2250.

Pediatr Transplantation 2006: 10: 766–767

Pediatric Transplantation
Doi:10.1111/j.1399-3046.2006.00572.x

Editorial

Protocol biopsies should not (yet) be the standard of care in pediatric renal transplant recipients

The care and management of renal transplant recipients, and especially of pediatric renal transplant recipients, is potentially complex and exacting. Balancing the amount of immunosuppression to prevent toxicity and to avoid rejection is not always straightforward. In addition, the specific needs of pediatric patients add another layer of complexity to their care. A reasonable question is whether routine protocol kidney biopsies (by definition, in patients with stable renal function) will help to optimize the management of pediatric kidney recipients, and whether the benefits justify making them the standard of care for all pediatric kidney recipients. I would argue that they do not, and that protocol biopsies should not yet be performed routinely in all patients.

There is no question that obtaining renal allograft biopsies to evaluate renal dysfunction is essentially mandatory. Without a biopsy to establish the diagnosis, any therapeutic intervention is a poorly educated guess. However, the use of invasive biopsies to evaluate all children with stable renal function is another matter. It is certainly possible, even likely, that such biopsies, preferably in combination with mechanistic studies of immunologic reactivity, represent important research tools. They can reveal whether important subclinical events are occurring that can impact on long-term patient and graft survival. Such studies should be performed in selected centers with the manpower and expertise to perform protocol biopsies safely and routinely. It is even reasonable for a given center to consider them as its standard of care. At issue is whether the results from studies that have performed protocol biopsies justify their expansion to every pediatric kidney transplant program.

There is a fairly substantial literature on protocol biopsies in adult renal transplant recipients, and a smaller literature on pediatric recipients. These studies show a variable incidence of subclinical acute rejection, ranging from 2.6–100%, with many reports in the 25–30% range (1–18). There is also a literature demonstrating an incidence of subclinical chronic allograft nephropathy (CAN) (6, 8, 10, 13, 14, 17–25), and a suggestion that the presence of CAN with vasculopathy is a poor prognostic factor for long-term outcome (8). However, the important issue in protocol biopsies is whether performing them will lead to management changes that will improve long-term graft survival and function. The only randomized trial that has demonstrated a benefit to diagnosing and treating subclinical acute rejection is the adult Winnipeg experience and, while it is persuasive, it is a relatively small, single center experience (3–6). The pediatric protocol biopsy experience from Winnipeg, which was not randomized, was associated with excellent three-yr graft survival and renal function, but was associated with an incidence of CAN of 86%, despite the aggressive treatment of subclinical rejection (26).

While the risks of protocol biopsies are low, they are not zero. Substantial morbidity, and even mortality, has been associated with kidney transplant biopsies; fortunately, these catastrophic complications are rare (12, 27). In patients with an indication for a biopsy, the low risk is justified by the benefit of knowing the cause of the renal dysfunction. In a protocol biopsy setting, it is a reasonable question to ask whether the risk is justified. By making protocol biopsies the standard of care in all programs, there is an increased risk of a serious biopsy-related adverse event, especially in centers without the

infrastructure and expertise to perform biopsies routinely and safely. There is additionally the issue of who will pay for the increased number of biopsies.

While protocol biopsies may be useful in centers where there is sufficient expertise to perform them and ideally where concomitant immunologic studies can be performed, it is not clear that there is enough benefit to expand their use to every pediatric transplantation program. It would certainly be worth considering a large, multicenter randomized trial of protocol biopsies in pediatric kidney transplant recipients, along the lines of the Winnipeg trial, to see if there would be a demonstrated benefit, in terms of graft survival and function. This would be a worthwhile project for either the International Pediatric Transplantation Association (IPTA) or North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) to consider, and would provide a real answer to this question.

Ron Shapiro
Thomas E. Starzl
Transplantation Institute
UPMC Montefiore
Pittsburgh
PA, USA
Tel: (412) 647-5730
Fax: (412) 647-5736
E-mail: shapiror@upmc.edu

