Molnupiravir: ineffective, carcinogenic, and a global threat

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Abstract

Molnupiravir's efficacy is marginal at best, but its mutagenicity and carcinogenicity are real. The tidbits of information published by the UK's MHRA include bone marrow toxicity, suggesting leukemia potential.

The re-analysis of the data in Merck's press release from October[1] shows much lower efficacy than claimed, even without questioning the conduct of the trial and reporting. Merck's failure to publish any paper containing that data is alarming. Merck also failed to disclose the outcomes from patients who were recruited after the cut-off date for the intermediate review.

The UK authorization also reveals that the population in Merck's trial was younger and less at-risk than the general population. Even so, after being treated with Molnupiravir, the trial population had worse outcomes than the comparable general population, who was not treated with Molnupiravir.

Molnupiravir damages bone marrow just when it is needed most – to produce B-cells producing antibodies against SARS-COV-2.

These facts are grounds for a strongly worded rejection of Molnupiravir.

The Molnupiravir's potential to rapidly create to more dangerous variants of SARS-COV-2 has already caught attention of the mainstream media[2].

Drugs having mutagenesis as the primary activity have never been used for acute respiratory diseases, or for any kind of coronavirus.

Lethal Mutagenesis has never worked and cannot work against Coronaviruses

Higher mutation rate can give the virus evolutionary rescue instead of extinctions[3], and *"higher mutation rate allows [virus] populations to withstand higher levels of stress"* [4].

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Ribavirin (with interferon) worked against coronaviruses only in vitro[5]. When they attempted to use ribavirin for MERS-CoV in humans, "*very few human cases who received a combination of IFN-α2b, ribavirin, and corticosteroids survived*"[6]. Ribavirin was also tried against SARS-CoV-2 in early 2020 and failed.

Favipiravir is an RNA chain terminator. Mutagenesis is its secondary mechanism against some viruses, but it has not seen much use prior to COVID-19. It was approved in Japan only for emergency use for pandemic influenza[7]. Favipiravir works against SARS-CoV-2 as a chain terminator because most mutations induced by it are eliminated in proofreading. Still, concerns about mutagenicity remain.

While Ribavirin is effective on as a part of a treatment for AIDS and Hepatitis C, they cannot be compared to COVID-19. HIV and HCV are small viruses without proofreading mechanism. SARS-COV-2 is a large virus with proofreading. AIDS and Hepatitis C are chronic, while COVID-19 is acute. Acceptable risk and harm are also very different.

Ineffective

Molnupiravir is not and cannot be effective against SARS-COV-2 in humans.

Theoretically, lethal mutagenesis might be effective against fast mutating viruses, existing near the error threshold[8]. Coronaviruses are far from any error threshold. Experiments have shown that coronaviruses can survive and thrive at an error rate 20x higher than their normal rate[9] (in vitro). Increased rate of error might have an opposite effect on the coronavirus, increasing its adaptability .

Lethal mutagenesis relies on "defectors" – unfit mutated virions that compete against fit ones[10]. However, a coronavirus infection is more likely to produce the opposite of defectors – let's call them "effectors". These "effectors" protect fit virions by binding neutralizing antibodies. This phenomenon cannot be observed in vitro, in bacteriophages, or in computer models. Further, the mutated "effectors" are likely to suppress the host's antiviral responses by the same mechanisms that fit virions do: downregulating or antagonizing tetherin[11] [12], STAT1 and STAT2 proteins, MHC I, interferon[13] etc.[11]. Smaller viruses lack most of these mechanisms.

Lethal mutagenesis is a long process, sometimes modeled as infinity[14]. That makes mutagenic drugs suitable for chronic diseases, but not for COVID-19, in which it can act only on 3-5 generations of the virus.

Bone Marrow Toxicity and Leukemia Potential

The UK regulator MHRA referenced[15] the following results from a previous study in dogs (emphasis is added):

*"Reversible, dose-related **bone marrow toxicity** affecting all haematopoietic cell lines was observed in **dogs** at ≥17 mg/kg/day (**0.4 times the human NHC exposure** at the recommended human dose (RHD))."*

0.4 times exposure can be rephrased as a *comparable exposure*. Molnupiravir's mutagenic effects can best be compared to the effects of ionizing radiation. A short-term exposure causes transitory injury, which may not even be felt. The long-term effects, depending on the dose, include cancer. The observed bone marrow toxicity suggests future leukemia.

