proximately 10% in critically ill patients without ESRD or AKI, 16% in the patients with ESRD, and more than 40% in the patients with AKI. In contrast to patients with AKI, ESRD status was not independently associated with mortality risk, and ICU length of stay and resource use were similar to those of the overall ICU population. ICU readmission rates, however, were approximately twice as high in both the patients with ESRD and the patients with AKI as in the general ICU population.

This study confirms and extends the findings of previous studies evaluating ICU use and outcomes in patients with ESRD.7–11 The majority of past studies were small, single-center analyses with limited inference to generalize. The only previous analysis of a large regional data set used the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme database from Great Britain.11 This analysis found patients with ESRD composed 1.3% of all 276,731 admissions to 170 adult ICUs in England, Wales, and Northern Ireland between 1995 and 2004. On the basis of the period prevalence of ESRD, the ICU use rate was approximately six admissions per 100 ESRD patient-years, a rate slightly less than half that observed by Strijack et al.6 A variety of reasons may account for this, including differences in case mix, criteria for ICU admission, and other ICU practice patterns as reflected by differences in age, frequency of nonsurgical ICU admissions, and ICU and hospital mortality rates in both general ICU and critically ill patients with ESRD. Although ESRD status was associated with an increased odds of in-hospital death (1.82; 95% confidence interval 1.13 to 1.37) in the ICNARC data set, after adjustment for demographics and case-mix factors, the odds of death (1.24; 95% confidence interval 1.69 to 1.96) were markedly attenuated, suggesting that underlying comorbidity rather than renal failure per se was the major determinant of increased mortality risk in patients with ESRD.

These data emphasize the need to include patients with ESRD in the spectrum of critical care nephrology. Patients with ESRD develop critical illness more frequently than the general population and have a greater severity of illness than those without renal disease. Moreover, patients with ESRD often present a unique set of clinical issues related to fluid and electrolyte management, mineral homeostasis, bleeding diatheses, and drug dosing that require the multidisciplinary expertise of nephrologists and critical care providers. Although renal failure seems to be, at most, only a minor contributor to the increased mortality risk associated with critical illness in patients with ESRD, the simple fact remains: Mortality in patients who have ESRD and develop critical illness is unacceptably high. To improve the care and outcomes of critically ill patients with ESRD, practitioners and investigators need to broaden the focus of critical care nephrology to include this patient population.

ACKNOWLEDGMENTS

Dr. Weisbord is supported by a Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development Service Career Development Transition Award and by Merit Review Project IIR 07-190.

DISCLOSURES

None.

REFERENCES


See related article, “Outcomes of Chronic Dialysis Patients Admitted to the Intensive Care Unit,” on pages 2441–2447.

Allograft Biopsies: Studying Them for All They’re Worth

Isaac E. Stillman*† and Martha Pavlakis†‡§

*Department of Pathology, †Renal Division, Department of Medicine, and ‡Transplant Institute, Beth Israel Deaconess Medical Center, Boston, Massachusetts; and §Harvard Medical School, Boston, Massachusetts


Advances in short-term renal allograft survival, as a result in large part of the use of calcineurin inhibitors (CNIs), have not

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Isaac E. Stillman, Department of Pathology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215. Phone: 617-667-4344; Fax: 617-667-7120; E-mail: istillm@bidmc.harvard.edu

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translated into increased organ longevity. For decades, researchers have tried to uncover the pathogenesis of chronic graft failure using histopathologic examination of human biopsies. Despite these efforts, biopsy evaluation in the setting of chronic graft failure is often a frustrating experience for nephrologist and nephropathologist alike. There is consensus that the most frequent biopsy findings in long-term graft failure (censored for death) result from cumulative injuries to the graft, which produce a pathologic pattern of scarring involving all renal compartments. Controversy over the term used to describe these findings (chronic allograft nephropathy versus interstitial fibrosis and tubular atrophy (IF/TA) is less important than the recognition that the dominant changes seen by routine microscopy represent a nonspecific common injury pathway, not a diagnosis, and that in most of those biopsies we lack the ability to determine the underlying cause.

There are many reasons for this imprecision, such as preexisting structural damage, the effects of comorbid conditions, and the structure/function interdependence of the renal compartments. Furthermore, comparisons across time and place are limited by the fact that every biopsy bears the imprint of the patient’s individual immunosuppression protocol. Nevertheless, significant progress has been made in identifying many of the underlying processes, and donor age and chronic CNI toxicity both emerge as major nonimmunologic factors. Dissecting the histopathology of these two processes from other causes of chronic injury, as well as from each other, is difficult, particularly in an individual biopsy. The pathology of chronic CNI toxicity is well defined in healthy rodents and typified by medullary ray (“striped”) fibrosis and arteriolar hyalinosis; however, the specificity of these lesions in human allograft biopsies is extremely limited, because these changes are commonly seen in diabetes, hypertension, hyperlipidemia, and renovascular disease.

Findings on implantation biopsies show promise as a predictive tool for clinical outcomes. Our group previously showed that a limited and hypothesis-driven PCR-based transcriptional profile of the 0-h kidney biopsy predicts early post-transplantation clinical outcomes, including delayed graft function, early acute rejection, and the quality of renal function 6 mo after transplantation. It is known that age increases susceptibility to CNI toxicity, but implantation biopsies may be of limited use in predicting long-term outcomes, especially in elderly donors. Better methods must be applied to all biopsies if we are to understand fully what they are showing us.

