Urinary-Cell mRNA Profile and Acute Cellular Rejection in Kidney Allografts


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BACKGROUND: The standard test for the diagnosis of acute rejection in kidney transplants is the renal biopsy. Noninvasive tests would be preferable.

METHODS: We prospectively collected 4300 urine specimens from 485 kidney-graft recipients from day 3 through month 12 after transplantation. Messenger RNA (mRNA) levels were measured in urinary cells and correlated with allograft-rejection status with the use of logistic regression.

RESULTS: A three-gene signature of 18S ribosomal (rRNA)-normalized measures of CD3ε mRNA and interferon-inducible protein 10 (IP-10) mRNA, and 18S rRNA discriminated between biopsy specimens showing acute cellular rejection and those not showing rejection (area under the curve [AUC], 0.85; 95% confidence interval [CI], 0.78 to 0.91; P<0.001 by receiver-operating-characteristic curve analysis). The cross-validation estimate of the AUC was 0.83 by bootstrap resampling, and the Hosmer-Lemeshow test indicated good fit (P=0.77). In an external-validation data set, the AUC was 0.74 (95% CI, 0.61 to 0.86; P=0.001) and did not differ significantly from the AUC in our primary data set (P=0.13). The signature distinguished acute cellular rejection from acute antibody-mediated rejection and borderline rejection (AUC, 0.78; 95% CI, 0.68 to 0.89; P<0.001). It also distinguished patients who received anti-interleukin-2 receptor antibodies from those who received T-cell-depleting antibodies (P<0.001) and was diagnostic of acute cellular rejection in both groups. Urinary tract infection did not affect the signature (P=0.69). The average trajectory of the signature in repeated urine samples remained below the diagnostic threshold for acute cellular rejection in the group of patients with no rejection, but in the group with rejection, there was a sharp rise during the weeks before the biopsy showing rejection (P<0.001).

CONCLUSIONS: A molecular signature of CD3ε mRNA, IP-10 mRNA, and 18S rRNA levels in urinary cells appears to be diagnostic and prognostic of acute cellular rejection in kidney allografts.