Reviews in Medical Virology - Manuscript ID RMV-2022-036 [email ref: SE-6-a]

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Cc: masyeniputu@yahoo.com; m.iqhram@oia.unsyiah.ac.id; andri.frediansyah@lipi.go.id; firzannainu@unhas.ac.id; trina_tallei@unsrat.ac.id; talhabmb@bgctub.ac.bd; talhabmb@gmail.com; yophinni@mgh.harvard.edu; kdhama@rediffmail.com; harapan@unsyiah.ac.id

Date: Thursday, 27 January 2022 at 01:33 pm GMT+8

27-Jan-2022

Dear Dr Harapan:

Your manuscript entitled "Molnupiravir: a lethal mutagenic drug against rapidly mutating SARS-CoV-2 – A narrative review" by Putu, Masyeni ; Iqhrammullah, Muhammad; Frediansyah, Andri ; Nainu , Firzan ; Tallei, Trina; Emran, Talha Bin; Ophinni, Youdiil; Dhama, Kuldeep ; Harapan, Harapan, has been successfully submitted online and is presently being given full consideration for publication in Reviews in Medical Virology.

Co-authors: Please contact the Editorial Office as soon as possible if you disagree with being listed as a co-author for this manuscript.

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Reviews in Medical Virology Editorial Office

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Date: Saturday, 12 February 2022 at 12:24 pm GMT+8

11-Feb-2022

Dear Dr. Harapan,

Your manuscript entitled "Molnupiravir: a lethal mutagenic drug against rapidly mutating SARS-CoV-2 – A narrative review" has been successfully submitted online and is presently being given full consideration for publication in Journal of Medical Virology.

Your manuscript number is JMV-22-15223. Please mention this number in all future correspondence regarding this submission.

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JMV-22-15223 - Decision on Manuscript

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Date: Sunday, 27 February 2022 at 04:07 am GMT+8

26-Feb-2022

Dear Dr. Harapan,

Manuscript ID JMV-22-15223 entitled "Molnupiravir: a lethal mutagenic drug against rapidly mutating SARS-CoV-2 – A narrative review" which you submitted to Journal of Medical Virology has been reviewed. The comments of the referee(s) are included at the bottom of this letter.

The reviewers recommend Major Revision at this time. A revised version of your manuscript that takes into account the comments of the referee(s) will be reconsidered for publication. We ask that you resubmit your manuscript within 21 days.

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Once again, thank you for submitting your manuscript to Journal of Medical Virology and I look forward to receiving your revision.

Kind regards,

Dr. Zhengqiang Wang
Associate Editor

Dr. Shou-Jiang Gao

Editor-in-Chief

Journal of Medical Virology

Referee(s)' Comments to Author:

Reviewing: 1

Comments to the Author (blind)
Molnupiravir: a lethal mutagenic drug against rapidly mutating SARS-CoV-2 – A narrative review

This review addresses the novel antiviral drug Molnupiravir, its discovery and development, its mechanism of action, its activity against SARS-2 and potential genotoxicity concerns. The mechanism of action of Molnupiravir, its broad-spectrum antiviral effect and its recent approval for SAR-CoV-2 infection treatment, makes this review of high interest for publication in the context of the COVID19 pandemic. Molnupiravir is one of the rare orally available drugs approved against SARS-CoV-2, the causative agent of the COVID19 pandemic. While the English is poor and require serious revision, the paper is well organized and mostly easy to read. However, multiple approximations and quick conclusions require major revisions. The paragraph addressing the "Concerns of Molnupiravir genotoxicity" is very short and is eluding a major debate regarding this drug.

