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cent). Finally, we observed no treatment failures for chlamydial infection among 57 men who reported not having had sexual intercourse during follow-up.

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Angiotensin II Type 1–Receptor Activating Antibodies in Renal-Allograft Rejection

TO THE EDITOR: Dragun et al. (Feb. 10 issue)¹ provide provocative data on the role of agonistic angiotensin II type 1 (AT₁)–receptor antibodies in patients with steroid-refractory renal-allograft rejection. We were surprised by the high incidence of biopsy-proved acute rejection among their patients (43 percent), which contrasts with the 15 percent previously reported with a similar immunosuppressive protocol.^{2,3} In addition, 16 of the 33 patients with steroid-refractory rejection in the study by Dragun et al. appeared to have malignant hypertension. The median blood pressure was 153/80 mm Hg in the 10 most recent patients with steroid-refractory rejection in our medical center, only 1 of whom had signs of hypertensive encephalopathy. Finally, information about the original renal disease of the patients is lacking — a relevant point because the AT₁-receptor antibodies were probably preexistent. We recently observed that patients who had the hemolytic–uremic syndrome are prone to have vascular rejection.⁴ Moreover, AT₁-receptor antibodies have been described in other microangiopathic conditions, such as preeclampsia and malignant hypertension.⁵ We propose that the combination of vascular rejection and AT₁-receptor antibodies occurs particularly in patients who have the hemolytic–uremic syndrome or malignant hypertension as their original renal disease.

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TO THE EDITOR: The incidence of severe hypertension after renal transplantation is primarily related to the presence of malignant hypertension in the pretransplantation period.¹ The original disease influences the outcome of kidney transplantation; in particular, recipients with malignant hypertension have poorer graft survival.² No information, however, is provided in the article by Dragun et al. about the original cause of end-stage renal disease, post-transplantation antihypertensive medication, or mean blood pressure before and after transplantation. Such data would be important, since hypertension was the sole clinical factor discriminating between the two groups. It was unclear in the paper by Dragun et al. whether this entity represents a subtype of acute rejection or recurrent disease. Preformed AT₁-receptor antibodies must have been present at the time of transplantation in at least some patients in whom clinical events occurred within days after transplantation. The failure to identify low levels of anti-HLA antibodies with sensitive solid-phase assays^{3,4} as well as levels of antibodies that are non–donor-specific⁵ may have affected both the accuracy of the subsequent analysis and the conclusions, which were dependent on the stratification of patients according to these criteria.

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THE AUTHORS REPLY: Our first patient, who did not have hypertension, was the recipient of a “full-house” matched transplant with no panel reactivity. Severe vascular rejection, malignant hypertension, and seizures developed after transplantation. We were struck by the fact that she had had preeclampsia nearly two decades earlier. We detected AT₁-receptor-activating autoantibodies in this patient, treated her blood pressure, and rescued the transplant with plasmapheresis and an AT₁-receptor blocker. We next screened serum samples from all patients with steroid-refractory rejection over a four-year period for anti-HLA reactivity, donor specificity, and AT₁-receptor antibodies. We minimized selection bias by testing all serum samples for all variables. We reported reactivity against HLA antigens in both groups of patients and also indicated that determinations of AT₁-receptor antibodies were performed. Although a few patients showed moderate HLA reactivity, these antibodies lacked donor specificity, as confirmed by the results of an HLA-antigen-specific enzyme-linked immunosorbent assay.¹ C4d-negative biopsy specimens argued against intragraft adsorption of donor-specific antibodies.²

End-stage renal disease was attributed to small, contracted kidneys in eight patients, in whom no biopsy was performed before transplantation. Other causes of end-stage renal disease were autosomal dominant polycystic kidney disease, juvenile nephronophthisis, focal segmental glomerulosclerosis, chronic tubulointerstitial nephritis, and, in just one patient, well-documented hypertensive nephrosclerosis.

None had end-stage renal disease due to the hemolytic-uremic syndrome. We believe that specific causes of end-stage renal disease and the presence or absence of hypertension before transplantation were not necessarily relevant, although we cannot prove that assumption with certainty. The hemolytic-uremic syndrome clearly warrants further study.

We documented 119 rejection episodes in 83 of 279 patients during a mean (\pm SD) of 26.2 \pm 15 months of follow-up. Seventy-three patients had a first rejection within six months after transplantation, for a rejection rate of 26.2 percent, which is similar to the rates in the reports cited by the correspondents.³ Most of the patients (13 of 16) did not have hypertension before vascular rejection occurred. This finding suggests that the post-transplantation hypertension was secondary to rejection. AT₁-receptor antibodies transferred to animals that had received transplants as part of our study induced first rejection and then hypertension. We suggest that the AT₁-receptor antibodies mediated hypertension by augmenting a local intrarenal renin-angiotensin system by way of activation of AT₁ receptors in a kidney with vascular rejection.⁴ However, our study did not test the relevance of hypertension in antibody-mediated rejection — an issue that warrants further investigation.

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