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Where Did We Leave Off in 2008? Conclusions From The 8th International Symposium

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ABSTRACT

Although short-term outcomes following kidney transplantation have improved in recent years, allograft viability beyond 1 year has changed little since the introduction of cyclosporine (CsA)-based immunosuppression. Chronic allograft nephropathy (CAN) is a continuing threat to improved long-term outcomes, and regimens that involve calcineurin inhibitors (CNI) are implicated as a result of the progressive fibrosis they promote in renal allografts. Although strategies to reduce the nephrotoxic effects of CNI exposure have shown some success, alternative approaches to reducing nephrotoxicity and graft failure are needed. Sirolimus (SRL) suppresses immune reactions in a mechanism distinct from that of other immunosuppressants and may therefore hold potential for reducing the risk of CAN and improving long-term graft survival. The Rapamune Maintenance Regimen study randomized patients at 3 months either to continue with a regimen of SRL, CsA, and steroids or to have CsA withdrawn and the dose of SRL increased. Patients who were randomized to CsA withdrawal had superior graft and patient survival, demonstrated improved renal function, better blood pressure control, and a lower rate of skin and nonskin posttransplantation malignancy. A key barrier to the wider clinical implementation of SRL in kidney transplantation has, however, been the understanding of its optimal incorporation into standard immunosuppressive protocols. The CONVERT study examined the late conversion (approximately 3 years posttransplantation) from CNI to SRL. Late conversion was associated with inferior outcomes in patients with poor graft function or significant proteinuria following conversion. In addition, a number of short-term adverse events, such as prolongation of delayed graft function and abnormal wound healing, have been more commonly associated with *de novo* approaches. In designing the optimal approach to achieving long-term CNI-free immunosuppression with SRL, it should therefore be considered how these adverse events may be avoided or minimized. This brings into focus the optimal timing for the introduction of SRL and the potential for a two-stage approach to immunosuppression, minimizing the different short- and long-term risks to both the graft and the patient.

IT IS well recognized that the introduction of calcineurin inhibitors (CNI) in renal transplantation has been associated with a dramatic decrease in the rate of acute rejection with consequential improvements in 12-month graft survival. The improvement in short-term outcomes has continued up until the present day, indicating that the incremental addition of other agents and clinical factors is continuing to have an impact. Perhaps our challenge is to now focus on the longer-term outcomes – for both patient and graft survival, and what strategies might offer potential to positively influence these most important parameters of our interventions. This challenge is highlighted by data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) for renal grafts performed from 1970 to 2006. The annual graft failure rates for the first year for the time periods from 1 to 4.9 years and from 5 to 10 years posttransplantation have improved over this time. However, for the time period beyond 10 years, annual graft failure rates have worsened (Fig 1). The major causes of

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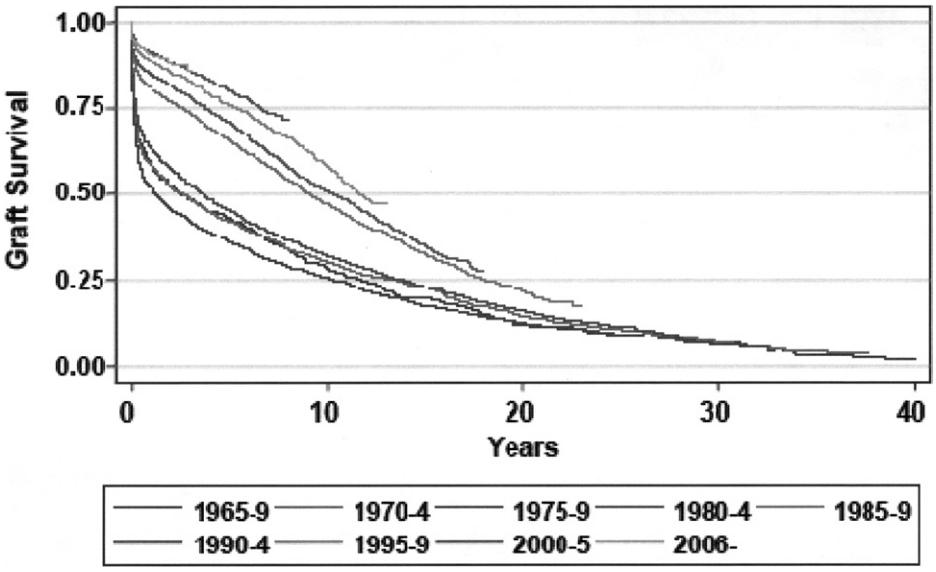

