

Received: 2012.06.12
Accepted: 2012.08.16
Published: 2012.12.31

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

Cost analysis of kidney transplantation in highly sensitized recipients compared to intermittent maintenance hemodialysis

Ahmed Al-Jedai^{1,2}^{ABCDE}, Mohammed Alsultan³^{ABE}, Khalid Almeshari⁴^{ADE},
Khalid Alshaibani⁵^{AE}, Hazem Elgamal⁴^{BE}, Delal Alkortas¹^{BE}, Fowad Khurshid³^{BE},
Mai Altalhi⁴^{BE}, Khaled Hamawi⁵^{ABCDE}

- ¹ Division of Pharmacy Services, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
- ² College of Medicine, Alfaisal University, Riyadh, Saudi Arabia
- ³ Pharmacoeconomics and Outcomes Research Unit, Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
- ⁴ Department of Kidney and Pancreas Transplantation, Organ Transplant Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
- ⁵ Multi Organ Transplant Center, King Fahad Specialist Hospital, Dammam, Saudi Arabia

Summary

Background:

Kidney transplantation in allosensitized recipients has recently increased. Studies performing cost analysis of desensitization protocols are scarce.

Material/Methods:

We performed an actual cost comparison between kidney transplantation following desensitization and maintenance hemodialysis. Group A (n=35) consisted of allosensitized recipients who underwent desensitization using immunoadsorption and/or plasmapheresis, intravenous immunoglobulin and anti-CD20 antibody who were followed for ≥ 2 years. Group B (n=49) consisted of matched patients who remained on hemodialysis throughout the study period. Actual costs of donor care, surgical procedures, out-patient visits, in-hospital admissions, medications, hemodialysis, immunoadsorption, plasmapheresis, and laboratory and radiology investigations were calculated. Health care services were provided by a single institution.

Results:

Mortality rate was similar between both groups. The average 4-year actual total cost was \$210,779 in group A and \$317,186.3 in group B; respectively (p=0.017). Average total cost per patient in group A was \$186,608; \$14,233; \$5,536; \$4,402 in the first, second, third and fourth years after transplantation respectively while the average total annual cost per patient in group B was \$79,296. The total cost in both groups became equal by month 31. The predicted annual cost savings in group A after 31 months was \$33,943.

Conclusions:

Despite using costly desensitization protocols, kidney transplantation in sensitized patients provides long-term cost savings compared to maintenance hemodialysis.

Key words:

allosensitization • cost analysis • desensitization • financial analysis • positive cross-match kidney transplantation

Full-text PDF:

<http://www.annalsoftransplantation.com/fulltxt.php?ICID=883698>

Word count:

3638

Tables:

5

Figures:

1

References:

42

Author's address:

Khaled Hamawi, King Fahad Specialist Hospital – Dammam, PO Box 15215, MBC# 067, Dammam 31444, Saudi Arabia, e-mail: Khaled.Hamawi@asu.edu

BACKGROUND

Kidney transplantation has become the treatment of choice for patients with stage V chronic kidney disease [1,2]. Transplantation provides superior patient survival and quality of life and is more cost effective when compared to intermittent maintenance hemodialysis [3–5]. The number of kidney transplantation surgeries across the globe has markedly increased in recent years and is associated with significant improvement in short- and long-term outcomes as a result of advances in medical skills, immunosuppressive medications and overall health care [6,7]. Most kidney transplant recipients have negative cross-match with potential donors and can undergo transplantation successfully if no other medical or surgical contraindications are present. On the other hand, a positive cross-match was considered an absolute contraindication for kidney transplantation. Transplanting a renal allograft to a recipient who has donor-specific anti-HLA antibodies with positive cross-match can result in a catastrophic outcome and immediate allograft rejection [8–11]. Sensitized kidney transplant candidates from previous transplants, blood transfusions or multiple pregnancies have the longest waiting time on the deceased donor waiting list and are less likely to receive a transplant [12,13]. These patients wait on average twice as long to receive an allograft compared to non-sensitized candidates [10].

Organ shortage is one of the greatest challenges facing the transplant community, and has led transplant programs to perform kidney transplantation across HLA antibodies from living or deceased donors.

In recent years, major transplant centers around the world have adopted innovative protocols trying to overcome the HLA antibody barrier and to perform kidney transplantation in sensitized recipients. Most desensitization protocols consist of highly specialized and expensive pre-conditioning modalities, including various combinations of antibody-depleting agents (eg, Rituximab, Antithymocyte globulin), intravenous immunoglobulin, total plasma exchange, or immunoadsorption and splenectomy. These protocols permitted kidney transplantation in highly sensitized subjects with relatively good short-term outcomes [14–18]. However, the rate of antibody-mediated rejection (AMR) following desensitization is significantly higher than in non-sensitized patients; many recipients require treatment of AMR with

total plasma exchange, high-dose intravenous immunoglobulin, and rituximab [19–26]. In addition, highly sensitized recipients need close monitoring with frequent office visits, surveillance allograft biopsies and anti-HLA antibodies monitoring. The use of rather expensive medications, procedures, laboratory investigations and close follow-up adds to the cost of standard negative cross-match kidney transplantation.

