Drug Therapy in the Heart Transplant Recipient
Part III: Common Medical Problems

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Continued improvement in the long-term survival of heart transplant recipients has resulted in a population of patients with prolonged exposure to immunosuppressive drugs.[1] This exposure, coupled with the increasing age of recipients, has resulted in an impressive prevalence of comorbidities in these patients. Indeed, by 5 years after transplantation, 95% of recipients have hypertension, 81% have hyperlipidemia, and 32% have diabetes.[1] In addition, 25% to 50% have coronary allograft vasculopathy (CAV), and up to 33% have chronic renal insufficiency.[2–5] As more drugs are developed to both prevent and treat these problems and common infectious complications after transplantation, it is likely that the heart transplant recipient will be taking an increasing number of drugs. Because standard immunosuppressive drugs have a high potential for drug–drug interactions, the heart transplant recipient is subject to an enormous risk for drug–drug interactions. In this article, we briefly review common medical problems in heart transplant recipients that are routinely addressed with drug therapy. In Part IV of this series, we provide specific details of known important and common drug–drug interactions, along with recommendations for management.

Coronary Allograft Vasculopathy

CAV was described in Part I of this series. The mechanism is incompletely understood but is likely a consequence of both immunologic and nonimmunologic factors.[3] CAV is present in 42% of heart transplant recipients at 5 years.[3] After the first posttransplantation year, CAV is responsible for ≈20% of all deaths.[1,6] CAV often involves the coronary arteries in a diffuse fashion, making percutaneous coronary interventions or bypass surgery less effective in many cases. Prognosis remains poor after the development of CAV.[7] No effective prevention for CAV is available, although statins seem to improve prognosis in heart transplant recipients, at least in part by ameliorating CAV.[8–10]

Hypertension

Hypertension is common after heart transplantation, occurring in 50% to 95% of heart recipients.[6,11,12] The excess risk of hypertension is attributable primarily to the use of calcineurin inhibitors (CIs) because of both direct effects and the associated renal insufficiency.[13,14] Although both are CIs, the incidence of hypertension is lower in patients treated with tacrolimus than with cyclosporine A (CSA).[15,16] No randomized trials in heart transplant recipients are large enough to evaluate the effect of antihypertensive therapy on morbidity, mortality, and graft survival, but it is likely that antihypertensive therapy has similar, if not greater, benefits in the heart transplant recipient than in the general population. One reason is that blood pressure after cardiac transplantation is characterized by a disturbed circadian rhythm without the normal nocturnal blood pressure fall and with a greater 24-hour hypertensive burden.[11,17,18] Most randomized trials comparing different antihypertensive drugs have been performed in kidney transplant recipients and have not demonstrated the superiority of any drug class.[19–23] A small, prospective, randomized study in heart transplant recipients compared lisinopril with diltiazem for 1 year and revealed no significant difference in blood pressure control, mortality, creatinine, or side effects between the 2 agents.[24] Among calcium channel blockers, diltiazem is often used because its inhibition of cytochrome P450 (CYP450) 3A4 allows a reduction in CI dose and because of reported favorable effects on VAC.[25] Posttransplantation hypertension frequently is difficult to control and often requires a combination of several antihypertensive agents.[24,26] Blood pressure after cardiac transplantation is sensitive to a low sodium diet.[27] In the heart transplant recipient, there are important pharmacokinetic interactions with the calcium channel blockers and important pharmacodynamic interactions with ACE inhibitors. Both are discussed in Part IV of this series.

