

Rapamycin for Cardiac Transplant Rejection and Vasculopathy One Stone, Two Birds?

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Pour faire d'une pierre deux coups¹

Heart transplantation can now be routinely performed. Acute rejection has been significantly reduced, and the limitations to the use of this procedure include the availability of organs, chronic rejection, and a late reaction that is driven by a unique vasculopathy. Post-transplant vasculopathy (PTV) shares features with the lipoprotein-driven native atherosclerosis and proliferation-driven postangioplasty restenosis, but it has been thought to be more sensitive to immune forces. These distinctions are critical, for they dictate our choice of therapy. Hypercholesterolemia dictates treatments that lower lipoproteins or their effects; thrombotic events require antiplatelet agents, antithrombotics, and even agents that interfere with the clotting cascade; proliferative and migratory events can be inhibited by directed agents; and an immune disease would suggest use of immunosuppressants. To date, statins and immunosuppressants have been the mainstay of therapy for patients with heart transplants. These drugs were intended to simultaneously reduce rejection and post-transplant vasculopathy by limiting excessive lipid accumulation and exuberant inflammation. Recent reports, including the findings by Mancini et al² reported in this issue of *Circulation*, suggest that although reduction in rejection may directly follow from direct control of the immune response, the same is not true for the vasculopathy. Vascular disease in heart transplant patients is effectively controlled by an agent classified as an immunosuppressant but not because of immune modulation, rather because of antiproliferative effects.²

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Post-Transplant Vasculopathy

PTV is an aggressive and diffuse coronary arteriopathy that occurs in heart transplant recipients. With an annual incidence rate of 5% to 10% and an unremitting course, it is the

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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Circulation is available at <http://www.circulationaha.org>
DOI: 10.1161/01.CIR.0000080228.97133.4D

major factor limiting long-term survival after heart transplantation. Because the donor heart is denervated, PTV often presents on routine follow-up angiographies or symptomatically as congestive heart failure and/or sudden death. This vasculopathy is generally diffuse, is initially in small vessels, and then spreads to the entire cardiac vasculature. Pathological findings include concentric intimal hyperplasia with intact internal elastic lamina and a cellular infiltrate composed of proliferating smooth muscle cells, macrophages, and T lymphocytes. The pathological characteristics, although not uniform, differ from native atherosclerotic lesions mainly in their diffuse localization and concentricity, in contrast to the focal lesions in native coronary disease. Other differences include lack of calcium deposition, an intact internal elastic lamina, and the scarcity of collateral vessel development, as well as the rapid progression of transplant vasculopathy.

PTV: Standard Medical Therapy

Current medical therapies for PTV are based on modification of cardiovascular disease risk factors. Hyperlipidemia, diabetes, and hypertension all increase PTV extent and severity.³ HMG-CoA reductase inhibitors reduce the occurrence of the vasculopathy and improve transplant survival. Wenke et al⁴ recently reported that simvastatin therapy started on the fourth postoperative day increased 8-year survival and reduced the occurrence both of vasculopathy and of severe transplant rejection. Of note is that these statins were initiated early; late commencement is not as effective and does not reduce the extent of arterial disease.^{4,5} Although immunologic factors are considered to play a major role in the PTV pathogenesis, current immunosuppressive regimens have made little impact on its development. Cyclosporine, the main agent in use in transplant recipients these days, has a minimal effect on disease occurrence. Mycophenolate mofetil, an antimetabolite with a direct antiproliferative effect on smooth muscle cells, reduces mortality and the need for rejection treatment but has no effect on the vasculopathy.⁶ Revascularization procedures, although often applied in PTV focal lesions, are usually of limited success because of the distal, diffuse, and recurrent nature of the disease.⁷⁻⁹

PTV: Future Therapies?

Immunosuppressants have been used in organ transplantation since the first recognition of the importance of rejection. Several reports described the effects of specific and nonspecific immunomodulation on the vasculopathy and rejection. The Stanford group has been investigating rapamycin for almost a decade, reporting that the drug limits both rejection

and vascular disease.^{10–12} What is unique about the Mancini et al² report is that the effect of rapamycin was seemingly independent of its immunosuppression. In this single-center, open-labeled trial 46 transplant recipients with demonstrable vasculopathy were randomized to standard therapy or rapamycin. Twenty-four patients continued with their immunosuppressants, cyclosporine A, azathioprine, tacrolimus, and/or mycophenolate mofetil. Twenty-two other patients were randomized to receive rapamycin as a 6-mg loading dose and a 2-mg daily maintenance dose. HMG-CoA reductase inhibitors and antihypertensive medications were maintained in all patients, as were cyclosporine and tacrolimus when applicable. In contrast, azathioprine and mycophenolate-mofetil were discontinued in those who received rapamycin. Rapamycin treatment significantly reduced the number of patients who reached the primary (death, myocardial infarction, need for revascularization, or angiographic deterioration) and secondary (cardiac hospitalizations) end points. There was no difference in anti-HLA antibody production or in T-lymphocyte growth. Unlike simvastatin, which suppressed the vasculopathy only when started immediately after transplantation,^{4,5} rapamycin inhibited the course of vascular disease in patients long transplanted and with existing vasculopathy.

