

■ clinical medicine

How Can We Manage Hyperlipidemia and Avoid Rhabdomyolysis in Transplant Patients?

Case Summary

A 25-year-old man with a history of perinuclear antineutrophil cytoplasmic antibodies-associated vasculitis presented to the ambulatory clinic with five days of diffuse myalgias and muscle tenderness. The patient had undergone kidney transplantation three years before presentation and had no post-transplant complications. He was maintained on cyclosporine, prednisone, and mycophenolate mofetil. Simvastatin 20 mg daily was started two months after transplantation for development of post-transplant hyperlipidemia. Three months before presentation, the creatinine concentration was 1.8 mg/dL. Two months before presentation, the simvastatin dosage was increased to 40 mg daily.

Results of laboratory studies done at presentation were remarkable for the following: creatine kinase, 25,000 U/L; aspartate aminotransferase, 767 U/L; alanine aminotransferase, 620 U/L; and creatinine, 2.3 mg/dL. Urinalysis revealed 4+ blood and 2+ protein. The cyclosporine concentration, 265 ng/mL, was above the normal range of 100 to 200 ng/mL.

A diagnosis of rhabdomyolysis was made on the basis of the symptom of myalgias in the setting of acute renal failure and an elevated creatine kinase concentration. Simvastatin was discontinued, and the patient was instructed to self-hydrate. At one day, five days, and two weeks after initial presentation, follow-up clinical evaluations found that symptoms had eased, and follow-up laboratory studies showed improvement.

Cyclosporine and Statins

Cardiovascular disease is the most significant cause of death in patients with a functioning renal allograft (Figure 1).¹ Hyperlipidemia is very common in these patients,² making strict lipid control a key to reduce

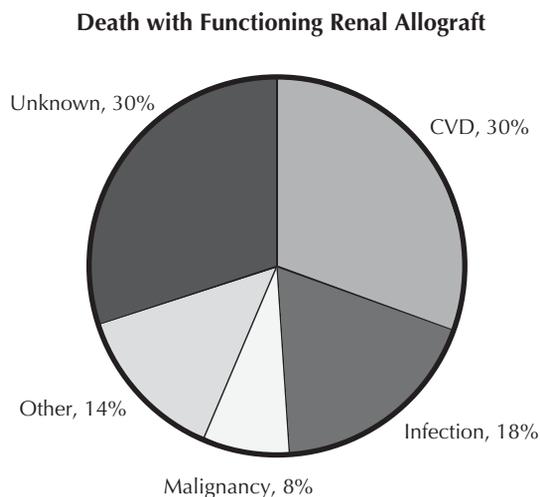


Figure 1. Causes of death in patients with functioning kidney allograft¹

mortality. Post-transplant hyperlipidemia is caused by many factors, including age, body mass index, genetic predisposition, and receipt of immunosuppressive agents such as cyclosporine, prednisone and rapamycin.

The increased daily dosage of simvastatin to 40 mg with concomitant use of cyclosporine caused rhabdomyolysis in the patient described in this case study. Thus, this case illustrates important facts about the concomitant use of statins and cyclosporine in transplant patients. First, these patients may present to the outpatient clinic with slight and minor complaints, making it important for the primary care provider to have a high index of suspicion of rhabdomyolysis. Second, patients taking cyclosporine and a statin medication are at risk for contracting rhabdomyolysis, a known drug-drug interaction.³ Finally, close monitoring and

Joseph M Kahwaji, MD, MPH
Ryszard R Dudek, MD

... patients taking cyclosporine and a statin medication are at risk for contracting rhabdomyolysis, a known drug-drug interaction.³



Joseph M Kahwaji, MD, MPH, (left) is a nephrology fellow at the KP Los Angeles Medical Center. E-mail: joseph.m.kahwaji@kp.org.
Ryszard R Dudek, MD, (right) is a staff nephrologist at the KP Los Angeles Medical Center. E-mail: riszard.r.dudek@kp.org.

Table 1. Characteristics of statins^{5,9}

Statin	Daily dosage (mg/day)	CYP metabolism	P-glycoprotein substrate	OATP2 substrate	Lipophilic
Atorvastatin	10-80	3A4	Yes	Yes	Yes
Fluvastatin	20-40	2C9	No	No	Yes
Lovastatin	20-80	3A4	Yes	Yes ^a	Yes
Pravastatin	10-80	None	Yes	Yes	No
Rosuvastatin	10-40	2C9 (minor)	No	Yes	No
Simvastatin	20-80	3A4	Yes	Possibly	Yes

^a Hsiang B, Zhu Y, Wu Y. A novel human hepatic organic anion transporting polypeptide (OATP2). Identification of a liver-specific human organic anion transporting polypeptide and identification of rat and human hydroxymethylglutaryl-CoA reductase inhibitor transporters. *J Biol Chem* 1999 Dec 24;274(52):37161-8.

patient education are important to help reduce the development of rhabdomyolysis.