Fig 1. Primary graft survival of deceased donors by year of transplantation to December 31, 2007 in Australia and New Zealand.

graft loss after the first year are chronic allograft nephropathy (CAN) and death with a functioning graft. The latter is predominantly contributed to by malignancy and cardiovascular disease, and analysis of the ANZDATA database shows that these contributory factors are the most common causes of death in transplant recipients in Australia.[1]

The current CNI-based regimens have been demonstrated to contribute to both of these long-term problems. An analysis of the ANZDATA of factors that influenced death-censored graft survival after 5 years showed that, on multivariate analysis, the only modifiable negative factors were if the recipient smoked or if the recipient received cyclosporine A (CsA) at 1 and 5 years posttransplantation.[2] The contribution of CNI nephrotoxicity to the development of CAN has been described by Nankivell et al.[3] In addition, the Australian Multicentre Cyclosporine A Renal Transplant Study has recently published follow-up results to 15 years that have demonstrated that patients randomized to ongoing CsA had an inferior outcome to those patients who received CsA for 3 months before converting to azathioprine and prednisolone.[4]

The contribution of CNIs to these late complications has led to the development of immunosuppressive regimens that either avoid, minimize, or withdraw CNIs. A number of these regimens have been based on the use of sirolimus (SRL) to allow these strategies without an appreciable reduction in immunosuppressive potency. Meta-analyses have confirmed that SRL is of adequate immunosuppressive potency[5] and has less nephrotoxicity compared with CNIs. This is evidenced by better renal function after conversion from a CNI to SRL.[6] However, when applying these strategies, consideration needs to be given to the risk factors of each individual patient, also noting the characteristics of the donor because these may affect the recipient's ultimate outcome. The other important and currently unresolved consideration is when to apply these strategies. The studies of protocol biopsies by Nankivell et al have shown that the risk of developing interstitial fibrosis and tubular atrophy is greatest in the first year as a result of acute rejection episodes, presence of subclinical rejection, and occurrence of delayed graft function. Later, vascular changes typical of CNI toxicity occur, with subsequent striped fibrosis and glomerulosclerosis. Hence, clinicians need to consider development of these pathological lesions when deciding the most appropriate time to minimize/withdraw CNI and to introduce SRL.

Two studies have shed light on the most appropriate time to consider these strategies posttransplantation. The Rapamune Maintenance Regimen study randomized patients at 3 months either to continue with a regimen of SRL, CsA, and steroids, or to have CsA withdrawn and the dose of SRL increased.[7] It is important to note that of the 525 patients entered into the study, 95 were not randomized either because of significant rejection in the first 3 months or poor renal function. Therefore, the randomized patients were a group selected for favorable outcomes in terms of immunological reactivity and graft function. Nevertheless, at 4 years those patients who were randomized to CsA withdrawal had superior graft survival.[8] In addition, this group also demonstrated higher glomerular filtration rate (GFR), less evidence at 3 years of CAN on graft biopsy,[9] better blood pressure control, and, surprisingly, a lower rate in the development of both skin and nonskin posttransplantation malignancies.[10]

The CONVERT study is a randomized controlled trial of more than 800 patients examining the late conversion (mean, approximately 3 years posttransplantation) from CNI to SRL. Results to 24 months have recently been published and suggest some benefit of conversion with improvement in graft function, but were not observed in all patients.[11] The factors associated with inferior outcomes were poorer graft function or significant proteinuria at