Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Statins in coronavirus outbreak: It's time for experimental and clinical studies

Taking into account the SARS-coronavirus 2 (SARS-CoV-2 also know as COVID-19) spreading and invasiveness in this critic period and the lack of therapeutic drugs and antiviral vaccines, it is necessary for all of us researchers to discuss about new therapeutic devices and quickly define if agents, other than that conventionally used, could offer true clinical benefits.

The interest in statins as an inexpensive, readily available and easily tolerated drugs useful to reduce the morbidity and mortality caused by influenza and viral diseases, has been provided from numerous scientific publications over the past 15 years [1,2] but for some reason it has never gone deep.

Statins, inhibitors of the HMG-CoA reductase an enzyme that limits the pathway of mevalonate and cholesterol, have pleiotropic effects, as we described in several publications and especially in a Thematic Issue "Statin: new life for an old drug" published in 2014 on Pharmacol Res in collaboration with the discoverer of these compounds, prof. A. Endo [3]. These are substances with anti-inflammatory and immuno-modulatory effects, which could certainly benefit patients with influenza and viral pathologies.

Experimental evidence suggested the effectiveness of statins in viral infections and their potential mechanisms of action (Table 1) [2]. In some viruses, statin-induced reduction of cholesterol in the plasma membrane results in lower viral titres and failure to internalize the virus. Such data suggest that in some viruses, cholesterol affects the early stages of infection. In particular, in the initial stage of infection, viruses bind specific receptors concentrated within lipid rafts, areas of plasma membrane rich in cholesterol. Statins, by reducing the percentage of cholesterol present in the membrane, alter the assembly of the receptors and dramatically reduce the possibility of adhesion of the viral agent to the host. Lipid rafts are also involved in the viral replication phases, as they constitute packets of vesicles capable of concentrating virus replication factors. These processes are also highly destabilized by statins [2].

Many viral pathogens encode substrates for mammalian prenylation pathway (mevalonate pathway). It is hypothesized that the pre-dilation of viral proteins is beneficial for the propagation of the virus and that in some viral infections the statins, by inhibiting HMG-CoAR and reducing the expression of prenylated proteins, carry out an evident antiviral activity [2].

A recent study has shown that the influenza A virus induces the formation of numerous lipid droplets in infected cells. In the experimental model used, Madin-Darby dog kidney cells were treated with atorvastatin (ATV, 5microM) before inducing the infection. Pretreatment reduced the infectious capacity and, consequently, the production of new influenza A viruses, with a percentage higher than 95 % [4].

Studies performed in other viral strains have shown that different statins perform antiviral activity with variable efficacy, probably due to the specific pharmacological and biochemical properties of the statins used in the analysis and, therefore, to the different antiviral power observed [5].

Furthermore besides statins there are also a series of mevalonate pathway inhibitors that could then be used in the next future with a more specific target and effectiveness.

It is certainly worth studying in detail the mechanism by which statins inhibit virus replication. Although unsuitable for prophylaxis in all patients [6], to study their efficacy as antivirals in vitro could provide a valuable tool to identify their mechanism of action in preventing virus reproduction and, therefore, pandemic spread.

These hypotheses are strongly supported by substantial meta-analyzes and retrospective studies showing reduced hospitalization rates and mortality in subjects already users of statins affected by flu diseases [7]. Of course, studies are needed to evaluate, in cellular and animal models, the direct effect of statins on different viral strains, and more than anything on coronavirus, obviously followed by clinical studies, largely dictated by the current clinical emergency. The analysis of the interaction with statins of viruses at very high costs, health and social, such as SARS-CoV-2, represents a valuable possibility. There is also to consider that the effects of statins on the family members of Coronaviridiae has never been investigated.

Positive results from these studies could provide the Health Services with an effective, safe and low-cost tool to improve the prognosis of this viral pathology, prevent pandemics and improve antiviral prophylaxis in "frail patients".

In conclusion with this letter, we want draw the attention from all researchers and physicians to this therapeutic perspective not yet and fully investigated.

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Table 1
Potential mechanisms triggered by statins as anti-virus compounds (see reference [2] for detailed studies).