Statin Metabolism

Statin vary in their characteristics (Table 1). Although statin serum concentrations increase when administered with cyclosporine,^{3,8} the reasons differ.

Cyclosporine is an inhibitor of the cytochrome P450 isoenzyme 3A4 (CYP3A4) and possibly of the active transport mechanisms OATP2 (organic anion transporting polypeptide-2) and P-Glycoprotein, which are involved in the biliary excretion of statins. Lovastatin, simvastatin, and atorvastatin are metabolized by CYP3A4. Lovastatin and atorvastatin are excreted into the bile, and simvastatin is likely to be excreted to the bile, causing increased serum concentrations when used with cyclosporine. Fluvastatin is metabolized primarily by the cytochrome P450 isoenzyme 2C9 (CYP2C9), but is also extensively excreted in the bile, causing increased serum concentration when used with cyclosporine. Pravastatin and rosuvastatin are not metabolized by CYP3A4; nonetheless, increased concentrations of these drugs have also been observed when administered with cyclosporine perhaps because these drugs are substrates of OATP2.^{5,9}

Managing Hyperlipidemia in Kidney Transplant Patients

Managing hyperlipidemia in kidney transplant recipients should follow the National Kidney Foundation Kidney Disease Outcome Quality Initiative guidelines,¹⁰ which state that kidney transplant recipients should be considered at high risk for cardiovascular disease. The guidelines consider that a low-density lipoprotein concentration of less than 100 mg/dL is optimal.

Statins are the mainstay of medical treatment in kidney transplant recipients. They not only improve the lipid profile but may also protect graft function and

directly impede atherosclerosis.¹¹ Depending on a patient's lipid profile, one may initially institute dietary modification, increased physical activity, and weight-reduction therapies.^{12,13} However, this is rarely enough to achieve target levels, and statin therapy should be initiated. Studies have shown the efficacy and safety of low dose statin therapy in this population.^{2,11,12,14} In particular, an average daily dosage of 10 mg simvastatin and 20 mg lovastatin had proved efficacy with minimal adverse outcomes.^{13,15} Fluvastatin and pravastatin have also proven to be of benefit in this population.^{3,16,17}

Other interventions are recommended in those with other types of dyslipidemias that cannot be controlled with statins.¹¹ The addition of fish oil by itself has been tried if the patient's lipid profile initially shows isolated hypertriglyceridemia or in combination with a statin in patients with mixed hyperlipidemia. Fish oil may reduce platelet aggregation, decrease blood pressure, and benefit graft function. Addition of a fibrate is not recommended because of the increased risk of myopathy in patients on statins. However, fibrates may be used as monotherapy for patients with low HDL associated with high triglycerides. Care must be taken to monitor creatinine and cyclosporine levels with fibrate use because their levels may decrease. The minimal dose needed to achieve the lipid goal is recommended. The use of niacin is limited mainly because of flushing and gastrointestinal side effects.

Giving antioxidant vitamins or folate to those with hyperhomocysteinemia to reduce the effects of oxidized LDL has not shown to be effective in preventing cardiovascular outcomes.¹¹ Cyclosporine increases homocysteine concentrations perhaps by disrupting folate-assisted remethylation.¹¹ Supplementing folic acid to correct this in patients on cyclosporine would not be beneficial because the folate cannot be utilized for remethylation.

... kidney transplant recipients should be considered at high risk for cardiovascular disease.

When target lipid levels cannot be achieved by medical management, thought is given to changing the patient's immunosuppression regimen. These adjustments are best made by the nephrologist. Prednisone can sometimes be tapered with or without a change in the azathioprine or mycophenolate mofetil dose. Cyclosporine can also be adjusted in such a manner. Sirolimus may also cause hyperlipidemia and can sometimes be discontinued or replaced. Tacrolimus has not been reported to cause hyperlipidemia.

