Cyclosporine A andLovastatin: the Good and the Bad, but who will be the winner?

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FOR THE PAST 30 YEARS, cyclosporine A (CsA) has played a significant role as an immunosuppressive agent in anti-rejection therapy for organ transplantation, including kidney transplants (2). CsA inhibits the protein phosphatase calcineurin, which suppresses the immune response (16). However, even with its many advantages as an anti-rejection drug, CsA exhibits a number of side effects, such as hypertension (7), nephrotoxicity (14, 17), increasing cholesterol [hypercholesterolemia (19)], K+ retention [hyperkalemia (1)], and apoptosis (18). All of these side effects are disconcerting to transplant patients and can confound kidney function and long-term quality of life. Therefore, a “fine” line needs to be drawn when administering drugs to patients, and the cost-benefit to the patient is of the utmost importance. Certainly, the posttransplant administration of CsA has made a major contribution to the reduction of organ transplant rejections of patients. Even though the major advantage of CsA might outweigh the potential side effects, it is vital that we determine ways to ameliorate the side effects of CsA, thus improving the management of postoperative care of the kidney transplant patient.

It is common for kidney transplant patients to suffer from abnormal lipid levels (dyslipidemia), which can result in cardiovascular abnormalities along with long-term kidney dysfunction (3, 10, 11). Statins, such as lovastatin, are a class of drugs that modulate the levels of cholesterol by inhibiting 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase, which blocks the cholesterol biosynthetic pathway, thus reducing cholesterol levels, resulting in controlled serum lipid levels. Unfortunately, the use of statins has unwanted side effects, such as rhabdomyolysis (breakdown of muscle) and apoptosis (4, 8), that need to be therapeutically managed.

A relatively standard posttransplant drug therapy regime is the simultaneous administration of CsA and statins to insure reducing possible organ rejection and modulating the potential abnormal cholesterol/lipid levels that might result in cardiovascular risks for the transplant patient. There has been research examining the interactions of CsA and statins, including lovastatin (5, 9), which has generated debate as to the effective doses of CsA and lovastatin and other statins that are safe and beneficial for the patient (11, 15). The debate about the use of CsA and lovastatin will, undoubtedly, continue at the level of the organ (e.g., kidney). However, there are other important questions to ask with regard to the coadministration of CsA and lovastatin on kidney function, such as: What are the effects of CsA and lovastatin at the level of the nephron and the renal epithelial cells? Also, do these drugs affect the membrane structure and/or result in nephrotoxicity (e.g., apoptosis) of the epithelial cells?

Unfortunately, there appears to be a dearth of experimental evidence that targets potential molecular mechanisms by which statins can alter the side effects of CsA at the cellular level. Additionally, is it possible that statins can lessen the side effects of CsA and vice versa? In this issue of American Journal Physiology-Renal Physiology, He-Ping Ma’s group (13) provides very exciting data that suggest that statins might benefit patients that receive CsA after an organ transplant and that CsA may be useful in reducing the side effects of extended statin-induced kidney nephrotoxicity. Ma and colleagues (13) used the mouse cortical collecting duct principal cell line (mpkCCD14 cells) to investigate the reciprocal effects of CsA and lovastatin on transepithelial resistance and cell topography, expression of the tight junctional protein zonula occludens (ZO)-1 via a cholesterol-dependent manner, levels of cholesterol in or around the tight junctional complex, and the induction of apoptosis and ROS levels of mpkCCD14 cells. Their significant findings include that, first, CsA, which has been shown to elevate levels of cholesterol (19), increased the transepithelial resistance of the epithelial monolayer of mpkCCD14 cells, which was antagonized by lovastatin. Second, using scanning ion conductance microscopy nanotechnology, for the first time, the authors demonstrated that CsA induced topographic changes in the tight junctional complex of the cell membrane, which increased membrane protrusions near the tight junctions, and this may be responsible for the altered paracellular permeability; these protrusions were alleviated by lovastatin. Third, furthermore, these authors demonstrated remodeling of the tight junctions as CsA increased the amount of ZO-1 in mpkCCD14 cells, which was abolished in the presence of lovastatin. Fourth, using the cholesterol-binding compound filipin, it was demonstrated that CsA enhanced the levels of cholesterol both in the tight junctional complex and in the apical membrane of mpkCCD14 cells and that lovastatin attenuated the effect of CsA on the levels of cholesterol. Fifth, lovastatin reduced the induction of apoptosis of mpkCCD14 cells by high concentrations of CsA. Sixth, sustained treatment of lovastatin resulted in apoptosis of mpkCCD14 cells, which was reduced in the presence of CsA. Seven, high concentrations of CsA caused oxidative stress, resulting in elevated levels of intracellular ROS in mpkCCD14 cells by activation of NADPH oxidase potentially via activation of p47phox expression. Finally, in contrast to CsA, lovastatin had no effect on the levels of ROS. Overall, this report provides very convincing evidence that the potential management of dose levels of CsA and lovastatin can be modulated to provide successful analgesic benefits for a kidney transplant patient. There are some extremely stimulating “take-home” messages from the Ma et al. study (13). Previously, Ma and

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demonstrated that tacrolimus (another calcineurin inhibitor) involving inhibition of the ATP-binding cassette transporter (e.g., increase transepithelial resistance). Second, their observations that CsA increased, whereas lovastatin decreased, the levels of cholesterol in the tight junctional complex is significant because these observations suggest that there may be local synthesis of cholesterol in renal epithelial cells and that the levels of cholesterol in the tight junctions can be modulated locally (13).

This report is very intriguing as we have two different modulators of cholesterol that, under specific conditions, can regulate basic physiology with potentially positive outcomes for the transplant patient. The implications of this report are very thrilling and certainly warrant further investigation into the interactions of CsA and lovastatin on the effect of other transport function by principal cells of the collecting duct. Coupled with those observations, Ma and co-workers (19) suggested that CsA may lead to hypertension by upregulating the epithelial Na+ channel via an increase in cytosolic or membrane cholesterol involving inhibition of the ATP-binding cassette transporter (ABCA1). Furthermore, these authors suggested that changes in cholesterol levels in the cell membrane might play a role downstream of ABCA1 (19). Ellison and co-workers (6) demonstrated that tacrolimus (another calcineurin inhibitor) increased activation of the Na+-Cl– cotransporter (NCC), which contributed to hypertension in mice. Furthermore, they reported that thiazides (inhibitors of NCC) reduced renal complications of hypertension in renal transplant patients who were receiving inhibitors of calcineurin (6). These studies suggest it would be very tempting for Ma and colleagues to examine the physiological dynamics of CsA and lovastatin on other ion transport proteins that play a role in overall Na+ and K+ transport function by principal cells of the collecting duct. Candidate ion transport proteins to pursue would certainly include the epithelial K+ channel and Na+-K+-ATPase.

Finally, we are assured that the use of CsA as an antirejection transplant drug is here to stay. CsA has major advantages to the long-term health benefits and outcome of a transplant patient. Therefore, in light of the various adverse actions of CsA, ameliorating the side effects of CsA is a major research pursuit that clinical and basic scientists must ingratiate. In the end, the health cost-benefit of the patient is our utmost principal concern.

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