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Can statins be applied for treating acute respiratory distress syndrome?

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Abstract: *Despite decades of research, no pharmacological therapy is effective in acute respiratory distress syndrome (ARDS). Fortunately, the pharmacogenetic evidence suggests that statins can be a candidate drug for ARDS. However, concerning ARDS, the potential effects of statin are controversial. This review summarizes current progress on the studies of statins therapy in ARDS.Recent finding ARDS is a highly heterogeneous disease. Two subphenotypes, hyper-inflammation subphenotype, and hypo-inflammation subphenotype have been confirmed recently. Additionally, statins have been shown to have different therapeutic effects on different subphenotypes. For instance, simvastatin can significantly improve the 28-day survival rate of the high inflammation group, whereas rosuvastatin does no effect on both subphenotypes. And during the new coronavirus epidemic, the use of statins has been reported to improve the prognosis of COVID-19 patients including those with ARDS. Existing studies suggest great potential of statins for the treatment of ARDS. However, its role in ARDS is not just as straightforward as previously thought. Further studies are urgently needed to investigate the role of statins among different ARDS subphenotypes, which is particularly important in the context of the COVID-19.*

Keywords: *Acute respiratory distress syndrome, statins, subphenotypes, COVID-19*

1. Introduction

In December 2019, the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is profoundly imperiling the health and daily life of people all over the world at an unthinkable scale and speed[1, 2]. Most individuals infected with SARS- CoV-2 remain asymptomatic or develop a mild to moderate illness, however, some patients especially the elderly or those with severe pneumonia rapidly develop ARDS and require to enter intensive care unit (ICU) for advance treatment[3, 4]. ARDS is the manifestation of systemic inflammatory response syndrome (SIRS) in the lungs. The uncontrollable inflammatory response in ARDS results in alveolar damage, causing the exudation of protein-rich pulmonary edema fluid in the alveoli, consequently, leading to respiratory failure[5].

Although the clinical symptoms of ARDS caused by the new coronavirus are slightly different from traditional ARDS[1], the pathogenesis is similar[6, 7]. The progression of ARDS has three stages. The first stage is the exudation phase, which is mainly characterized by interalveolar flooding, coagulation, and the formation of hyaline membranes. At this stage, damage to the endothelium and epithelium leads to the release of pro-inflammatory mediators and chemokines, and at the same time monocytes and macrophages are recruited by chemokines. The recruited leukocytes aggravate lung damage by releasing toxic mediators. In addition, damaged cells and inflammatory cells also produce nitric oxide, superoxide, and tissue factor, which are involved in oxidative stress and blood coagulation processes, respectively. The second stage is the proliferative phase, which is mainly characterized by the proliferation of airway progenitor cells and type II alveolar epithelial cells (AECII). The third stage is the fibrotic phase, which is mainly characterized by interstitial and interalveolar fibrosis[6, 8].

The major pathophysiological characteristics of ARDS include lung inflammation, oxidative stress, changes in coagulation and platelet function, and endothelial damage[6, 9]. Accordingly applying steroid, neutrophil elastase inhibitors, macrolides, surfactant, prostacyclin as well as statins on patients with ARDS has not to reach unanimous results[10]. Particularly for statins, these drugs have shown other lipid

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lowering-independent effects, such as extensive anti-inflammatory, downregulating blood coagulation and platelet-activating, inhibiting oxidative stress, and promoting endothelial growth[11-14]. Theoretically, statins should have beneficial effects on the recovery of ARDS. However, the results of clinical studies are contradictory. While an increasing amount of evidence proved that statins can be a viable candidate against ARDS[15-19], some studies have shown that statins are not effective for ARDS patients regardless of the subphenotypes of the disease [20, 21] Hence, the relationship between statins and recovery of ARDS is ambiguous and confusing, which needs to be clarified.

In this review, we summarized the studies of statin therapy in patients with ARDS and analyzed the reason underlying the paradox effects of statins on ARDS.

