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Molnupiravir Armageddon

Leo Goldstein

Abstract

Merck's Molnupiravir is a global catastrophic risk. Its broad use as a treatment for COVID-19 will create dangerous variants of SARS-COV-2. It is already in use in some countries.

Molnupiravir ("MOLN"), a presumed anti-COVID19 drug, acts by significantly increasing the RNA error rate in the coronavirus replication. That exponentially increases the probability of many mutations in a single copy. Copies containing a large set of new mutations are disproportionately likely to create dangerous mutations. Patients taking MOLN are expected to carry and shed the virus in almost equal volumes as untreated patients.

Estimates show that MOLN would increase the frequency of sets of 8 mutations by 3,000 times, and sets of 12 mutations by 240,000 times, per virus generation, per person. This does not include recombinations and many other effects which are likely to compound these results. Multiple rounds of replication and natural selection per person further increase the threat.

The impact cannot be detected immediately due to a possible lag between the appearance of a new variant and the necessary changes in external conditions, which lead to its spread.

At least some of the many artificial variants, induced by the MOLN treatment, are likely to combine immune escape, higher contagiousness, and higher virulence, just to mention a few. This would be a gain-of-function experiment, performed on the entire human race.

Introduction

Similar concerns about accelerating global evolution of SARS2 were expressed by (Ismagilov 2021) and (Nelson and Otto 2021) in the comments to the FDA.

MOLN is a mutagenic drug, which was expected to help body defeat SARS2 by causing lethal mutagenesis (Gordon et al. 2021) (Zhou et al. 2021) in the virus population. *"Lethal mutagenesis is the extinction of a viral population by artificially elevating its mutation rate"* (Bull et al. 2013). MOLN introduces errors in the coronavirus RNA after proofreading.

In addition to MOLN's mutagenicity for the virus, it has also been shown to be mutagenic for humans. Trials have also shown that MOLN is carcinogenic in humans and unsuccessful in preventing or treating COVID-19 (Goldstein 2021). The initial positive reports presented by Merk were based on only the first part of a trial, with several issues, invalidating the results.

Here, a *mutation* means a non-synonymous change in an amino acid, except where specifically noted otherwise.

Main

Frequent Misconceptions

The top three mistakes made by doctors (including AMDAC evaluators), regarding Molnupiravir's action on SARS2:

(1) Likening the variant creating action of MOLN with a resistance to antibiotics.

The evolution of pathogens happens by diversification (or entropy increase), through mutations and natural selection for fitness. Both parts of this process are required. Diversification is usually not noticed, because it is considered constant.

Unlike almost all existing drugs, MOLN increases the rate of mutations (diversification) of SARS2. This increase provides more raw material for natural selection.

This is very different from the resistance development, associated with antibiotics and some other drugs. A pathogen develops resistance to a drug via selection of pathogen genotypes that cannot be inhibited by this drug. MOLN increases the diversity of SARS2, allowing it to better adapt to all challenges and countermeasures.

A patient treated with MOLN has more diversified SARS2 RNA, starting a few hours from the very beginning of treatment. The patient is actively transmitting this diversified SARS2 RNA to others, throughout his/her entire infectious period.

(2) Not appreciating the rarity of the dangerous events.

A set of mutations that might become a new variant rises rarely. It is therefore unlikely to be detected by sequencing samples from a few hundred patients (less than 150 in the Merck's trials), or by observing the recovery of a few thousand patients. If MOLN causes a dangerous new variant once in a hundred thousand patients, Merck's trial would have completely missed it. However, it would be catastrophic when used on millions of people, as Merck plans to do.

(3) Not understanding that variants are not created by single mutations, but by simultaneously occurring mutation sets. MOLN exponentially increases the frequency of such large mutation sets.

If **m** is an increase in the mutation rate and **k** is the number of mutations in the set, then the frequency of sets of **k** mutations increases ~ $\mathbf{m}^{\mathbf{k}}$. Large mutation sets remain too rare to observe in a small trial of a few hundred, but are guaranteed to happen when MOLN is used on millions of people.

Merck has manufactured and shipped millions of MOLN 'treatment courses' all over the world and has licensed it for production in many countries. It intends to produce 10M 'treatment courses' by the end of the year. The Philippines are already using MOLN and heavily promoting it.

