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Primary Adult Liver Transplantation Under Tacrolimus: More Than 90 Months Actual Follow-Up Survival and Adverse Events

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Abstract

The introduction of tacrolimus has shown decreased rates of acute and steroid-resistant rejection after liver transplantation (LTx). The aim of the present study is to examine the long-term efficacy and safety of tacrolimus in primary liver transplant recipients. The first 121 consecutive adults (aged >16 years) who underwent primary LTx at a single center from August 1989 to February 1990 were followed up until August 1997. The mean follow-up was 93.2 ± 1.2 months (range, 90.5 to 96.5 months). Patient survival, graft survival, rate of rejection, and adverse events were examined. The actual 7-year patient survival rate was 67.8%, and the graft survival rate was 63.6%. Infections, recurrence of disease, de novo malignancies, and cardiovascular events constituted the main causes of graft loss and death in the long term. Graft loss related to acute or chronic rejection was rare. The rate of acute rejection beyond 2 years was approximately 3% per year, and most rejections were steroid responsive. Approximately 70% of the patients received only tacrolimus after 1 year. Four patients developed end-stage renal disease, and 2 patients underwent kidney transplantation. Hyperkalemia and hypertension were observed in one third of the patients. New-onset insulin-dependent diabetes mellitus was observed in 9% and 13% of the patients at the 1-year and 7-year follow-up, respectively. Seven patients developed de novo malignancies, including two skin malignancies. Six patients developed posttransplantation lymphoproliferative disorder during the entire follow-up period. Actual patient and graft survival at 7 years was excellent, and few adverse events developed after the first year. Graft loss from acute or chronic rejection was rare under tacrolimus, and approximately 70% of the patients were steroid free on tacrolimus monatherapy after the first year after LTx.

Tacrolimus is a macrolide isolated from the soil fungus, *Tsukubaensis*. It is a potent immunosuppressive agent. The first clinical trial with tacrolimus began at our institution in March 1989, initially as rescue treatment for failing liver allo-grafts under cyclosporine (CsA).[1-3] Subsequently, its use was evaluated by Todo et al[4,5] in primary liver transplantation (LTx). Reduced episodes of acute rejection were shown by 1990.[6,7] Three large prospective randomized trials were conducted: the University of Pittsburgh,[8] the United States multicenter, and European multicenter trials comparing tacrolimus with CsA.[9-11] Significantly lower rates of rejection and steroid-resistant rejection were shown in all three trials. Little is known, however, about the long-term impact of tacrolimus in liver transplant recipients.

The present study reports the long-term results of tacrolimus-based immunosuppression in primary adult liver transplant recipients with more than 90 months of follow-up. It examines patient survival, graft survival, causes of death, causes of retransplantation, rates of rejection, treatment of rejection, baseline immunosuppression, and adverse events.

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Patients and Methods

This study includes the first 121 consecutive adults (aged >16 years) who underwent primary LTx under tacrolimus-based immunosuppression between August 1989 and February 1990, There were 68 men and 53 women with a mean age of 46.3 ± 12.3 years. Ninety-eight patients (81%) were hospital bound at the time of LTx. All patients were followed up until August 31, 1997. The mean follow-up was 93.2 ± 1.2 months (range, 90.5 to 96.5 months). The indications for LTx are listed in Table 1. Our immunosuppressive protocol has been previously described.[6-8] The doses of tacrolimus used in this initial trial were three to five times greater than the current dosages.[8-11] All palients in this population received tacrolimus, 0.15 mg/kg intravenously, on the first day and then 0.075 mglkg twice daily over 2 to 4 hours as a constant infusion.[6,7] All intravenous tacrolimus has been administered as a continuous infusion at our institution since February 1991. Oral doses were administered when a patient could tolerate oral fluids. Adjustments in tacrolimus dosage were made on an individual basis, depending on the state of renal and liver function and the presence of rejection, infection, and neurotoxicity. The first 53 patients received 1 g of methylprednisone after perfusion of the liver, followed by a total of 600 mg of methylprednisone tapered over the next 5 postoperative days, starting with 200 mg on the first day (divided into four doses) and reduced to 40 mg/d over the next 4 days. The remaining 68 patients received only 20 mg of methylprednisone.[6, 7].