P-glycoprotein (PGP; synonyms include MDR1 and ABCB1), an energy-dependent, polyspecific efflux pump, has emerged from the study of multidrug resistance. PGP, a member of the ATP-binding cassette protein family, confers protection by both reducing cytoplasmic drug levels and blocking apoptotic pathways and is expressed in numerous normal tissues, particularly those functioning as epithelial and endothelial barriers. Renal PGP expression is most often seen in the proximal tubules, particularly along the brush border. Long-term cyclosporine (CsA) administration leads to PGP overexpression; in addition, supra-therapeutic concentrations of CsA competitively inhibit PGP activity, suggesting mechanisms for CsA toxicity. Koziolek et al. performed the first major study of PGP expression in allograft biopsies taken under a variety of conditions. Ischemia alone was found to induce reversibly intracellular redistribution of PGP. CsA treatment was associated with increased PGP expression in biopsies showing acute tubular necrosis and acute or chronic transplant rejection, but PGP was not increased in patients with CsA nephrotoxicity. This suggests CsA induces its own detoxification by upregulating PGP and that when upregulation is inadequate, nephrotoxicity results. Interestingly, the authors also noted intranidividual variability in endothelial and tubular PGP. CNIIs have a narrow therapeutic index, yet development of toxicity is variable, even at similar blood levels, suggesting differences in individual susceptibility and the importance of local rather than systemic concentrations.

CsA and tacrolimus are generally thought to display comparable incidence and mechanisms of nephrotoxicity, although the data supporting both assumptions are incomplete. Study of PGP expression in allograft biopsies show no differences in distribution of PGP between the two drugs, although intensity is significantly lower in the CsA group, in which CAN is significantly worse. Single-nucleotide polymorphisms in the CYP3A and MDR1 genes are associated with higher blood concentrations of CNIs. A recent prospective study with a homogeneous population found that, at comparable CsA exposure, carriers of the allelic variants in ABCB1 exon 21 or 26 were at increased risk for CsA-related adverse events, although donor genes were not evaluated and there were no biopsy correlations.

The prospective study published in this issue of JASN builds on this burgeoning base of knowledge by applying single-nucleotide polymorphism and gene product (PGP) analysis to a large population of transplant patients and their biopsies, producing a wealth of data and detailed clinicopathologic correlations for many parameters. CNI use was limited to tacrolimus, making this patient population more representative of modern protocols, although both the target tacrolimus levels and the observed rates of acute humoral rejection were high relative to our center’s experience. The rate of chronic graft loss was relatively low during the 3 yr of this study, necessitating the use of function and histology as surrogate end points. The histologic appearance at implantation and at 3 mo correlates significantly with graft function at all time points within the first 3 yr, a finding that might be expected, and does not point to a specific cause. Of course, the occurrence of acute rejection is a major determinant of outcome.

The data relating long-term injury to donor age and CNI toxicity and their interrelationship are particularly interesting, because they suggest distinctions beyond nonspecific histopathology. Age is a risk factor for the development of IF/TA, independent of initial pathology. The correlation of arteriolar hyalinosis with IF/TA is weaker, perhaps as a result of relatively low rates of posttransplantation hyalinosis, a possible advantage of tacrolimus over CsA. Furthermore, ABCB1 polymor-
phisms (particularly when donor and recipient were homozygous for the TT variant) are more strongly associated with IF/TA than CNI exposure. Interestingly, although donor genotype might be expected to dominate, the contribution of recipient genotype is similarly significant. Further important evidence for the impact of renal tissue (as opposed to blood), CNI concentration, and the variability of individual susceptibility was found by evaluation of PGP protein expression. Absence of apical staining at 3 mo is associated with higher IF/TA, independent of donor age and combined donor-recipient ABCB1 genotype, whereas systemic CNI exposure is not predictive of histopathology. PGP expression by immunohistochemistry is assumed to correlate with PGP pump function, although data supporting that are limited.

Unfortunately, some important areas of interest were insufficiently addressed in this study. A recent Banff meeting highlighted methodologic difficulties in the reproducible scoring of fibrosis; at a minimum, future studies must evaluate scarring using a trichrome stain. Increasing attention has been focused on the relationship between the angiogenesis of peritubular capillaries and the progression of allograft scarring. Although this article does not observe a relationship between acute humoral rejection and IF/TA, the relationship between \textit{de novo} or preexisting donor-specific antibodies and histopathologic outcomes needs to be addressed in the future. Quantification of renal epithelial PGP expression and the role of endothelial PGP regional expression deserve more detailed investigation. Finally, longer term follow-up of this patient cohort will be necessary.

The authors of this study have produced an outstanding summation of where we stand and suggestions for future investigation. The objective of this research should be the development of clinically useful tools to optimize allograft outcome. Our ongoing reliance on CNI blood concentrations for protection of long-term allograft function is of increasingly limited value in light of promising studies such as this.

**DISCLOSURES**

None.

**REFERENCES**


See related article, “Donor Age and Renal P-Glycoprotein Expression Associate with Chronic Histological Damage in Renal Allografts,” on pages 2468–2480.