While kidney transplantation has been shown to be cost effective for patients with stage V chronic kidney disease; there is insufficient data to show cost effectiveness of kidney transplantation in highly sensitized patients compared to intermittent maintenance hemodialysis. Short-term outcomes of kidney transplantation in highly sensitized candidates are acceptable, although long-term outcomes data is limited. With the rise in health care costs and the increased number of kidney transplantation surgeries in highly sensitized recipients worldwide, cost analysis of various desensitization protocols becomes important, knowing that long-term outcomes of kidney transplantation in this setting are limited.

The aim of this single-center study was to perform an analysis of the actual health care cost of kidney transplantation in recipients with positive cross-match, and to compare it to the cost of a matched group of hemodialysis patients who remained on hemodialysis throughout the study period.

MATERIAL AND METHODS

Settings

The health care system in Saudi Arabia is a national system in which the government provides health care services to all citizens through different health care sectors. King Faisal Specialist Hospital and Research Center (KFSH&RC) is the main tertiary care institution in the Kingdom of Saudi Arabia. The kidney transplant program at KFSH&RC was launched in 1981 and currently performs more than 170 kidney transplants annually [27]. We have previously reported our program description and transplant protocols [28]. All potential renal transplant candidates undergo a comprehensive medical, psychological and social evaluation prior to transplant surgery. Primary and post-transplant care is delivered to kidney transplant recipients exclusively at KFSH&RC. The hospital has one of the largest out-patient dialysis centres in the country and

provides all health care services to end-stage renal disease (ESRD) patients.

Patients and materials

Group A (n=35) consisted of all renal transplant candidates who had a positive cross-match with their prospective donor and who underwent desensitization using immunoadsorption and/or plasmapheresis, high dose immunoglobulin, anti-CD20, and polyclonal antibodies induction. Group B (n=49) consisted of patients who received HD during the same period of time. Hemodialysis patients were matched for age, sex and weight and remained on hemodialysis throughout the study period. All patients had at least 2-year follow-up. All health care related services for both groups during the study period were provided solely by this institution.

Actual healthcare costs for group A was calculated for all surgical procedures, out-patient visits, hospital admissions, medications, hemodialysis, immunoadsorption, plasmapheresis, laboratory and radiology investigations, including the pre-transplant evaluation period. Donor costs were added to recipients' first year total cost, including donor evaluation from the time of referral. In group B, the costs of hemodialysis sessions, laboratory, radiology, hospital admissions, clinic visits, all surgical interventions, and medications were included.

Cost calculations

We used hospital costs, not charges, to complete this analysis. A financial analyst performed current cost calculations for all procedures, including plasmapheresis, immunoadsorption, hemodialysis, hospital admissions, laboratory, radiology, biopsies, and transplant surgery. Cost components used for these calculations were manpower, supplies, equipment depreciation, hospital room, transplant center, and hospital overhead. The total cost was therefore the sum of direct and indirect components. Direct costs included direct manpower, supplies, and equipment depreciation. Indirect costs included management overhead of the transplant center, operating room, and hospital administration. Cost of medications was obtained from hospital pharmacy electronic records based on direct acquisition cost and did not include indirect charges.

Using the hospital's electronic health records, we calculated costs for every patient in both groups after retrieving all hospital encounters and visits

related to plasmapheresis, immunoadsorption, hemodialysis, hospital admissions, laboratory, radiology, biopsies, and transplant surgery.

Hemodialysis

All hemodialysis patients underwent an average of 4 hours in-center treatment sessions three times a week using Fresenius machines and high-flux single-use disposable filters. Comprehensive medical care for HD patients was provided exclusively by KFSH&RC. Actual cost was calculated similar to the other group for all procedures, hospitalizations, medications and hemodialysis treatments.

Desensitization

Candidates for desensitization of living donor kidney transplantation were risk-stratified for AMR according to Complement Dependant Cytotoxicity (CDC) and flow cross-match results as follows:

1. High risk candidates: patients with positive T cell and/or B cell IgG CDC cross-match.
2. Intermediate risk candidates: patients with negative CDC cross-match but positive T and/or B cell IgG flow cross-match.