The diagnosis of rejection was determined by an increase in serum bilirubin and hepatic enzyme levels in the absence of any technical complication, ischemic injury, or development of hepatitis (hepatitis B, hepatitis C, or cytomegalovirus). All patients also underwent protocol liver biopsies between postoperative days 10 and 14.[6-8,11] Episodes of acute rejection were treated with 1 g of hydrocortisone or 1 g of methylprednisone with or without 600 mg of methylprednisone tapered over the next 5 days. Steroid-resistent rejections were treated with OKT3, 10 mL, over 5 to 7 days.

Results

Patient and graft survival rates are shown in Figure 1. Mortality was more prominent in the first year after LTx. Thereafter, it averaged 3% every year, with an actual patient survival rate of 67.8% and graft survival rate of 63.6% at 7 years. Causes of death are shown in Table 2. Infection was the most common cause of death, particularly during the first year. Thereafter, recurrence of disease, de novo malignancies, and cardiovascular events constituted important causes of death. In 2 patients, the cause of death could not be established; both died suddenly and unexpectedly at home with normal liver function.

Causes for Retransplantation

Twenty patients lost their first graft and underwent a second transplantation. Seven patients required a third transplant, and 2 patients needed a fourth transplant. Primary nonfunction, hepatic artery thrombosis, and recurrence of disease were the most common indications for retransplantation (Table 3).

Rate of Rejection

The highest incidence of rejection occurred in the first 3 months after LTx. The rates of rejection, as listed in Table 4, progressively decreased over time from 45% in the first 3 months to 18% from 3 to 12 months, 13% in the second year, and 2% per year after the second year.

Fifty-four episodes of rejection requiring treatment occurred between 3 and 84 months after LTx in 52 patients. These episodes were controlled with l-g boluses of methylprednisone in 42 instances (78%) and l-g boluses of hydrocortisone in 12 instances (22%). One patient also

received OKT3. Two primary grafts were lost because of acute and chronic rejection. Three second transplants were lost because of acute rejection in 1 patient and chronic rejection in 2 patients during the entire study period.

Liver Function

Liver function test results in all surviving patients were stable. The mean serum bilirubin, alanine aminotransferase, aspartate aminotransferase, gama glutamyl transferase (GGT), and alkaline phosphate levels at each year are shown in Table 4.

Maintenance of Immunosuppression

Tacrolimus—The mean tacrolimus dose was less each year and decreased from 0.15 mg/kg/d during the first year to 0.04 mg/kg/d at vear 7. Similarly, mean plasma tacrolimus trough concentrations were 0.76 ng/mL at 1 year and 0.5 ng/mL at 4 years. Since August 1994, we measured trough whole-blood tacrolimus concentrations, and mean concentrations were 8.8, 6.4, and 6.2 ng/mL at 5, 6, and 7 years, respectively (Table 4).

Cyclosporine—One patient, because of severe headaches, was switched to CsA in the first year and has remained on CsA. None of the patients received CsA and tacrolimus simultaneously.

Prednisone—Approximately 70% of the patients were maintained without prednisone. For those who received prednisone at 1 year, the dose of prednisone decreased in subsequent years. Fifteen percent of the patients were receiving greater than 5 mg/d of prednisone at 1 year, and this declined to 5% at 7 years (Table 4).

Azathioprine—Azathioprine was not used in the first year after LTx. It was used after the first year to improve renal function by reducing the dose of tacrolimus. The number of patients receiving azathioprine varied from 8 patients during the second year to 15 patients in the seventh year. At most times, more than two thirds of the patients were receiving 50 mg/d or less of azathioprine. None of the patients received more azathioprine than 100 mg/d at any time (Table 4).

Adverse Events

Nephrotoxicity—Nephrotoxicity was the most common complication of tacrolimus, as previously described. However, there was little change in the mean serum creatinine and blood urea nitrogen levels over 7 years when dialysis-dependent patients were excluded (Table 4). More than 80% of the patients had serum creatinine levels of 2.0 mg/dL or less. Two patients, however, underwent kidney transplantation for end-stage kidney disease attributable to tacrolimus toxicity at 12 and 28 months after LTx. Two other patients are currently undergOing hemodialysis.

Neurotoxicity—In this population, the initial doses of tacrolimus were three to five times greater than those currently used. Transient confusional state and tremor were common; however, these complications were not properly documented. Major neurological complications have been reported on a larger population from our institution.[12] The majority of neurotoxicity occurred in the immediate postoperative period and was dose dependent.

