



Evaluating Strategies to Extend and Maximize Patient and Graft Survival

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Boston - For initial maintenance therapy following transplantation, guidelines recommend first-line use of calcineurin inhibitors (CNIs) with an antiproliferative agent, with or without steroids. However, experts now strive to achieve adequate immunosuppression to promote long-term allograft survival with the least possible risk of toxicity. To that end, various strategies, including the use of CNI monotherapy, reduced-dose CNIs and steroid withdrawal, are all being explored. The development of donor-specific antibodies has now been associated with poorer long-term graft survival and risk factors for their development, most notably non-adherence to the immunosuppressive regimen, must be taken into consideration. Strategies to improve adherence may include conversion to once-daily dosing, now possible with a prolonged-release formulation of the CNI tacrolimus.

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The calcineurin inhibitors (CNIs) are potent immunosuppressive agents, effectively preventing acute rejection and enhancing overall survival. However, immunosuppression is associated with a number of adverse outcomes over time and strategies to minimize them are increasingly being used in order to optimize patient well-being. One such strategy is to use only one immunosuppressive agent for maintenance therapy.

CNI Monotherapy

In one study cited here at the ATC by Dr. David Baran, Clinical Associate Professor, Beth Israel Medical Centre, Newark, New Jersey, 90 out of 124 cardiac transplant recipients initially treated with tacrolimus and corticosteroids were weaned to tacrolimus monotherapy without the use of an antiproliferative agent. Another 69 cardiac transplant recipients from the same institution were treated with either a tacrolimus- or cyclosporine-based regimen. As the authors reported (*J Heart Lung Transpl* 2006;25(6):699-706), actuarial survival rates for patients in the arm weaned to tacrolimus at 1, 3 and 5 years were 99%, 93% and 87% vs. 65%, 55% and 53% for the comparator group, which was statistically significant ($P < 0.01$). Prevalence of high-grade rejection and the incidence of cardiac allograft vasculopathy within the first year were similar between groups.

Combination immunosuppression needed to be restarted in just 10 patients on monotherapy, at an average of 768 days post-transplantation. Nevertheless, investigators felt that tacrolimus monotherapy is attainable in most cardiac transplant recipients.

Another strategy that may successfully decrease long-term exposure to CNIs is to use a lower dose. Favi et al. (abstract 55) presented findings in the setting of kidney transplant recipients. A regimen of low-dose, extended-release tacrolimus plus low-dose everolimus once daily was compared to standard-dose, extended-release tacrolimus plus once-daily mycophenolate mofetil (MMF).

All patients received the same induction regimen and all study medications were given orally once a day, starting on day 4 post-operatively. Three months after transplantation, steroids were selectively withdrawn in patients who had had no acute rejection episodes, whose serum creatinine was < 2 mg/dL and whose proteinuria levels were < 300 mg/L/24 hours. At 6 months, there were no differences in patient or graft survival (95% for the low-dose group compared to 100% in the standard-dose/MMF group), biopsy-proven acute rejection (BPAR) (0% in the low-dose group vs. 5% in the standard-dose/MMF group), or in rates of steroid-resistant acute rejection (0% in both groups). Serum creatinine levels and calculated creatinine clearances were virtually identical in both



groups, as were rates of proteinuria, although patients on the low-dose everolimus regimen did have higher serum cholesterol levels than the comparator regimen and required more statin therapy.

Exploratory Regimen

In another study presented here, Russ et al. (abstract 3) explored the 6-month efficacy and safety of giving kidney transplant recipients sotrastaurin (STN), a novel immunosuppressant that blocks early T-cell activation, plus reduced-exposure tacrolimus in low- to moderate-risk renal transplant patients. A total of 298 patients were randomized to either STN 100 mg or 200mg b.i.d. plus standard-dose tacrolimus (5 to 12 ng/mL trough level) or to higher-dose STN (300 mg b.i.d.) plus a reduced daily dose of tacrolimus (2 to 5 ng/mL trough level). These groups were compared to a control group who received enteric-coated mycophenolic acid (MPA) plus standard-dose tacrolimus. All patients also received basiliximab and steroids.

