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the
PRUDENT
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Oral Antivirals for Covid-19 Treatment:

Game Changers or Grand Gambles?

“Thor’s Hammer,” Molnupiravir

Molnupiravir has been in development as a broad-spectrum antiviral for approximately 10 years. It was first tested as an Ebola drug in Liberia’s 2016–2017 outbreak. At the onset of Covid-19, it was in trials as a therapy for seasonal influenza. Interesting fact: the drug is named after the Norse thunder god Thor’s hammer, Mjölner.



Merck’s Confusing Rollout of Molnupiravir

In June of 2021, our federal government agreed to buy 1.2 million doses of molnupiravir (trade name Lagevrio). In November 2021, they exercised their option to purchase another 1.4 million doses. Total cost: \$2.2 billion. At the planned interim analysis, Merck promised one level of efficacy (a meaningless relative risk reduction that won’t cross my lips), but later in their final analysis decided that the drug was much less efficacious. Finally, on December 16, 2021— in the first peer-reviewed look— Merck’s Phase 3 trial MOVE-AHEAD was published in the *NEJM*. We’re still waiting for the complete results from the 10 ongoing studies in India (8 studies in mild COVID-19, 2 studies in moderate COVID-19). (*J Infect Dis.* 224 (3) (2021 Aug 2), pp. 415-419).

The MOVE-AHEAD Trial

The trial was a double-blind, randomized, placebo-controlled study carried out in 170 sites in 20 countries.

Methods: Eligible participants included individuals who were **unvaccinated** for Covid-19, with confirmed Covid-19 infection, not hospitalized, and had mild-moderate symptoms. Eligibility required at least one risk factor for developing severe illness from Covid-19 (age >60 years [17.2%]; active cancer; chronic kidney disease; chronic obstructive pulmonary disease; obesity, defined by a body-mass index ≥ 30 [73.7%]; serious heart conditions [heart failure, coronary artery disease, or cardiomyopathies]; or diabetes mellitus [15.9%]). **Treatment had to be initiated within 5 days of symptom onset.** Participants were randomly assigned to receive 800 mg of molnupiravir or placebo twice daily for 5 days. The primary efficacy end point was hospitalization or death by day 29.

Results: A total of 1,433 participants underwent randomization; 716 were assigned to receive molnupiravir and 717 to receive placebo. At the interim analysis, the risk of hospitalization for any cause or death through day 29 was lower with molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]). **NNT to prevent one hospitalization/ death was 15.** In the final analysis, the percentage of participants who were hospitalized or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709] vs. 9.7% [68 of 699]). **The NNT to prevent one hospitalization/death was 35.** Among those who received molnupiravir or placebo, most (95.2% in the molnupiravir group and 94.7% in the placebo group) received at least 9 doses. Overall, 47.7% of the participants had had onset of signs or symptoms 3 days or less before randomization and 44.5% had moderate Covid-19 (Individuals who showed evidence of lower respiratory disease and who had oxygen saturations greater than or equal to 94% on room air.).

The point estimate for the difference in the risk of hospitalization or death through day 29 favored placebo over molnupiravir only in patients with SARS-CoV-2 nucleocapsid antibodies at baseline; patients with low viral

load at baseline; patients with diabetes at baseline; patients who identified themselves as Asian only, Black only, Native American only, or mixed Black–Native American–White; and patients enrolled in the Asia-Pacific region.

One death was reported in the molnupiravir group and 9 were reported in the placebo group through day 29. Adverse events were reported in 216 of 710 participants (30.4%) in the molnupiravir group and 231 of 701 (33.0%) in the placebo group. The most frequently reported adverse events that were deemed to be related to the trial regimen were diarrhea (1.7% vs. 2.1%), nausea (1.4% vs. 0.7%), and dizziness (1.0% vs. 0.7%)

Molnupiravir was also shown in a [separate trial](#) to accelerate the clearance of infectious Covid-19 virus from the nose and throat, indicating that it may also help reduce the spread of the virus.



Timing is Everything: Severe cases of Covid-19 tend to unfurl in two stages—one dominated by the virus, and a second by the immune system's reaction. The point of antivirals is to act early and fast. There are three Phase 3 Merck trials of molnupiravir (one in severely ill hospitalized Covid-19 patients and two in moderately ill Covid-19 patients.) All three studies were stopped because of futility. ([Diabetes & Metabolic Syndrome: Clinical Research & Reviews Volume 15, Issue 6, 2021](#)) Molnupiravir is largely useless once patients have descended into the second phase.



FDA Advisory Committee: The FDA's Antimicrobial Drugs Advisory Committee voted 13 to 10 to recommend emergency authorization of molnupiravir. Many members of the advisory committee described the vote as a difficult one, in which they had to carefully weigh the risks and benefits of a drug that could help those most at-risk but raised many unanswered questions. Merck could not explain why the same phase 3 study produced significantly differing results roughly seven weeks apart. Several committee members recommended that Merck's emergency use authorization be revisited and potentially withdrawn if another treatment becomes available later.