All patients had HLA donor-specific antibodies (DSA), determined by either phenotype or single antigen analysis by solid phase immunoassay (Luminex[®] Platform). High-risk patients received full desensitization treatment, which consisted of:

- Anti-CD20 antibody (Rituximab, MabThera[®] F. Hoffman-La Roche Ltd. Basel, Switzerland): single dose of 500 mg IV over 10 hours, at least 2 weeks prior to transplant.
- Immunoadsorption or plasma exchange based on availability. For plasma exchange, 1.5 plasma volumes was exchanged every other day for a total of 3–5 treatments, and albumin was used as a replacement fluid. For immunoadsorption, protein A column or Therasorb[®] system was used. Treatments were given daily for a total of 5–7 treatments.
- High-dose (2 gm/kg) intravenous immunoglobulin (IVIg) (Octagam[®], Octapharma Pharmazeutika Produktionsges.m.b.H., Austria) was administered at 100 mg/kg after completion of each plasma exchange or immunoadsorption treatments. The remaining dose of 2 gm/kg was infused over 48 hours at least 2 days before surgery.

Successful desensitization for high-risk patients was defined by abrogation of positive CDC

cross-match prior to transplantation, which was a pre-requisite for transplantation. Intermediate risk patients received single-dose Rituximab and high-dose IVIG, similar to high-risk patients but without plasma exchange or immunoadsorption. Transplantation was performed after the completion of the high-dose IVIG. Splenectomy is not part of the desensitization protocol at KFSHRC.

Immunosuppression

All highly sensitized renal transplant recipients received induction with rabbit antithymocyte globulin (Thymoglobulin® Genzyme, Cambridge, MA) 1.5 mg/kg/day, rounded off to the nearest 25 mg, intravenous infusion through a central line, arteriovenous (AV) fistula/graft, or peripheral line. The infusion of the first dose started prior to reperfusion of the renal allograft. Patients received 3–6 doses (total maximum dose of 9 mg/kg). The first 3 doses were given regardless of T-lymphocyte absolute counts or CD markers. The remaining doses were adjusted according to T-lymphocyte counts and/or CD2. Patients were pre-medicated prior to each dose of Thymoglobulin® with 25–50 mg of diphenhydramine (Major Pharmaceuticals, Livonia, MI, USA) and Acetaminophen (MAPAP®) (Major Pharmaceuticals, Livonia, MI, USA). Duration of induction was 5–10 days, with a target absolute lymphocyte count (ALC) of less than 0.2×10^9 /L or a CD2 of <20. The total number of doses was determined based on daily monitoring of the ALC, which was performed daily by manual differential on peripheral blood smear.

All patients in group A received maintenance immunosuppression therapy, consisting of 3 daily doses of methylprednisolone (Solu-Medrol®) (Pfizer Inc. NY, NY, USA) at 500, 250, and 90 mg on postoperative day 0, 1, and 2, respectively, followed by oral prednisone (Roxane Laboratories, Inc. Columbus, Ohio) at 80 mg/day, reduced by 10 mg/day until 20 mg/day is reached and continued up to 6 weeks post-transplant. After 6 weeks, prednisone was tapered down by 2.5 mg every 2 weeks until the maintenance dose of 5 mg/day was reached. Patients in group A were also started on Mycophenolate Mofetil (Cellcept® F. Hoffmann-La Roche Ltd. Basel, Switzerland) with a target dose of 2000 mg/day on POD #1, and dose was adjusted based on adverse effect profile. Tacrolimus (Prograf®), (Astellas Pharma US, Inc. Deerfield, IL, USA) was started on all highly sensitized recipients on POD #3. In patients with delayed (dialysis required within 7

days post-transplant) or slow graft function (less than 25% reduction in serum creatinine (SCr) during the first 48 hours and not requiring dialysis), tacrolimus introduction was deferred until SCr reached <300 µmol/L (3.4 mg/dl) and/or daily urine output was ≥3L. Target trough levels of tacrolimus were 12–15 ng/ml during the first 3 months post-transplant and 10–12 ng/ml thereafter. Drug monitoring was performed using the liquid chromatography-mass spectrophotometry method (LC-MS-MS).

Statistical analysis

The statistical package IBM SPSS Statistics version 20 (formerly called SPSS Advance Statistics, SPSS Inc., Chicago, Illinois) was used to analyze data. A 2-tailed paired Student's t-test was used for continuous data, and chi-square for categorical variables of both groups. Analysis of variance (ANOVA) was used to calculate difference in cost between the 3 different regimens used for desensitization. A probability of $p < 0.05$ was considered statistically significant.