2. Key point

(1) Statin treatment is controversial in ARDS, and its therapeutic effect varies with the type of statins

(2) ARDS is a highly heterogeneous disease. Two subphenotypes which responds differently to statins therapy has been found.

(3) Statins are one of the potential treatment options for patients with COVID19, including ARDS caused by SARS-CoV-2.

2.1 Inconsistency of the therapeutic effect of statins in ARDS

The benefits of statins for ARDS or acute lung injury (ALI) are reflected in basic research and clinical research. By verifying the cytoskeleton activation and gene expression changes of simvastatin in endothelial barrier regulation, Jacobson et al got the conclusion that statins can be a treatment option for a variety of vascular pathologies, including acute lung injury[22]. The same authors showed that simvastatin inhibits inflammation and vascular leakage in murine inflammatory lung injury models [23]. Similar results have also been found in other studies[24-27]. In clinical trials, the first randomized controlled trial(RCT) demonstrated that compared with placebo, atorvastatin can significantly delay the development of sepsis to severe sepsis which predominantly had a respiratory failure[28]. Another study provides that simvastatin pretreatment has significant anti-inflammatory effects in ALI patients induced by lipopolysaccharide[19]. In addition, the preventive effect of statins on ARDS patients has been reported in other studies [17, 18].

However, the research of statins therapy in ARDS is not taken in the direction we thought. HARP-2 trial confirmed that the use of simvastatin does not improve the prognosis of ARDS patients even if it does not induce serious adverse events[21]. Another clinical trial (SAILS trial) of rosuvastatin was stopped for the lack of benefit in 60-day mortality in patients with sepsis-relate ARDS, and the observation that rosuvastatin may have contributed to hepatic and renal organ dysfunction[20]. Additionally, a one-year follow-up study of the SAILS trial population indicated that randomization to rosuvastatin did not affect survival[29]. Due to the contradictory results from previous studies, the use of statins for the treatment of ARDS has become a controversy. Thus, continuous investigation on this topic is needed.

2.2 Statins are effective for treating ARDS with high inflammation

In 2014, a study. verified that there are indeed two different subphenotypes in the patient with ARDS, one of the subphenotypes is associated with high plasma concentrations of inflammatory biomarkers, severe shock, and metabolic acidosis, another subphenotype is associated with less severe inflammation and shock, and these two subphenotypes have a different response to differing ventilator strategies[30]. And, two biologically distinct clusters of patients with ARDS, which named ‘uninflamed’ and ‘reactive’ respectively, were identified with a set of 20 biomarkers of inflammation, coagulation, and endothelial activation[31]. For further research of statins in the two subphenotypes patients, in 2018, Calfee et al. got the conclusion that compared with placebo, simvastatin therapy significantly improved 28-day survival(P=0.008) in the hyper-inflammatory subphenotype after they conducted a second analysis of the HARP-2 trial[15]. In the same year, the study based on using latent class analysis (LCA) to make a secondary analysis of the SAILS trial from Sinha et al found that rosuvastatin has no treatment effect on ARDS people, but once again proved the existence of the two subphenotypes[32]. After that, the stability of the two subtypes has also been verified by researchers [33].In general, the secondary analysis of the HARP-2 trial and SAILS trial brought mixed results. We know there are two subphenotypes in the ARDS patients, which will provide a new direction for future research on ARDS treatment, but on the other

