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Cyclosporine , but not tacrolimus, intracellular concentration is affected by simvastatin through MRP1 inhibition in jurkat cells.

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Objectives : Calcineurin inhibitors are very useful in the treatment of glomerulonephritis and prevention of graft rejection in transplantation. They are usually coadministered with lipid-lowering agents in these patients. However, when multiple drugs are administered simultaneously, patients have an increased risk of drug-drug interactions. Drug-metabolizing enzymes or transporters, which mediate the influx or efflux of drugs, are important for the pharmacokinetics of substrate drugs and may affect the intracellular drug concentration in target cells. It is known that statins can modulate drug transporters. Therefore, the aim of this study is to investigate whether intracellular cyclosporine or tacrolimus concentration may be affected by statins through transporters expressed in lymphocytes or not.

Methods : We performed real-time quantitative RT-PCR to analyze the jurkat cell expression of drug transporters (MDR, MRP1, MRP2, BCRP, OATP1B1, OAT1, and OCT1). To test drug-drug interactions, jurkat cells were incubated with 0.1-mL ND96 buffer and 1 μM [3H]cyclosporine A or 50 nM [3H]tacrolimus in the absence and presence of 100 μM verapamil, 0.1-100 μM simvastatin, or 0.1-100 μM pravastatin. The intracellular cyclosporine and tacrolimus concentrations were measured using a MicroBetaTriLux 96-well Scintillation/ Luminescence detector (PerkinElmer). To interpretate the results, we assessed the inhibitory effect of statins on MRP1 using MRP1-overexpressing MDCK cells and we performed transporter-based interaction studies by measuring the net flux ratio (the ratio of basal-apical permeability to apical-basal permeability) in MRP1-overexpressing LLCPK cells.

Results : In jurkat cells, the mRNA expression levels were in the following order: MRP1>>>BCRP, MRP2, and OCT1, while MDR1, NTCP, OATP1B1, and OAT1 were not detected. Cells treated with simvastatin (10 μM), simvastatin (100 μM) revealed significantly higher intracellular cyclosporine accumulations with 808.2 ± 110.71 fmol/min/1×10^6cells ($p < 0.001$), 705.7 ± 40.43 fmol/min/1 × 10^6cells ($p < 0.01$) in the jurkat cells, respectively. However, pravastatin showed no difference compared to control($p > 0.05$). In contrast, all

concentrations of tacrolimus treated with two statins were not showed significant difference compared to control ($p > 0.05$).
Simvastatin resulted in higher calcein-AM(substrate of MRP1) accumulation, compared to the control or pravastatin. MRP1 were involved in the transport of cyclosporine with showing net flux ratio of cyclosporine over 2 (B to A/ A to B= 2.36). In contrast, tacrolimus transport was not mediated by MRP1 with showing the net flux ratio of tacrolimus in MRP1 less than 2(B to A/ A to B= 1.81)

Conclusions : The intracellular cyclosporine concentration might be affected by simvastatin via MRP1 inhibition. However, the intracellular tacrolimus concentration is not , because of the relatively low net flux ratio of tacrolimus in MRP1 in Jurkat cells.

Keywords : Drug transporter, calcineurin inhibitor, statin