Rare events are disregarded as outliers, even when observed. Variant causing mutation sets appear rarely, like once per million cases. But among less than 150 sequenced patients in Merk's trial, one patient had 7 mutations in the spike protein (FDA CDER Briefing 2021), p. 32. This is very alarming. If such a massive mutation set was found in about less than 150 patients tested, what would happen when it is used on millions? Neither the FDA nor AMDAC looked at this case closely, and they allowed the sponsor to simply dismiss it.

AMDAC Meeting

AMDAC is not suitably composed to evaluate global risks. Only one doctor in the AMDAC meeting understood the global risk of MOLN and spoke about it.

MOLN is mutagenic for viruses and for humans. Some AMDAC doctors were confused by that.

All the data presented to AMDAC come from the sponsor (Merck & Ridgeback). There has been no independent testing and no peer review of the data.

Teleconferencing is not a suitable way to conduct meetings of such importance.

The Benefit of Errors to SARS2

SARS2 globally benefits from an increased mutation rate, because of the fast-changing conditions necessitating faster adaptation.

RNA mutations (or errors) are necessary for viral evolution. A mutation/error rate that is too low, reduces the natural selection ability of the virus. Experiments with production of artificial antibodies and other synthetic proteins by randomly mutating the DNA have shown that higher rates of mutation/error produced a larger number of useful proteins (Drummond and et al. 2005).

Lethal mutagenesis is a lengthy process. It is unlikely to work on SARS2 after the onset of symptoms, when there are likely only 1-3 generations of the virus, before the virus is cleared, the patient is hospitalized, or both. MOLN does not significantly decrease the SARS2 viral load during that time.

Numeric Estimates

Variants of Concern

The following Table 1 is useful in making guesses about the sizes of variant-creating mutation sets.

Table 1. Numbers of new mutations in variants of concern and Lambda (Outbreak.info 2021)

Variant	First detected	Parent	**New Mutations in total**	New mutations in S-protein
Omicron (B.1.1.529)		B.1.1	**45**	32
Delta (B.1.617.2)	7/14/2020	B.1 (sic)	**26**	7
Lambda (C.37)	7/31/2020	B.1.1.1	**14**	7

Gamma (P.1)	4/7/2020	B.1.1.28	**19**	10
Beta (B.1.351)	2/15/2020	B.1	**14**	6
Alpha (B.1.1.7)	2/7/2020	B.1.1	**17**	8
B.1 (not a variant)	1/28/2020	---	**---**	---

Data from November 14, 2021. The consensus sequences change occasionally, but not much. Outbreak.info is based on GISAID, which is strongly biased by sampling. It contains mostly SARS2 RNA sequences from North America and Western Europe. There is almost no data from China. Nevertheless, because SARS2 spreads quickly, it is assumed sufficient for rough estimates.

The *New Mutations* column is how many mutations distinguish the variant from its immediate parent in the Pango classification. Reverse mutations can be disregarded because of low probability. Absence of intermediate nodes suggests that intermediate (between the variant and its parent) RNA sequences were either absent or not evolutionary fit. Thus, there likely has been a "leap" from the vicinity of the parent lineage to the "attraction basin" of the VOC. This provides some basis to the estimation of 8-12 mutations.

Poisson Distribution

For the mutation frequency λ, the probability of exactly k mutations in one replication of a virus is described by the Poisson distribution:

$$p(k, \lambda) = \lambda^k * e^{-\lambda} / k! \qquad (1)$$

When it is increased by a factor of **m** by a mutagen, the formula becomes:

$$p(k, m*\lambda) = (m*\lambda)^k * e^{-m*\lambda} / k!$$

which can be re-written as:

$$p(k, m*\lambda) = p(k, \lambda) * m^k / e^{(m-1)*\lambda} \qquad (2)$$

Thus, the increase in probability of large sets of mutations grows very sharply by **k**.

$\lambda \approx 0.4$, including mutations caused by host editing. Formula (2) is sensitive to **m** and **k**, but not to λ. (Zhou et al. 2021) suggests **m ≈ 2.5**, but the assumption that MOLN has above zero therapeutic activity requires **m > 4**. Let's set **m = 3** as a reasonable compromise between the two values.

Considering these parameters, as an example, MOLN would increase the frequency of **8** mutations occurring simultaneously by 3,000 times, and the frequency of **12** mutations occurring simultaneously by 240,000 times.