RESULTS

There were a total of 35 subjects with positive cross match in group A and 49 hemodialysis patients in group B. With the exception of having being more females in group A (84%) *vs.* group B (58.7%), there was no statistically significant difference between the 2 groups ($p > 0.05$) (Table 1). Nineteen patients in group A were considered high-risk candidates and received immunoadsorption (16/19) or total plasma exchange (3/19). The rate of successful desensitization was 71.5% (25/35). Of those who achieved desensitization and underwent successful renal transplant, 7/25 (28%) had acute antibody-mediated rejection in the first year.

For group A, the total health care related cost, including the cost for patients who failed desensitization, was \$5,269,494. Average annual cost of medical care per patient after transplantation in the first, second, third and fourth year was US \$133,291, US \$14,233, US \$5,536 and US \$4,402; respectively (Table 2). During the 4 years post-transplantation, more than US \$4.6 million (88.5% of total costs) was spent in the first year only, followed by US \$355,833 (6.75%) in the second year, US \$138,405 (2.6%) in the third year and US \$110,056 (2.1%) in the fourth year (Table 2). Procedure costs were US \$1,630,884 (30.9% of total expenditure),

Table 1. Baseline patients' characteristics.

	HSP renal transplant n (%)	Hemodialysis patients n (%)	p-value
Female gender	28 (80%)	27 (55.1%)	0.026
Weight (kg, mean)	61.5	66.7	0.157
Age (yr, median)	47.0	49.5	0.21
Height (cm, mean)	155.1	159.3	0.27

Table 2. Annual Health care cost in highly sensitized transplant candidates including those who failed desensitization (group A, n=35)*.

Cost type/year	1 st year	2 nd year	3 rd year	4 th year	Total
Radiology	131,520.1	5,542.7	3,786.6	9,145.3	149,994.70
Laboratory	1,167,477.5	106,986.7	41,110.1	20,265.3	1,335,839.6
Visit	474,357.4	39,946.7	14,733.3	15,080	544,117.4
Procedures**	1,576,394.8	41,280.0	13,209.6	0,000.0	1,630,884.4
Medications	1,315,449.4	162,077.1	65,566.1	65,566.1	1,608,659
Total	4,665,199.1	355,833.2	138,405.7	110,056.7	5,269,494.7
Average total cost/patient [#]	186,607.9	14,233.3	5,536.2	4,402.3	210,779.7

* US Dollars; ** including transplant procedure; # successful desensitization (25 patients only).

followed by medication costs of US \$1,608,659 (30.5%) and laboratory cost of US \$1,335,839 (25.4%). Itemized total annual cost of transplantation procedures in highly sensitized recipients per patient is shown in Table 3. The cost of 5 sessions of immunoadsorption was US \$58,952, and single treatment with total plasma exchange was US \$3,911. Total annual cost of procedures in highly sensitized recipients per case is summarized in table 4. The cost for different desensitization protocols was different than expected. The range of first year overall cost for patients who received high-dose intravenous immunoglobulin and anti-CD20 was US \$73,002-\$170,615 per patient. The range of first year cost per patient for those who underwent immunoadsorption, high-dose intravenous immunoglobulin and anti-CD20 was US \$167,792-\$306,763, while the range of first year cost for patients who received total plasma exchange, high-dose intravenous immunoglobulin and anti-CD20 was US \$171,857-\$225,827 per patient. There was a statistically significant difference between the average cost at 1 year for patients who received only high-dose intravenous immunoglobulin and anti-CD20 *vs.* those who underwent immunoadsorption or total plasma exchange ($p=0.001$).

For group B, the extrapolated cost of all medical care for all patients for 4 years was US

\$15,542,128. The average cost of care per patient during 4 years was US \$317,186. Average annual cost of medical care per patient was US \$79,296 (Table 5). Hemodialysis cost accounted for US \$2,044,510 or 52.6% of total first year expenditure (Table 5), followed by laboratory costs (US \$704,249; 18%), and procedure cost (US \$547,964; 14%).

The average 4-year actual total cost per patient was US \$210,779 and US \$317,186.3 in group A and B; respectively ($p=0.017$). The total cost in both groups became equal in month 31 (Figure 1). The predicted annual cost savings in group A after 31 months is \$33,943.

DISCUSSION

Recent advances in transplant immunology, anti-HLA antibody detection, and the availability of newer humanized anti-lymphocytic antibodies in the era of organ shortage led to the expansion of desensitization protocols and allowed the performance of kidney transplantation in highly sensitized individuals. There are various desensitization protocols applied by different transplant programs in the United States and worldwide to overcome the anti-HLA antibodies barrier. Most of these protocols involve the use of various combinations of intravenous immunoglobulin, anti-CD20, thymoglobulin,

Table 3. Itemized cost of transplantation procedures per patient*.

