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## HLA-Mismatched Renal Transplantation without Maintenance Immunosuppression

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**TO THE EDITOR:** We previously reported results of our study of combined kidney and bone marrow transplantation without maintenance immunosuppression. We extended the study to include five additional patients. Here we report longer follow-up of the initial five patients and observations made after 3 years in the later cohort (Table 1). Both trials were sponsored by the Immune Tolerance Network and are currently closed to further enrollment.

The first five patients received the previously described conditioning regimen (regimen 1): cyclophosphamide, thymic irradiation, anti-CD2 monoclonal antibody, and an 8-to-14-month course of a calcineurin inhibitor.<sup>1</sup> After irreversible acute humoral rejection was observed in Patient 3, who was retrospectively found to have preformed antidonor HLA class I antibodies, the regimen was modified to include two doses of rituximab before transplantation (regimen 2). Since low levels of donor-specific antibodies developed in Patients 4 and 5, the regimen was further modified to include two additional doses of rituximab (regimen 3).

Patient 1 remained well, without rejection for more than 10 years. Patient 2 also remained rejection-free for more than 9 years, although mycophenolate mofetil was added after 7 years because of recurrence of his original disease, membranoproliferative glomerulonephritis. Kidney-allograft function remained stable for more than 7 years in Patient 4, but mycophenolate mofetil was initiated, since chronic humoral rejection was diagnosed at 5 years. Patient 5 remained rejection-free for 6 years, despite the development of low levels of donor-specific antibodies after discontinuation of immunosuppression. His most recent biopsy specimen at 6.8 years, however, showed minor transplant glomerulopathy (C4d-negative), which could indicate the incipient onset of chronic rejection.

Patients 6, 7, and 9 received regimen 3 and successfully discontinued immunosuppression. Their condition remained stable, without evidence of rejection or donor-specific antibodies,

for 3 to 4 years. Patient 8 resumed dialysis after losing kidney function due to thrombotic microangiopathy 6 months after transplantation. Immunosuppression was reinstated in Patient 10 when cellular rejection was diagnosed 2 months after withdrawal of immunosuppression. His renal function improved but remained compromised.

Although early development of donor-specific antibodies was observed, especially in the patients who received regimen 2, no donor-specific antibodies have been detected in any of the patients who received regimen 3 with intensified B-cell depletion. The risk of recurrence of original kidney disease, which occurs in patients receiving long-term immunosuppression,<sup>2</sup> could be increased if immunosuppression is withdrawn.<sup>3</sup> To overcome “the engraftment syndrome,” which causes transient renal dysfunction,<sup>4</sup> we have considered the use of low-dose total-body irradiation rather than cyclophosphamide; to our knowledge, low-dose total-body irradiation has never caused the engraftment syndrome when used in nonhuman primates.<sup>5</sup>

In conclusion, long-term, stable tolerance can be induced in a substantial proportion of treated patients despite induction of only transient chimerism by means of combined kidney and bone marrow transplantation. Results in the second group of five patients suggest that the current B-cell depletion regimen adequately controlled the development of donor-specific antibodies but that additional modifications of the treatment regimen are needed to overcome the obstacle of the engraftment syndrome.

## References

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**Table 1**

Patient Characteristics and Results of Laboratory Tests.\*

Outcome and Regimen No.	Patient No.	Time to Discontinuation of Immunosuppressive Therapy after Transplantation	Graft Survival	Duration without Immunosuppression	Pathologic Status	Current Serum Creatinine Level	Time to Appearance of Post-Transplantation Donor-Specific Antibodies Detected on ELISA	Current Immunosuppression
Long-term discontinuation of immunosuppression								
1	1	9	>10.0 yr	>9.2 yr	No rejection	1.1	Not detectable	None
1	2	14	>9.4 yr	5.8 yr	No rejection; recurrence of membranoproliferative glomerulonephritis	2.1	Not detectable	Mycophenolate mofetil after 7 yr
2	4	9	>7.7 yr	4.2 yr	Chronic rejection (after 5 yr)	1.9	1.0 yr	Mycophenolate mofetil after 6 yr
2	5	9	>6.8 yr	>6.0 yr	Early transplant glomerulopathy (after 6.8 yr)	2.3	1.7 yr	None
3	6	8	>3.8 yr	>3.2 yr	No rejection	1.5	Not detectable	None
3	7	8	>3.6 yr	>3.0 yr	No rejection	0.8	Not detectable	None
3	9	8	>3.2 yr	>2.6 yr	No rejection	1.1	Not detectable	None
No discontinuation of immunosuppression								
1	3	Not applicable	10 days	Not applicable	Acute humoral rejection	1.2 after retransplantation	10 days	Mycophenolate mofetil, tacrolimus, and corticosteroids
3	8	Not applicable	0.5 yr	Not applicable	Thrombotic microangiopathy	5-7 with dialysis	Not detectable	None after reinstitution of dialysis
3	10	Not applicable	>3.1 yr	2 mo	Acute cellular rejection	4-6	Not detectable	Dactinomycin and corticosteroids

\* ELISA denotes enzyme-linked immunosorbent assay.