Hyperkalemia—As shown in Table 4, more than 50% of the patients in the first 3 years had hyperkalemia ($K^+ > 5.0$ mEq/L) requiring treatment. Approximately one third of the patients had hyperkalemia by 7 years (Table 4). In all cases, hyperkalemia was readily controlled with fludrocortisone.

Hypertension—Thirty-one percent of the patients developed new-onset hypertension, defined as the need for any hypertension medication to control blood pressure. Patients who received diuretics alone were excluded because these were administered more often for fluid retention with renal impairment at our center. In more than 75% of the patients, hypertension was controlled with a small dose of a single antihypertensive agent, usually a calcium channel blocker (Table 4).

New-onset insulin-dependent diabetes mellitus—Nine percent of the patients at 1 year and 13% of the patients at 7 years were on insulin therapy. None of these patients were known to have diabetes before transplantation (Table 4). In addition, 4 patients are currently receiving oral hypoglycemic agents.

In patients with renal impairment or hyperglycemia, there was some difference in the dosages of tacrolimus and steroids. In this population, the tacrolimus dose was usually reduced. No statistical significance, however, has been attributed to these variations.

De novo malignancies—Seven patients developed de novo malignancies, 2 of which were skin cancer (one basal cell carcinoma and another squamous cell carcinoma). Three patients developed lung cancer, 1 developed breast cancer, and 1 developed glioblastoma of the brain. The lung cancer types included one small cell, one oat cell, and one adenocarcinoma, which were diagnosed at 84, 61, and 37 months after LTx at the patient ages of 53, 49, and 67 years, respectively. These 3 patients had a history of smoking; however, 1 patient had stopped smoking 12 years before LTx.

Posttransplantation lymphoproliferative disorders—Six patients developed posttransplantation lymphoproliferative disorders (PTLDs) involving the tonsils (2 patients), colon (2 patients), liver (1 patient), and hepatic hilum (1 patient). One patient with colonic PTLD and another with hepatic hilum PTLD received three liver transplants and had a cytotoxic-positive cross-match with donor lymphocytes. Both patients died, 1 of overwhelming cytomegalovirus infection, and the other of sepsis, respectively. The other 4 patients are currently alive and disease free (Table 4).

Discussion

Introduction of CsA in the early 1980s led to major improvements in patient and graft survival, and the incidence and severity of rejection were reduced considerably.[13, 14] A more potent immunosuppressive agent, tacrolimus, has contributed to further significant reductions in the number of episodes of rejection and in the severity of rejections in liver transplant recipients.[8-11] Because many patients in randomized trials have been converted from CsA to tacrolimus in the event of rejection, it is not possible to evaluate the true incidence of improvement in patient and graft survival. However, a European multicenter randomized study[9] and a large series from our center by Todo et al[15] have shown improved patient and graft survival. The initial successes described in these initial trials appear to be sustained beyond 7 years of follow-up. Rejection rates remain low, and these episodes are readily controlled in most instances. The maintenance dose of steroids is also low, and nearly 70% of the patients are on mono therapy. Late graft losses and/or death are mostly related to a recurrence of disease (hepatitis B virus, hepatitis C virus, sclerosing cholangitis) or patient noncompliance.

In this series, all patients initially received a tacrolimus dose three to five times greater than that currently used. Long-term chronic nephrotoxicity remains a major concern; however. end-stage renal disease requiring dialysis or kidney transplantation was still less than 4% after 7.5 to 8 years of follow-up. The mean serum creatinine levels observed in this series were similar to those reported from the US Multicenter Study Group comparing CsA with tacrolimus.[16]

Hyperkalemia was observed in a significant number of patients and was readily controlled with fludrocortisone. Hypertension appeared to be less frequent and less severe clinically compared with published data on CsA.[16,17] The incidence of new-onset insulin-dependent diabetes mellitus was 13% after 7 years in the adult population. This adverse event was not observed in children.[18] Stegall et al[19] reported a 13% incidence of new-onset diabetic mellitus when using CsA. Knobler et a120 reported that 23% of the patients were hyperglycemic after LTx and found no difference between CsA- and tacrolimus-based immunotherapy. De novo malignancy rates were 5.8% in the long-term follow-up. One such report on CsA after LTx by Levy et al[21] reported de novo malignancy rates of 4.5%, with a mean follow-up of 35 months. [21] We have published a similar incidence of 5.7% in the larger population taking tacrolimus, which compares that risk with the nontransplant population matched for age, sex, and length of follow-up.[22] Six patients (5%) developed PTLD in our series, and these patients tended to receive higher doses of tacrolimus. The rate of PTLD in the larger population taking tacrolimus is 1.9% for adults and 11.4% for children, as reported from our center. [23] This rate is similar to that reported using CsA.[24]

In conclusion, the benefits of tacrolimus observed in the initial clinical trials are sustained in the long term. Approximately 70% of the patients can be maintained on monotherapy. Primary graft loss caused by either acute or chronic rejection is rare under tacrolimus-based immunosuppression. The overall toxicity of tacrolimus is not worse than that reported with CsA.

