of Rabbit Antithymocyte Globulin versus Basiliximab in Renal Transplantation – a German perspective

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INTRODUCTION:

Use of induction regimens in kidney transplantation to prevent organ rejection has significantly contributed to the success of cadaveric kidney transplantation in Germany. However, there remain limited assessments of the economic consequences of induction regimens. The current study was designed to quantify health care resources, costs and health outcomes of kidney transplant patients receiving anti-thymocyte globulin versus basiliximab. The study combined a 12 month follow-up of transplant patients[1,2] with a 10-year Markov model of costs and health outcomes.

BACKGROUND:

- Kidney transplantation has evolved to become the most proven, safe and effective therapeutic modality for end stage renal disease (ESRD). A major cost of transplantation is the induction regimens. As different therapies are available for induction, cost effectiveness analysis may be used to inform choice in this clinical setting.
- In the kidney transplant setting, cost effectiveness analysis should consider drug costs as well as costs associated with the use of induction regimens, including their effects on delayed graft function, rejection, infection, graft failure and return to dialysis. It should also consider impact to quality of life and patient survival.
- Induction with anti-thymocyte globulin (Thymoglobulin®), a lymphocyte-depleting polyclonal antibody that targets multiple immunologic epitopes and, as a result, is associated with delay in the time to initial rejection, reduction in the frequency of steroid-resistant rejection episodes, and improved graft survival compared with conventional regimens, including cyclosporine. Basiliximab (Simulect®) is a chimeric (murine/human) recombinant monoclonal antibody (IgG_{1k}) that competitively inhibits IL-2-mediated activation of lymphocytes, a critical pathway in the cellular immune response involved in allograft rejection.
- To date, limited health economic assessments have assessed the costs and health benefits of anti-thymocyte globulin and basiliximab induction agents. The current study was designed to provide a health economic perspective associated with varying treatment strategy.

OBJECTIVE:

- The goal of this non-interventional study is to quantify the costs and health outcomes of cadaveric kidney transplantation using anti-thymocyte globulin versus basiliximab as induction therapy. Costs and health outcomes occurring within 12 months of transplant are estimated using the Brennan database[1] and supplemented with data from 3 German hospitals. Costs and health outcomes predicted to occur in the following decade are estimated based on a Markov model and literature-derived estimates for cost, utility scores (QoL) and clinical outcomes.
- Health economic analyses included drug costs as well as costs associated with avoidance of acute post-transplant graft failure, reduction in use of dialysis and dialysis costs, improved quality of life, improved survival and other cost-benefits.

METHODS: DATA COLLECTION, MODELING AND STATISTICAL ANALYSIS

- This health economic study analyzed the Brennan[1,2] et al study database. The study population included patients aged ≥ 18 years diagnosed with chronic renal failure who underwent cadaveric kidney transplantation and received either thymoglobulin or basiliximab induction regimens. The original SAS database from the Brennan study was used as source clinical information to estimate treatment costs during the 365 days following transplantation.
- Demographic characteristics of the two treatment groups were compared using Chi Square and Student's t tests. The incidence of delayed graft function, graft failure and death within 365 days of transplantation were compared using Chi Square. Because the numbers of rejection episodes and infections experienced per patient were determined to be not normally distributed by Kolmogorov D, comparisons were made using Wilcoxon rank sum.
- Treatment costs incurred within 365 days of transplantation were estimated by applying mean internal hospital costs from three German centers to counts of: mild, moderate and severe cellulitis, urinary tract infection, sepsis, upper respiratory infection, pneumonia, nephritis, oral cavity and intra-abdominal infection; antibody-treated, other confirmed and suspected rejection episodes; and graft failure events with and without nephrectomy.
- Health economic modeling to determine cost-effectiveness was conducted using a 4-state Markov model with the following 3 cohorts: transplant patients receiving anti-thymocyte globulin, transplant patients receiving basiliximab, and ESRD patients who do not receive a transplant and instead remain on dialysis. In the model, patients are predicted to transition between 4 heath states: never transplanted, alive with functioning graft, alive following graft failure, and deceased. The model makes several simplifying assumptions, including that patients with graft failure never receive a second transplant, and that only one health state transition (dialysis to death, functioning graft to failed graft, functioning graft to death, graft failure to death) may occur each year.

