
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.

Medical Hypotheses 144 (2020) 110046

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Letter to Editors

# Reposition of montelukast either alone or in combination with levocetirizine against SARS-CoV-2

A B S T R A C T

It has been hypothesised that antiallergic medications (AAMs) like montelukast and levocetirizine both the two bitter chloro compounds could be repurposed either alone or combinedly as an antiviral against SARS-CoV-2, like chloroquine/hydroxychloroquine (CQ/HCQ), another two bitter chloro compounds. Both AAMs and CQ/HCQ are bitter tasted chloro compounds. Depending on their these two similar physical properties and the safety and efficacy of AAMs by controlling over post viral episodes as comparing with viral inhibitory activities including SARS-CoV-2 by CQ/HCQ, a reposition of AAMs either alone/combinedly could be rationalised as an antiviral approach to nCoV.

*To the editor*

**COVID-19**: Commonly referred to as the "novel coronavirus" (nCoV) or simply the "coronavirus", a new virus showing a respiratory illness like pneumonia, or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a causative agent for corona disease 2019 (COVID-19). WHO declared a highest global health emergency on COVID-19 on 30th January 2020, that time outside of the China only 98 case of positive were found [1]. But today, the 16th June 2020 the figure is totally opposite that the world is overwhelmed by more than 80.0 lacks infections and 4.3 lacks death. The rate curve of world confirmed cases of COVID-19 and confirmed death from COVID-19 showed still steeper. No flattening the curves were observed (source: Johns Hopkins CSSE Note, data updated on yesterday, 15th June 2020) [2]. Medical professionals are facing direct challenge due to unprecedented power of spreadibility of the virus. At this moment Humanity and world economy are totally paralysed by lockdown. There are no other ways except masking, hand washing and social distancing. Only the way to wait for a specific medication and or a vaccine to defeat the virus. Currently there are no FDA approved vaccines available for covid-19. Clinical trials and case reports have yield moderate results repurposing antiviral therapies used in unrelated viral infections, but further investigation is required [3].

**Antiallergic medications**: Antiallergic medications (AAMs), a combination of montelukast (MLK) and levocetirizine (LCZ) could be effective antiviral against COVID-19. Montelukast, a known antiasthmatic/antileukotriene/antiallergic drug may have some viral inhibitory role to control COVID-19, need to explore, as recently reported by Yongkang Chen et al., 2020, that it can irreversibly inhibit the infectivity of Zika like flavivirus [4] and reported by Ahmad A et al., 2018, that it can reduce dengue (like flavivirus) shock syndrome [5]. Levocetirizine may stop cytokine storm as it inhibits the production of intercellular adhesion molecule-1 (ICAM-1) and secretion of interleukin IL-6 and IL-8, which may have beneficial effects on the pathophysiologic changes related to human rhinovirus (HRV) infection in airway epithelial cells [6]. Flaviviruses, HRV and nCoV have common type of genetic material that is single stranded RNA. Both montelukast and levocetirizine, the two bitter [7] chloro compounds [8,9], like chloroquine/hydroxychloroquine (CQ/HCQ) as CQ has bitter taste, that was described by Hans D Nothdurft and Kevin C Kain [10] and HCQ- it leaves a horrible bitter taste in the mouth, reported in India Today Insight [11]. CQ exerts direct antiviral effects inhibiting pH dependent steps of the replication of several viruses including members of the flaviviruses, retroviruses and coronaviruses [12]. Also montelukast, can treat recurrent respiratory symptoms of post-respiratory syncytial virus bronchiolitis in children [13]. Montelukast attenuates the frequency and severity of episodic wheezing in child patients due to upper respiratory tract infection caused by adenovirus, influenza, metapneumovirus, coronavirus [14]. Inventor, Bruce Chandler described in his European patent that combination of LCZ and MLK formulations are effective for treating influenza, common cold and associated acute inflammation [15]. Mi-Kyeong Kim et al., 2018 reported that a 4-week double-blind, randomized, multicenter phase 3 study was conducted to compare montelukast monotherapy vs combination therapy with montelukast plus levocetirizine in a cohort of patients with perennial allergic rhinitis and mild to moderate asthma. Resulting a fixed-dose combination of montelukast plus levocetirizine was found to be safe and effective for the treatment of perennial allergic rhinitis and asthma compared with montelukast alone, according to research [16]. SM Adsule et al., 2010 has reported in his review that the new generation antihistaminics are all safe, with negligible sedative effects, excellent tolerability and have no influence on cardiac parameters. Montelukast when used as monotherapy is efficacious and improves quality of life. Combination therapy (montelukast plus levocetirizine) is a more effective strategy than monotherapy in the treatment of persistent allergic rhinitis [17].