At 6 months, the composite end point of BPAR, graft loss, death or loss to follow-up was reached by 16% and 11% of patients in the STN 100 mg and 200 mg plus standard-dose tacrolimus groups, respectively, and in 10.8% for the STN 300 mg plus reduced-dose tacrolimus group and 9.8% for the MPA plus standard-dose tacrolimus group. Most rejections were considered mild and the frequency and pattern of infections were comparable between groups.

Graft loss or death rates were significantly higher at 6.8% in the STN 200 mg plus standard-dose tacrolimus group than in the other 3 groups. The estimated glomerular filtration rates (eGFRs) were also significantly lower for this group at a median of 48.6 mL/min/1.73 m². In contrast, eGFRs were highest in the STN 300 mg plus reduced tacrolimus group. Study authors concluded that all STN-based regimens were well tolerated, and that discontinuation rates due to adverse events (AEs) were dose-proportional.

Steroid Withdrawal

Steroids are usually included in the initial immunosuppressive regimen but are associated with AEs. A number of protocols have been advanced to either reduce or fully withdraw steroid use. One strategy to minimize steroid-related AEs is rapid discontinuation of prednisone in kidney transplantation recipients but concerns exist regarding long-term allograft outcomes using this approach.

In a presentation by Matas et al. (abstract 293), investigators in Austria followed 591 primary transplant recipients whose kidney allograft was still intact out to 5 years post-transplant. Prednisone had been discontinued on day 5 in all recipients and 10-year actuarial recipient and graft survival rates were compared with historical controls (Table 1).

Table 1. 10-year Outcome in Patients with 5-year Graft Survival After Rapid Prednisone Discontinuation

	Rapid discontinuation of prednisone	Historical controls
	10 years	10 years
Living donor	(n=432)	(n=317)
Patient survival (%)	93	83
Graft survival (%)	78	75
Deceased donor	(n=159)	(n=189)
Patient survival (%)	79	76
Graft survival (%)	81	65

Adapted from Matas et al. ATC 2012, abstract 293.

Patients in whom prednisone had been rapidly discontinued did not have an excess of late graft loss relative to historical controls. The authors also noted that mean eGFR rates were significantly higher and mean serum cholesterol and triglyceride levels significantly lower between years 5 and 9 for recipients in whom prednisone had been rapidly discontinued compared to historical controls. Findings suggested that the practice of discontinuing prednisone on day 5 post-transplantation appeared to be associated with better long-term renal function and improved lipid control than standard immunosuppressive strategies.

However, a large retrospective cohort of 2244 first kidney allograft recipients captured in the Austrian Dialysis and Transplant Registry suggests that withdrawal of steroids too early following transplantation may be associated with poorer outcomes, at least during the first post-transplant year. The Registry tracked steroid use and withdrawal every quarter in the first year following transplantation and annually thereafter (abstract 292).

A propensity score adjusted for comorbidity, comorbidity and specific laboratory values was calculated, while a landmark Cox model for actual graft loss and mortality was computed at yearly intervals and included the propensity score to account for confounding by steroid indication. As Haller et al. reported, modelling analyses showed that the risk of graft loss and mortality

was higher when steroids were withdrawn within the first year post-transplantation. However, the risk of graft loss and mortality declined after the first year and was lower over the next 5 years among those who were not on steroids than for those on steroid maintenance. Based on these results, the optimal time for steroid withdrawal appears to be one year following transplantation. As these 2 studies indicate, the optimal time point at which steroids may be safely withdrawn following kidney transplantation has yet to be determined.

