SUPPLEMENTAL DIGITAL CONTENT (SDC)

Methods:

Early CSWD Regimen:

Exclusion criteria: Patients who had lost a previous transplant due to immunologic reasons within one year of the transplant, requiring maintenance corticosteroid therapy for other conditions (e.g., on steroids for SLE) or with donor-specific antibodies were not eligible for CSWD.

Panel reactive antibody (PRA) was determined via complement dependent cytotoxicity (CDC) assay.

Opportunistic Infection Prophylaxis:

All patients received a standard opportunistic infection prophylaxis; cytomegalovirus (CMV) prophylaxis consisted of ganciclovir (3 grams/day) or low-dose valganciclovir (450 mg/day) therapy for 6 months when the donor and/or recipient were CMV-positive prior to transplant. In cases where both donor and recipient were CMV-negative, acyclovir or valganciclovir was used for three months. All doses were adjusted based on renal function. Prophylaxis against *Pneumocystis jiroveci* consisted of sulfamethoxazole-trimethoprim 400mg/80mg daily for one year. Pentamidine inhalations or oral dapsone were substituted in patients with sulfa allergy. All patients received clotrimazole troches for the first three months after transplant to prevent oropharyngeal candidiasis.

Treatment of Acute Rejection:

All acute rejection episodes were treated with a corticosteroid pulse and maximization of maintenance immunosuppression, when applicable. Patients with borderline or Banff 1a or 1b rejections may have had prednisone added to their maintenance regimen at the discretion of their transplant physician. Banff 2a or 2b rejections were treated with rabbit anti-thymocyte globulin (rATG) or muromonab OKT3 and addition of maintenance prednisone. Patients with antibody-mediated rejection (ABMR) were treated with intravenous immunoglobulin ± plasmapheresis and rituximab and had corticosteroids reinstituted; those with concurrent cellular rejection also received rATG. When necessary, these

regimens were tailored for patient-specific factors such as concurrent polyomavirus infection or other indications.

Cardiovascular Risk Analysis:

Demographic and baseline pre-transplant characteristics such as incidence of hypertension, diabetes, and hyperlipidemia, as well as clinical laboratory markers of these diseases and number of medications used to treat hypertension and hyperlipidemia were collected. Patients were compared to their baseline laboratory values, vital signs (weight, blood pressure), and medications at 6, 12, 24, 36, 48, and 60 months after transplant to determine blood pressure control and number of anti- hypertensive medications, and presence and treatment of dyslipidemia. Incidence of new-onset diabetes mellitus (NODM) (defined as need for insulin and/or oral hypoglycemic agent for more than 1 month post-transplant) was also recorded. All laboratory, medication-requirement and co-morbidity related data (blood pressure, weight, lipid profile, etc.) was censored at the time of graft loss or when permanent corticosteroid therapy was introduced.