Since AAMs [7–9] and CQ/HCQ [10,11] both possess bitter taste and chloro group, depending on their these two similar properties, I would like to hypothesise that there is a chance for repositioning the these two bitter chloro MLK and LCZ compounds, alone or combinedly against SARS-CoV-2 like chloroquine/hydroxychloroquine as both CQ and HCQ can inhibit SARS-CoV (SARS-2003) and SARS-CoV-2 (2019-nCoV) before and after infection, which was reported by Katelyn A Pastick et al., 2020 [18]. It is partinent to say, recently a hypothesis was reported by Cihan Fidan et al., 2020 where author has described that as a potential treatment of COVID-19, montelukast has an anti-

https://doi.org/10.1016/j.mehy.2020.110046
Received 16 June 2020; Received in revised form 22 June 2020; Accepted 24 June 2020
Available online 28 June 2020

inflammatory role [19]. Whereas in the present hypothesis I would like to clearly emphasize that repurpose possibility of AAMs either alone (MLK/LCZ) or combination (MLK + LCZ) as antiviral against SARS-CoV-2 with special reference to CQ/HCQ. Also combination (MLK + LCZ), another option of therapy may be more effective than monotherapy (MLK/LCZ) [15–17]. Further more it has been strengthening the hypothesis from the reported evidences [4–6,13–17] that as the individual components (MLK/LCZ) of AAMs either alone or in a combination posing positive role in controlling different post viral manifestations [4–6,13–17] showing significant safety and efficacy [15–17] resulting need to see what happens when alone/combinedly it would be treated as preventive/prophylactic/curative of COVID-19.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

None.

## Funding and support

None.

