CORRESPONDENCE

Chronic Allograft Nephropathy

TO THE EDITOR: Nankivell et al. (Dec. 11 issue)[1] report that serial renal biopsies in recipients of kidney and pancreas transplants who were given calcineurin inhibitors showed that chronic rejection was rare but that, over time, these drugs led to irreversible lesions. The authors conclude that calcineurin inhibitors are unsuitable for long-term immunosuppression.

The authors should be congratulated for their informative contribution, but their conclusions may be challenged. With a regimen based on calcineurin inhibitors, Nankivell et al. report that the survival rate for kidney grafts, with data censored for patients who died, was 95.2 percent at 10 years. I wonder whether immunosuppressive regimens without calcineurin inhibitors would have prevented chronic rejection, which represented by far the most common cause of late graft failure before the introduction of calcineurin inhibitors. On the other hand, the nephrotoxicity of calcineurin inhibitors does not necessarily lead to the failure of kidney grafts over time. On the basis of our own cumulative experience with cyclosporine, my colleagues and I reported a graft half-life, with data censored for patients who died, of 31 years.[2] Caution should be recommended before calcineurin inhibitors are abandoned.

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Editor's note: Dr. Ponticelli currently serves as an external consultant for Novartis.

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TO THE EDITOR: Nankivell et al. analyzed the deleterious effect of ischemia on graft outcome at one year. They found an increased incidence of chronic allograft nephropathy among patients with acute tubular necrosis, predominantly with a new onset of tubulointerstitial damage. We recently assessed the distinct contributions of alloreactivity and cold ischemia to the progression of chronic allograft nephropathy.[1] Our findings suggest that although immune activation plays the most critical role, ischemia added to the allogeneic background turns into a strong inflammatory insult that accelerates the involved cellular mechanisms, leading to severe tubulointerstitial damage. The usual immunosuppressive schedule used in this well-established model of chronic allograft nephropathy could not control the early immune inflammatory response. These findings suggest that the introduction of new drugs to interfere with these initial mechanisms might be an exciting strategy to explore. In fact, there is some evidence of a promising beneficial effect of antiinflammatory or immunomodulatory strategies on long-term graft outcome.[2,3] We think it is time to consider the treatment of post-trans-

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plantation inflammatory T-cell–mediated cellular changes associated with renal ischemic injury to prevent chronic allograft nephropathy most effectively.

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1. Herrero-Fresneda I, Torras J, Cruzado JM, et al. Do alloreactivity and prolonged cold ischemia cause different elementary lesions in chronic allograft nephropathy? Am J Pathol 2003;162:127-37.
2. Reutzel-Selke A, Zschockelt T, Denecke C, et al. Short-term immunosuppressive treatment of the donor ameliorates consequences of ischemia/reperfusion injury and long-term graft function in renal allografts from older donors. Transplantation 2003;75:1786-92.
3. Kusaka M, Zandi-Nejad K, Kato S, et al. Exploitation of the continuum between early ischemia/reperfusion injury and host alloresponsiveness: indefinite kidney allograft survival by treatment with a soluble P-selectin ligand and low-dose cyclosporine in combination. Transplantation 1999;67:1255-61.

TO THE EDITOR: Chronic allograft nephropathy has previously been suggested to cause graft loss in 30 to 40 percent of cases in which the allograft failed more than one year after transplantation.[1] However, calcineurin-inhibitor toxicity was implicated in less than 10 percent of cases. In contrast, Nankivell et al. report that 10 years after transplantation, 100 percent of patients had calcineurin-inhibitor nephrotoxicity, and the authors therefore suggest calcineurin-inhibitor–free immunosuppression for long-term treatment. In view of the major implications for the treatment of chronic allograft nephropathy, the sensitivity and specificity of the histopathological diagnosis of calcineurin-inhibitor nephrotoxicity, as well as interobserver variation, should be provided. Previous studies have already shown a very high rate of interobserver variation in the interpretation of findings on renal-transplant biopsy, especially with respect to chronic allograft nephropathy.[2] Furthermore, since whole-blood concentrations of calcineurin inhibitors, and presumably also the type of calcineurin inhibitor used, affect nephrotoxicity, trough levels of cyclosporine and tacrolimus should be presented.[3,4]

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Editor's note: Dr. Krämer reports having received grants from Fujisawa and Novartis; having participated in clinical trials sponsored by Fujisawa, Novartis, and Wyeth; and having received lecture fees from Fujisawa, Novartis, and Wyeth.