Risk Factors in Developing Donor-specific HLA Antibodies

Current immunosuppressive regimens have improved acute rejection responses but adaptive immune responses to grafted organs still frequently undermine long-term success. Among the most important of these adaptive responses is the development of donor-specific HLA antibodies (DSAs), now known to be involved in both acute and late rejection. Here at the ATC, Dr. David Rush, Medical Director, Transplant Manitoba Adult Renal Program, Winnipeg, and colleagues demonstrated the importance of DSAs for long-term graft survival. As reported also in a recent issue of the *American Journal of Transplantation* (2012;12:1157-67), the prevalence of *de novo* DSA (*dn*DSA) increases over time but their appearance depends on a number of risk factors which have now been identified.

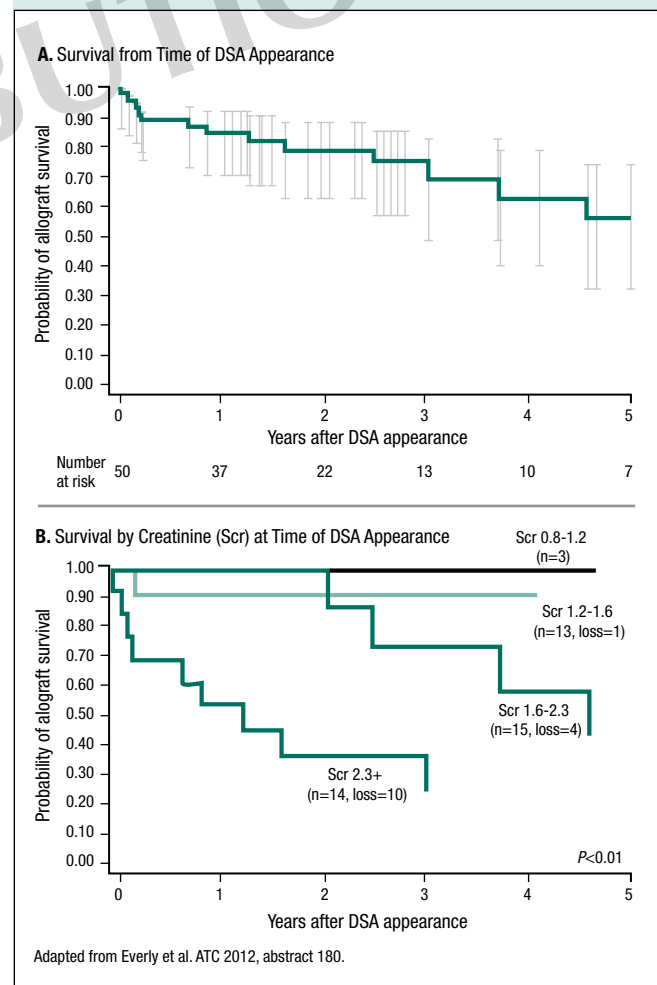
The Winnipeg-based study involved 315 kidney transplant recipients with no DSA evidence prior to transplantation followed out to 10 years. The study indicated that despite being a low-risk, well-treated transplant population, *dn*DSAs developed at a surprisingly high rate of 15% over a mean of 4.6 years of follow-up. Moreover, the 10-year survival rate of patients who developed *dn*DSAs was inferior at approximately 57% compared to approximately 96% for patients who did not ($P < 0.0001$). By far, the strongest risk factor for the development of *dn*DSAs by year 10 was non-adherence to the immunosuppressive regimen (adjusted odds ratio [OR] 8.75, $P < 0.001$), followed by mismatching of certain class 2 antigens (OR 5.66, $P < 0.006$). There was also a strong trend towards clinical rejection episodes preceding the development of *dn*DSAs (OR 1.57, $P = 0.061$) as being an important risk factor.

In commenting on their findings, Dr. Rush noted that in the Winnipeg transplantation program, “we follow our patients much more frequently than other centres.” Up to 6 months’ post-transplantation, patients

are seen almost weekly and every time patients attend clinic, “they have blood levels taken. If [patients] don’t show up, they are phoned by nurses at home. So failure to have a good blood level or patients not showing up repeatedly for clinic or lab assessment or patient’s own admission to not taking their drugs are all part of our criteria for being non-adherent,” he explained. “Once patients develop DSAs, there is nothing you can do about it, which is why prevention is so important.”