Molnupiravir's Trials and Tribulations

Merck's Press Release

Merck's press release[1] announced "successful trial results" in 775 patients. It also announced that they end enrollment of new patients, after the study had already enrolled more than 90% of prospective patients (or ~1,400). Because of the short observation time of only 29 days, including the five days of treatment, Merck had complete results from all ~1,400 patients (the original 775 plus those recruited after the interim analysis) before October 25. Yet, none of this data has been published. That further raises suspicions that the data does not support Merk's claims.

Selection of Low-Risk Patients

Merck's press release gives the impression that the trial population was a high-risk population. In fact, the study patients were at lower risk than the general population[15]:

*"At baseline, in all randomised subjects, the **median age was 44 years** (range: 18 to 88 years); **14%** of subjects were 60 years of age or older and **3% were over 75 years** of age; ..."*

More than 30% of the general adult population is 60 years old or older, compared with only 14% in the study population. 86% of the subjects were ages 18 - 59. They had at least one of the following conditions: "*diabetes, obesity (BMI >30), chronic kidney disease, serious heart conditions, chronic obstructive pulmonary disease, or active cancer.*" Except for obesity, no information about the severity of these conditions is available. More than 40% of the US population 18 - 59 are obese (BMI>30), per ref [16], Table. 2. Non-severe obesity (35>BMI>30) increases the risk of COVID-19 hospitalization by only 7% [17].

Even with this questionable patient selection, the rate of hospitalization in the Molnupiravir treatment group was 7.8%. This is ***higher*** than the hospitalization rate found in the general population. The general pooulation, who had not been treated with Mulnupiravir, had a hospitalization rate of less then 7% in January 2021, and even lower during the summer. Thus, the treatment group's hospitalzation rate of 7.8% is ***significantly higher*** than the hospitalization

rate of the general population during the time of the trial (although it is hard to compare because of the lack of data from the trial).

Absence of Rationale to Stop the Trial Prematurely

The truncation of the trial was not justified. Although the efficacy was reported as 48% (relative risk reduction or RRR), the lower bound of the 95% confidence interval was only **17%** (per ref [15], Table 2). For a novel drug, with potentially very serious adverse effects, this is an unsatisfactory result.

It is well known in the industry that truncated trials significantly overestimate the reported effect[18]. When applying this overestimation to this rial, the estimated RRR drops to **27%**, and lower bound to **<0** (i.e., worsened outcome).

Thus, the results of intermediary analysis did not justify stopping the trial. The decision to stop recruiting was made after more than 90% of the planned number of participants were already recruited. If the sponsor believed that the drug is effective and safe for the intended population, they should have spent another 5-6 weeks to complete the study as planned[19]. None of the justifications given for truncating the trial were valid. Even taken as is, the efficacy data from the interim analysis was not sufficient for Molnupiravir ‘s authorization.

Additional Problems and Lack of Information

Molnupiravir was not successful in animal trials. For example, human lung mice[20] were treated for SARS-COV-2 infection with Molnupiravir at various dose. Symptomatic improvement was observed only at the dose equivalent **1,500 mg/m^2**, 4x recommended human dose (**370 mg/m^2**).

Some important studies were **not** conducted. According to MHRA[15]:

- *“Carcinogenicity studies with molnupiravir have not been conducted.”*
- *“No drug interactions have been identified based on the limited available data.”*
- *“No clinical interaction studies have been performed with molnupiravir.”*

The Global Threat

Used broadly, Molnupiravir will sharply increase SARS-COV-2 diversity and will cause multiple immune escape variants with higher contagiousness and virulence than the current Delta.

We also hope that you issue a strong warning about the global risks of using Molnupiravir. Many foreign countries have acquired the license from Merck and intend to manufacture and broadly

use Molnupiravir. But a dangerous variant of this virus appearing anywhere is a threat for people everywhere.

Disclosure

I have no competing interest. This comment was not funded or solicited by any third party.

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