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.

Molecular pharmacology of ciclesonide against SARS-CoV-2

To the Editor:

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has suddenly emerged, resulting in a pandemic. At present, there is no known safe and effective antiviral agent for COVID-19 treatment. Matsuyama et al[1] suggested that ciclesonide (Alvesco [(11β, 16α)-16, 17-[[(R)-cyclohexylmethylene]bis(oxy)]-11-hydroxy-21-(2-methyl-1-oxopropoxy)-pregna-1, 4-diene-3, 20-dione]), an inhaled glucocorticoid, could inhibit the replication of SARS-CoV-2 genomic RNA by targeting the viral endonuclease NSP15. However, there is no information concerning the detailed pharmacological and/or molecular mechanisms underlying this response. Here, we present an *in silico* study that elucidates a mechanism whereby ciclesonide might inhibit SARS-CoV-2 replication.

The full-length nucleotide sequences of *NSP15* and *RdRp* (RNA-dependent RNA polymerase) genes identified in GenBank (accession no. MN908947) were used for homology modeling. The 3-dimensional structures used for the docking simulation analysis were obtained from the PubChem database, including the structural data for nonesterified ciclesonide (compound identification [CID] number 6918155), esterified ciclesonide (desisobutyryl-ciclesonide [des-CIC], CID number 6918281), and fluticasone propionate (CID number 444036). Protein structure models of NSP15 and RdRp proteins (Protein Data Bank identification numbers 6VWW and 6NUR, respectively) were constructed as previously described.[2] AutoDock Vina software was used for computationally simulating the molecular recognition process (docking simulation) of the proteins and these drugs.[3] Detailed procedures of the docking simulations have been previously reported.[4]

As shown in Fig 1, our docking simulations revealed that des-CIC could bind to the active site of NSP15 endonuclease with a binding energy of −8.5 kcal/mol. The des-CIC binding sites within NSP15 included His236, His251, Lys291, Ser295, Thr342, and Tyr344 (Fig 1). Most of the interactions between NSP15 and des-CIC were estimated as hydrogen bonds. Similarly, nonesterified ciclesonide could also interact with active-site residues of NSP15 (−7.5 kcal/mol, data not shown). In contrast, neither ciclesonide variant could bind to the active site of SARS-CoV-2 RdRp (data not shown). Moreover, fluticasone propionate, another inhaled glucocorticoid, could not bind to NSP15 or RdRp (data not shown). These results suggested that both esterified and nonesterified derivatives of ciclesonide had the capacity to interact with NSP-15, thereby possessing the capacity to inhibit replication of the SARS-CoV-2 viral genome.

Nonesterified ciclesonide is metabolized by tissue esterases, resulting in des-CIC.[5] Thus, des-CIC may be the predominant form of ciclesonide *in vivo*. Interestingly, we found that both nonesterified ciclesonide and des-CIC were capable of interacting with NSP15, and the interaction of des-CIC with NSP15 involved the larger of the 2 predicted binding energies. As such, replication inhibition of the viral genome may relate primarily to the actions of des-CIC. However, it is critical to recognize that there is scarce information available with respect to the RNA replication mechanisms catalyzed by RdRp and NSP15. Ciclesonide is currently approved for the treatment of asthma and allergic rhinitis and has few to no adverse effects.[6,7] Conclusively, this agent is an important candidate for consideration as potential therapy for COVID-19, and our study results may contribute to the design of other antiviral drugs against SARS-CoV-2.

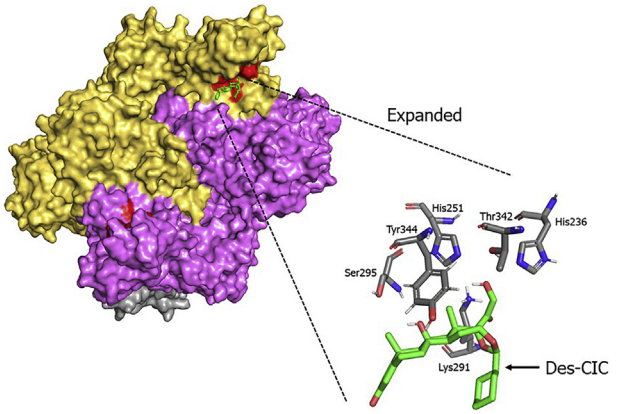

FIG 1. Detailed interaction between esterified ciclesonide (des-CIC) and active sites (*red regions*) of SARS-CoV-2 NSP15 endonuclease. Structure mappings of des-CIC and NSP15 endonuclease were constructed using the space-filling or stick model.

