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To:
Editor in Chief
World J Virol

Dear Editor,

Thank you for giving us the possibility to resubmit the manuscript. We revised the letter with particular regard to the following points raised by the reviewers.

Reviewer 03441022

The manuscript by Finsterer et al. in a form of a Letter to Editor criticizes the claims made in the work by Dominari et al. I fully agree with the authors however I recommend the authors to minor revised their manuscript at the following: “NAC cannot neutralise the virus and cannot reduce the virus load. Thus, NAC may have, at best, a complementary but no curative effect in SARS-CoV-2 infections as all infections are associated with increased oxidative stress and cytokine activation. Second, there are no reports about studies demonstrating that NAC was capable to reduce the virus load, preventing the infection, alleviating the severity of COVID-19, or reducing mortality.” Though I might agree with the authors that there is no scientific proof that NAC influences SARS-CoV-2 virus replication or viral load, it does not mean that in the future such studies will not appear. There are reports showing that NAC inhibits virus replication e.g. H5N1 please see: Biochem Pharmacol. 2010 Feb 1;79(3):413-20.

Thank you for this point. It was added to the discussion as well as the reference.

Last sentence: “In a situation in which the whole world suffers from this scourge of humanity we do not need speculations or dazzling but facts we can rely upon.” This sentence should be softened, hypotheses or speculations are needed in science because progress is made as a result of their verification.

The sentence was softened accordingly.

Reviewer 05393454

The English need improvement since there are few grammatical and syntax errors in the manuscript (For example, the words “N-acetyl cystein” may be as “N-acetyl cysteine”; “an antiviral” as “the antiviral”; “glutathion” as “glutathione”; “the oxidative” as “oxidative”; “NAC have” as “NAC to have the”; “in sputum” as “sputum”; “a strong” as

“strong”). There are some typing mistakes as well, and authors are advised to carefully proof-read the text (For example, the words “Key words” may be as “Keywords”; “interest” as “interest.”). The grammar mistakes and typos not mentioned here also to be checked and corrected properly.

Thank you for your vigilance. The English was improved and all grammatical and typographical errors, whenever detected, were corrected.

Check the abbreviations throughout the text and introduce the abbreviation when the full word appears the first time in the text and then use only the abbreviation (For example, N-acetyl cysteine – NAC, MMP-1, MMP-4, ICAM-1, NF-kB, Nrf2, etc.,). And it should be in both abstract as well as in the remaining part of the manuscript.

All abbreviations were written in full at their first occurrence in the abstract and main text.

The authors should change the signs in the chemical name either superscript or subscript all over the text. For example, “RO₂” should be as “RO²”.

Was changed accordingly

The authors may referred the following references published in Medical Hypotheses, in 2020 and the doi: 10.1016/j.mehy.2020.109862, which may support the protocols of using heparin along with N-acetyl cysteine, which has been developed by a Seattle-based biotherapeutics researcher may support to treat COVID-19. And there is no published data regarding with this hypothesis.

Thank you for this valuable information. This point was added to the discussion.

Reviewer 03261315

In reviewed the letter to the Editor by Josef Finsterer et al, regarding the review article by Dominari et al. about the putative therapeutic effect of N-acetyl cysteine (NAC) in SARS-CoV-2 infected patients. In my opinion the authors should balance the arguments regarding the possibility of therapeutic role of NAC in SARS-CoV-2 infection. The arguments against NAC as a potential therapeutic drug for SARS-CoV-19 are not solid. NAC could act as a potential therapeutic agent in the treatment of COVID-19 through a variety of potential mechanisms, including increasing glutathione, improving T cell response, and modulating inflammation. There are evidence to support the use of NAC as a treatment for COVID-19.

Radtke K.K., Coles L.D., Mishra U., Orchard P.J., Holmay M., Cloyd J.C. Interaction of N-acetylcysteine and cysteine in human plasma. J Pharm Sci. 2012;101:4653–4659. [PubMed] [Google Scholar]

Scheffel M.J., Scurti G., Wyatt M.M., Garrett-Mayer E., Paulos C.M., Nishimura M.I. N-acetyl cysteine protects anti-melanoma cytotoxic T cells from exhaustion induced by rapid expansion via the downmodulation of Foxo1 in an Akt-dependent manner. Cancer Immunol Immunother. 2018;67:691–702.

Malorni W., Rivabene R., Lucia B.M., Ferrara R., Mazzone A.M., Cauda R. The role of oxidative imbalance in progression to AIDS: effect of the thiol supplier N-acetylcysteine. AIDS Res Hum Retroviruses. 1998;14:1589–1596. [PubMed] [Google Scholar]

De Rosa S.C., Zaretsky M.D., Dubs J.G., Roederer M., Anderson M., Green A. N-acetylcysteine replenishes glutathione in HIV infection. Eur J Clin Invest. 2000;30:915–929. [PubMed] [Google Scholar]

Liu Y., Yao W., Xu J., Qiu Y., Cao F., Li S. The anti-inflammatory effects of acetaminophen and N-acetylcysteine through suppression of the NLRP3 inflammasome pathway in LPS-challenged piglet mononuclear phagocytes. Innate Immun. 2015;21:587–597.

Lee S.I., Kang K.S. N-acetylcysteine modulates lipopolysaccharide-induced intestinal dysfunction. Sci Rep. 2019;9:1004.

There are clinical trials on going regarding the potential role of NAC in Covid-19 infection. Therefor a final conclusion could be not undertaken.

We agree. The discussion was modified accordingly. The references were added to the reference list.

We hereby submit the manuscript “Repurposing the antioxidant and anti-inflammatory agent N-acetyl cysteine for treating COVID-19” by Finsterer J et al. for publication as a “Letter to the Editor” in the “World J Virol”.

The manuscript has not been published in print or electronic format, submitted, or is not simultaneously being under consideration by another publication or electronic medium, and no portion of the data has been or will be published in proceedings or transactions of meetings or symposium volumes.

There is no financial support or other benefits from commercial sources for the work reported on in the manuscript, or any other financial interest of the authors, which could create a potential conflict of interest or the appearance of a conflict of interest with regard to the work. Both authors approved submission of the revised manuscript.

Please confirm receipt of the manuscript.

Sincerely Yours,

J. Finsterer, MD, PhD

Vienna, 23rd June 2021