Statins	Experimental Models	Mechanism of action and observed effects
Atorvastatin, Rusovastatin	Madin-Darby Canine Kidney (MDCK) cells infected with influenza A (strains- H3N2 and H1N1) viruses	-down-regulation of Rho/Rho kinase pathway; -inhibition of the virus proliferation
Atorvastatin	C57BL/6 mice infected with influenza A virus (strains H3N2 and H1N1)	-reduced lung virus titers; -reduced mortality rates in infected mice
Atorvastatin, Simvastatin	Crandell Feline Kidney (CrFK) cells infected with influenza A virus (strain H1N1)	-reduced TNF-α and IL-6 in supernatants of infected cells
Simvastatin	Primary normal human bronchial epithelial (NHBE) cells stimulated with synthetic dsRNA viral analogue; Human lung epithelial cell line A549 stimulated with synthetic dsRNA viral analogue	-suppressed dsRNA-induced STAT3 activation; -inhibition of RANTES expression
Simvastatin	synthetic dsRNA-induced pneumonia in BALB/c mice	-reduced STAT3 activation; -reduced RANTES release; -reduced neutrophilia in the lungs
Atorvastatin	Madin-Darby Canine Kidney (MDCK) cells infected with influenza A virus (strain H1N1)	-inhibition of the early stage of virus multiplication; -reduced virus infectivity by decreasing the virus titer from infected cells; -increased cell viability of virus infected cells
Simvastatin	Madin Darby canine kidney (MDCK) cells infected with Influenza A virus (strain H1N1)	-inhibition of the early stage of virus multiplication; -decreased virus-induced cytotoxicity in infected cells; 2-fold decrease of secreted pro-inflammatory cytokines (TNF-α, IL-6, INF-γ); decrease of virus replication through inhibition of Rab/RhoA GTPase activity and LC3 membrane localization
Lovastatin	HEp-2 cells infected with Respiratory Syncytial Virus (RSV, strain A2) C57BL/6 and BALB/c mice infected with RSV	-reduced RSV replication in HEp-2 cells; -reduced cell-to-cell fusion in cell culture (through inhibition of RhoA); -decreased RSV virus replication in mice; -decreased virus-induced weight loss and illness in mice
Simvastatin	BALB/c mice infected with Influenza A virus (strain H5N1)	-decrease of secreted pro-inflammatory cytokines and chemokines (IFNγ, IL-10, TNFα);
Simvastatin	Leukocytes from HIV-infected patients	-depletion of cell membrane cholesterol and dissociation of lipid-rafts; -decrease of subpopulations and macrophages acting as Antigen Presenting Cells -decrease of highly efficient HIV-1 infection transferred by macrophages to $CD4^+$T cells
Mevastatin, Simvastatin	Human hepatocarcinoma (Huh7) cells containing subgenomic HCV replicons	-dose-dependent inhibition of HCV replicon replication (measured as luciferase signal); -additive antiviral activity in short-term used in combination with IFNα or HCV nonstructural (NS)5B polymerase or NS3 protease inhibitors

Declaration of Competing Interest

The authors declare no conflicts of interest.

References

[1] F.J. Frost, H. Petersen, K. Tollestrup, B. Skipper, Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins, Chest 131 (2007) 1006–1012, https://doi.org/10.1378/chest.06-1997.

[2] P. Mehrbod, A.R. Omar, M. Hair-Bejo, A. Haghani, A. Ideris, Mechanisms of action and efficacy of statins against influenza, Biomed Res. Int. (2014) 872370, , https://doi.org/10.1155/2014/872370.

[3] M. Bifulco, A. Endo, Statin: new life for an old drug, Pharmacol. Res. 88 (2014) 1–2, https://doi.org/10.1016/j.phrs.2014.06.005.

[4] D. Episcopio, S. Aminov, S. Benjamin, G. Germain, E. Datan, J. Landazuri, R.A. Lockshin, Z. Zakeri, Atorvastatin restricts the ability of influenza virus to generate lipid droplets and severely suppresses the replication of the virus, FASEB J. 33 (2019) 9516–9525, https://doi.org/10.1096/fj.201900428RR.

[5] K.P. Hui, D.I. Kuok, S.S. Kang, H.S. Li, M.M. Ng, C.H. Bui, J.S. Peiris, R.W. Chan, M.C. Chan, Modulation of sterol biosynthesis regulates viral replication and cytokine production in influenza A virus infected human alveolar epithelial cells, Antiviral Res. 119 (2015) 1–7, https://doi.org/10.1016/j.antiviral.2015.04.005.

[6] H.L. van den Hoek, W.J. Bos, A. de Boer, E.M. van de Garde, Statins and prevention of infections: systematic review and meta-analysis of data from large randomised placebo controlled trials, BMJ 343 (2011) d7281, https://doi.org/10.1136/bmj.d7281.

[7] Y. Ma, X. Wen, J. Peng, Y. Lu, Z. Guo, L. Jiahai, Systematic review and meta-analysis on the association between outpatient statins use and infectious disease-related mortality, PLoS One 7 (2012) e51548, , https://doi.org/10.1371/journal.pone.0051548.

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