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THE AUTHORS REPLY: We do not propose the complete abandonment of calcineurin inhibitors in the absence of alternative approaches to immunosuppression that have been proved effective. As noted by Dr. Ponticelli, our excellent 10-year rate of graft survival, with data censored for patients who died, was facilitated by the use of calcineurin inhibitors, agents that probably alter the histologic pattern of transplanted kidneys. However, any projected improvement in graft half-life must be contrasted with actual graft-survival curves, which still show a progressive and inexorable attrition, despite more potent therapies.[1] Whether calcineurin inhibitors can be administered at an effective and safe dose is problematic. Our data indicated that a dose of 5 mg of cyclosporine per kilogram of body weight per day or a higher dose led to progressive arteriolar hyalinosis in pairs of specimens from sequential biopsies, suggesting a threshold dose for cyclosporine nephrotoxicity in this population (but not necessarily in individual patients). This dose is remarkably similar to the widely cited optimal cyclosporine dose that has been suggested to prevent chronic immunologic graft failure,[2] indicating an overlap of the nephrotoxic and therapeutic ranges. Hence, we reaffirm our conviction that cyclosporine is unsuitable for long-term therapy in a broad population of kidney-transplant recipients.

We agree with Dr. Pietrzyk and colleagues that interobserver variation occurs in the assessment of renal-transplant biopsy specimens, particularly with acute rejection, which, with the use of the Banff schema, hinges on the finding of relatively scarce tubulitis. In contrast, the changes of chronic allograft

nephropathy are relatively easy to recognize and there is correspondingly better agreement between pathologists on these changes. Our interobserver kappa statistics for chronic allograft nephropathy, calcineurin nephrotoxicity, and subclinical rejection were 0.61, 0.48, and 0.76, respectively, and the intraobserver kappa statistics were 0.93, 0.83, and 0.80, respectively. Variation was easily compensated for by the large numbers of biopsies. The specificity and sensitivity for the diagnosis of chronic allograft nephropathy were not calculated, since histologic examination itself is the gold standard. The mean (±SD) cyclosporine dose and trough levels at 1, 5, and 10 years were 5.1±1.5, 4.7±1.5, and 4.1±1.0 mg per kilogram per day and 221±115, 178±102, and 121±51 ng per milliliter, respectively. The one-year tacrolimus dose and trough levels were 0.12±0.06 mg per kilogram per day and 12.4±4.6 ng per milliliter, respectively. Substantial calcineurin-inhibitor nephrotoxicity still occurred with conventional doses and trough levels.

Our study showed an independent effect of both ischemic injury and acute rejection in contributing to tubular damage, results that were similar to the experimental histologic findings of Dr. Torras and colleagues, but we cannot discriminate between an additive and a synergistic mode of action. The greatest burden of tubulointerstitial damage occurred within three months after transplantation and was reduced by tacrolimus and mycophenolate therapy. Hence, controlling early immune-mediated injury and ischemia–reperfusion damage remains the best strategy for preserving functional nephrons.

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Surgeon Volume and Operative Mortality

TO THE EDITOR: Birkmeyer et al. (Nov. 27 issue)[1] demonstrated that an individual surgeon's volume was a better predictor of lower mortality for certain high-risk operations than hospital volume. Kizer, in an accompanying editorial,[2] interpreted these data to conclude that patients and health plans should preferentially choose high-volume surgeons for certain procedures or should at least avoid low-volume surgeons.

As a surgeon and surgical educator, I do not doubt the validity of the data reported by Birkmeyer et al., nor do I disagree with Kizer's recommendations. However, we must remember that every high-volume surgeon began practice as a low-volume surgeon, who subjected some number of patients to the increased risk associated with undergoing an operation performed by a low-volume surgeon. So, as Kizer states, we are faced with an ethical conundrum. An educated, informed patient with the means to choose will prefer a high-volume surgeon. But on whom will the low-volume surgeons operate in order to become high-volume surgeons? Patients of modest knowledge and means? And if there is no opportunity to practice on less choosy patients, where will future high-volume surgeons come from?

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TO THE EDITOR: Birkmeyer et al. infer from Medicare statistics that a higher surgical-case volume accounts for improved outcomes of various surgical procedures. Is it possible that the cart has been placed before the horse?

From my view as a referring physician, a somewhat different perspective may be obtained. There is a well-developed grassroots information network at every institution, which provides dynamic information on surgical skills, experience, and unexpected outcomes. This network drives referrals to surgeons with good outcomes and is the basis of the relationship between outcome and volume. Birkmeyer et al. have not established that volume begets quality, rather than the other way around.

Gifted, high-volume surgeons must at some