References:

1. Brennan DC, Daller JA, Lake KD et al. Rabbit Antithymocyte Globulin versus Basiliximab in Renal Transplantation/ N Engl J Med 2006; 355:1967-1977. ***2.*** Brennan DC, Schnitzler MA. Long-Term Results of Rabbit Antithymocyte Globulin and Basiliximab Induction. N Engl J Med 2008; 359:1736-8. ***3.*** US Renal Data (USRD) . http://www.ajkd.org/issue/S0272-6386(15)X0014-X. ***4.*** Icks A, Haastert B, Gandjour A, et al. Costs of dialysis – a regional population-based analysis. Nephrol Dial Transplant 2010; 25:1647–52. ***5.*** Matas AJ, Schnitzler M. Payment for living donor (vendor) kidneys: a cost-effectiveness analysis. Am J Transplant 2004; 4:216-21. ***6.*** von der Schulenburg JM, Greiner W et al. German Recommendations on Health Economic Evaluation: Third and Updated Version of the Hanover Consensus. International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 2008.

- The following estimates based on US Renal Data System data[3] were used to model health state transitions: dialysis patients on the transplant wait list face a 5.6% annual risk of death; patients with a functioning graft face a 2.1% annual risk of death; patients with a failed graft face a 12.3% annual risk of death. Patients with a functioning graft were assumed to face a 1.1% annual risk of nonfatal graft failure.[2]
- The following estimates were assigned as treatment costs: Patients awaiting transplant and those with graft failure incur annual dialysis costs of € 54,777[4]. Based on data from the study centers costs were estimated based on hospital tariffs and utilization estimates, 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.
- To calculate cost/quality-adjusted life year (Cost/QALY), a common health economic metric, utility scores were obtained from the literature. Utility values range from 0-1, 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 on dialysis[5].
- 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 QALYs were assumed, consistent with German guidelines[6].
- All site specific data were de-identified. No Ethics Committee approval was required for this study.

RESULTS:

- Using the published Brennan data at 12 months, the incidence of the composite end point was similar in the two groups (P = 0.34). The anti-thymocyte globulin group, as compared with the basiliximab group, had significantly lower incidences of acute rejection (15.6% vs. 25.5%, P =0.02) and of acute rejection that required treatment with antibody (1.4% vs. 8.0%, P = 0.005).
- The anti-thymocyte globulin group and the basiliximab group had similar incidences of graft loss (9.2% and 10.2%, respectively), delayed graft function (40.4% and 44.5%), and death (4.3% and 4.4%) [Table 2]. Though the incidences of all adverse events, serious adverse events, and cancers were also similar between the two groups, patients receiving anti-thymocyte globulin had a greater incidence of infection (85.8% vs 75.2%, P = 0.03) but a lower incidence of cytomegalovirus disease (7.8% vs. 17.5%, P = 0.02).
- Table 3 lists treatment costs within 12 months of transplant. While induction costs associated with anti-thymocyte globulin are €5,378 greater per patient, this difference is partially offset by a reduction (€1,044) in the cost of treating rejection episodes (P=0.02). Costs of delayed graft function, nonfatal graft failure events and post-graft failure dialysis are lower among anti-thymocyte globulin-treated patients (P=NS). Infection treatment costs are nearly identical in the two groups (P=NS). Anti-thymocyte globulin-treated patients incurred higher graft maintenance costs and lower post graft failure dialysis costs, consistent with their longer graft survival (P=NS). At 1 year, total estimated treatment costs were 2.6% greater for anti-thymocyte globulin- treated patients : €85,306 versus €83,144 (P<0.01).
- Cumulative incremental costs and QALYS are presented in Figures 1 and 2, respectively. Since fewer anti-thymocyte globulin patients return to dialysis within 12 months of transplant, long term costs are projected to be lower with anti-thymocyte globulin versus basiliximab. By the end of year 2, costs are projected to be €51,446 less for each 100 patients in the anti-thymocyte globulin cohort, with savings reaching €440,544 for each 100 patients by year 10.
- Anti-thymocyte globulin-treated patients are projected to enjoy a modest gain in total QALYs compared to basiliximab-treated patients over the 10 year model time horizon (Figure 2). The initial utility difference of 0.007 QALYs per patient grows to 0.096 QALYs by year 10.