Cost item	Manpower	Transplant center overhead	OR supply	Laboratory	OR equipment depreciation	Room charges	Subtotal	Hospital overhead	Total
Living donor renal transplant surgery									
\$	1,276.3	1,424.8	62.7	0.0	404.5	2,600	5,768.0	3,845	9,613.3
%	13.2	14.8	0.6	0.0	4.2	27.0	60.0	40.0	100%
Deceased donor renal transplant surgery									
\$	1,733.9	1,935.7	62.7	0.0	294.1	3,400.0	7,643.5	5,095.7	12,739
%	13.6	15.2	0.5	0.0	2.3	26.7	60.0	40.0	100%
Donor nephrectomy									
\$	957.6	1,093.6	62.7	0.0	147.5	1,800	4,219.7	2,813.1	7,033
%	13.6	15.5	0.9	0.0	2.1	25.6	60.0	40.0	100%
Kidney biopsy									
\$	238.4	266.1	362.4	68.3	45.1	0.0	990.7	660.5	1,651.2
%	14.4	16.1	21.9	4.1	2.7	0.0	60.0	40.0	100%
Liver biopsy									
\$	238.7	266.4	362.4	68.3	45.1	0.0	990.9	660.8	1,651.7
%	14.4	16.1	21.9	4.1	2.7	0.0	60.0	40.0	100%
Total plasma exchange									
\$	52.5	58.7	623.5	0.0	9.9	1,600.0	2,346.7	1,564.5	3,911.2
%	1.3	1.5	15.9	0.0	0.3	40.9	60.0	40.0	100%
Immunoadsorption									
\$	1,250.9	1,396.5	26,263.2	142.7	3863.2	2,400.0	35,371.2	23,580.8	58,952.3
%	2.1	2.4	44.5	0.2	6.6	4.1	60.0	40.0	100%

* US Dollars.

Table 4. Total Annual Cost of procedures in highly sensitized recipients per case*.

Procedure	# of procedures/year	Med cost	Hospital overhead	Total cost
Immunoadsorption (5 sessions)	22	35,371.3	23,580.9	58,952.2
Liver biopsy	35	991.0	660.7	1,651.7
Plasmapheresis (session)	13	2,346.8	1,564.5	3,911.3
Renal transplant biopsy	110	990.8	660.5	1,651.3
Renal transplant surgery (living donor)	105	5,768.1	3,845.4	9,613.4
Renal transplant surgery (deceased donor)	35	7,643.4	5,095.6	12,739.1
Donor nephrectomy	105	4,219.8	2,813.2	7,033.0
Total	416	57,331.2	38,220.8	95,552.0

* US Dollars.

total plasma exchange, immunoadsorption and splenectomy [18,23,29,30].

The results of our study show that despite the high expense of desensitization, there is a potential

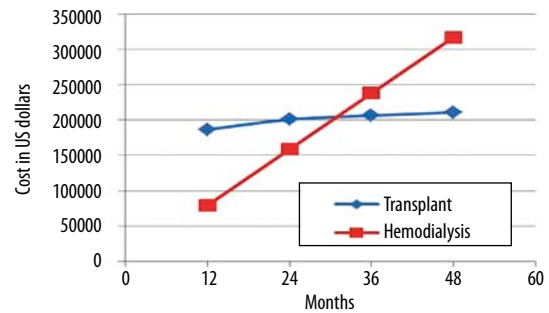
Table 5. Hemodialysis Health-Related Costs including hospital overhead (Group B $n=49$)*.

Cost type	1 st year	Total 4 year cost
Hemodialysis	2,044,510	8,178,040
Laboratory	704,249	2,816,996
Procedure	547,964	2,191,856
Visit	393,423	1,573,692
Radiology	110,286	441,144
Medications	85,100	340,400
Total	3,885,532	15,542,128
Average total cost/patient	79,296	317,186.2

* US Dollars.

health care cost savings of kidney transplantation in highly sensitized patients when compared to maintenance hemodialysis beyond 2 years. These savings are achieved even when considering failed desensitization cases. Our study shows that health care cost becomes equal at 31 months post-transplantation, with projected savings after this period. Previous studies comparing the cost of kidney transplantation to hemodialysis in non-sensitized recipients have shown similar results [31–35]. An earlier study showed that kidney transplantation was a more beneficial treatment modality than hemodialysis and reported that initial higher costs of transplantation were exceeded by hemodialysis after 2 years and 10 months [36]. Another study reported that treatment cost over the 3-year period was significantly less for transplant recipients than for patients maintained on hemodialysis, and concluded that on average hemodialysis was US \$38,900 more costly than transplantation [32].

