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Induced Immune Tolerance for Kidney Transplantation

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TO THE EDITOR

Recipients of kidney transplants require the lifelong use of immunosuppressive drugs to prevent graft rejection, but immunosuppressive medications are associated with cumulative side effects, including increased risks of heart disease, infection, cancer, and diabetes.[1] Despite maintenance immunosuppression, chronic rejection results in gradual long-term graft loss.[1] Eliminating the lifelong need for immunosuppressive medications that result in freedom from rejection remains an elusive and important goal.

The induction of immune tolerance achieved this goal in pilot clinical studies based on pre-clinical models of combined organ and hematopoietic-cell transplantation.[2–5] In the current proof-of-concept study, 12 patients who received HLA-matched kidney transplants received a donor-cell infusion of highly enriched CD34+ hematopoietic progenitor cells mixed with CD3+ T cells, and a conditioning regimen of total lymphoid irradiation and anti–T-cell antibodies according to a protocol described in detail in a previous case report of the successful induction of tolerance.[5]

Patients received a conditioning regimen of 10 doses of total lymphoid irradiation (80 to 120 cGy) targeted to the lymph nodes, spleen, and thymus, and 5 doses of rabbit antithymocyte globulin during the first 10 days after kidney transplantation. The duration of hospitalization for transplantation surgery was 4 to 7 days, and no patients were hospitalized again for viral or opportunistic infections. Donor CD34+ selected cells (5×10^6 to 16×10^6 per kilogram of body weight) and a defined dose of T cells (1×10^6 to 10×10^6 per kilogram) were injected intravenously on day 11 in the outpatient infusion center. All patients received mycophenolate mofetil (2 g per day after cell infusion) for 1 month and cyclosporine starting at day 0 for at least 6 months. Cyclosporine was discontinued 6 to 17 months after transplantation as long as chimerism persisted for at least 6 months according to short-tandem-repeat analysis of DNA from blood granulocytes and lymphocytes[5] and there was no evidence of graft-versus-host disease, clinical rejection, or rejection on microscopical assessment of surveillance biopsy specimens at the time of withdrawal.

In eight patients, antirejection drugs were discontinued, and patients were observed thereafter for at least 12 to 36 months (mean, 25) without subsequent rejection episodes (Table 1). There was no evidence of chronic rejection or graft injury according to subsequent creatinine clearances (57 to 107 ml per minute per 1.73 m^2 of body-surface area), proteinuria (<250 mg of protein per 24 hours), and histopathological scoring of tubular atrophy, fibrosis, and injury on repeat surveillance biopsies 6 to 18 months after discontinuation. Four of the patients were tested for the mixed leukocyte reaction, and all

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showed a specific unresponsiveness pattern to donor cells similar to that reported previously.[5] Patient 1, who discontinued antirejection drugs for 3 years, died suddenly while exercising, 4 months after a myocardial infarction. Four patients continued to receive immunosuppressive drugs because of the recurrence of focal segmental glomerulosclerosis in one (Patient 2) and rejection episodes during the tapering of cyclosporine in the others (Table 1). Rejection episodes were reversed with standard medications, serum creatinine levels returned to baseline, and maintenance immunosuppressive agents were resumed without evidence of graft dysfunction or chronic rejection thereafter.

In conclusion, the majority of patients were able to discontinue antirejection medications, and all patients had excellent graft function at the last observation point. We are applying the protocol to patients who were mismatched for one HLA haplotype on the basis of the safety profile of the current study.

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Table 1

Patient Characteristics and Outcomes.

Patient No.	Age	Sex	Duration of Follow-up after Transplantation	Serum Creatinine Level at Last Observation	Interval since Discontinuation of Antirejection Drugs at Last Observation*
	yr		*mo*	*mg/dl*	*mo*
1	48	M	42	1.3	36
2	39	F	68	0.9	
3	24	M	62	1.3	
4	52	M	46	1.4	28
5	34	M	44	1.2	36
6	61	F	43	1.2	
7	23	F	39	0.7	28
8	33	M	36	0.9	30
9	29	F	30	1.0	
10	52	F	29	0.9	17
11	37	F	21	1.0	14
12	36	F	18	1.4	12

* Patients for whom no months are shown continued to receive immunosuppressive drugs (Patient 2, mycophenolate mofetil and cyclosporine; Patient 3, cyclosporine alone; Patient 6, mycophenolate mofetil and tacrolimus; and Patient 9, tacrolimus alone). To convert values for creatinine to micromoles per liter, multiply by 88.4.