ABSTRACT

The incidence of posttransplantation comorbidities related to use of immunosuppressive agents is extremely high. As rates of survival have progressively improved after heart transplantation, the implications of these treatment-related comorbidities on long-term health, patient survival, and healthcare costs have become clear. This article reviews the major nonvasculopathy complications of immunosuppressive therapy, including hypertension, metabolic abnormalities, infection, malignancy, and renal insufficiency. Several strategies aimed at minimizing side effects of immunosuppressive regimens (such as limitation of calcineurin inhibitor [CNI] use) are described. Although newer agents, such as the proliferation signal inhibitors, appear to have beneficial effects in limiting comorbidities, especially of nephrotoxicity in CNI-sparing protocols, the full therapeutic profile of these agents has yet to be defined.


Despite progressive improvements in cardiac transplant outcomes, significant morbidities persist, including hypertension, metabolic abnormalities, infection, malignancy, renal insufficiency, and cardiac allograft vasculopathy (CAV). Many of these complications are mediated by specific immunosuppressants or via synergistic toxicities between agents. In particular, the calcineurin inhibitors (CNIs) cyclosporine and tacrolimus are known to have significant adverse impacts on renal function and cardiovascular disease in solid organ transplantation. New immunosuppressants offer the possibility of enhanced efficacy with less toxicity, but clinicians need to maintain an awareness of all potential complications that limit long-term survival and cause morbidity. This article and the ensuing discussion highlight the nonvasculopathy complications of immunosuppressive therapy and describe evolving strategies for managing the main comorbidities associated with the complex multidrug regimens in use today.

POSTTRANSPLANTATION COMORBIDITIES IN PERSPECTIVE

Survival rates for patients transplanted over the past 7 years are significantly higher than the rates for patients transplanted in the 1980s or 1990s. These progressively improving outcomes are due in part to the availability of newer immunosuppressive drugs with better efficacy and less toxicity. The improved survival is also attributable to improved management of comorbidities.

Despite this positive trend, the cumulative prevalence of posttransplantation comorbidities is alarmingly high (Table). By year 5, approximately 9 of every 10 patients have hypertension and/or hyperlipidemia, and more than 3 of 10 have some degree of renal dysfunction; 1 in 3 patients has diabetes. These rates of dis-
ease are high even allowing for the fact that the transplant population has a high baseline prevalence of coronary artery disease with antecedent problems related to blood pressure, lipids, or sugar. Also disturbing are new registry data showing that the rates of malignancy in 1-, 5-, and 10-year survivors are 2.9%, 15.1%, and 31.9%, respectively. More than 50% of these malignancies in heart transplant recipients are skin cancers.

Comorbidities take a clear and progressive toll on long-term survival. Unlike mortality from acute rejection, with its predictable early rise in the 6 to 12 months after transplantation followed by a long plateau, many of the other leading causes of death in this population show a relentless linear increase over time (Figure 1). Again, the steadily rising rate of cancer mortality is particularly evident and is very likely related to immunosuppressive therapy. Even deaths due to infection continue to increase linearly over time despite the usual reduction in immunosuppression in later years.

The goal for clinicians is to be aware of the natural history of these overlapping comorbidities in cardiac transplant recipients and to modify risks and select therapies in ways that will alter these trajectories. As a basis for that awareness, we review several studies that have compared the impacts of various immunosuppressive regimens on complication rates—some as part of a focused analysis on minimization of specific side effects (eg, avoiding CNIs) and others within the broader context of a trial examining overall drug efficacy and safety.