Our cost calculation is comparable to previously published figures in Europe and other parts of the world. In Austria, Haller et al carried out a study that showed a mean annual treatment cost for hemodialysis of €43,600 during the first 12 months, €40,000 between 13 and 24 months, and €40,600 beyond 25 months after initiation of treatment. On the other hand, mean annual therapy costs for kidney transplantation during the first 12 months were €50,900 from living donor, €51,000 from a deceased donor, and mean total costs of kidney transplantation were €17,200 between 13 and 24 months, and €12,900 beyond 25 months after transplantation [33]. In Finland, Salonen et al conducted a retrospective study between January 1, 1991, and December 31, 1996,

**Figure 1.** Comparison of cumulative cost between transplant and hemodialysis over four years.

which showed direct health care costs for the first 6 months in the HD and transplant groups were US \$32,566 and US \$38,265, respectively, and US \$26,272 and US \$7,420, respectively, for the next 6 months. During subsequent years, annual costs were US \$54,140 and US \$54,490 in the HD group, and US \$11,446 and US \$9,989 in the transplant group [34]. You et al estimated the costs of patients with HD in the “Top End” of Australia’s Northern Territory for the financial years 1996/97 and 1997/98 using a hospital costing model. The average cost per routine hemodialysis treatment was US \$78,600 per patient treatment year [35]. In another study carried out in Hungary, treatment cost of transplantation per patient over the 3-year study period during 1994–1997 was US \$70,297, and concluded that although transplantation requires early investment compared with hemodialysis, cost equalizes at 12.6 months, after which the level of cumulative expenses favors transplantation [32].

It is important to note that there is a difference between cost-effectiveness and cost savings procedures. Taking patient survival and quality of life into consideration, a treatment can be cost-effective even if it translates into higher overall cost. In our study, the annual health care cost for stage V chronic kidney disease patients undergoing in-center maintenance hemodialysis 3 times per week was not significantly different during the first, second, third and fourth year of follow-up. On the other hand, the cost of kidney transplant using desensitization protocols was highest during the first year post-transplant and significantly dropped during subsequent years of follow-up. These findings were expected, knowing that most desensitization cost is incurred in the pre-transplant and the first year post-transplant period when antibody-mediated rejection usually occurs [37,38]. Most of the cost in the highly sensitized group was a result of expensive medication

regimens and procedures (plasmapheresis or immunoadsorption). On the other hand, the cost in the hemodialysis group was mainly due to hemodialysis treatments, although hospitalization constitutes a significant portion of the annual health care cost for the hemodialysis group. It is also notable that the costs of different desensitization protocols were not equal. The cost of total plasma exchange is significantly less than the cost of immunoadsorption [39]. In our study, a single treatment of total plasma exchange cost US \$3,911 (5 treatments cost about US \$19,555). In comparison, the cost of 5 sessions of immunoadsorption was US \$58,952. The higher cost of immunoadsorption is due to expensive adsorption columns. These columns can be used up to 20 times for an individual patient. Assuming that the efficacy of both modalities in removing anti-HLA antibodies is the same, and based on these findings, the use of immunoadsorption for desensitization is more plausible when more than 15 treatments of plasmapheresis are anticipated in the pre- and post-transplant course.

Although there was no difference in survival between the 2 groups, the study was not designed to examine this. Montgomery et al showed a survival benefit of transplantation in highly sensitized recipients compared to patients on the United Network of Organ Sharing (UNOS) waiting list [41].

Schwartz et al. [41] studied the economics of the use of ABO-incompatible living donors at the Mayo Clinic. Their comparison group was ABO-compatible living donor transplants. They showed that the costs were greater for ABO-incompatible patients by an average of \$37,800. In their study there was no dialysis comparison group, and the cost savings of transplant to dialysis was projected. Although kidney transplantation across the ABO and HLA barriers utilizes similar desensitization protocols, the number of plasma exchange treatments and post-operative complications may be different.

Our study is the first to directly look at the financial aspect of kidney transplantation utilizing various desensitization protocols in comparison to hemodialysis. We calculated actual health care cost and not hospital billing charges incurred at our center. Because the study subjects of both groups received all their health care at a single center, including their primary and non-transplant medical care, we were able to calculate the actual health care cost with reasonable accuracy.

This study was not designed to examine cost-effectiveness and, hence, patient/graft survival and quality of life. This is an inherent limitation, since we selected patients who survived on hemodialysis during the study time. On the other hand, the study allowed us to investigate the health care cost of hemodialysis patients and compare it to kidney transplantation in highly sensitized recipients, assuming that hemodialysis patients survived for that length of time. Health care cost of hemodialysis patients could be higher if we included end-of-life expenses. Hemodialysis patients received treatments three times a week, with an average of 4 hours per session. The cost in the hemodialysis group could be higher if more intense regimes (eg, daily nocturnal hemodialysis) are used.

