Cyclosporine A and lovastatin: the good and the bad, but who will be the winner?

Kirk L. Hamilton
Department of Physiology, Otago School of Medical Sciences, University of Otago, Dunedin, New Zealand
Submitted 6 June 2013; accepted in final form 7 June 2013

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 andLovastatin 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, 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 byLovastatin. 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 filpin, 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...
demonstrated that tacrolimus (another calcineurin inhibitor) a role downstream of ABCA1 (19). Ellison and co-workers (6) changes in cholesterol levels in the cell membrane might play porter (ABCA1). Furthermore, these authors suggested that terol involving inhibition of the ATP-binding cassette trans-

Acknowledgments

The author acknowledges Dr. Fiona J. McDonald for providing comments on this manuscript.

Disclosures

No conflicts of interest, financial or otherwise, are declared by the author(s).

Author Contributions

Author contributions: K.L.H. drafted manuscript; K.L.H. edited and revised manuscript; K.L.H. approved final version of manuscript.

References