References

1. Starzl TE, Todo S, Fung JJ, Demetris AJ, Venkataramanan R, Jain AB. FK506 for liver, kidney, and pancreas transplantation. Lancet 1989;2:1000–1004. [PubMed: 2478846]
2. Fung JJ, Todo S, Jain AB, McCauley J, Alessiani M, Scotti C, et al. Conversion of liver allograft reipients with cyclosporine-related complications from cyclosporine to FK506. Transplant Proc 1990;22:6–12. [PubMed: 1689901]
3. Fung JJ, Todo S, Tzakis A, Demetris A, Jain AB, Abu-Elmagd K, et al. Conversion of liver allograft recipients from cyclosporine to FK506-based immunosuppression: Benefits and pitfalls. Transplant Proc 1991;23:14–21. [PubMed: 1703682]
4. Todo S, Fung JJ, Venkataramanan R, Todo S, Starzl TE. Early trials with FK506 as primary treatment in liver transplantation. Transplant Proc 1990;22:13–16. [PubMed: 1689886]
5. Todo S, Fung JJ, Tzakis A, Demetris A, Jain AB, Alessiani M, et al. 110 consecutive primary orthotopic liver transplantations under FK506 in adults. Transplant Proc 1991;23:1399–1404.
6. Jain AB, Fung JJ, Alessiani M, Takaya S, Abu-Elmagd K, Tzakis A, Stazl TE. Incidence and treatment of rejection episodes in primary orthotopic liver transplantation under FK506. Transplant Proc 1991;23:928–930. [PubMed: 1703354]
7. Jain AB, Todo S, Fung JJ, Venkataramanan R, Day R, Bryant J, et al. Correlation of rejection episodes with FK506 dosage, FK S06 level and steroid following primary orthotopic transplant. Transplant Proc 1991;23:3023–3025. [PubMed: 1721347]
8. Fung JJ, Eliasziw M, Todo S, Jain AB, Demetris AJ, McMichael JP, et al. The Pittsburgh Randomized Trial of Tacrolimus compared to cyclosporine for hepatic transplantation. J Am Coll Surg 1996;183:117–125. [PubMed: 8696542]
9. European FK S06 Multicentre Liver Study Group. Randomized trial comparing tacrolimus (FK506) and cyclosperine in prevention of liver allograft rejection. Lancet 1994;344:423–428. [PubMed: 7520105]
10. The US Multicenter FK506 Liver Study Group. Randomized trial comparing tacrolimus (FK506) and cyclosporine for immunosuppression in liver transplantation. N Engl J Med 1994;331(17):110–115.
11. Starzl TE, Donner A, Eliasziw M, Stitt P, Meier P, Fung JJ, et al. Randomized trialomania?: The multicenter liver transplant trials. Lancet 1995;346:1346–1350. [PubMed: 7475777]
12. Eidelman BH, Abu-Elmagd K, Wilson J, Fung JJ, Alessiani M, Jain AB, et al. CMV infection in liver transplantation under CyA of FK506. Transplant Proc 1991;23:3175–3178. [PubMed: 1721398]

13. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982;2:614–636. [PubMed: 6749635]

14. Iwatsuki S, Starzl TE, Todo S, et al. Experience in 1,000 liver transplants under cyclosporine-steroid therapy: A survival report. Transplant Proc 1988;20(suppl 1):498–504. [PubMed: 3279643]

15. Todo S, Fung JJ, Starzl TE, Tzakis A, Doyle H, Abu-Elmagd K, et al. Single center experience with primary orthotopic liver transplantation under FK506 immunosuppression. Ann Surg 1994;220:297–309. [PubMed: 7522431]

16. Porayko MK, Gonwan TA, Klintmalm GB, Weisner RH, US multicenter liver study group. Comparing nephrotoxicity of FK 506 and cyclosporine regimen after liver transplantation. Transplant Proc 1995;27:1114–1116. [PubMed: 7533358]

17. Jain AB, Fung JJ. Cyclosporine and tacrolimus in clinical transplantation. A comparative review. Clin Immunther 1996;5:351–373.

