Inhibitory effect of rosuvastatin on SARS-CoV-2

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ABSTRACT

Based on *in silico* studies statins could be efficient SARS-CoV-2 Mpro inhibitors, especially rosuvastatin. It has been also showed that rosuvastatin can significantly decrease the rate of deep vein thrombosis (JUPITER trial), and that it can improve lung pathological changes by decreasing T helper cells Th2 and Th17-mediated cytokines. Therefore, rosuvastatin might be an useful adjunct therapy in patients with COVID-19, especially in those who already have an indication for statin use (homozygous familial hypercholesterolemia, hyperlipidemia, mixed dyslipidemia, primary dysbetalipoproteinemia, hypertriglyceridemia, prevention of cardiovascular disease).

INTRODUCTION

Rosuvastatin is a statin medication used as a lipid-lowering agent. The mechanism of action of rosuvastatin is inhibition of 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase. This enzyme is the rate-limiting step in cholesterol synthesis, which reduces the production of mevalonic acid from HMG-CoA. Furthermore, this results in an increase of low-density lipoprotein receptors on hepatocyte membranes and stimulation of low-density lipoprotein catabolism. HMG-CoA reductase inhibitors also decrease levels of high sensitivity C-reactive protein (CRP). They also possess pleiotropic properties, including inhibition of platelet aggregation, anticoagulant effects, reduced inflammation at the site of a coronary plaque, and improved endothelial function. The FDA-approved indications are homozygous familial hypercholesterolemia, hyperlipidemia, mixed dyslipidemia, primary dysbetalipoproteinemia, hypertriglyceridemia, and prevention of cardiovascular disease. The non-FDA approved uses are in non-cardioembolic stroke, secondary prevention in transient ischemic attack (TIA), and as perioperative therapy for cardiac risk reduction in noncardiac surgeries[1]. Rosuvastatin exhibits high hydrophilicity and hepatoselectivity, as well as low systemic bioavailability, while undergoing minimal metabolism via the cytochrome P450 system. Therefore, rosuvastatin has an interesting pharmacokinetic profile that is different from that of other statins[2].

INHIBITORY EFFECT ON SARS-CoV-2

Molecular docking was performed in a study published by Reiner and coworkers using AutoDock/Vina, a computational docking

program. SARS-CoV-2 Mpro was docked with all statins, while antiviral and antiretroviral drugs – favipiravir, nelfinavir, and lopinavir – were used as standards for comparison. The binding energies obtained from the docking of 6LU7 with native ligand favipiravir, nelfinavir, lopinavir, simvastatin, rosuvastatin, pravastatin, pitavastatin, lovastatin, fluvastatin, and atorvastatin were –6.8, –5.8, –7.9, –7.9, –7.0, –7.7, –6.6, –8.2, –7.4, –7.7, and –6.8 kcal/mol, respectively. The number of hydrogen bonds between statins and amino acid residues of Mpro were 7, 4, and 3 for rosuvastatin, pravastatin, and atorvastatin, respectively, while other statins had two hydrogen bonds. Authors concluded that these results indicate, based upon the binding energy of pitavastatin, rosuvastatin, lovastatin, and fluvastatin, that statins could be efficient SARS-CoV-2 Mpro inhibitors[3].

Statins can limit SARS-CoV-2 cell entry and replication by inhibiting both the main protease (Mpro) and RNA-dependent RNA polymerase (RdRp). The cytokine storm can be ameliorated by lowering serum IL-6 levels; this can be achieved by inhibiting Toll-like receptor 4 (TLR4) and modulating macrophage activity. Statins can also reduce the complications of COVID-19, such as thrombosis and pulmonary fibrosis, by reducing serum PAI-1 levels, attenuating TGF-β and VEGF in lung tissue, and improving endothelial function. Despite these benefits, statin therapy may have side effects that should be considered, such as elevated creatinine kinase (CK), liver enzyme and serum glucose levels, which are already elevated in severe COVID-19 infection. The effectiveness of statins in COVID-19 patients with high cardiovascular risk indicates that they should not be withdrawn during the infection, but there is no evidence from randomized controlled trials which would clearly support statins de novo initiation in SARS-CoV-2 infection[4].

As patients with COVID-19 infection have an increased risk of cardiovascular complications and thrombotic events, and statins are known for their pleiotropic, anti-inflammatory, antithrombotic and immunomodulatory effects, they may have a potential role as adjunctive therapy to mitigate endothelial dysfunction and dysregulated inflammation in patients with COVID-19 infection[5].

The JUPITER trial, which studied relatively healthy patients with high CRP levels, reported a significantly decreased rate of deep vein thrombosis in those who received rosuvastatin compared to placebo[6].

A study showed that rosuvastatin improves lung pathological changes by decreasing T helper cells Th2 and Th17-mediated cytokines where this action is not related to its lipid-decreasing activity[7].

Another study by Farag and coworkers, in a

structure-based drug design approach aiming at targeting COVID-19 virus revealed that rosuvastatin on docking along with COVID-19 virus Mpro substrate-binding pocket (PDB ID: 6LU7) showed outstanding binding affinity regarding free energy with S score of −12.3096 kcal mol−1. Concerning binding mode, it experienced hydrophobic interactions and hydrogen bonding with Gly143 and Glu166 amino acids[8].

Statins, especially rosuvastatin are advised by some authors to be given to acute COVID-19 patients because of their role in decreasing cardiovascular problems like the fatal myocardial infarction associated with COVID-19 infection[9, 10].

CONCLUSION

Statins can limit SARS-CoV-2 cell entry and replication by inhibiting the main protease (Mpro) and RNA-dependent RNA polymerase (RdRp). The cytokine storm can be ameliorated by lowering serum IL-6 levels. Statins can also reduce the rate of complications of COVID-19, such as thrombosis and pulmonary fibrosis, by reducing serum PAI-1 levels, attenuating TGF-β and VEGF in lung tissue, and improving endothelial function. Therefore, statins should not be withdrawn during the COVID-19 infection. Rosuvastatin was associated in the JUPITER trial with significantly decreased rate of deep vein thrombosis. It has been also showed that rosuvastatin improves lung pathological changes by decreasing T helper cells Th2 and Th17-mediated cytokines. In few *in silico* studies rosuvastatin was showed to be a potent SARS-CoV-2 Mpro inhibitor. Rosuvastatin is undergoing minimal metabolism via the cytocrome P450 system, and therefore, it has relatively less pharmacokinetic drug-drug interactions in comparison with other statins. Rosuvastatin might be an useful adjunct therapy in patients with COVID-19, especially in those who already have an indication for statin use (homozygous familial hypercholesterolemia, hyperlipidemia, mixed dyslipidemia, primary dysbetalipoproteinemia, hypertriglyceridemia, prevention of cardiovascular disease).

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