Reviewer's major criticisms

Page 5 line 76 "Since its first transmission to humans in 2019" , there is no proof of a first transmission to humans in 2019, the infection may have been undetected for months, maybe years at low infection rates. Suggesting " Since its first observation in humans in 2019"
Page 5 line 83 "the repurposing of drugs is expected to turn the tide of the pandemic" it is just one of the strategies expected to turn the tide.
Page 5 Line 84 "broad-spectrum antivirals are preferable because it is not impossible for the new human-infecting virus to cause another outbreak" unclear, rephrase
Page 5 line 89 "Remdesivir, an RdRp inhibitor, is the only drug approved for the treatment of COVID-19" there are now several approved drugs. Update
Page 6 line 102 "the antiviral agent should also be tasked to make the virus hardly resistant" unclear and inaccurate, rephrase
Page 6 line 104 "error catastrophe" the authors alternate between "error catastrophe " and lethal mutagenesis terms in the entire document which are essentially similar. These terms should be defined. Using only one of them would make things clearer. Additionaly, the authors often use the term mutagenic activity but it is not clear if they are talking about mutagenic activity against the virus or host DNA.
Page 6 line 104 "how it acts as a barrier against SARS-CoV-2 resistance" the reviewer disagree with this statement, while barrier to viral drug development has been observed, the reasons behind this effect have yet to be established. Rephrase
Page 6 line 117 "The ester group in molnupiravir functions as a blockage for the 5′-OH to escape phosphorylation until the molecule reaches the bloodstream." The reviewer highly doubts the veracity of this statement, else provide a reference or rephrase.
Page 6 line 124 "Molnupiravir was specifically designed as a broad-spectrum antiviral agent" Molnupiravir and its precursor NHC have not been designed to have broad antiviral effect but rather observed to have a broad effect before the mechanism was explained. Rephrase.
Page 7 line 125 "Molnupiravir was specifically designed as a broad-spectrum antiviral agent against RNA viruses, thus preventing the virus to develop resistance against the drug." This is completely unrelated. Viruses always tend to develop drug resistance regardless of the broad-spectrum antiviral effect.
Page 7 line 137 "This protein or its equivalent is absent in humans" this is not true, humans do have RNA ploymerases. Rephrase
Page 7 line 138 Remdesivir is an RdRp inhibitor while Favipiravir possesses multiple mechanisms of action. Rephrase.
Page 7 line 141 "In case of coronaviruses (CoVs), RdRp inhibitors cannot be designed to rely only on the termination of RNA chain elongation" this is an overstatement, there is no proof for this. The proof reading mechanism makes it difficult but not impossible.
Page 8 line168 "ExoN proofreading would be a simple task for molnupiravir to circumvent " unclear, rephrase.
Page 10 line 204 "the superiority" suggesting "the advantages" or the efficacy
Page 15 line 336 "inconclusive findings" these results are actually very conclusive on the mutagenic effect on the host DNA of Molnupiravir compared to other drugs in the parameter of the study. The authors should be much more cautious since this aspect of Molnupiravir is highly scrutinized. We suggest a much more cautious approach for this entire paragraph. The mutagenic potential of Molnupiravir for the host is to be taken very seriously. To illustrate this, Molnupiravir is not prescribed for the treatment of pregnant women, a negative pregnancy test is required before treatment is performed. Protected intercourse is recommended.
Page 25 Figure 1 the 5' carbon of each nucleoside is missing, redraw the structures

Reviewer's minor criticisms

Page 4 line 61 "the key therapeutic" suggesting "a key therapeutic"
Page 4 line 63 "Molnupiravir is a proposed nucleoside analogue" suggesting "Molnupiravir is a nucleoside analogue"
Page 4 line 64 "in silico" suggesting "in vitro"
Page 5 line 77 "in 2020", remove, the pandemic is still ongoing in 2022
Page 5 line 80 "respond" suggesting "responded"
Page 5 line 92 phrase is unclear, rephrase
Page 9 line 185, define ex vivo
Page 15 line 342 "have suggested" suggesting "demonstrated"
Page 26 Figure 2 : NHC-TP competes with CTP but the reverse is true to, suggesting NHC-TP is incorporated as CTP analogue.

Reviewing: 2

Comments to the Author (blind)
In the present narrative review, Masyeni, Sri et al. have discussed results from recent clinical trials, and research studies to address the mechanism of action, efficacy in subjects and safety concerns of new investigational drug – molnupiravir for the treatment of SARS-CoV-2. Molnupiravir is a broad spectrum antiviral targeting viral RNA-dependent RNA polymerase (RdRp), the enzyme critical for viral replication. In this review, authors have presented the outcomes of clinical studies to demonstrate that molnupiravir is a potent antiviral drug with good oral bioavailability, safety and tolerability. It is capable of inhibiting the replication of SARS-CoV-2 by inducing the error catastrophe and has found to be significant in patients with mild or moderate COVID-19 and also could reduce the risk of hospitalization or death in non-hospitalized adults. Authors have also discussed the concerns that molnupiravir might cause mutations in host cells.
Overall, authors do a good job of summarising the recent outcomes of clinical studies of molnupiravir. The review is written reasonably well and recommended for publication after major revision. Listed below are few suggestions to improve the review to gain more attention and interest from the readers of "Journal of Medical Virology".