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hand, the difference in the treatment effect between simvastatin and rosuvastatin remind us that we should profoundly rethink the specific mechanism of action of statins. Therefore, the prediction model of subphenotypes in the secondary analysis uses the Z-scale value, this means that the premise of the model is prior knowledge, implicated that it is not suitable for prospective use. The recent model which used three-variable (IL-8, bicarbonate, and protein C) or four-variable (IL-8, bicarbonate, protein C, and vasopressor use) has good prospect [34], The AUC of the three-variable model and the four-variable model are 0·94 (95% CI 0·92–0·95) and 0·95 (95% CI 0·93–0·96) respectively. The three-variable model has higher specificity, correspondingly, the four-variable model has higher sensitivity when setting the Youden Index as the probability cut off to assign subphenotype. When the probability cutoff was set at 0.5, specificity increases and is >0.9 in both models, the difference is the three-variable model has higher specificity. Despite the relationship between statins and ARDS is ambiguous, combining prior studies of statins in ARDS, the determination of the subphenotype undoubtedly points out a new direction for the study of statins therapy in ARDS. The differences in the ARDS population and the effectiveness of statins determine that the treatment of this disease cannot be one size fits all, but individualized specific medications. Clinical research of statins in ARDS or COVID-19 is shown in table1.

Table 1: Clinical research on statins in ARDS or COVID-19

	Disease	Drug	Dose	Key finding
Shyamsundar 2009[19]	pulmonary inflammation	Simvastatin	40 or 80mg/day	Pretreatment with simvastatin might be of benefit in ALI
Kor 2009[35]	ALI/ARDS	statins	References	Statins therapy has no effect in ALI/ARDS
Craig 2011[36]	ALI	simvastatin	80mg/day	Simvastatin may be benefit in organ dysfunction in ALI
Patel 2012[28]	sepsis	atorvastatin	40mg/day	Atorvastatin may prevent sepsis progression
Bajwa 2012[37]	critically ill	statins	unknown	Statins are not beneficial in the prevention of ARDS
Kruger 2013[38]	critically ill	atorvastatin	20mg/day	Continuation of atorvastatin was associated with improved survival
Ou 2014[39]	sepsis	statins	High-potency:(rosuvastatin≥10 mg, atorvastatin≥20 mg, simvastatin≥40 mg)	High-potency statin use is associated with a lower risk of sepsis-related mortality
Yadav 2014[40]	patients undergoing high-risk surgery	statins	unknown	Preoperative statin therapy was not associated with a statistically significant reduction in postoperative ARDS
Truwit 2014[20]	ARDS	Rosuvastatin	20mg/day	Rosuvastatin did not improve clinical outcomes in patients with sepsis -associated ARDS
McAuley 2014[21]	ARDS	simvastatin	80mg/day	Simvastatin did not improve clinical outcomes in patients with ARDS
Mansur 2015[41]	ARDs	statins	unknown	A history of prior statin therapy and continuous statin therapy benefie for ARDS
Schurr, 2016[41]	sepsis	statins	unknown	Prior use of statins may can prevent sepsis
Dinglas 2016[29]	ARDS	Rosuvastatin	unknown	rosuvastatin had no effect in patients with sepsis-associated ARDS
Sinha 2018[32]	ARDS	Rosuvastatin	20	No treatment effect was observed with rosuvastatin in ARDS subphenotypes
Calfee 2018[15]	ARDS	simvastatin	80	Compared with placebo, simvastatin had improved survival in hyperinflammatory subphenotype
Zhang 2020[42]	COVID-19	statins	Unknown	Statins are beneficial to hospitalized patients with COVID-19
Spiegeleer 2020[43]	COVID-19	statins	unknown	Statin treatment is associated with beneficial effects on COVID-19-related clinical symptoms in in elderly nursing home residents
Rodriguez-2020[44]	COVID-19	atorvastatin	40	Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU

2.3 Potential mechanisms underlying the inconsistency of statins' effects in ARDS

The liposolubility affects statins therapeutic efficacy. In the research of endothelial repair of statins, simvastatin in type 2 diabetes patients is stronger than that of rosuvastatin[45] ,which is consistent with the difference between simvastatin and rosuvastatin in the treatment of ARDS. This may be because hydrophilic statins have weaker effects on endothelial oxidative metabolism than hydrophobic statins[46].In anti-inflammatory research, a study showed that lipophilic statins are significantly better than hydrophilic statins in improving cardiac function and reducing inflammation in patients with heart failure[47]. Moreover, lipophilic statins have been proven to inhibit Volume-activated Cl^- channels by inhibiting NADPH oxidase and reduce the inflammation of monocytes caused by hypotonicity, which have not been found in hydrophilic statins[48].In the research of statins in cancer treatment, studies have shown that Lipophilic statins are more protective than hydrophilic statins for patients with pancreatic