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Hyperlipidemia

Lipid abnormalities are present in 60% to 81% of heart transplant recipients.[28–30] Hyperlipidemia is thought to play a role in the development of CAV, cerebrovascular disease, and peripheral vascular disease.[30,31] Characteristically, total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides increase by 3 months after transplantation and then generally fall somewhat after the first posttransplantation year.[8,32,33] Immunosuppressive drugs, loop diuretics, and renal insufficiency all contribute to posttransplantation hyperlipidemia.[30,32,33] CIs, prednisone, and the target of rapamycin inhibitors sirolimus and everolimus all exacerbate hyperlipidemia.[33,34] One randomized trial and several nonrandomized studies have demonstrated that tacrolimus has similar, although less marked, effects on cholesterol, LDL cholesterol, and triglycerides as CSA.[33,35]

The HMG-CoA reductase inhibitors (statins) are as effective in reducing LDL cholesterol in heart transplant recipients as in the nontransplant population.[8,9] Two randomized trials comparing pravastatin (20 to 40 mg) or simvastatin (5 to 20 mg) with placebo in heart transplant recipients have demonstrated benefits of statins on mortality, rejection associated with hemodynamic compromise, and CAV.[8–10] The benefits of statins in heart transplant recipients have been suggested to be even greater than in the general population and may be due to both cholesterol lowering and immune modulating effects.[8,29] From these data, statins are routinely prescribed to heart transplant recipients according to guidelines provided in Part IV of this series and other reviews.[29] However, there is considerable controversy as to which statin and what doses to use in transplant recipients taking CIs, primarily because of the risk of rhabdomyolysis when these drugs are used together. Rhabdomyolysis was not observed in the 2 randomized trials discussed above using pravastatin and simvastatin.[8–10] One observational study that compared simvastatin (20 mg/d) with pravastatin (40 mg/d) demonstrated an increased risk of rhabdomyolysis with simvastatin, but another study did not.[36,37] In general, pravastatin is used at doses of 20 to 40 mg, whereas other statins are used at lower than the maximally approved dose for the nontransplant population. Pravastatin may have a lower incidence of rhabdomyolysis because it is not metabolized by cytochrome enzymes like the other statins.[38] The incidence of rhabdomyolysis increases substantially when statins are used in high doses in these patients or when fibrates or niacin is added, and these combinations are generally contraindicated in patients taking CIs.[29] If statins cannot be used and bile acid sequestrants are prescribed, care must be taken to separate the timing of administration to prevent the bile acid sequestrants from interfering with the absorption of CSA. Ezetimibe is a reasonable alternative in patients who cannot tolerate statins because it does not cause rhabdomyolysis. However, ezetimibe has not been compared with statins to determine whether it results in equivalent efficacy on rejection, graft atherosclerosis, or mortality. Although elevated triglycerides may be important in the development of CAV, no randomized trials have evaluated triglyceride lowering in these patients.[29] Fibrates may decrease CSA levels, and the combination of a statin and a fibrate significantly increases the risk for rhabdomyolysis.[29] The specific mechanisms and magnitude of drug–drug interactions with the lipid-lowering agents are discussed in Part IV of this series.

Diabetes

Diabetes occurs in 32% of heart transplant recipients.[6] A number of factors, including pretransplantation diabetes, glucocorticoids, and CIs, contribute to the high prevalence of diabetes.[39] Tacrolimus is associated with a higher incidence of posttransplantation diabetes than CSA, especially in blacks and when used in higher doses.[40] Diabetes is associated with a poorer long-term survival in both renal and heart transplant recipients.[39,41] There are remarkably few data about the treatment of diabetes in the heart transplant recipient and few reports of drug–drug interactions between hypoglycemic and immunosuppressive drugs. Indeed, even a recent consensus guideline on diabetes in transplant patients did not address specific drug therapy.[41] With the increased prevalence of renal insufficiency in heart transplant recipients, one would expect relative contraindications to metformin and fluid retention and weight gain with the thiazolinediones.[42] Shorter-acting sulfonylureas are preferred over longer-acting sulfonylureas in patients with renal insufficiency.