Hirokazu Kimura, PhD[a]
Hiromu Kurusu, MSc[b]
Mitsuru Sada, MD[b]
Daisuke Kurai, MD[c]
Koichi Murakami, PhD[d]
Wataru Kamitani, PhD[e]
Haruyoshi Tomita, MD[f]
Kazuhiko Katayama, PhD[g]
Akihide Ryo, MD[h]

From [a]the Department of Health Science, Gunma Paz University Graduate School of Health Sciences, Gunma, [b]the Advanced Medical Science Research Center, Gunma Paz University, Gunma, [c]the Department of Respiratory Medicine, Kyorin University School of Medicine, Tokyo, [d]the Infectious Disease Surveillance Center, National Institute of Infectious Diseases, Tokyo, [e]the Department of Infectious Diseases and Host Defense, Gunma University Graduate School of Medicine, Gunma, [f]the Department of Bacteriology, Gunma University Graduate School of Medicine, Gunma, [g]the Laboratory of Viral Infection I, Kitasato Institute for Life Sciences Graduate School of Infection Control Sciences, Kitasato University, Tokyo, and [h]the Department of Microbiology, Yokohama City University School of Medicine, Kanagawa, Japan. E-mail: kimhiro@nih.go.jp.

This work was partly supported by a commissioned project for Research on Emerging and Re-emerging Infectious Diseases from the Japan Agency for Medical Research and Development (AMED, grant no. 20fk0108103h0202).

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Matsuyama S, Kawase M, Nao N, Shirato K, Ujike M, Kamitani W, et al. The inhaled corticosteroid blocks coronavirus RNA replication by targeting viral NSP15. BioRxiv 987016 [Preprint]. 2020. https://doi.org/10.1101/2020.03.11.987016.
2. Aso J, Kimura H, Ishii H, Saraya T, Kurai D, Matsushima Y, et al. Molecular evolution of the fusion protein (F) gene in human respirovirus 3 [published online ahead of print January 15, 2020]. Front Microbiol 2020;10:3054. https://doi.org/10.3389/fmicb.2019.03054.
3. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem 2010;31:455-61.
4. Forli S, Huey R, Pique ME, Sanner M, Goodsell DS, Olson AJ. Computational protein-ligand docking and virtual drug screening with the AutoDock suite. Nat Protoc 2016;11:905-19.

5. Nave R, Meyer W, Fuhst R, Zech K. Formation of fatty acid conjugates of ciclesonide active metabolite in the rat lung after 4-week inhalation of ciclesonide. Pulm Pharmacol Ther 2005;18:390-6.
6. Vogelmeier CF, Hering T, Lewin T, Sander P, Bethke TD. Efficacy and safety of ciclesonide in the treatment of 24,037 asthmatic patients in routine medical care. Respir Med 2010;105:186-94.
7. Ratner PH, Wingertzahn MA, van Bavel JH, Hampel F, Darken PF, Shah T. Efficacy and safety of ciclesonide nasal spray for the treatment of seasonal allergic rhinitis. J Allergy Clin Immunol 2006;118:1142-8.

Available online June 13, 2020.
https://doi.org/10.1016/j.jaci.2020.05.029

COVID-19: Time to embrace MDI+ valved-holding chambers!

To the Editor:

Because of the great transmissibility of the virus causing coronavirus disease 2019 (COVID-19), the use of small-volume nebulizers (SVNs) in these days may constitute a serious hazard.

There is much evidence that pressurized albuterol metered-dose inhalers (pMDIs) with valved-holding chambers (VHCs) are efficient, effective, and associated with less side effects than SVNs for the treatment of obstructive pulmonary exacerbations.[1,2] VHCs help to ensure aerosol delivery in infants and toddlers (3-5 years) and in the elderly or cognitively impaired by means of facemasks and tidal breathing. In older children, adolescents, and adults, aerosols should be inhaled by means of the VHC mouthpiece and well-defined respiratory maneuvers designed to maximize deposition of medical aerosol particle (mass median aerodynamic diameter 1-5 μm) in the lower respiratory tract.[3]

In contrast to many other countries that have replaced SVN bronchodilator therapy with pMDIs with VHCs, the United States has continued to use SVN in asthma and chronic obstructive pulmonary disease.

The main impetus for continuing to use SVNs was perceived financial considerations. Because the MDI unit used to cost about $200 and had to be single-patient use (not reimbursed), it was "clearly more cost-effective" to use the SVN. However, this is true only if one considers the devices and not the true cost of the longer emergency department and often intensive care unit stay. Recent studies showed a significant cost saving with MDIs/VHCs because patients improved faster, were sent home more quickly, and could be taught in the emergency department to use the MDIs/VHCs, thus decreasing early readmission.[4,5]

VHCs have numerous additional advantages including an up to 80% decrease in the upper respiratory tract deposition of inhaled medication, and generation of significantly smaller particles that better penetrate into the lung periphery.[3] Furthermore, they are totally self-contained and do not require an external, expensive, and bulky source of energy.