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cancer or breast cancer[49, 50]. Another study of human pancreatic cancer lines, lipophilic statins have stronger effects in drug concentration of intracellular, bioavailability and genes expression changing than hydrophilic statins[51]. Additionally, Sahebkar et al. also found that lipophilic statins are significantly better than hydrophilic statins in the regulation of cortisol and hemophilia factor[52, 53]. In short, the main effect of statins is to lower lipids, but their other biological results are obviously different, and it is likely to depend on whether the statin is hydrophilic or lipophilic. This is also one of the directions that need to be paid attention to in the future of statin drug research.

The therapeutic effect of statins will be affected by a specific disease. A study showed that simvastatin, rosuvastatin and pravastatin can significantly increase the expression of heme oxygenase-1(HMOX1) in primary endothelial cells, but among the exogenous placenta of women with premature preeclampsia, only simvastatin can increase the expression of HMOX1[54]. Compared with several other statins, simvastatin can increase heme oxygenase mRNA expression through an indirect mechanism, which via the p38 and Akt pathways, while other statins can only directly increase heme oxygenase promoter activity[12]. Moreover, HMOX1 promoter was associated with a risk decreasing of ARDS[55]. Combining with the difference between simvastatin and rosuvastatin in the treatment of ARDS, when the regulation of statins on HMOX1 is linked to specific disease states, the effects of different types of statins might be different, but the process of the regulation of HMOX1 by statins under different pathological mechanisms are not clear, which needs further research.

ARDS population is heterogeneous. The difference in prior research was also reflected in the choice of population. Previous RCTs did not consider the phenotypic differences in the cohort. HARP-2 population may have severe ARDS for its baseline characteristics showed a lower PaO2/FiO2, and SAILS select a narrower group for systemic inflammatory response as an inclusion criteria[56]. It is a confounding factor that the effect of statins might depend on the severity of ARDS or subphenotype [15, 31, 41]. Therefore, a recognized diagnostic model to identify the two subphenotypes in patients with ARDS is essential.

2.4 Can statins be a tool against ARDS caused by SARS-CoV-2?

SARS-CoV-2 transmitted through respiratory droplets like other respiratory viruses and mainly manifested in pathophysiology as damage to the airway as a result of aggressive inflammatory responses strongly[57]. The infection process can be briefly summarized as the virus enters the host cell through membrane surface receptor, causing the pyroptosis of the host cell[58] , then inducing the generation of pro-inflammatory cytokines and chemokines which can recruit monocytes, macrophages, and T cells to promote the inflammatory response. The IFN-γ from T cell can produce positive feedback on inflammation, and cytokine storm which damages the organs start when the inflammatory factors are overloaded[7], as a result, severe SARS-CoV-2 infection, ARDS, or multiple organ damage occurs throughout the body. Similar to other two coronaviruses such as SARS-CoV and MERS-CoV, the mechanism including cytokine storm, chemokine release, renin-angiotensin system (RAS) activation, coagulation and endothelial damage, among them coagulation and endothelial damage are closely related to high inflammation and RAS activation[59]. Based on current clinical studies, statins have shown their potential benefits on COVID-19[42-44, 60], but how do statins participate in this process?

Statins can hinder the maturation of the SARS-CoV-2 virus, A molecular docking study indicated that statins could efficiently inhibit SARS-CoV-2 Mpro(main protease) which is important in proteolytic maturation in virus, and the binding ability of statins especially pitavastatin is even stronger than protease or polymerase[61]. Statins treatment for COVID-19 by impeding SARS-CoV-2 maturation in autolysosomes and thus induce the accumulation of autolysosome is under clinic trial [62].

