

DR SIMIN DASHTI-KHAVIDAKI (Orcid ID : 0000-0003-2004-7845)

PROFESSOR HOSSEIN KHALILI (Orcid ID : 0000-0002-1590-6396)

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### **Letter to the Editor**

### **Considerations for statin therapy in patients with COVID-19**

Simin Dashti-Khavidaki<sup>1</sup>, Hossein Khalili<sup>2\*</sup>

<sup>1</sup>Professor of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. E-mail: [dashtis@sina.tums.ac.ir](mailto:dashtis@sina.tums.ac.ir). ORCID: 0000-0003-2004-7845

<sup>2</sup>Professor of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran. E-mail: [khalilih@sina.tums.ac.ir](mailto:khalilih@sina.tums.ac.ir)

### **Corresponding Author**

Hossein Khalili,

Professor of Clinical Pharmacy,

Faculty of Pharmacy,

Tehran University of Medical Sciences, Tehran, Iran.

P.O.Box: 1417614411

Tel/Fax: +98-21-66954709,

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E-mail: khalilih@sina.tums.ac.ir

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Current coronavirus pandemic named coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is the third coronavirus outbreak during the current century after severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses.<sup>1</sup>

Acute respiratory distress syndrome (ARDS) is an immunopathologic event and main cause of death following COVID-19. The main mechanism of ARDS is uncontrolled systemic inflammatory response and cytokine storm following release of proinflammatory cytokines (such as interferons (IFN), interleukines (IL), tumor necrosis factor (TNF)- $\alpha$ ) and chemokines.<sup>2-3</sup> So, some Chinese researchers proposed or used anti-inflammatory agents in the treatment regimen of patients with COVID-19.<sup>3-4</sup>

Statins are well known for their anti-inflammatory effects<sup>5</sup> and some hospitals included them in the COVID-19 treatment protocol.<sup>6</sup> Here, we summarize main points that should be considered before incorporating this class of drugs in COVID-19 treatment regimen.

#### **Potential mechanistic effects/adverse effects of statins on ARDS**

Toll-like receptors (TLR), a family of sensor proteins, assist immune system to discriminate between “self” and “non-self”. In mice model, Totura *et al* demonstrated that TLR signaling through TRIF adaptor protein mitigate ARDS as a main cause of death in SARS-CoV disease.<sup>7</sup> Gene expression of myeloid differentiation primary response 88 (MyD88) acts downstream of TLRs and is induced by SARS-CoV infection.<sup>7</sup> Both over-expression<sup>7</sup> and under-expression of MyD88 gene<sup>8</sup> were related to increased mortality after MERS-CoV infection. Downstream of TLRs-MyD88 pathways, NF- $\kappa$ B is activated by coronavirus infections. In mice model, inhibition of NF- $\kappa$ B improved lung infection and

Accepted Article  
survival after SARS-CoV infection.<sup>9</sup> Statins preserve MyD88 at normal level during hypoxia<sup>10</sup> and mitigate NF- $\kappa$ B activation<sup>11</sup>, therefore some investigators hypothesized the idea of using statins for treatment of MERS-CoV infection<sup>12</sup> and COVID-19.<sup>13</sup> But animal studies have shown that aberrant inhibition of TLR adaptor TRIF or MyD88 signals results in severe lung damage and death.<sup>7,14</sup> This may be due to the compensatory activation of other innate immune factors. In addition, animal studies on SARS-CoV and MERS-CoV infections revealed that abolished TLR pathway leads to increased viral load that persists for longer time and increase risk of human to human transmission.<sup>7,14</sup> So, statins by the potential to stop TLR and NF- $\kappa$ B signaling carry the potential risk of exacerbating compensatory immune signals and poor disease outcome. Although some human and animal studies have shown lung injury improvement of statins by their anti-inflammatory effects.<sup>15-16</sup>, a retrospective analysis of the findings of a multicenter clinical trial on efficacy of rosuvastatin against infection-induced ARDS showed higher IL-18 level and mortality in statin treated patients.<sup>17</sup> The findings on the effects of statin on community acquired<sup>18</sup> and ventilator-associated pneumonia<sup>19-20</sup> are conflicting as well.