This study has the limitation of any retrospective analysis. Another limitation is the exclusion of peritoneal dialysis (PD) patients. It is possible that health care cost is different in PD than HD patients. On the other hand, the majority of patients in the United States and in our center were on HD.

Of note, our study did not analyze the cost of kidney paired donation (KPD) as a valid treatment option for sensitized patients with end-stage renal disease.

Health care costs are diverse around the world. Our transplant center health care costs may not be applicable to other countries. It was notable, however, that the health care cost of HD patients in our center were comparable to the reported cost of CMS in the United States [42].

CONCLUSIONS

Despite the higher cost of desensitization procedures, kidney transplantation appears to provide cost savings over maintenance hemodialysis after 31 months post-transplantation. With increasing health care expenditure, cost-effectiveness and survival studies in highly sensitized kidney transplant recipients are needed to answer the question of whether this treatment offers not only financial benefit, but also survival advantage. Future studies should also address the potential cost difference for KPD programs.

Disclosure: Conflict of interest

The authors of this manuscript have no conflicts of interest.

Abbreviation

AMR – Antibody Mediated Rejection; **CDC** – Complement Dependant Cytotoxicity; **DSA** – Donor Specific Antibodies; **ESRD** – End Stage Renal Disease; **HD** – Hemodialysis; **IVIg** – Intravenous Immunoglobulin; **KFSH&RC** – King Faisal Specialist Hospital and Research Center; **PD** – Peritoneal Dialysis; **SCr** – Serum Creatinine; **UNOS** – United Network of Organ Sharing.

REFERENCES:

- Sayegh MH, Carpenter CB: Transplantation 50 years later – progress, challenges, and promises. *N Engl J Med*, 2004; 351: 2761–66
- Wolfe RA, Ashby VB, Milford EL et al: Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*, 1999; 341: 1725–30
- Evans RW, Manninen DL, Garrison LP Jr et al: The quality of life of patients with end-stage renal disease. *N Engl J Med*, 1985; 312: 553–59
- Port FK, Wolfe RA, Mauger EA et al: Comparison of survival probabilities for dialysis patients vs cadaveric renal transplant recipients. *JAMA*, 1993; 270: 1339–43
- Russell JD, Beecroft ML, Ludwin D, Churchill DN: The quality of life in renal transplantation – a prospective study. *Transplantation*, 1992; 54: 656–60
- Yen EF, Hardinger K, Brennan DC et al: Cost-effectiveness of extending Medicare coverage of immunosuppressive medications to the life of a kidney transplant. *Am J Transplant*, 2004; 4: 1703–8
- Marcen R: Immunosuppressive drugs in kidney transplantation: impact on patient survival, and incidence of cardiovascular disease, malignancy and infection. *Drugs*, 2009; 69: 2227–43
- Patel R, Terasaki PI: Significance of the positive crossmatch test in kidney transplantation. *N Engl J Med*, 1969; 280: 735–39
- van Kampen CA, Roelen DL, Versteeg-van der Voort Maarschalk MF et al: Activated HLA class I-reactive cytotoxic T lymphocytes associated with a positive historical crossmatch predict early graft failure. *Transplantation*, 2002; 74: 1114–19
- Terasaki PI, Ozawa M, Castro R: Four-year follow-up of a prospective trial of HLA and MICA antibodies on kidney graft survival. *Am J Transplant*, 2007; 7: 408–15
- Terasaki PI, Ozawa M: Predicting kidney graft failure by HLA antibodies: a prospective trial. *Am J Transplant*, 2004; 4: 438–43
- Gebel HM, Bray RA, Nickerson P: Pre-transplant assessment of donor-reactive, HLA-specific antibodies in renal transplantation: contraindication *vs.* risk. *Am J Transplant*, 2003; 3: 1488–500
- Zhou YC, Cecka JM: Sensitization in renal transplantation. *Clin Transpl*, 1991: 313–23
- Glantz D, Antoine C, Julia P et al: Desensitization and subsequent kidney transplantation of patients using intravenous immunoglobulins (IVIg). *Am J Transplant*, 2002; 2: 758–60
- Hiesse C, Kriaa F, Rousseau P et al: Immunoabsorption of anti-HLA antibodies for highly sensitized patients awaiting renal transplantation. *Nephrol Dial Transplant*, 1992; 7: 944–51
- Jordan SC, Vo A, Bunnapradist S et al: Intravenous immune globulin treatment inhibits crossmatch positivity and allows for successful transplantation of incompatible organs in living-donor and cadaver recipients. *Transplantation*, 2003; 76: 631–36
- Thielke J, DeChristopher PJ, Sankary H et al: Highly successful living donor kidney transplantation after conversion to negative of a previously positive flow-cytometry cross-match by pretransplant plasmapheresis. *Transplant Proc*, 2005; 37: 643–44
- Jin Q, Liu H, Song LY et al: Protein A immunoabsorption therapy in the highly sensitized kidney transplant candidates. *Chin Med J (Engl)*, 2011; 124: 780–82
- Montgomery RA, Zachary AA, Racusen LC et al: Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. *Transplantation*, 2000; 70: 887–95
- Tanriover B, Wright SE, Foster SV et al: High-dose intravenous immunoglobulin and rituximab treatment for antibody-mediated rejection after kidney transplantation: a cost analysis. *Transplant Proc*, 2008; 40: 3393–96
- Kaposztas Z, Podder H, Mauiyyedi S et al: Impact of rituximab therapy for treatment of acute humoral rejection. *Clin Transplant*, 2009; 23: 63–73
- Faguer S, Kamar N, Guilbeaud-Frugier C et al: Rituximab therapy for acute humoral rejection after kidney transplantation. *Transplantation* 2007; 83: 1277–80
- Jordan SC, Vo AA, Toyoda M et al: Post-transplant therapy with high-dose intravenous gammaglobulin: Applications to treatment of antibody-mediated rejection. *Pediatr Transplant*, 2005; 9: 155–61