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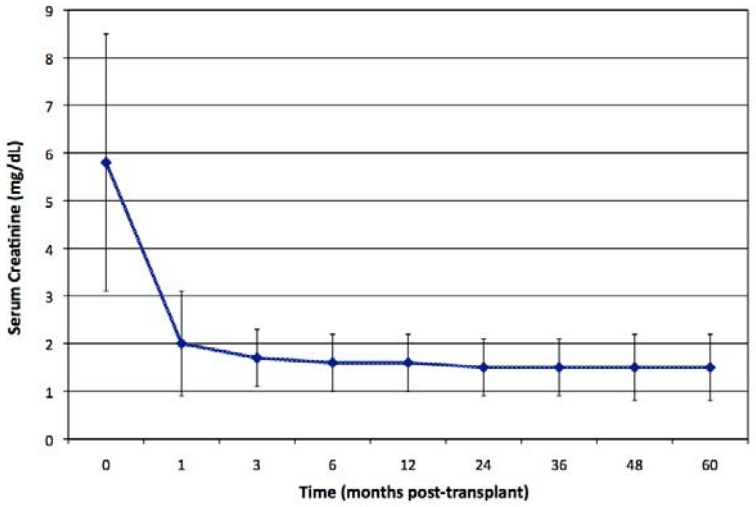
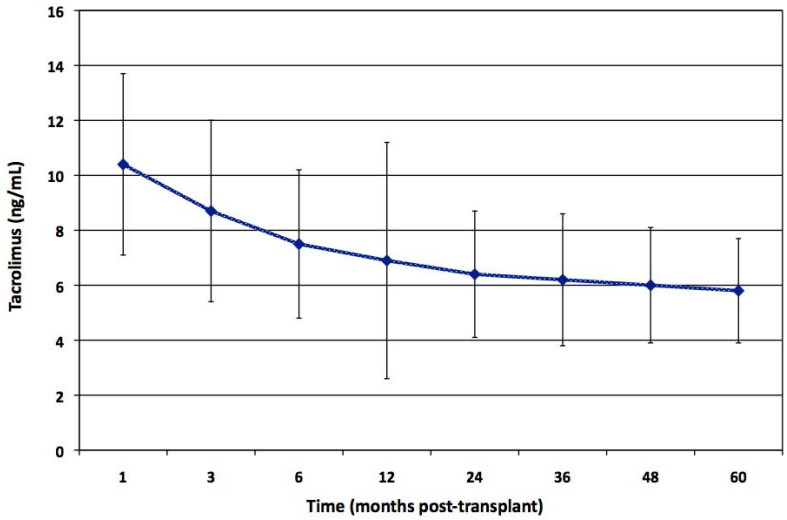
Results:

SDC Figure S1: Mean (±SD) serum creatinine (A) and tacrolimus (B) concentrations in patients managed with an early CSWD regimen and with a functioning graft through 5 years post-transplant.

A



B



SUPPLEMENTAL DIGITAL CONTENT (SDC)

SDC Table S1: Univariate Cox Proportional Hazards Model: Analysis for Risk Factors for Acute Rejection

Variable	HR	95% CI	P value
Age ≥ 60 years (vs. < 60 years)	0.378	0.205-0.698	0.002
African American (vs. non African American)	1.959	1.242-3.088	0.004
Diabetes Mellitus type 2 (yes)	0.677	0.493-0.930	0.02
Peak PRA ≥ 20% (yes)	1.656	1.027-2.670	0.04
Diabetes Mellitus type 1 (yes)	1.731		0.20
Gender (male) (vs. female)	0.748		0.24
Deceased Donor (vs. living donor)	1.218		0.40
Expanded Criteria Donor (vs. standard criteria)	1.237		0.48
DGF (yes)	1.173		0.55
Transplant number (primary vs. repeat)	0.816		0.78
DR mismatches ≥ 1 mismatch (vs. 0 mismatch)	1.062		0.85
Transplant PRA ≥ 20% (yes)	0.926		0.92
AB mismatches ≥ 1 mismatch (vs. 0 mismatch)	1.000		1.0

SUPPLEMENTAL DIGITAL CONTENT (SDC)

SDC Table S2: Univariate Cox Proportional Hazards Model: Analysis for Risk Factors for Graft Loss

Variable	HR	95% CI	P value
Acute Rejection (yes)	5.064	3.143-8.147	<0.0001
DGF (yes)	4.455	2.505-7.074	<0.0001
African American (vs. non African American)	2.499	1.575-3.965	0.0001
Deceased Donor (vs. living donor)	2.342	1.391-3.942	0.001
Peak PRA $\geq$ 20% (yes)	1.842	1.142-2.969	0.01
Transplant PRA $\geq$ 20% (yes)	2.437	0.984-6.035	0.056
Age $\geq$ 60 years (vs. < 60 years)	0.780		0.34
Diabetes Mellitus type 1 (yes)	0.523		0.37
Expanded Criteria Donor (vs. standard criteria)	0.781		0.37
Gender (male) (vs. female)	0.848		0.51
AB mismatches $\geq$ 1 mismatch (vs. 0 mismatch)	1.201		0.72
DR mismatches $\geq$ 1 mismatch (vs. 0 mismatch)	1.123		0.74
Transplant number (primary vs. repeat)	0.833		0.80
Diabetes Mellitus type 2 (yes)	1.031		0.82