Finally, for COVID-19 outbreak, although some US hospitals included statin in COVID-19 treatment [6] and some proposed their use for this condition<sup>13</sup>, some others worry regarding statin-induced increase in IL-18 and deterioration of SARS-CoV-2 induced ARDS and mortality.<sup>21</sup>

### **Considerations in real situation**

We have to notice that patients with common comorbidities including hypertension, cardiovascular diseases and diabetes are at greater risk for SARS-CoV-2 infection and its related ARDS and mortality.<sup>22</sup> Most of these patients are taking statins routinely based on diabetes and cardiovascular guidelines. There is no evidence for discontinuing statins in these patients during COVID-19 episode.

### **Common adverse effects between COVID-19 and statins**

Although usually well-tolerated, statins may cause myotoxicity in some patients. Features of statin-induced myotoxicity differ from myalgia (more common) to myopathies and rarely rhabdomyolysis. Rhabdomyolysis can cause acute kidney injury.<sup>23</sup> Myalgia, increased creatine phosphokinase, rhabdomyolysis and acute kidney injury occur in patients with COVID-19 as well.<sup>2</sup> In addition, some risk factors such as advanced age and liver and kidney impairments are common between statin-

induced myopathies and infection with SARS-CoV-2.<sup>2,23</sup> So, initiating statin in patients with COVID-19 may increase the risk and severity of myopathies and acute kidney injury. Furthermore, statin therapy and COVID-19 both increase liver enzymes that are hard to differentiate from each other, if statin therapy starts at the episode of COVID-19.<sup>2</sup>

### **Drug interaction between statins and antiviral agents for COVID-19 treatment**

Most available statins are substrate for cytochrome (CYP) 450 system especially 3A isoenzymes and P-glycoproteins (P-gp). Protease inhibitors (*e.g.* lopinavir, darunavir) and their pharmacokinetic enhancers (ritonavir and cobicistat) are potent inhibitors of both CYP3A and P-gp and their concomitant administration results in markedly increased statin exposure and adverse effects. Coadministration of simvastatin or lovastatin with ritonavir/cobicistat boosted protease inhibitors should be avoided. Maximum daily doses of 20mg for atorvastatin and 10-20mg for rosuvastatin have been proposed in patients receiving ritonavir/cobicistat boosted protease inhibitors.<sup>24-25</sup>

### **Conclusion**

Taken together, although there is an urgent need for finding safe and available options for treatment of COVID-19 and its related fatal ARDS, we must balance our expectation from these immunomodulatory drugs against the potential of disease exacerbation by these agents.

We recommend guideline-directed continuation of statin therapy among COVID-19 patients with history of atherosclerotic cardiovascular disease or diabetes. We recommend guidance-directed initiation of statin in patients with COVID-19 who show acute cardiac injury. But, *de novo* initiation of statin therapy for management of COVID-19 episode can be done only as clinical trial not routinely.

### **References**

1. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020. doi:10.1016/j.jpha.2020.03.001.

- Accepted Article
2. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. doi:10.1056/NEJMoa2002032.
  3. Conti P, Ronconi G, Caraffa A, Gallenga CE, Ross R, Frydas I, et al. Induction of proinflammatory cytokines (IL-1 and IL-6) and lung inflammation by coronavirus-19 (COVID-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents*. 2020; 34(2). doi: 10.23812.CONTI-E.
  4. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the experience of immunologists from China. *Clin Immunol*. 2020. doi: 10.1016/j.clim.2020.108393.
  5. Schönbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? *Circulation*. 2004; 109(21 Suppl 1):II18-26. doi:10.1161/01.CIR.0000129505.34151.23.
  6. Massachusetts General Hospital COVID-19 Treatment Guidance Version 1.0 3/17/2020. Available at: <https://medtube.net/infectious-diseases/medical-documents/26086-covid19-treatment-guidelines-by-massachusetts-general-hospital>
  7. Totura AL, Whitmore A, Agnlhram S, Schäfer A, Katze MG, Heise MT, et al. Toll-like receptor 3 signaling via TRIF contributes to a protective innate immune response to severe acute respiratory syndrome coronavirus infection. *mBio*. 2015; 6(3): e00638-15. doi: 10.1128/mBio.00638-15.
  8. Sheahan T, Morrison TE, Funkhouser W, Uematsu S, Akira S, Baric RS, et al. MyD88 is required for protection from lethal infection with a mouse-adapted SARS-CoV. *Plos Pathog*. 2008; 4:e1000240. doi: 10.1371/journal.ppat.1000240.
  9. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jimenez-Guardeño JM, Fernandez-Delgado R, Fett C, et al. Inhibition of NF- $\kappa$ B-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increase survival. *J Virol*. 2014; 88: 915-924. doi:10.1128/JVI.02576-13.
  10. Yuan X, Deng Y, Guo X, Shang J, Zhu D, Li H. Atorvastatin attenuates myocardial remodeling induced by chronic intermitten hypoxia in rats: partly involvement of