## References

[1] Global health emergency declared by WHO, available from https://www.bbc.com/news/world-51318246.
[2] www.theguardian.com/world/2020/jun/16/coronavirus-world-map-which-countries-have-the-most-covid-19-cases-and-deaths.
[3] https://www.psychologytoday.com/sg/blog/experience-engineering/202003/can-supplements-help-combat-covid-19, posted on March 20, 2020.
[4] Chen Yongkang, Li Yuan, Wang Yiaohuan, Zou Peng. Montelukast an anti-asthmatic drug inhibits Zika virus infection by disrupting viral integrity. Front Microbiol 2019;10:3079. https://doi.org/10.3389/fmicb.2019.03079.
[5] Ahmad A, Waseem T, Butt NF, Randhawa FA, Malik U, Shakoori TA. Montelukast reduces the risk of dengue shock syndrome in dengue patients. Trop Biomed 2018;35(4):1115–22.
[6] Jang Ju Yong, Wang Jong Hwan, Kim Ji Sun, Kwon Hyun Ja, Yeo Nam-Kyung, Lee Bong-Jae. Levocetirizine inhibits rhinovirus-induced ICAM-1 and cytokine expression and viral replication in airway epithelial cells. Antiviral Res 2009;81(3):226–33. https://doi.org/10.1016/j.antiviral.2008.12.001. Epub 2008 Dec 25.
[7] Gupta MM, Gupta Niraj, Chauhan Bhupendra S, Pandey Shweta. Fast disintegrating combination tablet of taste masked levocetrizine dihydrochloride and montelukast sodium: formulation design, development, and characterization. J Pharm (Cairo) 2014:568320. https://doi.org/10.1155/2014/568320. Published online 2014 Mar 30.
[8] https://pubchem.ncbi.nlm.nih.gov/compound/Montelukast-sodium.
[9] https://pubchem.ncbi.nlm.nih.gov/compound/Levocetirizine.
[10] Nothdurft HD, Kain KC. Malaria prevention. The Travel and Tropical Medicine Manual. fifth ed. 2017. (www.sciencedirect.com/topics/medicine-and-dentistry/malaria-control).
[11] https://www.indiatoday.in/india-today-insight/story/covid-19-the-bitter-truth-about-using-hydroxychloroquine-as-a-preventive-drug-1659116-2020-03-24.
[12] Savarino A, Boelaert JR, Cassone A, Majori O. Effect of chloroquine on viral infections: An old drug against today's diseases. Lancet Infect Dis 2003;3(11):722–7.
[13] Bisgaard H, Flores-Nunez A, Goh A, Azimi P, Halkas A, Malice M-P, Marchal J-L, Dass SB, Reiss TF, Knorr BA. Study of montelukast for the treatment of respiratory symptoms of post–respiratory syncytial virus bronchiolitis in children. Am J Respir Crit Care Med 2008;178(8):854–60. PubMed PMID: 18583576, Epub 2008/06/28.
[14] Brodlie M, Gupta A, Rodriguez-Martinez CE, Castro-Rodriguez JA, Ducharme FM, McKean MC. Leukotriene receptor antagonists as maintenance and intermittent therapy for episodic viral wheeze in children. Cochr Database Syst, Rev 2015. CD008202, PubMed PMID: 26482324, Pubmed Central PMCID: PMC6986470, Epub 2015/10/21.
[15] Inventor: Bruce Chandler, Levocetirizine and montelukast for the treatment of influenza, common cold and inflammation, European Patent office, Publication no. EP2799071B1, Granted on 17 Oct., 2018.
[16] Kim Mi-Kyeong, Lee Sook Young, Park Hae-Sim, Yoon Ho Joo, Kim Sang-Ha, Cho Young Joo, Yoo Kwang-Ha, Lee Soo-Keol, Kim Hee-Kyoo, Park Jung-Won, Park Heung-Woo, Chung Jin-Hong, Choi Byoung Whui, Lee Byung-Jae, Chang Yoon-Seok, Jo Eun-Jung, Lee Sang-Yeub, Cho You Sook, Jee Young-Koo, Lee Jong-Myung, Jung Jina, Park Choon-Sik. A randomized, multicenter, double-blind, phase III study to evaluate the efficacy on allergic rhinitis and safety of a combination therapy of montelukast and levocetirizine in patients with asthma and allergic rhinitis. Clin Ther 2018;40(7):1096–1107.e1. https://doi.org/10.1016/j.clinthera.2018.04.021.
[17] Adsule SM, Misra D. Long term treatment with montelukast and levocetirizine combination in persistent allergic rhinitis: Review of recent evidence. J Indian Med Assoc 2010;108(6):381–2.
[18] Pastick Katelyn A, Elizabeth C, Okafor, Wang Fan, Lofgren Sarah M, Skipper Caleb P, Nicol Melanie R, Pullen Matthew F, Rajasingham Radha, McDonald Emily G, Lee HTodd C, Schwartz Ilan S, Kelly Lauren E, Lother Sylvain A, Mitjà Oriol, Letang Emili, Abassi Mahsa, Boulware David R. Hydroxychloroquine and Chloroquine for Treatment of SARS-CoV-2 (COVID-19). Open Forum Infectious Diseases 2020;7(4). https://doi.org/10.1093/ofid/ofaa130.
[19] Fidan Cihan, Aydoğdu Ayşe. As a potential treatment of COVID-19: montelukast. Med Hypotheses 2020. https://doi.org/10.1016/j.mehy.2020.109828. Published online 2020 May 11.

Dipankar Bhattacharyya
*Chichuria Institute of Medical Science & Research, Thakurpara, Chichuria, Bethuadahari-II (XVI), Nadia, West Bengal 741 126, India*
*E-mail address:* bhattacharyya952@gmail.com.