Dr. Sankar Swaminathan, an infectious disease specialist at the University of Utah School of Medicine, voted against endorsing Merck's medication because the efficacy was "modest at best." Swaminathan also said he worried that the drug's potential effect on human DNA wasn't adequately understood. "Given the large potential population affected, the risk of widespread effects on potential birth defects, especially delayed effects on the male, has not been adequately studied," he said.

FDA approval: The FDA granted use of molnupiravir under a EUA on December 23, 2021. UK approved use on November 4, 2021 and will allow use in both vaccinated and unvaccinated Brits. A dozen countries have expressed interest in purchasing the drug.

Safety: The clinical safety database for molnupiravir (593 subjects) is significantly smaller than the safety databases that the FDA has authorized for other treatments (1350-2100 subjects) for mild-moderate Covid-19.

The mutagenic effect of molnupiravir has been shown in animal cell cultures (J Inf Dis (2021), 10.1093/infdis/jiab247), raising concerns on the potential risk of molnupiravir-induced tumors and the emergence of detrimental mutations in sperm precursor cell generation and embryo development.

Merck's FDA briefing document for molnupiravir states:

MOV (molnupiravir) may affect bone and cartilage development. In a chronic (3-month) rat study, abnormal bone (growth plate) and cartilage formation were noted. Also, in embryo-fetal development (EFD) studies in rats and rabbits, delayed and incomplete ossification was noted in fetuses.

Escape mutant concern: Molnupiravir works by prompting the virus that causes Covid-19 to mutate and produce errors inhibiting its ability to replicate and spread.

Merck's FDA briefing document for molnupiravir states:

Collectively, these analyses indicate MOV (molnupiravir) treatment may increase the rate of emergence of SARS-CoV-2 (Covid-19) populations with amino acid changes in the viral spike protein, consistent with its mutagenic mechanism of action. However, there remain many uncertainties regarding these findings and their clinical and public health implications.

Dr. James Hildreth, CEO of Meharry Medical College in Nashville, Tennessee, told the FDA panel: "Even if the probability is very low, 1 in 10,000 or 100,000, that this drug would induce an escape mutant from which the vaccines we have do not cover, that could be catastrophic for the whole world."

Nicholas Kartsonis, Merck's senior vice president of clinical research, said the company does not have data on the chances such a mutation could evolve.

Costs: A 5-day course of molnupiravir costs \$17.74 to produce according to a study issued by drug pricing experts at the Harvard School of Public Health and King's College Hospital in London. Merck is charging the U.S. government \$712 for the same amount of medicine.



No one should approach the temple of science with the soul of a money changer.

- Thomas Browne

Paxlovid nirmatrelvir/ritonavir

The Pfizer drug **nirmatrelvir** was developed two decades ago as a treatment for SARS, but the epidemic ended before it could be used in trials. Nirmatrelvir is prescribed with the HIV drug ritonavir, which slows the body's metabolism of nirmatrelvir.

EPIC-HR Trial

Methods: The primary data supporting this EUA for Paxlovid are from EPIC-HR, a randomized, double blind, placebo-controlled clinical trial studying Paxlovid for the treatment of non-hospitalized, symptomatic adults with a laboratory confirmed diagnosis of Covid-19 infection. Patients were adults 18 years of age with a pre-specified risk factor for progression to severe disease or were 60 years regardless of pre-specified chronic medical conditions. **All patients had not received a Covid-19 vaccine and had not been previously infected with Covid-19.** The main outcome measured in the study was the proportion of people who were hospitalized due to Covid-19 or died due to any cause during 28 days of follow-up.

Results: In this analysis, 1,039 patients received Paxlovid and 1,046 patients received placebo. Among these patients, 0.8% who received Paxlovid were hospitalized or died during 28 days of follow-up compared with 6% of the patients who received placebo. **NNT to prevent one hospitalization/death = 19. There were no deaths in the patients who received Paxlovid, as compared to 10 deaths in patients who received placebo. For patients who were started on Paxlovid within 3 days, the NNT to prevent one hospitalization/death was 16.**


| Drug | molnupiravir | nirmatrelvir/ritonavir |
|---------------------------------|---|---|
| Manufacturer/ Trade Name | Merck Lagevrio | Pfizer Paxlovid |
| Mechanism of Action | Stops the coronavirus from replicating by inserting errors into its genetic code; molnupiravir acts as a mutagenizing agent that causes an "error catastrophe" during viral replication. In other words, it mutates the virus to kill itself. | Nirmatrelvir disrupts the replication of Covid-19 in the body by binding to the 3CL-like protease, an enzyme crucial to the virus' function and reproduction. Ritonavir slows the metabolism of nirmatrelvir. |
| FDA Status | CDC EUA approval on December 23, 2021. UK approved Nov 4, 2021 and will allow use in both vaccinated and unvaccinated Brits. | EUA approval December 22, 2021. |
| Cost per course of Treatment | ~\$700 is the presumptive list price, although the US government will provide free to Americans who meet the criteria. | \$530 is the presumptive list price, although the US government will provide free to Americans who meet the criteria. |