DISCUSSION:

Based on data from Brennan[1,2] and clinical care sites in Germany, this study found anti-thymocyte globulin induction costs €5,378 more than basiliximab. However, reduced costs associated with delayed graft function, rejection episodes, nonfatal graft failure events and post-graft failure dialysis substantially reduced the cost advantage of basiliximab within 12 months .

To further evaluate differences between the two regimens we projected costs and QALYs during the subsequent decade. After 10 additional years, each anti-thymocyte globulin-treated patient is projected to enjoy an additional 0.096 QALYs versus a basiliximab-treated patient. Also after 10 years, each 100 anti-thymocyte globulin patients would cost **€59,652** less than 100 basiliximab patients.

While substantial, the differences in costs and QALYs between anti-thymocyte globulin and basiliximab pale in comparison with the overall savings achieved by substituting transplantation for a long-term dialysis regimen. According to our model, dialysis costs €91,284 per QALY gained, transplantation with basiliximab costs €26,268 per QALY gained, and transplantation with anti-thymocyte globulin costs €25,142 per QALY gained.

Comparing anti-thymocyte globulin with basiliximab, the former is the dominant treatment choice-providing more QALYs and lower long term costs. The QALY advantage is evident within 12 months. Cost reduction occurs during year 2, and grows to approximately €440,000 for every 100 patients within a decade following transplantation.

Table 1 Patient Demographics

	Thymolglobulin (n=141)	Basiliximab (n=137)	p value
Age in Years			
Mean (SD)	50 (13)	50 (13)	
Median (q1-q3)	53 (43 - 63)	49 (40 - 61)	
Range	22 - 74	23 - 73	0.30 (a)
Race - N (%)			
White	85 (60%)	89 (65%)	
Nonwhite	56 (40%)	48 (35%)	0.43 (b)
Gender - N (%)			
Male	79 (56%)	82 (60%)	
Female	62 (44%)	55 (40%)	0.52 (b)

(a) Student's t-test
(b) Chi Square test

Table 2 Graft Events and Deaths within 12 Months of Transplant

	Thymolglobulin (n=141)	Basiliximab (n=137)	p value
Delayed Graft Function - N (%)			
Did Not Occur	84 (60%)	76 (55%)	
Occurred	57 (40%)	61 (45%)	0.49 (b)
AB Treated Rejection Episodes			
Mean (SD)	0.01 (0.08)	0.09 (0.31)	
Median (q1-q3)	0 (0 - 0)	0 (0 - 0)	
Range	0 - 1	0 - 2	<0.01 (c)
Other Rejection Episodes			
Mean (SD)	0.16 (0.52)	0.19 (0.48)	
Median (q1-q3)	0 (0 - 0)	0 (0 - 0)	
Range	0 - 4	0 - 2	0.44 (c)
Suspected Rejection Episodes			
Mean (SD)	0.07 (0.26)	0.09 (0.31)	
Median (q1-q3)	0 (0 - 0)	0 (0 - 0)	
Range	0 - 1	0 - 2	0.76 (c)
Graft Failure within 365 days - N (%)			
	128 (91%)	120 (88%)	
Did Not Occur	13 (9%)	17 (12%)	0.40 (b)
Occurred			
Deaths within 365 days - N (%)			
Did Not Occur	135 (96%)	131 (96%)	
Occurred	6 (4%)	6 (4%)	0.96 (b)