### HYPERTENSION AND HYPERLIPIDEMIA

In a study of 60 heart transplant patients who had developed CNI-related complications during maintenance immunosuppression (mean 5.4 ± 3.2 years from procedure), switching from cyclosporine to everolimus led to significantly reduced blood pressure after 3 months (Figure 2), in addition to marked improvements in tremor, peripheral edema, hirsutism, and gingival hyperplasia. There were no significant changes in cholesterol subfractions or triglycerides. However, in a larger study (N = 634) documenting the efficacy of everolimus versus azathioprine in preventing vascuropath while preventing rejection, analysis of 12-month serum lipids showed a statistically significant increase in total cholesterol and triglycerides (but not high- or low-density lipoprotein subfractions) in patients taking the proliferation inhibitor versus those taking azathioprine (P = .01). Overall, based on these

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**Table. Morbidity in Cardiac Transplant Survivors: Cumulative Prevalence Data from ISHLT Registry**

<table>
<thead>
<tr>
<th></th>
<th>1-Year Survivors (n = 6556–7640)</th>
<th>5-Year Survivors (n = 5944–9237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension, %</td>
<td>74.4</td>
<td>93.8</td>
</tr>
<tr>
<td>Renal dysfunction, %</td>
<td>30.4</td>
<td>32.6</td>
</tr>
<tr>
<td>Abnormal creatinine</td>
<td>22.4</td>
<td>21.2</td>
</tr>
<tr>
<td>Creatinine &lt;2.5 mg/dL</td>
<td>5.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>1.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Renal transplant</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>67.8</td>
<td>87.1</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>31.5</td>
<td>34.8</td>
</tr>
<tr>
<td>Vasculopathy, %</td>
<td>7.1</td>
<td>31.5</td>
</tr>
</tbody>
</table>


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**Figure 1. Leading Causes of Death in Adult Heart Transplant Recipients: Data from ISHLT Registry (Transplants January 1992–June 2005)**

CAV = cardiac allograft vasculopathy; CMV = cytomegalovirus; ISHLT = International Society of Heart and Lung Transplantation; PTLD = posttransplant lymphoproliferative disorder. Reprinted with permission from Taylor et al. J Heart Lung Transplant. 2007;26:769-781.©
and similar studies, most centers currently strive to limit exposure to CNIs but also maintain an awareness of the possible lipid effects of agents such as sirolimus and everolimus.

**INFECTIONS**

Three studies provide insight into infectious complications after heart transplantation. In the first study, high-dose (3 mg) everolimus was associated with significantly more bacterial infections (37.9%) versus azathioprine (24.8%, \( P = .001 \)); however, the incidence of viral infections was significantly lower in everolimus-treated patients (14.8% and 17.1% in the 1.5-mg and 3-mg groups, respectively) than in the azathioprine group (31.3%, \( P = .001 \)).4 The second study showed no difference in sepsis rates between sirolimus and azathioprine groups but pneumonia incidence was higher in both sirolimus groups (11.8% and 10.3% in the 3-mg and 5-mg groups, respectively) versus the azathioprine group (0, \( P < .05 \)); systemic cytomegalovirus (CMV) infections were significantly reduced in the high-dose sirolimus group (1.7% vs 13.6%, \( P < .05 \)).5 In the most recent study, postsurgical wound complications and symptomatic pleural effusion were significantly more common (52% and 25%, respectively) in patients taking sirolimus versus those taking mycophenolate mofetil (MMF; 28.2% and 8.7%, \( P = .019 \) and \( P = .035 \)).6 Based on such results, many transplant centers remain concerned about the risks of starting proliferation signal inhibitors (PSIs) too early after transplantation.

**RENAL INSUFFICIENCY**

Nephrotoxicity, with an incidence of 30% at 1 year posttransplantation, is one of the most common and serious comorbidities of immunosuppression. Because this problem is associated with CNI-mediated vasoconstriction of the afferent arteriole, resulting in chronic ischemic injury, several studies have evaluated the potential benefits of CNI-sparing regimens.

In the already mentioned conversion trial involving 60 patients transitioned from CNI to everolimus,3 the mean serum creatinine was reduced from 1.8 mg/dL to 1.5 mg/dL at 6 months (\( P = .001 \)) with concomitant rises in glomerular filtration rates (GFRs) (\( P < .02 \)). Another trial showed that conversion from CNI to sirolimus because of either renal insufficiency (\( n = 58 \)) or vasculopathy (\( n = 20 \)) significantly increased GFR (from 47 mL/min to 61 mL/min, \( P = .0001 \)) versus CNI maintenance (\( n = 51 \)) 24 months after sirolimus initiation (Figure 3).7 Similar levels of GFR improvement were seen in both CNI conversion groups.