To the best of our knowledge, this is the first human study to demonstrate efficacy of pharmacological regulation in patients with existing advanced cardiac transplant vasculopathy. The results are in accordance with a previous animal model experiment that showed reduction of heart allograft vasculopathy in animals treated with rapamycin.¹² Taken together, it seems that drugs that appear to target elevated cholesterol metabolism or inflammation can reduce PTV independent of their anticipated primary effects. PTV in animals and patients was reduced with HMG-CoA reductase inhibitors and immunosuppressants independent of reduction in lipoproteins and immunomodulation, and with calcium channel blockers and angiotensin-converting enzyme inhibitors independent of effects on blood pressure. As all of these classes of drugs influence smooth muscle migration and proliferation, one is left wondering whether smooth muscle events must now be reconsidered as paramount to PTV.

Rapamycin: Mechanism of Action

Rapamycin is an immunosuppressive agent with potent antiproliferative and antimigratory properties on vascular smooth muscle cells.^{13–15} Yet its biggest claim to fame is not in its role as an immunosuppressant, but as the active agent in drug-eluting endovascular stents. Rapamycin-eluting stents reduce the development of in-stent restenosis.^{16,17} Rapamycin cellular actions are mediated through binding to the intracellular FK506 binding protein (FKBP12). FKBP12 binds drugs within a class of agents generally analogous to FK506 (tacrolimus). However, rapamycin is somewhat unique. Other agents in this class form a complex that inhibits calcineurin but has no antiproliferative and antimigratory effects. Rapamycin-FKBP12 does not inhibit calcineurin but rather suppresses TOR (target of rapamycin) kinase, which in turn regulates the cell cycle through an increase in p27^{kip1} protein and inhibition of retinoblastoma protein phosphorylation (see

ref 15 for a review). This unique aspect of rapamycin may explain the observed results. The question that arises is whether the difference in mechanism of action leads to a difference in activity against PTV. Current immunosuppressive regimens do not effectively control vasculopathy, and the immunosuppressive efficacy of rapamycin is not significantly different from that of these other agents. Moreover, in this current study, rapamycin slowed vasculopathy progression and reduced cardiovascular events while not affecting B- and T-lymphocyte-associated immunologic parameters. Thus, its efficacy against PTV may well be attributed to its antiproliferative and antimigratory actions.^{14,18} Nevertheless, a PTV-suppressive effect that is mediated mainly through the FK-506 binding protein cannot be totally negated on the basis of this study. Although FK-506 holds no antiproliferative and antimigratory capacities on smooth muscle cells in vitro^{13,14} and did not reduce transplant vasculopathy in animals,¹⁰ the clinical findings against PTV are mixed.^{19,20} In a recently reported study of heart transplant patients treated by tacrolimus as a sole immunosuppressive agent, the incidence of cardiac transplant vasculopathy was much lower than that reported by others.²¹ In the present small-scale study, no differentiation was made between tacrolimus- and rapamycin-treated patients. Future studies are warranted to clarify whether there is a difference between tacrolimus and rapamycin and whether TOR binding is the major mechanism by which rapamycin therapy achieves suppression of cardiac transplant vasculopathy. Furthermore, although immunomodulation through B- and T-cell function is probably not the underlying mechanism for the beneficial effect of rapamycin in suppressing vasculopathy, innate immunomodulation, which is exerted by rapamycin,²² may be associated with reduced vasculopathy.^{23,24}

Questions and Concerns

*Thomas Hobbes thinks to kill two birds with one stone, and satisfy two arguments with one answer, whereas in truth he satisfieth neither.*²⁵

The report in this issue of the journal² of a beneficial effect of rapamycin in patients with documented cardiac transplant vasculopathy may be a breakthrough in the treatment of this daunting complication of heart transplantation. The findings may shed further light on whether PTV is an immune or a proliferative disease or a mixture of both. Larger, multicenter studies are warranted to confirm the results, to investigate the efficacy of rapamycin when initiated immediately after cardiac transplantation, and to examine whether the positive effects can be extended to all patients or just to specific subsets, eg, to define whether the benefit is greatest in patients who have active vasculopathy, but are not new transplants, and whether coincident rejection offers greater responsiveness to the drug. Similarly, it will be fascinating to determine whether rapamycin is more effective, or less effective, with other drugs, such as antihypertensive or antilipid drugs, immunosuppressants, etc, and what the mechanism of any synergistic effect is. Finally, an investigation of the adverse effects that are associated with rapamycin in this subset of patients is warranted. A recent pilot study of

systemic rapamycin in recalcitrant in-stent restenosis did not report any beneficial effect in treated patients.²⁶ The study population consisted of a small number of patients, but the rate of adverse effects that called for cessation of therapy was 50%, much higher than that reported by Mancini et al.²

Although questions remain, the study by Mancini et al² continues our evolving understanding and treatment of the complex diseases associated with heart transplantation. It is appealing to believe that we can kill two birds, organ rejection and vasculopathy, with one stone. Only time will tell if we satisfy both arguments with one answer.

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KEY WORDS: Editorials ■ transplantation ■ rejection ■ vasculature