The current COVID-19 pandemic has been shown to require much greater infection control not only with proven infected persons but even more in unknown, as yet undiagnosed, or asymptomatic COVID-19 carriers.

With continuously operating SVNs, aerosols are released into the room air throughout exhalation. The risk of transmission further increases because SVNs generate a large, potentially "respirable" aerosol mass propelled over a greater distance than the natural dispersion pattern.[6] Recent reports indicated that the coronavirus may be disseminated by airborne transmission.[7-9] Furthermore, the aerosol particles generated by SVNs can stimulate patients' or by-standers' cough reflex, further increasing the risk of spreading the disease.

The change from SVNs to MDIs/VHCs has been going on in Canada for many years. Given the current pandemic of COVID-19, Canadians have further restricted the delivery of aerosol by nebulizers, with Global Initiative for Asthma[10] and many other international authorities following suit. On April 8, 2020, the Food and Drug Administration approved the first generic albuterol inhaler in the United States. This is a major step that promises to make pMDIs/VHCs increasingly favored over SVNs for treating reversible airflow obstruction. It is our view that caregivers worldwide should also adopt the conversion from SVNs to pMDIs/VHCs for bronchodilator therapy.

Israel Amirav, MD[a]*
Michael T. Newhouse, MD, MSc[b]

From [a]the Pediatric Department, University of Alberta, Edmonton, Alberta, and [b]the Firestone Institute for Respiratory Health, St Joseph's Hospital, McMaster University, Hamilton, Ontario, Canada. E-mail: amirav@ualberta.ca.

*Israel Amirav, MD, is currently at Dana-Dwek Children's Hospital, Tel Aviv, Israel.

Disclosure of potential conflict of interest: M. T. Newhouse is employed by InspiRx Pharmaceuticals, Inc, as the Chief Medical Officer and has patents through InspiRx Pharmaceuticals, Inc (6,470.882; 8,119,016; D 689,602; D 685,085; and D 686725; Pending: US 2012/0318261 and 2012/0318265). I. Amirav declares no relevant conflicts of interest.

REFERENCES

1. Amirav I, Newhouse MT. Metered-dose inhaler accessory devices in acute asthma: efficacy and comparison with nebulizers: a literature review. Arch Pediatr Adolesc Med 1997;151:876-82.
2. Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev 2013;9:CD000052.
3. Vincken W, Levy ML, Scullion J, Usmani OS, Dekhuijzen PR, Corrigan CJ. Spacer devices for inhaled therapy: why use them, and how? ERJ Open Res 2018;4.
4. Spin P, Sketris I, Hill-Taylor B, Ward C, Hurley KF. A cost analysis of salbutamol administration by metered-dose inhalers with spacers versus nebulization for patients with wheeze in the pediatric emergency department: evidence from observational data in nova scotia. CJEM 2017;19:1-8.
5. Rodriguez-Martinez CE, Sossa-Briceño MP, Castro-Rodriguez JA. Metered-dose inhalers vs nebulization for the delivery of albuterol in pediatric asthma exacerbations: a cost-effectiveness analysis in a middle-income country. Pediatr Pulmonol 2020;55:866-73.
6. Tang JW, Li Y, Eames I, Chan PKS, Ridgway GL. Factors involved in the aerosol transmission of infection and control of ventilation in healthcare premises. J Hosp Infect 2006;64:100-14.
7. Fineberg HV. Rapid expert consultation on the possibility of bioaerosol spread of SARS-CoV-2 for the COVID-19 pandemic (April 1, 2020). In: The National Academies Press N.R.C., ed. Washington, DC: The National Academies Press, National Research Council; 2020.
8. Morawska L, Cao J, Airborne transmission of SARS-CoV-2: the world should face the reality [published online ahead of print April 10, 2020]. Env Int. https://doi.org/10.1016/j.envint.2020.105730.
9. Lewis D. Is the coronavirus airborne? Experts can't agree. Nature 2020;580:175.
10. Global INitiative for Asthma. COVID-19: GINA answers to frequently asked questions on asthma management March 25, 2020. Available at: www.ginasthma.org. Accessed May 10, 2020.

Available online May 22, 2020.
https://doi.org/10.1016/j.jaci.2020.04.046

The bimodal SARS-CoV-2 outbreak in Italy as an effect of environmental and allergic causes

To the Editor:

We read with attention the very recent Editorial by Navel et al[1] in the latest issue of the *Journal*. The topic intrigued us because we are currently investigating how come Italy is cropped into 2 great coronavirus disease 2019 (COVID-19)-infected macro