(b) Chi Square test
(c) Wilcoxon Rank Sum test

Table 3 Treatment Costs within 12 Months of Transplant

	Thymoglobulin (n=141)	Simulect (n=137)	p value
Organ Procurement			
Mean (SD)	15,190 (0)	15,190 (0)	
Median (q1-q3)	15,190 (15,190 - 15,190)	15,190 (15,190 - 15,190)	1.00 (c)
Routine Transplant Stay			
Mean (SD)	45,526 (0)	45,526 (0)	
Median (q1-q3)	45,526 (45,526- 45,526)	45,526 (45,526- 45,526)	1.00 (c)
Induction Regimen			
Mean (SD)	7,792 (0)	2,414 (0)	
Median (q1-q3)	7,792 (7,792 - 7,792)	2,414 (2,414 - 2,414)	<0.01 (c)
Delayed Graft Function			
Mean (SD)	1,526 (1,859)	1,680 (1,883)	
Median (q1-q3)	0 (0 - 3,774)	0 (0 - 3,774)	0.49 (c)
Rejection Episodes			
Mean (SD)	471 (1,428)	1,515 (3,906)	
Median (q1-q3)	0 (0 - 0)	0 (0 - 1,646)	0.02 (c)
Infections			
Mean (SD)	3,933 (5,792)	3,890 (7,914)	
Median (q1-q3)	1,586 (0 - 5,606)	1,552 (0 - 5,689)	0.15 (c)
Routine Graft Maintenance			
Mean (SD)	8,905 (1,589)	8,539 (2,406)	
Median (q1-q3)	9,348 (9,348 - 9,348)	9,348 (9,348 - 9,348)	0.34 (c)
Graft Failure Events			
Mean (SD)	471 (1,816)	620 (2,112)	
Median (q1-q3)	0 (0 - 0)	0 (0 - 0)	0.56 (c)
Post-Graft Failure Dialysis			
Mean (SD)	1,493 (7,363)	3,770 (13,778)	
Median (q1-q3)	0 (0 - 0)	0 (0 - 0)	0.53 (c)
Total 12 Months Costs			
Mean (SD)	85,306 (10,933)	83,144 (18,567)	
Median (q1-q3)	82,512 (79,408 - 86,494)	76,252 (72,478 - 82,542)	<0.01 (c)

(c) Wilcoxon Rank Sum test

Figure 1 Cumulative QALYS Per Patient

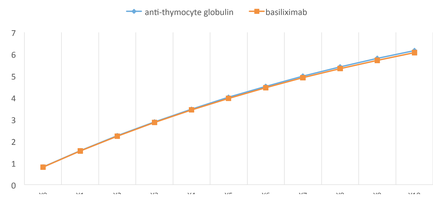
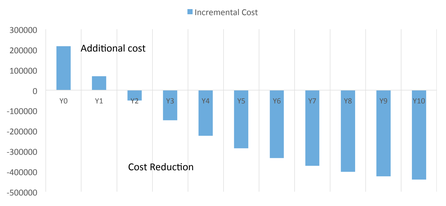


Figure 2 Cumulative Incremental cost of 100 anti-thymocyte globulin patients vs 100 basiliximab patients



CONCLUSION:

This analysis offers an important and increasingly relevant health economic perspective for patients undergoing cadaveric kidney transplant induction therapy receiving anti-thymocyte globulin compared with those receiving basiliximab with a one-year post-transplant follow-up. Health economic modeling, including cost/QALY analysis is valuable to reflect the long term cost and consequences, including the patient benefit, that may be achieved with different immunosuppressive agent intervention. As improved graft survival mitigates the growing demand for cadaveric kidneys, improved long term clinical outcomes may support healthcare institutions to realize more cost-effective care. Lastly, because funding for ESRD therapy is in the public domain, it is appropriate for healthcare institutions as well as individual countries to investigate if policy and reimbursement changes might result in more cost-effective care.

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