18. Reyes J, Jain A, Mazariegos G, Kashap R, Fung J. Primary liver transplantation in children under tacrolimus: 3 to 8 years actual follow-up [abstract 178]. Pediatr Transplant 1998;2:75.

19. Stegall MD, Everson G, Schroter G, Bilir B, Karrer F, Kam I. Metabolic complications after liver transplantation. Diabetes, hypercholesterolemia, hypertension and obesity. Transplantation 1995;60:1057–1060. [PubMed: 7491685]

20. Knobler H, Stagnaro-Green A, Wallenstein S, Schwartz M, Roman S. Higher incidence of diabetes in liver transplant recipients with hepatitis C. J Clin Gastroenterol 1998;26:30–36. [PubMed: 9492860]

21. Levy M, Backman L, Husber B, Goldstein A, McMillan R, Gibbs JU, et al. De novo malignancy following liver transplantation: A single center study. Transplant Proc 1993;25:1397–1399. [PubMed: 8442153]

22. Jain AB, Yee LD, Nalesnik MA, Youk A, Marsh G, Reyes J, et al. Comparative incidence of de novo nonlymphoid malignancies after liver transplantation under tacrolimus using surveillance epidemiologic end result data. Transplantation 1999;66(9):1193–1200. [PubMed: 9825817]

23. Jain A, Reyes J, Kashap A, Rohal S, Cacciareili T, McMichael J, et al. Liver transplantation under tacrolimus in infants, children, adults and seniors: Long-term results, survival and adverse events in 1000 consecutive patients. Transplant Proc 1998;30:1403–1404. [PubMed: 9636567]

24. Nalesnik M, Locker J, Jaffe A, Reyes J, Cooper M, Fung J, Stazl TE. Experience with posttransplant lymphoproliferative disorders in solid organ transplant recipients. Clin Transpl 1992;6:249–252.

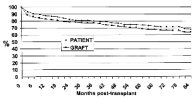

Figure 1.
Actual patient and graft survival rates over time.

Table 1

Indications for Adult Liver Transplantation

Indications	No.	%
Alcoholic cirrhosis	29	24
Hepatitis non-A non-B	19	16
Hepatitis B	15	12
Hepatitis C	12	10
Primary biliary cirrhosis	12	10
Cryptogenic cirrhosis	10	8
Sclerosing cholangitis	10	8
Miscellaneous	14	12
Primary liver malignancy	3	
Toxic hepatitis	2	
Crigler-Najjar disease	1	
Biliary atresia	1	
Secondary biliary cirrhosis	1	
Budd-Chiari syndrome	1	
Caroli’s disease	1	
Hemochromatosis	1	
Trauma	1	
Alagille syndrome	1	
Wilson’s disease	1	
Total	121	100

Table 2

Causes of Death

	Months Posttransplantation									
Causes	**0-≤3**	**>3-≤12**	**>12-≤24**	**>24-≤36**	**>36-≤48**	**>48-≤60**	**>60-≤72**	**>72-≤84**	**>84-≤96***	**Total**
Infection	5	4	2	1	2			2	1	17
Sepsis	5				2			1	1	9
Fungal		3		1				1		5
CMV		1	1							2
Protozoal-cryptococcal			1							1
Recurrent disease		1			1	2	1	1	1	7
HBV					1	2	1			4
HCV								1	1	2
HCC		1								1
Cardiovascular	1		1					2		4
Cerebrovascular	2		1							3
De novo malignancy				1	1		1			3
Noncompliance		1				1				2
Pancreatitis							1		1	2
Uremia			1							1
Retransplantation bleeding			1							1
Unknown†		1	1							2
Total	8	7	6	3	4	3	3	5	3	42

Abbreviations: CMV, cytomegalovirus; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

*Current follow-up.

†Sudden unexpected death at home.

