Editorial

Strategies in Immunosuppression After Heart Transplantation

Is Less Better?

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In this issue of Circulation: Heart Failure, Baran and colleagues' report on 150 de novo adult heart transplant patients randomized to tacrolimus monotherapy or tacrolimus and mycophenolate mofetil therapy (dual therapy). Corticosteroids were weaned and discontinued in all patients by 8 weeks posttransplantation. Intravascular ultrasound (IVUS) was performed at baseline and at follow-up. The authors find that the primary end point of a composite biopsy score at 6 months was similar for both study groups. They also report no significant difference between groups in 3-year survival and the development of cardiac allograft vasculopathy (CAV) by coronary angiography and IVUS. No patient required reinsti-
tution of corticosteroids or a switch to another immunosuppres-
sive drug during the follow-up period. The authors conclude that early corticosteroid weaning, tacrolimus mono-
therapy, or dual therapy are potential viable options for heart transplant patients.

For many cardiac transplant physicians, there is a pervasive unease that we have been overimmunosuppressing our pa-
tients. To this end, the authors are to be congratulated for pursing an aggressive reduced immunosuppression regi-
men early after heart transplantation in the form of tacrolimus monotherapy and dual therapy with mycophenolate mofetil. However, although the basic idea of the study was well conceived, there are several concerns. The most important of these is that the study was underpowered to demonstrate true differences in the primary and secondary end points. Rejec-
tion rates were low at 5%, which is consistent with what many centers are now reporting; thus, the number of patients needed to power this study was underestimated. The primary end point of 6-month composite biopsy score is another concern. The authors used the older 1990 International Society for Heart & Lung Transplantation biopsy grading scale. This grading scale is not linear, and the biopsy grading score, although used in other publications, has never been validated as a useful outcome tool. To further demonstrate that the older biopsy grades were either redundant or irrele-
vant, the revised 2004 International Society for Heart & Lung Transplantation biopsy grading scale reduced the number of

abnormal biopsy grades from 6 to 3. Finally, the IVUS data are not consistent, as the follow-up IVUS study was done at variable times, ranging from 12 to 24 months after transplant. Comparison of cross-sectional IVUS data is not reliable in such a small number of patients.

In addition, a control arm of routine triple-drug immuno-
suppression for comparison with the 2 study arms is lacking in the present study. Without a control arm in this study, it is not possible to assess the true benefit of tacrolimus mono-
therapy or dual therapy. The advantage of reduced immuno-
suppression appears logical, but is it truly beneficial in the long term? The use of tacrolimus monotherapy relied on maintaining a higher tacrolimus blood trough level through-
out the study, which appeared to result in reduced renal function. During the first year of this study, mean serum creatinine levels rose from 1.24 mg/dL at baseline to 1.64 mg/dL at month 12, begging the question of whether tacroli-
mus monotherapy (with higher trough levels) has fewer long-term adverse effects (eg, renal dysfunction) than lower tacrolimus trough levels with low-dose antiproliferative agents and corticosteroids. A study in 2007 reported on 33 select heart transplant patients (all with a creatinine level <2 mg/dL and no left ventricular assist device) who received tacrolimus and sirolimus with corticosteroids.3 To reduce both nephrotoxicity and CAV, both tacrolimus and sirolimus exposure were kept low (6 to 8 ng/mL). Corticosteroids were withdrawn successfully from all patients by 6 months. Only 1 acute rejection occurred, and there was 100% survival and no CAV at 2 years. Mean serum creatinine level was unchanged from baseline to 2 years, remaining at 1.3 mg/dL. Lower-dose triple-drug therapy with later corticosteroid wean (which is currently being done by many programs) may not be inferior to tacrolimus monotherapy with its higher targeted blood trough levels.

Although there are problems with the study design and plan, some of the clinical outcomes are noteworthy. Reduced immunosuppression with tacrolimus monotherapy and dual therapy administered to both study arms was associated with low incidences of rejection and infection, mortality, and the development of CAV. Another important observation from this study is that early steroid weaning appears practical and possible without adverse consequences, and this was ob-
erved in both study arms where all patients were withdrawn from corticosteroids by 8 weeks after transplant. Further, the study patients included relatively large numbers of high-risk (for rejection) subpopulations such as black patients (19%), women (19%), sensitized patients with panel-reactive anti-
body >10% (30%), and status 1A patients (57%). Finally, over the course of the 3-year median follow-up, there were no

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cases of corticosteroid reinstitution or a switch to another immunosuppressive medication.