24. Wadstrom J, Gannedahl G, Bersztel A et al: Successful kidney transplantation after suppression of HLA alloantibodies with intravenous immunoglobulin in a highly sensitized patient. *Transplant Proc*, 1995; 27: 3463-64
25. Tyan DB, Li VA, Czer L et al: Intravenous immunoglobulin suppression of HLA alloantibody in highly sensitized transplant candidates and transplantation with a histoincompatible organ. *Transplantation*, 1994; 57: 553-62
26. Glotz D, Haymann JP, Sansonetti N et al: Suppression of HLA-specific alloantibodies by high-dose intravenous immunoglobulins (IVIg). A potential tool for transplantation of immunized patients. *Transplantation*, 1993; 56: 335-37
27. Al-Meshari K, Al-Shaibani K, Hamawi K et al: The Kidney Transplant Program at King Faisal Specialist Hospital and Research Center. *Clin Transpl*, 2005: 119-29
28. Simon DG: A cost-effectiveness analysis of cyclosporine in cadaveric kidney transplantation. *Med Decis Making*, 1986; 6: 199-207
29. Bohmig GA, Wahrmann M, Regele H et al: Immunoabsorption in severe C4d-positive acute kidney allograft rejection: a randomized controlled trial. *Am J Transplant*, 2007; 7: 117-21
30. Glotz D, Antoine C, Julia P et al: Intravenous immunoglobulins and transplantation for patients with anti-HLA antibodies. *Transpl Int*, 2004; 17: 1-8
31. Jordan S, Cunningham-Rundles C, McEwan R: Utility of intravenous immune globulin in kidney transplantation: efficacy, safety, and cost implications. *Am J Transplant*, 2003; 3: 653-64
32. Kalo Z, Jaray J, Nagy J: Economic evaluation of kidney transplantation versus hemodialysis in patients with end-stage renal disease in Hungary. *Prog Transplant*, 2001; 11: 188-93
33. Haller M, Gutjahr G, Kramar R et al: Cost-effectiveness analysis of renal replacement therapy in Austria. *Nephrol Dial Transplant*, 2011; 26: 2988-95
34. Salonen T, Reina T, Oksa H et al: Cost analysis of renal replacement therapies in Finland. *Am J Kidney Dis*, 2003; 42: 1228-38
35. You J, Hoy W, Zhao Y et al: End-stage renal disease in the Northern Territory: current and future treatment costs. *Med J Aust*, 2002; 176: 461-65
36. Loubeau PR, Loubeau JM, Jantzen R: The economics of kidney transplantation versus hemodialysis. *Prog Transplant*, 2001; 11: 291-97
37. Mauiyyedi S, Colvin RB: Humoral rejection in kidney transplantation: new concepts in diagnosis and treatment. *Curr Opin Nephrol Hypertens*, 2002; 11: 609-18
38. Lefaucheur C, Nochy D, Hill GS et al: Determinants of poor graft outcome in patients with antibody-mediated acute rejection. *Am J Transplant*, 2007; 7: 832-41
39. Schwenger V, Morath C: Immunoabsorption in nephrology and kidney transplantation. *Nephrol Dial Transplant*, 2010; 25: 2407-13
40. Montgomery RA, Lonze BE, King KE et al: Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med*, 2011; 365: 318-26
41. Schnitzler MA, Lentine KL, Burroughs TE: The cost effectiveness of deceased organ donation. *Transplantation*, 2005; 80: 1636-37
42. U.S. Renal Data System, *USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010