Table 3

Causes of Retransplantation

Causes	No. of Cases		
	First Graft	Second Graft	Third Graft
Primary nonfunction	6	2	0
Hepatic artery thrombosis	4	0	2
Biliary necrosis	2	0	0
Acute rejection	1	1	0
Chronic rejection	1	2	0
Recurrence of disease	5	1	0
HCV	3		
PSC	2	1	
Portal vein stenosis	1	0	0
Lymphoproliferative disorder	0	1	0
Total	20	7	2

Abbreviations: HCV, hepatitis C virus; PSC, primary sclerosing cholangitis.

Table 4

Complete Results of the Study

	Months Post–Liver Transplantation						
	12	**24**	**36**	**48**	**60**	**72**	**84**
Survival							
Patients (%)	87.6	82.6	80.2	76.9	74.4	71.9	67.8
Grafts (%)	82.6	78.5	76.9	72.7	68.6	66.9	63.6
Patients at fisk (no.)	106	100	97	93	90	87	82
Rejection no. (%)	22 (18)*	16 (13)	4 (3)	4 (3)	2 (2)	3 (3)	1 (1)
Immunosuppression							
Tacrolimus dose (mg/kg/d)	0.15 ± 0.09	0.12 ± 0.06	0.09 ± 0.06	0.08 ± 0.06	0.08 ± 0.06	0.06 ± 0.03	0.04 ± 0.03
Tacrolimus level (ng/mL)	0.76 ± 0.5	0.73 ± 0.54	0.73 ± 0.39	0.53 ± 0.3	8.8 ± 5.9†	6.4 ± 7.3†	7.5 ± 4.5†
Prednisone dose (mg/d)							
0 (%)	72	70	64	70	62	70	74
1-5 (%)	13	17	23	19	24	21	22
6-10 (%)	11	9	10	8	9	6	4
11-20 (%)	4	4	3	3	6	4	1
Azathioprine (mg/d)							
25-50 (no.)	0	6	5	4	9	9	6
75 (no.)	0	1	1	1	3	1	1
100 (no.)	0	1	3	3	3	2	1
Liver function							
Total bilirubin (mg/dL)	0.7 ± 0.7	0.7 ± 0.3	0.7 ± 0.4	0.7 ± 0.3	0.8 ± 0.3	0.7 ± 0.3	0.8 ± 0.9
AST (U/L)	36 ± 28	56 ± 81	46 ± 46	36 ± 21	38 ± 24	36 ± 31	38 ± 22
ALT (U/L)	37 ± 28	52 ± 94	45 ± 45	38 ± 30	41 ± 31	46 ± 34	42 ± 29
GGT (U/L)	93 ± 144	154 ± 302	122 ± 225	96 ± 157	113 ± 152	87 ± 142	116 ± 162
Alkaline phosphatase (U/L)	114 ± 58	113 ± 85	118 ± 68	117 ± 72	113 ± 54	117 ± 106	119 ± 94
Renal function							
BUN (mg/dL)‡	26 ± 11	27 ± 11	26 ± 11	25 ± 5	25 ± 11	27 ± 17	24 ± 10
Creatinine (mg/dL)‡	1.6 ± 0.5	1.6 ± 0.5	1.7 ± 0.5	1.6 ± 0.4	1.6 ± 0.5	1.7 ± 0.7	1.5 ± 0.5
<1.5 (%)	49	43	42	43	55	44	58

	Months Post–Liver Transplantation						
	12	**24**	**36**	**48**	**60**	**72**	**84**
≥1.5-≤2.0 (%)	35	36	42	43	25	36	31
≥2.0-≤2.5 (%)	9	18	11	10	14	11	6
≥2.5 (%)	7	3	4	3	6	9	6
Kidney tx (total)							2
Dialysis (current)							2
Cholesterol (mg/dL)	173 ± 43	180 ± 48	181 ± 47	181 ± 46	182 ± 50	178 ± 50	196 ± 61
Hyperkalemia (K > 5.0 mEq/L)	54	56	50	43	40	33	30
Hypertension	23	24	29	23	32	31	31
Insulin-dependent diabetes mellitus	9	15	18	15	10	13	11
De novo malignancy (total)							7
Skin cancer (total)							2
Other malignancy (total)							5
PTLD (total)							6

NOTE. Bilirubin, 1 mg/dL = 17 μmol/L, SI units; BUN, 1 mg/dL = 0.357 μmol/L, SI units; creatinine, 1 mg/dL = 88.4 μmol/L, SI Units. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GGT, gamma-glutamyl transferase.

*From 3- to 12-month interval.

†Whole-blood level (level <5 calculated as 5)

‡Patients on dialysis censured from calculation.