Statins can work on the cell membrane of host cells, SARS-CoV-2 infects host cells including airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, and macrophages in the lung resulting in a decrease of ACE2 in the cell surface, which can upregulate Ang-II causing inflammation, tissue damage, fibrosis, and lung injury[63]. And statins can benefit lung injury by normalizing the AEC2[64]. A novel finding that CD147 is a receptor for the S-protein in the SARS-CoV-2[65], statins mainly downregulate CD147 through inhibiting protein isoprenylation and N-glycosylation [66], provides a possible way that statins might prevent SARS-CoV-2 from infecting cells including lung cells. Lipid rafts are cholesterol-rich areas of the plasma membrane and essential for flavivirus and coronavirus entries in the human cell[67]. And its composition can be modulated by HMG-CoA reductase inhibitor. During an RNA virus infection, a high amount of cellular cholesterol correlated with increased activity of HMG-CoA reductase [68].

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Statins can induce cell autophagy to reduce virus replication. Coronavirus membrane-associated papain-like protease PLP2 (PLP2-TM) can interact with key autophagy regulators microtubule-associated protein light chain 3(LC3) and Beclin1 to inhibit autophagy[69]. And the degradation of SKP2 can prevent beclin1 ubiquitination and improve the reduction of autophagy caused by MERS-CoV, thereby reducing virus production[70]. Furthermore, statins can downregulate SKP2 result in increasing of beclin1 and directly upregulate LC3-II or beclin1 to induce cell autophagy[71-73] In summary, stains can inhibition of SKP2 and cause upregulate beclin1, or directly upregulate LC3-II or beclin1 to induce cell autophagy, as a result, reducing virus replication.

Statins are involved in immunomodulation. The observation that statins reduce the content of farnesyl pyrophosphate, geranyl pyrophosphate, and cholesterol results from the inhibition of prenylation of a variety of important cell signaling small G-proteins, leading to the slowness of protein isoprenylation which turns down the response stringency of signaling pathways [12, 74]. One of the signaling pathways is the Toll-like receptor (TLR)–MYD88–NF-κB pathway which is known for inducing the pro-inflammatory caused by coronaviruses. And statins can stabilize the level of MYD88 to alleviate NF-κB action, thereby mitigating inflammation[75]. SARS-CoV-2 might directly activate NLRP3 inflammasome[76], and treatment with statins can not only downregulate the expression of NLRP3 but also the downstream cytokines[77, 78] . Low-density lipoprotein cholesterol (LDL-C) is a stronger promoter of inflammation in NLRP3[79]. As a lipid-lowering agent, statins can lower LDL-C implicated that statins can be anti-inflammatory while lipid-lowering.

Statins participate in the regulation of heme oxygenase-1 enzymes(HO-1).SARS-CoV-2 can bind porphyrins astonishingly, even stronger than ACE-2 receptors, leading to a situation of the upregulation of free heme and decrease levels of heme oxygenase-1 enzymes, and the free heme is an oxidant, which associated with severe reactive oxygen species (ROS) formation[80]. HO including HO-1 and HO-2 can decompose heme into free iron, biliverdin, and carbon monoxide, which participate in the synthesis of ferritin, and are quickly reduced to bilirubin to participate in anti-oxidation and anti-apoptosis[81]. As stated above, statins can directly or indirectly increase the expression of heme oxygenase mRNA, thereby increasing heme oxygenase, as a result, the process of heme decomposition is enhanced, so is the effect of anti-oxidative stress[12]. In a word, statins can increase heme oxygenase, which modulated oxidative stress including induced by SARS-CoV-2.

Statins can inhibit the formation of thrombosis. Virus infection can cause platelet activation and upregulation of tissue factor(TF) expression [82]， leading to exogenous coagulation and thrombosis. Statins can downregulate TF by inhibiting RaC1 or Rho (both belong to small GTPase), which downregulated blood coagulation cascade and reduced thrombin generation[82, 83]. And statins can reduce platelet activity through lipid-lowering and lipid-independent mechanisms[13]. The regulation of statins in COVID-19 is shown in figure1.