Recommendations

On the basis of current evidence, we recommend the following:

- Periodically check levels of aspartate aminotransferase and alanine aminotransferase.
- Check activities of aspartate aminotransferase, alanine aminotransferase, and creatine kinase upon
 - Start of statin therapy.
 - Change of statin dose.
 - Start of drugs known to interfere with cytochrome P450.
 - Complaints of symptoms.
 - Higher than therapeutic cyclosporine levels.
- Start statin daily dosage at 50% of the daily dosage for nontransplant patients and titrate up to no more than 25% of the maximal dose in nontransplant patients. (Statin medications have been safely used at these dosages.^{13,14})
- Monitor symptoms of rhabdomyolysis while patients are on statin therapy.
- Educate patients about their symptoms so they can report them to their doctor when they occur.
- Discontinue a statin if rhabdomyolysis develops and check cyclosporine and serum creatinine levels.
- Hospitalize a patient in the following situations:
 - Increase in creatine kinase more than mild.
 - Oliguria or acute kidney failure develop.
 - Pain more than mild; overall functioning decreases; self-hydration not reliable.

Consider prescribing fluvastatin or pravastatin as suitable alternatives to other statins because few side effects related to myopathy for these two have thus far been reported.³❖

Acknowledgment

Michael S Altus, PhD, ELS, provided editorial assistance.

References

1. US Renal Data Service. USRDS Annual Data Report 2005: Atlas of End Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda (MD), 2005, p 152.
2. Massy ZA. Hyperlipidemia and cardiovascular disease after organ transplantation. *Transplantation* 2001 Sep 27;72(6 suppl):S13-5.
3. Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med* 2003;163(13):1615-6.
4. Goldberg R, Roth D. Evaluation of fluvastatin in the treatment of hypercholesterolemia in renal transplant recipients taking cyclosporine. *Transplantation* 1996 Dec 15;62(11):1559-64.
5. McKenney JM. Efficacy and safety of rosuvastatin in treatment of dyslipidemia. *Am J Health Syst Pharm* 2005 May 15;62(10):1033-47.
6. Muck W, Mai I, Fritsche L, et al. Increase in cerivastatin systemic exposure after single and multiple dosing in cyclosporine-treated kidney transplant recipients. *Clin Pharmacol Ther* 1999 Mar;65(3):251-61.
7. Arnadottir M, Eriksson LO, Thysell H, Karkas JD. Plasma concentration profiles of simvastatin 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitory activity in kidney transplant recipients with and without cyclosporin. *Nephron* 1993;65(3):410-3.
8. Olbricht C, Wanner C, Eisenhauer T, et al. Accumulation of lovastatin, but not pravastatin, in the blood of cyclosporine-treated kidney graft patients after multiple doses. *Clin Pharmacol Ther* 1997 Sep;62(3):311-21.
9. Launay-Vacher V, Izzedine H, Deray G. Statins' dosage in patients with renal failure and cyclosporine drug-drug interactions in transplant recipient patients. *Int J Cardiol* 2005 May 11;101(1):9-17.
10. Kasiske B, Cosio FG, Beto J, et al; National Kidney Foundation. Clinical practice guidelines for managing dyslipidemias in kidney transplant patients: a report from the Managing Dyslipidemias in Chronic Kidney Disease Work Group of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative. *Am J Transplant* 2004;4 Suppl 7:13-53.
11. Arnadottir M, Berg AL. Treatment of hyperlipidemia in renal transplant recipients. *Transplantation* 1997 Feb 15;63(3):339-45.
12. Kobashigawa JA, Kasiske BL. Hyperlipidemia in solid organ transplantation. *Transplantation* 1997 Feb 15;63(3):331-8.
13. Kobashigawa JA, Murphy FL, Stevenson LW, et al. Low-dose lovastatin safely lowers cholesterol after cardiac transplantation. *Circulation* 1990 Nov;82(5 Suppl):IV281-3.
14. Massy ZA, Kasiske BL. Post-transplant hyperlipidemia: mechanisms and management. *J Am Soc Nephrol* 1996 Jul;7(7):971-7.
15. Cheung AK, DeVault GA Jr, Gregory MC. A prospective study on treatment of hypercholesterolemia with lovastatin in renal transplant patients receiving cyclosporine. *J Am Soc Nephrol* 1993 Jun;3(12):1884-91.
16. Holdaas H, Hartmann A, Stenstrom J, Dahl KJ, Borge M, Pfister P. Effect of fluvastatin for safely lowering atherogenic lipids in renal transplant patients receiving cyclosporine. *Am J Cardiol* 1995 Jul 13;76(2):102A-106A.
17. Goldberg RB, Roth D. A preliminary report of the safety and efficacy of fluvastatin for hypercholesterolemia in renal transplant patients receiving cyclosporine. *Am J Cardiol* 1995 Jul 13;76(2):107A-109A.