References

1. Burdick JF, Beschorner WE, Smith WJ, et al. Characteristics of early routine renal allograft biopsies. Transplantation 1984: 38: 679–684.
2. Burdick JF, McGraw D, Bender W, Beschorner WE, Williams GM, Solez K. Renal allograft infiltrate in the absence of rejection. Transplant Proc 1984: 16: 1580–1582.
3. Rush DN, Jeffery JR, Gough J. Protocol biopsies in stable renal transplant patients under triple immunosuppression: Results at 6 months. Transplant Proc 1994: 26: 2576.
4. Rush DN, Jeffery JR, Gough J. Sequential protocol biopsies in renal transplant patients. Clinico-pathological correlations using the Banff schema. Transplantation 1995: 59: 511–514.
5. Rush DN, Nickerson P, Gough J, et al. Beneficial effects of treatment of early subclinical rejection: A randomized study. J Am Soc Nephrol 1998: 9: 2129.
6. Rush D, Nickerson P, Jefferey J. Protocol biopsies in the management of renal allograft recipients. Curr Opin Nephrol Hyptertens 2000: 9: 615.
7. Seron D, Moreso F, Bover J, et al. Early protocol renal allograft biopsies and graft outcome. Kidney Int 1997: 51: 310–316.
8. Seron D, Moresco F, Ramon JM, et al. Protocol renal allograft biopsies and the design of clinical trials aimed to prevent or treat chronic allograft nephropathy. Transplantation 2000: 69: 1849–1855.
9. Lipman ML, Shen Y, Jeffery JR, et al. Immune-activation gene expression in clinically stable renal allograft biopsies: Molecular evidence for subclinical rejection. Transplantation 1998: 66: 1673–1681.
10. Legendre C, Thervet E, Skhiri H, et al. Histologic features of chronic allograft nephropathy revealed by protocol biopsies in kidney transplant recipients. Transplantation 1998: 65: 1506–1509.
11. Jain S, Curwood V, White SA, Furness PN, Nicholson ML. Subclinical acute rejection detected using protocol biopsies in patients with delayed graft function. Transpl Int 2000: 13: S52–S55.
12. Shapiro R, Randhawa P, Jordan ML, et al. An analysis of early renal transplant protocol biopsies – The high incidence of subclinical tubulitis. Am J Transplant 2001: 1: 47–50.
13. Nankivell BJ, Fenton-Lee CA, Kuypers DR, et al. Effect of histological damage on long-term kidney transplant outcome. Transplantation 2001: 71: 515–523.
14. Veronese FV, Noronha IL, Manfro RC, et al. Protocol biopsies in renal transplant patients: Three-years' follow up. Transplant Proc 2002: 34: 500–501.
15. Gloor JM, Cohen AJ, Lager DJ, et al. Subclinical rejection in tacrolimus-treated renal transplant recipients. Transplantation 2002: 73: 1965–1968.
16. Qureshi F, Rabb H, Kasiske BL. Silent acute rejection during prolonged delayed graft function reduces kidney allograft survival. Transplantation 2002: 74: 1400–1404.
17. Shishido S, Asanuma H, Nakai H, et al. The impact of repeated subclinical acute rejection on the progression of chronic allograft nephropathy. J Am Soc Nephrol 2003: 14: 1046–1052.
18. Bohmig GA, Regele H, Horl WH. Protocol biopsies after kidney transplantation. Transpl Int 2005: 18: 131–139.
19. Isoniemi H, Taskinen E, Hayry P. Histological chronic allograft damage index accurately predicts chronic renal allograft rejection. Transplantation 1994: 58: 1195–1198.
20. Dimeny E, Wahlberg J, Larsson E, Fellstrom B. Can histopathological findings in early renal allograft biopsies identify patients at risk for chronic vascular rejection? Clin Transplant 1995: 9: 79–84.
21. Bicknell GR, Williams ST, Shaw JA, Pringle JH, Furness PN, Nicholson ML. Differential effects of cyclosporine and tacrolimus on the expression of fibrosis-associated genes in isolated glomeruli from renal transplants. Br J Surg 2000; 87: 1569–1575.
22. Lehtonen SR, Taskinen EI, Isoniemi HM. Histological alterations in implant and one-year protocol biopsy specimens of renal allografts. Transplantation 2001: 72: 1138–1144.
23. Moreso F, Lopez M, Vallejos A, et al. Serial protocol biopsies to quantify the progression of chronic transplant nephropathy in stable renal allografts. Am J Transplant 2001: 1: 82–88.
24. Baboolal K, Jones GA, Janezic A, Griths DR, Jurewicz WA. Molecular and structural consequences of early renal allograft injury. Kidney Int 2002: 61: 686–696.
25. Seron D, Moreso F, Fulladosa X, Hueso M, Carrera M, Grinyo JM. Reliability of chronic allograft nephropathy diagnosis in sequential protocol biopsies. Kidney Int 2002: 61: 727–733.
26. Birk PE, Stannard KM, Konrad HB, et al. Surveillance biopsies are superior to functional studies for the diagnosis of acute and chronic renal allograft pathology in children. Pediatr Transplant 2004: 8: 29–38.
27. Furness PN, Philpott CM, Chorbadjian MT, et al. Protocol biopsy of the stable renal transplant: A multicenter study of methods and complication rates. Transplantation 2003: 76: 969–973.