SUPPLEMENTAL DIGITAL CONTENT (SDC)

Cardiovascular Risk Analysis:

Two hundred fifty eight (258) patients receiving the corticosteroid withdrawal regimen were analyzed. Data for the measures below are presented in Table S3.

New Onset Diabetes Mellitus

Of the 184 patients who did not have diabetes at the time of transplant, 13 (7.1%) developed NODM. The majority of NODM cases (n=9; 69%) were diagnosed within the first 6 months after transplant. The remaining 4 cases occurred late with two patients diagnosed between 12 and 24 months post-transplant and two patients diagnosed between 24 and 36 months. Distribution of the 13 cases of NODM between previously non-diabetic recipients of different ethnic groups included: 4/32 Hispanic (12.5%), 4/52 African American (7.7%), 4/69 Caucasian (5.8%) and 1/31 all other patients (3.2%) (p=NS).

Hypertension

Compared to baseline values, systolic and diastolic blood pressure values improved significantly after transplantation through post-transplant year 4. This improvement occurred along with significant reduction in anti-hypertensive requirements at months 6, 12, and 48, and similar anti-hypertensive requirements at other time points.

Dyslipidemia

Total cholesterol, LDL, HDL, and triglyceride values remained stable throughout the follow-up period. The number of patients prescribed a lipid-lowering agent did increase over time from pre-transplant values (35% at baseline to maximum of 58.8% at year 4).

Weight Gain

Weight gain from baseline values occurred up to 3 years after transplantation ($p<0.05$). Beginning at 4 years post-transplantation, weight was significantly lower than it had been at baseline ($p<0.05$).

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SDC Table S3: Cardiovascular Risk Analysis

Lab value/Co-Morbidity	Pre- transplant	6 mo	12 mo	24 mo	36 mo	48 mo	60 mo
Glucose (mg/dL)	110 ± 46	124 ± 55*	117 ± 54*	115 ± 48*	108 ± 46*	109 ± 54*	110 ± 43*
Total Cholesterol (mg/dL)	170 ± 47	166 ± 38	172 ± 35	163 ± 33	169 ± 39	174 ± 32	182 ± 32
LDL (mg/dL)	83 ± 36	90 ± 30	94 ± 29	89 ± 26	92 ± 32	97 ± 25	99 ± 22
HDL (mg/dL)	48 ± 17	46 ± 15	46 ± 14	47 ± 14	47 ± 13	49 ± 15	40 ± 8
Triglycerides (mg/dL)	192 ± 140	147 ± 81*	157 ± 108	142 ± 82	145 ± 75	145 ± 80	214 ± 104
Systolic blood pressure (mmHg)	146 ± 21	131 ± 19*	133 ± 19*	130 ± 15*	127 ± 13*	131 ± 18*	131 ± 12
Diastolic blood pressure (mmHg)	81 ± 12	78 ± 9*	78 ± 10*	77 ± 9*	78 ± 9*	76 ± 12*	84 ± 10
# of blood pressure medications	1.9 ± 1.2	1.6 ± 1.0*	1.8 ± 1.0*	1.7 ± 1.1	1.6 ± 1.0	1.5 ± 1.0*	1.2 ± 0.8
On lipid-lowering agent (%)	35.0%	36.1%	41.2%	53.5%	55.3%	58.8%	33.3%
Weight (kg)	78 ± 19	81 ± 19*	83 ± 21*	83 ± 24*	82 ± 21*	75 ± 14*	75 ± 13*

* $p<0.05$ compared to pre-transplant value