Finally, conversion from low-dose cyclosporine to sirolimus was studied in 39 cardiac transplant patients (mean 8.2 years from transplantation) with evidence of renal dysfunction (serum creatinine >1.7 mg/dL).8 In the 19 patients randomized to CNI discontinuation, renal function improved markedly after 6 months (serum creatinine from 2.08 mg/dL to 1.67 mg/dL and GFR 48.5 mL/min to 61.7 mL/min; both \( P < .001 \)) whereas there was no change in the control group randomized to continued low-dose CNI (Figure 4).8 Although there were no significant changes in laboratory values (including lipids) in this study, 5 patients discontinued sirolimus as a result of gastrointestinal adverse events (3), pulmonary embolism (1), or pneumonia (1).

Thus, although PSIs do not have a direct renal-protective effect,4,5 these agents may allow a conversion to a CNI-based regimen in selected patients, a switch that has been associated with positive changes in renal function.
Although strategies for CNI minimization, avoidance, or withdrawal are fairly well documented in the setting of renal transplantation, more clinical experience and pathophysiologic insight is needed in the context of heart transplantation.

Caution is also warranted because of the known side effects of the main alternatives to CNIs. For example, in a study comparing adverse events in 136 patients randomized to sirolimus or azathioprine, the sirolimus patients were less likely to have rejection or vasculopathy but they also had higher incidences of anemia and thrombocytopenia, gastrointestinal toxicity (particularly diarrhea), hyperlipidemia, epistaxis and mouth ulcerations, abnormal wound healing, and abnormal renal function. Those patients on azathioprine had higher rates of arrhythmia, atrial fibrillation, and nausea.

CONCLUSIONS

Early studies with PSIs in CNI-sparing protocols indicate that these agents may have a beneficial impact on renal insufficiency and hypertension. However, clinicians are still learning the nuances of using these agents in combination with other immunosuppressives in heart transplant patients. In particular, the effects of sirolimus and everolimus on renal function, wound healing, infections, malignancy, hyperlipidemia, anemia, and thrombocytopenia must be further defined. Achieving the best long-term clinical outcomes with new agents, such as the PSIs, will require finding the least toxic and most effective combination of agents, determining the best timing for therapy initiation, diligently monitoring the immunosuppressive course, and changing the regimen as required. The array of studies reviewed here makes clear the need to balance the risk-benefit profile of each regimen based on the particular needs of the patient.

Figure 3. Impact of CNI Withdrawal and Sirolimus Addition on Renal Function

![Graph showing impact of CNI withdrawal and sirolimus addition on renal function.]

Figure 4. Impact on Renal Function of Conversion from Low-Dose Cyclosporine to Sirolimus in Combination Immunosuppression Therapy

![Graph showing impact of conversion from low-dose cyclosporine to sirolimus.]

CNI = calcineurin inhibitor; GFR = glomerular filtration rate; Group A = switched due to renal insufficiency; Group B = switched due to cardiac allograft vasculopathy; Siro = sirolimus.

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**DISCUSSION**

**Dr Kobashigawa:** Nephrotoxicity is clearly a large risk factor for increased mortality late after transplantation. We have talked about minimizing or withdrawing CNIs but what about avoiding them from the very beginning?

**Dr Rogers:** There is still concern about using PSIs early after transplantation because of risks related to wound healing and also the risk of pleural and pericardial effusions. The notion of avoiding aggregate nephrotoxicity by using these drugs earlier is interesting but has not been studied in large trials. The real question today is how early in the posttransplant course should we institute the therapy.

**Dr Kobashigawa:** There are actually 2 questions. One is how early do you switch. The other is how gradually do you switch. One preliminary study involving abrupt withdrawal of CNIs at month 3, with addition of sirolimus and MMF, led to high rates of early rejection. Perhaps 3 months is too early and/or perhaps a gradual switch is needed.

**Dr Rogers:** It is hard to make a recommendation based on the current literature. Switching protocols vary from center to center and many studies on this topic are single-center. We definitely need a large randomized trial. That said, I will point out that the successful studies presented earlier all weaned the drug over several weeks to months.