In a separate study by Everly et al. (abstract 180), investigators tracked survival following the onset of *dn*DSAs in a consecutive series of 224 low-risk renal transplant recipients. Patients underwent DSA testing prior to transplantation and again at 1, 3, 6, 9 and 12 months, and annually thereafter. As investigators reported here, 50 patients followed for up to 10 years developed *dn*DSA post-transplantation. From the time of *dn*DSA detection, 15% of patients had lost their graft at one year, 28% had lost their graft at 3 years and 42% had lost their graft at 5 years (Figure 1).

Figure 1. Graft Survival After Onset of *dn*DSA



Interestingly, among those patients who tested positive for *dn*DSA, above-normal baseline creatinine levels (>1.6 mg/dL) were predictive of poorest response.

The development of acute rejection after the appearance of *dn*DSA was also associated with a poorer prognosis (HR 3.43).

Strategies to Improve Adherence

As was discussed by investigators at the Joint International Congress of ILTS, ELITA and LICAGE in Valencia, Spain, in 2011, drugs with a relatively narrow therapeutic window such as the CNIs often perform better when offered in extended- or prolonged-release formulations. This may be because release of the active moiety in the gastrointestinal tract can be controlled and peaks in absorption avoided. With controlled absorption, steady plasma concentrations are often easier to maintain and the risk of toxicity may be reduced. Extended-release formulations also allow drugs to be dosed once a day, a feature that may help promote better adherence.

Stable immunosuppressive blood levels are an important principle underpinning allograft management, and safety issues are paramount in any conversion from twice-daily to once-daily dosing. A retrospective single-centre study addressing this issue was presented here by Slatinska et al. (abstract 1023). Their aim was to compare renal function and the incidence of acute rejection in 589 b.i.d. tacrolimus kidney transplant patients prior to, and after, conversion to q.d. tacrolimus. The median time of conversion was 4.1 years post-transplantation. There was no deterioration in graft function as reflected by eGFR (52.8 mL/min/1.73 m² before conversion and 46.2 mL/min/1.73 m² post-conversion). There was no significant change in tacrolimus trough levels at 5.07 µg/L prior to conversion vs. 4.93 µg/L after conversion. The incidence of acute rejection was low, and graft survival

at one year was 97%. Investigators concluded that once-daily morning dosing with extended-release tacrolimus may help facilitate adherence and improve long-term outcomes.

Jannot et al. (abstract 586) sought to evaluate the flexibility of using the extended-release formulation of tacrolimus during the initial period of transplantation, when dose adjustments may be necessary. They compared the safety and efficacy of an early conversion strategy to once-daily therapy vs. the conventional twice-daily regimen. Patients received steroids and MMF in both groups as well as a sequential induction therapy. Conversion to the once-daily tacrolimus strategy was initiated on average 12.4 days following transplantation.

As investigators reported, exposure to tacrolimus was not significantly affected by conversion to a once-daily strategy. Nor were there any differences observed in acute rejection rates, levels of renal function, mean albuminuria levels, new-onset diabetes or the proportion of patients with high blood pressure and cholesterol levels between patients who had been converted to the once-daily strategy and those who remained on conventional dosing. One-year post-transplant, patient and graft survival rates were also similar in both groups.

Summary

In the transplant patient, achieving the right balance between adequate levels of immunosuppression and minimizing the risk of adverse outcomes remains difficult. The optimal time to steroid withdrawal needs to be confirmed. More short- and long-term data presented here at the ATC confirmed the importance of adherence to immunosuppressive therapy. By promoting adherence with optimal simplified immunosuppressive regimens, physicians can help reduce the risk of patients developing *dn*DSA, which are implicated in acute and late graft rejection. □

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