Chronic Renal Insufficiency

Renal insufficiency is a common adverse effect of CIs, and no effective therapy has been developed to prevent this problem. Creatinine levels >2 mg/dL occur in 24% to 33% of heart transplant recipients at 4 to 5 years after transplantation, and 3% to 8% ultimately develop end-stage renal disease.[4,5,43,44] It is not known whether ACE inhibitors or angiotensin receptor blockers are effective in decreasing the progression of CI-induced renal disease. The decrease in glomular filtration rate after transplantation results in an increased potential for drug–drug interactions with drugs secreted or eliminated by the kidney.

Antiplatelet Therapy

CAV causes as many deaths in years 1 to 3 after transplantation as do infections or rejection and is responsible for 17% of all deaths occurring after the third posttransplantation year.[6] Routine use of antiplatelet agents, especially aspirin, in cardiac transplant recipients is based on their utility in nontransplant patients with ischemic heart disease, along with data suggesting that enhanced platelet activity may be important in the pathogenesis of CAV.[45]

There are no randomized trials evaluating the benefits of antiplatelet therapy in heart transplant recipients. Animal studies using antiplatelet agents and studies in human heart transplant recipients using warfarin and dipyridamole have shown conflicting results for CAV.[46–48] Studies suggest that heart transplant recipients appear to be aspirin resistant compared with a nontransplant population even at aspirin doses as high as 500 mg/d.[49] Evaluation of ticlopidine at a dose of 250 mg BID in 12 patients showed profound suppression of platelet aggregation.[50] Ticlopidine, however, decreases CSA levels, which can lead to rejection.[50] Rhabdomyolysis has been reported with clopidogrel.[51] Currently, it remains uncertain whether heart transplant recipients should continue to use standard doses of aspirin, use higher doses of

aspirin, switch to thienopyridines, or abandon the use of antiplatelet agents altogether. Additional interactions between CIs and thienopyridines are discussed in Part IV of this series.

Infection Prophylaxis

Infections cause ≈20% of deaths in the first year after transplantation and remain a common cause of morbidity and mortality after the first year.[6] With the advent of routine prophylaxis, the predominant infections seen in the first month after transplantation are nosocomial bacterial and fungal infections related to mechanical ventilation, catheters, and the surgical site. Before routine use of prophylaxis during periods of increased immunosuppression, reactivation of herpes simplex and infections with opportunistic infections such as *Pneumocystis jiroveci (carinii)* (PCP), cytomegalovirus (CMV), *Aspergillus* species, and *Nocardia* species were common.[52,53] Prophylaxis against CMV, PCP, herpes simplex virus, and oral candidiasis now is used routinely during the first 6 to 12 months after transplantation when the risk of these infections is high. After the initial 6 posttransplantation months, the most common infections are community acquired, and prophylactic antibiotics can generally be discontinued.

Pneumocystis jiroveci (carinii)

Before the institution of prophylaxis, PCP was seen in 9% to 11% of all heart transplant recipients, with a mortality rate of 11% to 38%.[53] The prophylactic use of trimethoprim-sulfamethoxazole (1 double-strength tablet 3 to 7 times per week) has eliminated PCP.[52,53] This prophylactic regimen is also highly effective for preventing *Nocardia* infection and toxoplasmosis. Trimethoprim-sulfamethoxazole prophylaxis is generally reinstituted during episodes of increased risk for PCP such as enhanced immunosuppression with antilymphocyte agents or acute and chronic rejection.[54] Potential side effects include rash, renal insufficiency, hyperkalemia, and bone marrow suppression.[55]

Fungal Infections

Aspergillosis and *Candida* species are the most common fungal infections after heart transplantation. Nystatin oral solution or clotrimazole troches are routinely used in the first 6 to 12 posttransplantation months or with enhanced immunosuppression to prevent oral candidiasis. In patients who present a higher risk for systemic fungal infections, fluconazole, itraconazole, or occasionally amphotericin-B may be prescribed prophylactically. Voriconazole, fluconazole, and itraconazole have a high potential for drug–drug interactions with CIs and sirolimus and are discussed in detail in Part IV of this series. Caspofungin has not yet been evaluated as prophylactic therapy.