(1) It will be a good addition if authors include discussion to address the concerns over molnupiravir that it could trigger the upsurge of new and more dangerous viral variants.
(2) On Page 4, Line 64: Authors mentioned about the "in silico experiments have reported that molnupiravir will inhibit the replication of SARS-CoV-2". The "in vivo" experimental studies provide sound evidence over "in silico", so authors should delete term "in silico".
(3) On page 4, Line 68: Authors claim that they have discussed with recent findings from published reports and clinical trials. Though authors made good summary of clinical study outcomes, it will be good if they provide discussion on the limitations of the present clinical studies to establish the safety of molnupiravir and what safety measures should be applied to reduce mutagenic effects of molnupiravir to the host and how the labelling and cautious use can reduce the risk of teratogenic effects. A more detailed discussion is recommended instead of only summarizing the clinical study outcomes.
(4) On Page 5, Line 89: Authors claim "Remdesivir, an RdRp inhibitor, is the only drug approved for the treatment of COVID-19". However, this is not true: 1) molnupiravir and paxlovid are now authorized / approved for the treatment of COVID19; and 2) numerous non-antiviral, disease-modifying drugs have been approved for treating COVID-19 (COVID-19 described the disease, not the virus).
(5) On Page 6, Line 109 to 121: Correct the abbreviation "NCH" to "NHC" for β-d-N4-hydroxycytidine.
(6) On Page 7, Line 127: Authors claim that, "ivermectin is repurposed to treat COVID-19". This is not correct as US-FDA has not authorized or approved ivermectin for use in preventing or treating COVID-19 in humans or animals. Ivermectin is approved for human use to treat infections caused by some parasitic worms and head lice and skin conditions like rosacea. Currently available data do not show ivermectin is effective against COVID-19.
(7) On Page 7, Line 128: Authors claim that, "favipiravir have been repurposed and approved for COVID-19 treatment". Again this is not true. Favipiravir is not approved for the treatment of COVID-19, as it exerted no significant beneficial effect in the term of mortality in the general group of patients with mild to moderate COVID-19 (ref.: Sci Rep. 2021; 11(1):11022. doi: 10.1038/s41598-021-90551-6.).
(8) On Page 7, Line 142: Authors claim that, "Chain terminating antiviral agents are often ineffective against the proofreading activities of the virus." This is not true as delayed chain termination is one of the chain termination mechanisms, as exemplified by remdesivir, which is still a chain terminator.
(9) On Page 7, Line 149: Authors write Favipiravir is a "nucleotide analog", however the more precise term is "nucleobase/nucleoside analog".
(10) On Page 8, Line 150-153: As Favipiravir is not an antiviral against SARS-CoV-2, it is not necessary to discuss how it will escape the proof reading activity to improve the efficacy against SARS-CoV-2. It's fair to discuss its MOA of lethal mutagenesis.
(11) On Page 8, Line 156: Authors claim that, "The active form of molnupiravir, NHC-TP, forms NHC-MP by acting as a cytosine analog during the transcription of negative sense genomic RNA (-gRNA) through RdRp". This is not

true, The NHC-TP does not form NHC-MP. Once inside the cells, NHC is phosphorylated to form the active ribonucleoside triphosphate (NHC-TP). Viral RNA polymerase (nsp12) then incorporates NHC-TP (as NHC-monophosphate [NHC-MP]) into SARS-CoV-2 RNA. Authors need to digest the work of, Gordon et al. (J. Biol. Chem. 2021, 297(1):100770. doi: 10.1016/j.jbc.2021.100770.) demonstrating that once incorporated, primers having NHC monophosphate at their 3' end were efficiently extended, particularly at high rNTP concentrations. Moreover, like other mutagenic nucleotides, NHC-TP likely exists in different tautomeric forms that affect base pairing. The hydroxylamine form acts like C and enables base pairing with G, whereas the oxime form (C=NOH) acts like U and allows base pairing with A. The NHC-TP substrate exists predominantly in its hydroxylamine form and acts like CTP; however, when present as NHC-MP in the template, both tautomeric forms seem to coexist and act like CTP or UTP, favoring incorporation of GTP and ATP, respectively. Authors need to discuss the mutagenesis mehanism of molnupiravir with clear understanding.

(12) On Page 9, Line 175: Authors claim that, "Favipiravir is weakly incorporated into the RNA template (-gRNA) ....". This is not correct, as nucleotides get incorporated in "primer" and not "template".

(13) On Page 10, Line 206: Authors write, "A meta-analysis of in vivo studies on anti-SARS-CoV-2 drugs, coupled with a molecular docking investigation, suggested....". It suggested that Authors should eliminate "molecular docking" as its not strong evidence when compared to in vivo studies.

(14) On Page 13, Line 296-300: Authors can eliminate "Molnupiravir is a poor electron acceptor, suggesting that ..... improve its performance in COVID-19 treatment

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- Conflict of Interest statement
- Author contribution statement

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Date: Monday, 14 March 2022 at 08:43 pm GMT+8

14-Mar-2022

Dear Dr. Harapan,

Your manuscript entitled "Molnupiravir: a lethal mutagenic drug against rapidly mutating SARS-CoV-2 – A narrative review" has been successfully submitted online and is presently being given full consideration for publication in Journal of Medical Virology.

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Date: Friday, 18 March 2022 at 10:53 pm GMT+8

18-Mar-2022

Dear Dr. Harapan,

It is a pleasure to accept your manuscript entitled "Molnupiravir: a lethal mutagenic drug against rapidly mutating SARS-CoV-2 – A narrative review" in its current form for publication in Journal of Medical Virology. The comments of the referee(s) who reviewed your manuscript are included at the bottom of this letter.

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Associate Editor

Dr. Shou-Jiang Gao
Editor-in-Chief
Journal of Medical Virology

Referee(s)' Comments to Author:

Reviewing: 1

Comments to the Author (blind)
The modifications are satisfactory.

Reviewing: 2

Comments to the Author (blind)
The Authors have revised the manuscript thoroughly and carefully based on all the comments provided by the reviewers. So far, the reviewer is very satisfied with the revised manuscript. It is recommended to publish the manuscript as it is.

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