The 100% success of corticosteroid weaning without any patient requiring reinstitution of corticosteroids in this study is laudable. Previous studies, albeit in earlier times, have reported between 40% to 60% of corticosteroid weaning failures, with these patients being restarted on corticosteroids. There may be many reasons for this successful corticosteroid weaning in the current study, including the use of higher target tacrolimus trough levels, more experienced pathology reading of biopsy specimens, and confidence of managing physicians to maintain corticosteroid-free immunosuppression despite a rejection episode. Early corticosteroid weaning also may be more successful because patients do not become corticosteroid dependent, as with long-term use. Patients are less likely to suffer from withdrawal symptoms that could lead to reinstitution when corticosteroids are weaned later.

The concept of early corticosteroid withdrawal is well established. In the mid 1980s, Yacoub et al demonstrated encouraging results with a steroid-free regimen. This pioneering work was quickly followed with several variations on the theme by other investigators weaning corticosteroids both early and late after transplantation. Most of these studies reported successful corticosteroid weaning in 50% to 80% of patients, all of whom were on cyclosporine-based immunosuppression. A more recent report evaluated corticosteroid weaning in 41 heart transplant patients treated with tacrolimus and mycophenolate mofetil, with 25 (62%) patients being successfully weaned within 1 year. These patients weaned from corticosteroids were then followed for 1 year and found to have a lack of metabolic benefits. The reason for this finding is because tacrolimus-based regimens have been shown to decrease hypertension and hyperlipidemia compared with cyclosporine-based regimens. In addition, early statin therapy is widely used in heart transplant patients, thus maintaining relatively lower lipid levels.

The concept of tacrolimus monotherapy has been previously reported. An initial retrospective study reported in 2001 revealed that of 43 patients initiated with tacrolimus and prednisone alone, 32 were subsequently weaned off steroids at a mean of 246 days posttransplant (range, 106 to 730 days). The freedom from treated rejection was 69% at 90 days and 52% at 1 year. The achievement of early tacrolimus weaning in 50% to 80% of patients, all of whom were on cyclosporine-based immunosuppression. A more recent report evaluated corticosteroid weaning in 41 heart transplant patients treated with tacrolimus and mycophenolate mofetil, with 25 (62%) patients being successfully weaned within 1 year. The achievement of early tacrolimus monotherapy in the current study with subsequent low rejection and CAV rates suggests that the immunosuppression protocol may be a key factor.

The authors speculate on the advantage of early lower immunosuppression and good outcome by mentioning an interesting protocol for administering immunosuppression. There is evidence that interruption of immunosuppression for 72 hours 1 day after transplant and subsequent engagement of donor and recipient effector cells in this initial period posttransplant (otherwise referred to as a WOFIE [window of opportunity for immunologic engagement]) allows the development of an immunoregulatory cell population. Indirect allore cognition, demonstrated to be the dominant immunologic pathway used by CD4+CD25+ T regulatory cells, bears strong impact on the development of chronic graft rejection. Thus, this mode of immunotherapy may not only protect the recipient from acute graft rejection, but also prevent chronic graft failure. A pilot study of 20 kidney transplant patients used induction with daclizumab with initiation of tacrolimus, mycophenolate mofetil, and prednisolone. After 1 day, mycophenolate mofetil and prednisolone immunosuppression was interrupted for 72 hours. Corticosteroid withdrawal followed within 12 to 16 weeks posttransplant. Compared to controls, this group of patients experienced less acute rejection episodes and developed better graft function. The treatment group also demonstrated an increase of CD4+CD25+ T regulatory cells that correlated with a significantly higher expression level of forkhead box P3 mRNA, which is the most definitive marker for this population. In the current study, no induction therapy was administered; however, relatively low doses of tacrolimus (target levels of 8 to 10 ng/dL within the first 7 to 10 days posttransplant) and mycophenolate mofetil (started at 500 to 1000 mg twice daily) were given. It is conceivable that this low level of immunosuppression in the first few days post-transplant (while tacrolimus levels were becoming therapeutic) allowed engagement of donor and recipient effector cells, possibly leading to an operational tolerance. It is, of course, speculation to believe that this process is actually occurring in the present study patients. Further investigation needs to be pursued.

Tacrolimus monotherapy and dual therapy may not be applicable for everyone. Patients who develop early antibody-mediated rejection are at risk for poor outcome as seen in this study and as reported by others. With only 1 immunosuppressive agent, medical compliance is paramount and could result in a disastrous outcome if trough blood levels become subtherapeutic. Certainly, this form of therapy cannot be broadly extended to all heart transplant patients. Nonetheless, it is encouraging to know that tacrolimus monotherapy or dual therapy early after transplant can be considered an option if this is needed for special cases such as intolerance to antiproliferative medications, severe infections, and severe existing side effects to corticosteroid therapy. There is growing conviction that today’s “standard” immunosuppression will someday be replaced by immunosuppression individualized for each patient on the basis of genomic profile, baseline risks for rejection and infection, and perhaps serial assessments of immune response after transplantation.

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References


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