Productive recombination events would further increase this effect. Additionally, other factors are underestimated in this assumption. For example, the concentration of NHC (the active metabolite of MOLN) is variable. Its half-life is 3.3 hours (per (Merck 2021), slide 39), compared to the recommended 12 hours between drug intakes. Thus, the drug concentration varies over 10x in the body. This should cause larger than expected mutagenicity at peaks, and almost no mutagenicity at throughs.

MOLN also significantly changes relative frequencies of nucleotide substitutions.

Nucleotide Transition Frequencies

MOLN increases probabilities of some nucleotide changes more than other changes. The following Table 2 shows that the frequencies of **G > A** and **A > G** transitions were increased **12x** and **4.3x**, respectively. This further increases relative likelihood of variant-creating mutation sets, because it explores parts of the mutations space, underexplored naturally.

Table 2. Nucleotide transitions frequencies, MOLN vs. Placebo

	MOLN	**Placebo**	***ratio***
#	47	72	
C > U	7.1	3.5	**2.0**
U > C	2.1	0.7	**2.8**
G > A	3.6	0.3	**12.0**
A > G	2.0	0.5	**4.3**

Notice that these are not raw nucleotide mutations, but those that underwent selection.

This is derived from the following Table 2B.

Table 2B. Raw frequencies of nucleotide transitions from Merck and FDA documents

	MOLN*	**Placebo***	**MOLN***	**Placebo***	**MOLN****	**Placebo****
#	13	10	14	20	42	50
C > U	5.9	3.1	9.0	2.6	6.6	4.1
U > C	2.0	0.2	2.5	0.2	1.8	1.1
G > A	1.5	0.1	5.7	0.2	3.6	0.4
A > G	0.9	0.6	2.6	0.3	2.2	0.5

(*) (FDA CDER Brief2 2021), Table 3, based on the data provided by Merck

(**) (FDA CDER Briefing 2021), Table 7, based on the data provided by Merck

Conclusion

Because SARS2 spreads so fast, the use of MOLN anywhere threatens people everywhere. It should be stopped immediately.

Annex 2. Links

FDA Materials: https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-30-2021-antimicrobial-drugs-advisory-committee-meeting-announcement-11302021-11302021#event-materials

The video of the AMDAC meeting: https://www.youtube.com/watch?v=fR9FNSJT64M

Selected comments from Regulations.gov docket

https://virological.org/t/mutagenic-antivirals-the-evolutionary-risk-of-low-doses/768

https://www.regulations.gov/comment/FDA-2021-N-0758-0040

https://www.regulations.gov/comment/FDA-2021-N-0758-0024

https://www.regulations.gov/comment/FDA-2021-N-0758-0020

https://www.regulations.gov/comment/FDA-2021-N-0758-0017

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Drummond A, et al. Why High-error-rate Random Mutagenesis Libraries are Enriched in Functional and Improved Proteins - ScienceDirect. 2005 https://www.sciencedirect.com/science/article/abs/pii/S0022283605005541

FDA CDER Briefing. FDA Briefing Document. 2021 Nov 26; https://www.fda.gov/media/154418/download

FDA CDER Brief2. FDA CDER Brief2. 2021 Nov 29; https://www.fda.gov/media/154421/download

Goldstein L. Re-analysis of Molnupiravir Trials, Phase II/III. TrialSiteNews; 2021 Nov 28; https://trialsitenews.com/re-analysis-of-molnupiravir-trials-phase-ii-iii/

Gordon CJ, Tchesnokov EP, Schinazi RF, Götte M. Molnupiravir promotes SARS-CoV-2 mutagenesis via the RNA template. J Biol Chem. 2021 Jul 1. https://www.jbc.org/article/S0021-9258(21)00563-9/abstract

Ismagilov R. Regulations.gov Comment 2021. https://www.regulations.gov/comment/FDA-2021-N-0758-0015

Merck. Molnupiravir. 2021. https://www.fda.gov/media/154472/download

Nelson C, Otto S. Mutagenic antivirals: the evolutionary risk of low doses - SARS-CoV-2 coronavirus Virological. 2021. https://virological.org/t/mutagenic-antivirals-the-evolutionary-risk-of-low-doses/768

Zhou S, Hill CS, Sarkar S, Tse LV, Woodburn BMD, Schinazi RF, et al. β-d-N4-hydroxycytidine Inhibits SARS-CoV-2 Through Lethal Mutagenesis But Is Also Mutagenic To Mammalian Cells. J Infect Dis 2021 Aug 1. https://doi.org/10.1093/infdis/jiab247