Viral Infections

Viral infections, especially CMV, are a major cause of morbidity and mortality, with an incidence of CMV as high as 24% in CMV IgG-negative recipients of CMV IgG-positive donor hearts (D+/R−).[56] CMV infection has been associated with CAV, rejection, and enhanced immunosuppression, resulting in additional opportunistic infections such as fungal disease and end-organ disease (eg, pneumonitis, retinitis, and bone marrow involvement).[54,56–61] Use of prophylactic intravenous ganciclovir or oral valganciclovir in the CMV-seronegative recipient of a CMV-positive donor has been shown to effectively prevent CMV infection in this high-risk population.[59,62–64] In addition, preemptive use of oral valganciclovir or intravenous ganciclovir in all transplant recipients with evidence of active CMV viremia on routine monitoring has been shown to prevent symptomatic disease.[59,63] Ganciclovir may result in bone marrow suppression, and routine complete blood count monitoring is required. Reactivation of herpes simplex virus 1 and 2 and herpes zoster occurs commonly after transplantation, so patients who are seropositive routinely receive prophylaxis with acyclovir, famciclovir, or valacyclovir. In patients taking ganciclovir or valganciclovir for CMV, no additional prophylaxis for herpes simplex virus is necessary.

Gout

The high risk of drug–drug interactions makes gout a particularly vexing therapeutic problem.[65] Causes of gout after heart transplantation include pretransplantation gout, use of CI, frequent use of loop diuretics, and renal insufficiency.[66] Because there are significant pharmacokinetic and pharmacodynamic drug–drug interactions with nonsteroidal anti-inflammatory drugs and colchicine, glucocorticoids are often used to treat episodes of acute gout. Colchicine may be used to treat acute gout, but there appears to be an increased risk of colchicine myoneuropathy, which is discussed in more detail in the drug–drug interaction section.[66] Nonsteroidal anti-inflammatory drugs often result in worsening renal insufficiency and hyperkalemia, especially in patients taking CIs. Prophylaxis of recurrent gout with allopurinol is effective, but doses of allopurinol and azathioprine must be reduced significantly when used together, and this combination usually is avoided because of the potential for life-threatening neutropenia.[67] There is no interaction between mycophenolate mofetil and allopurinol. Uricosuric agents may be effective in some patients.

Osteoporosis

Osteoporosis resulting in vertebral fractures is a common and debilitating problem after heart transplantation. The cause is multifactorial, compounded by the nearly 50% pretransplantation prevalence of osteopenia and osteoporosis in patients with advanced heart failure.[68,69] Glucocorticoids are the major factor in additional bone loss after transplantation, with contributions from renal insufficiency and CIs. Two years after heart transplantation, as many as 28% of recipients have osteoporosis in the lumbar spine, with vertebral fractures reported in up to 30%.[70–72] The risk for fractures is highest in those with osteoporosis, but fractures may develop even in those with normal bone density before transplantation.[71,72] Most bone loss occurs in the first 6 to 12 months after transplantation when steroid doses are highest.[73] Bisphosphonates have been shown to prevent bone loss and fractures in nontransplant patients receiving glucocorticoids.[74,75] Several, but not all, studies suggest that bisphosphonates can prevent bone loss and fractures after cardiac and liver transplantation.[69,76,77] Bisphosphonates have a lower risk of hypercalciuria than calcitriol.[77] Recommendations for patients receiving

>5 mg/d prednisone for 3 months include calcium (1500 mg/d) and vitamin D (800 IU/d), regular weight-bearing exercise, and a bisphosphonate.[78,79]

Depression

Depression has been reported in up to 25% of cardiac transplant recipients at 1 to 3 years after transplantation, with most episodes seen in the first year.[80] There is an 18% prevalence of depression even at 5 and 10 years after transplantation.[81] Thus, a large number of heart transplant recipients are likely to be taking antidepressant drugs. There are substantial differences in the effect of various selective serotonin reuptake inhibitors on CSA levels, as discussed in Part IV of this series.

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