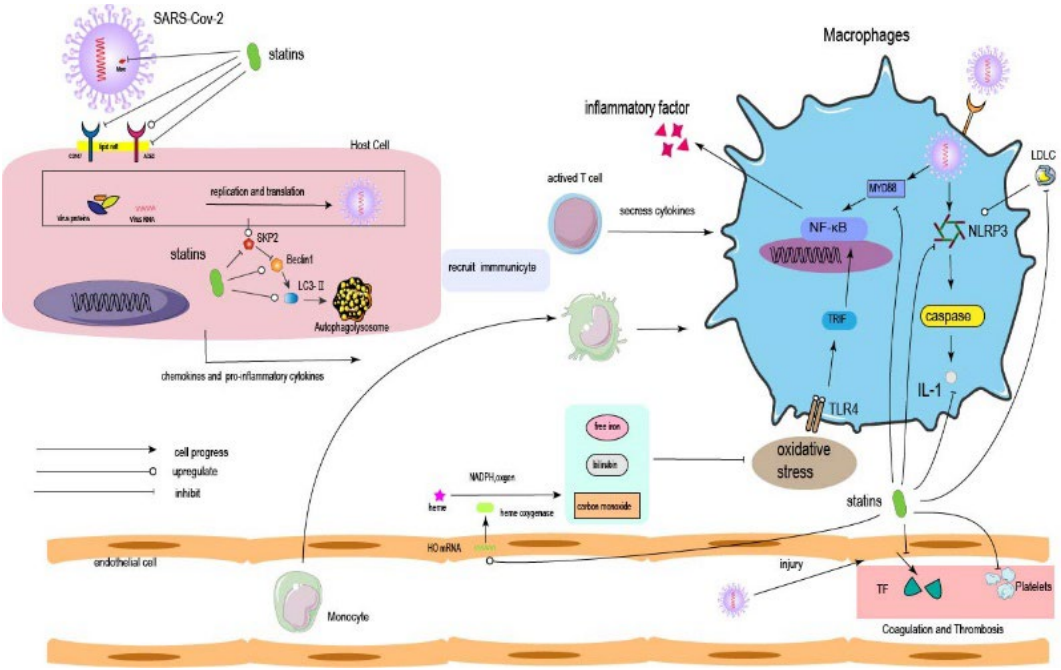

Figure 1: The regulation of statins in COVID-19

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3. Perspective and Conclusions

The outbreak of COVID19 may be a juncture for research on the treatment of statins in ARDS, especially since existing studies have shown that statins might be effective against SARS-CoV-2 infection for it can against ARDS from three main aspects: anti-inflammation, anti-coagulation, and endothelial repair. Even though there is controversy about whether statins are effective for ARDS, but with the proposal of the concept of subphenotype, and the existing evidence of statins can effective for a certain subphenotype, statins are still a promising pharmaceutical treatment for ARDS. However, there are still some unsolved problems. First, the study on the role of statins in ARDS is not enough, especially when the subphenotype viewpoint is put forward. The classification of the animal model of ARDS has not yet been found[84], which will be a big obstacle to animal experiments. Future studies want to gain insight into the mode of action of statins in ARDS patients, and reliable animal models are necessary. Second, the mechanism of action of statin in ARDS is not yet fully understood, the dose of statin[39], the type of statin, and selection of time node for statins use[38] will affect the treatment effect, which will determine unique effects of different statins. Third, whether the racial difference would affect subphenotype classification is unclear.

In conclusion, with the accurate and feasible subphenotype model is stable, statins can be a choice for ARDS drugs therapy, future research should concentrate on the subphenotypes of ARDS for targeted therapy, including the preventive effect or/and the therapeutic effect of statins, which is also consistent with the purpose of precision medicine.

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