**Dr Eisen:** It is crucial to avoid an abrupt cessation of CNI and also to maintain consistently therapeutic levels of sirolimus and of mycophenolate if those are the additional agents.

**Dr Rogers:** Do we know the mechanism behind the lower risk of CMV infections in a PSI-treated population?

**Dr Eisen:** It has certainly been a striking result in clinical trials but we do not know if the anti-CMV effect is a result of lower aggregate immunosuppression or something more specific and mechanistic—perhaps a reduced impact on the late-type hypersensitivity that controls herpes viruses. Also, if we believe that CMV plays a role in development of CAV, then anything that inhibits CMV infection should have a beneficial effect, but again we do not really know. In the early sirolimus and everolimus trials, the synergistic adverse effect between the PSIs and the CNIs was surprising. Back then, of course, CNIs were being used at full dose. In a more recent European trial involving randomization to everolimus and low-dose cyclosporine, the adverse renal effects were reduced, at least at 6 months, versus full-dose cyclosporine and mycophenolate. We still need the data from this and other similar trials but my impression is that the renal issues with PSIs may be diminishing.

**Dr Kobashigawa:** Renal dysfunction was definitely the biggest problem in the original everolimus trials. However, if that stumbling block to use of everolimus early after transplant has been removed by reducing cyclosporine doses, then we may have a drug that decreases CAV (by all IVUS [intravascular ultrasound] parameters), decreases rejection compared to the azathioprine, and decreases CMV infection, which is also a risk factor for allograft vasculopathy.

**Dr Eisen:** Yes, if we can avoid renal insufficiency while also achieving less rejection, less CMV, and less CAV, that would be a desirable drug. One problem with the ongoing European trial is the lack of IVUS and thus we are missing data on perhaps the most important end point.

**Dr Kobashigawa:** There is one ongoing trial that is randomizing between mycophenolate and everolimus both in combination with cyclosporine and corticosteroids. This should help to reveal any differences between these antiproliferative drugs in terms of development of CAV.

**Dr Rogers:** Yes, PSI comparisons against azathioprine are no longer very informative. We need to design future trials using contemporary immunosuppressant regimens as comparators.

**Ms Carter:** Based on all of the data that we have talked about today, is there a “perfect regimen” for a patient 6 months out from transplantation?

**Dr Kobashigawa:** Currently, based on evidence-based medicine, I would select tacrolimus, MMF, and corticosteroids. This is the combination that did best overall in terms of efficacy and safety in the recent 3-arm trial. This may change based on new evidence. Eventually we may use everolimus instead of mycophenolate along with lower-dose cyclosporine. Or perhaps we will use everolimus with tacrolimus. It is truly the combination regimen, and not so much the individual drug, that we need to watch because certain drugs will have interactions with each other. We need to find the immunosuppression regimen that is most beneficial and for that we will have to wait for clinical trials.
Dr Russell: Also, our ideal choice at month 3 may be very different than it is at month 0. For example, the poor wound healing associated with everolimus and sirolimus may not allow use of those agents from day 0. But perhaps we will be able to switch patients at month 1 or month 2. We need data from a clinical trial to find the best time to switch.

Dr Eisen: And as a caveat for that proposed trial, if you believe that the PSI impact on response to injury in terms of smooth muscle cell proliferation also occurs in the first 3 months, then it may be too late to intervene against CAV at 3 months.

Dr Russell: Might there be a benefit to bathing the donor heart in a preservative solution that contains one of those inhibitors?

Dr Conte: It may be worth thinking about. Unfortunately, most preservation research on limiting reperfusion injury or coronary disease has not translated from the animal models into clinical use.

Dr Eisen: Also, looking ahead, a recent small study in renal transplantation gave donor-specific bone marrow to recipients along with radiation; there was tolerance and minimal or no need for maintenance immunosuppression in 4 of 5 patients. Similar approaches were tried without success about 10 years ago in heart transplantation but this may be worth revisiting. Also worth exploring is an approach using antibodies that block Signal 2; given early enough after transplantation, this may allow much less immunosuppression.

REFERENCES