TLR4/MYD88 pathway. *Biochem Biophys Res Commun.* 2014; 446: 292-297. doi: 10.1016/j.bbrc.2014.2.091.

11. Chansrichavala P, Chantharaksri U, Sritara P, Chaiyaraj SC. Atorvastatin attenuates TLR-4-mediated NF-kappa B activation in a MyD88-dependent pathway. *Asian Pac J Allergy Immunol.* 2009; 27: 49-57.
12. Yuan S. Statins may decrease the fatality rate of Middle East respiratory syndrome infection. *mBio.* 2015; 6(4): e01120-15. doi:10.1128/mBio.01120-15.
13. Fedson, DS, Opal SM, Rordamc OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. *mBio.* 2020; 11 (2): e00398-20. doi:10.1128/mBio.00398-20.
14. Totura AL, Baric RS. Reply to “statins may decrease fatality rate of MERS infection. *mBio.* 2015; 6(5): e01303-15. doi:10.1128/mBio01303-15.
15. Shyamsundar M, McKeown STW, O’Kane CM, Craig TR, Brown V, Thickett DR, et al. Simvastatin decreases lipopoly-saccharide-induced pulmonary inflammation in healthy volunteers. *Am J Respir Crit Care Med.* 2009; 179:1107–1114. doi:10.1164/rccm.200810-1584OC.
16. Chen W, Sharma R, Rizzo AN, Siegler JH, Garcia JG, Jacobson JR. Role of claudin-5 in the attenuation of murine acute lung injury by simvastatin. *Am J Respir Cell Mol Biol.* 2014. 50:328–336. doi: 10.1165/rcmb.2013-0058OC.
17. Rogers A, Guan J, Trtchounian A, Hunninghake G, Kaimal R, Desai M, et al. Association of elevated plasma interleukin-18 level with increased mortality in a clinical trial of statin treatment for acute respiratory distress syndrome. *Crit Care Med.* 2019; 47: 1089-1096. doi: 10.1097/CCM.0000000000003816.
18. Garnacho-Montero J, Barrero-García I, Gómez-Prieto MG, Martín-Loeches I. Severe community-acquired pneumonia: Current management and future therapeutic alternatives. *Expert Rev Anti Infect Ther.* 2018; 16(9): 667-677. Doi: 10.1080/14787210.2018.1512403.
19. Makris D, Manoulakas E, Komnos A, Papakrivou E, Tzovaras N, Hovas A, et al. Effect of pravastatin on the frequency of ventilator-associated pneumonia and on intensive care unit

- mortality: open-label, randomized study. *Crit Care Med.* 2011; 39(11): 2440–2446. doi:10.1097/CCM.0b013e318225742c.
20. Papazian L, Roch A, Charles PE, Pento-Regon C, Perrin G, Roullet P, et al. Effect of statin therapy on mortality in patients with ventilator-associated pneumonia: a randomized clinical trial. *JAMA.* 2013; 310(6): 1692–1700. doi:10.1001/jama.2013.280031.
  21. Goldstein MR, Graeber CW, Poland GA. Are certain drugs associated with enhanced mortality in COVID-19. *QJM: An International Journal of Medicine.* Hcaa. doi:10.1093/qjmed/hcaa103.
  22. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med* 2020. doi: 10.1001/jamainternmed.2020.0994.
  23. Turner RM, Pirmohamed M. Statin-related myotoxicity: a comprehensive review of pharmacokinetic, pharmacogenomics and muscle components. *J Clin Med.* 2020. doi:10.3390/jcm9010022.
  24. Liverpool COVID-19 drug interactions. <http://www.covid19-druginteractions.org/>. Accessed 20 March 2020.
  25. Lexicomp. March 2020.