| Drug | molnupiravir | nirmatrelvir/ritonavir |
|---------------------------|--|---|
| Indications | Mild illness in first 5 days of the illness in patients with at least one risk factor for severe disease in adult outpatients. | Mild illness in first 5 days of the illness in patients with at least one risk factor for severe disease in adult outpatients. |
| Dosing | Four 200mg capsules twice a day for five days. | Three tablets (two tablets of nirmatrelvir and one tablet of ritonavir) taken together orally twice daily for five days. |
| Adverse Events | Drug related adverse events were similar (12% molnupiravir, 11% placebo). Fewer people in the molnupiravir group discontinued treatment because of an adverse event (1.3%) than in the placebo group (3.4%). (BMJ 2021; 375) | Impaired sense of taste, diarrhea, high blood pressure, and muscle aches were the most common side effects. Using Paxlovid in people with uncontrolled or undiagnosed HIV-1 infection may lead to HIV-1 drug resistance. |
| Drug Interactions | No substantial risks for clinically important drug interactions when dosing with molnupiravir 800 mg every 12 hours for 5 days have been identified based on the limited available in-vitro data. | Concomitant use of Paxlovid with certain other drugs can be associated with significant drug interactions. ** |
| Contra-indications | Not tested in pregnant women, women intending to get pregnant or breastfeeding moms or kids. It will be interesting to see how restrictive the FDA is in allowing this drug to be prescribed for childbearing aged women and the men who have sex with them. | Paxlovid is not recommended during pregnancy and in people who can become pregnant and who are not using contraception. Breastfeeding should be interrupted during treatment. These recommendations are because laboratory studies in animals suggest that high doses of Paxlovid may impact the growth of the fetus. Ritonavir may cause liver damage. Avoid giving Paxlovid to patients with preexisting liver disease. Avoid in patients with severely compromised renal function. |
| Clinical Studies | The MOVE-AHEAD Trial In the final analysis, of the 1,433 unimmunized patients, the percentage of participants who were hospitalized or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709] vs. 9.7% [68 of 699] NNT to prevent one hospitalization/death was 35 . One death was reported in the molnupiravir group and 9 were reported in the placebo group through day 29. | EPIC-HR Trial 1,039 patients received Paxlovid, and 1,046 patients received placebo and among these patients, 0.8% who received Paxlovid were hospitalized or died during 28 days of follow-up compared to 6% of the patients who received placebo. NNT to prevent one hospitalization / death = 19 . In the overall study population, no deaths were reported in patients who received Paxlovid as compared to 10 deaths in patients who received placebo. |

** [Follow the hyperlink for more information regarding concomitant use of Paxlovid with certain other drugs that can be associated with significant drug interactions.](#)



MY TAKE

- The woeful lack of access to timely Covid-19 testing in the US will put the kibosh on molnupiravir and nirmatrelvir/ritonavir for a large segment of Americans. The tight therapeutic window of initiation of both drugs within 5 days of onset of symptoms in the clinical trials is not compatible with our real-world diagnostic bottleneck. Recall that once the body's immune response to Covid-19 kicks in, both drugs appear worthless.
- Clearly, Paxlovid is the superior of the two oral drugs both in terms of efficacy (NNT~ 19 vs NNT~35) and safety (The FDA Advisory panel caught the Merck scientists with their pants down).
- It is my opinion that the FDA erred in approving molnupiravir and should take it off the market NOW. Is this another “Aduhelm for Alzheimer’s, because it’s a bad disease and there is nothing else?” **OR** is it “We just spent \$2.2 billion and we’re gonna use these damn pills (Cost Sunk Fallacy)?”
- Merck’s marketing hype about the Thunder god Thor’s hammer (“a devastating weapon and a divine instrument” per Wikipedia) fell flat. A more accurate metaphor would promote molnupiravir as an “expensive, potentially dangerous feather duster.” 
- Prescribing Paxlovid to patients on other meds will require careful checking for drug interactions.
- The Brits are prescribing molnupiravir to immunized patients in spite of the largely unimmunized participants in both drug trials. Whither the FDA? And what will American docs do?
- **Other alternatives for mild-moderate Covid-19 in outpatients:** Recall that the NNTs (22,33,45) for monoclonal antibodies are comparable in mild-moderate outpatient Covid-19 patients and the 10-day window of opportunity for treatment is longer. In a study with a demographically similar outpatient population to those with the oral pills, IV remdesivir (200mg on day 1 and 100mg on days 2 and 3) was administered within 7 days of symptom onset. The NNT to prevent one hospitalization/death was 22. (NEJM December 22, 2021) And finally, off label prescription of generic Luvox (fluvoxamine) with similar demographics of patients studied and with a 7-day treatment window resulted in a NNT of 20 to prevent one hospitalization/death.



Pre-Exposure Prophylaxis for the Immunocompromised: Evusheld

About 2% of the global population is considered at increased risk of an inadequate response to a Covid-19 vaccine. The FDA has granted emergency use authorization (EUA) for AstraZeneca's antibody therapy Evusheld for the pre-exposure prophylaxis to Covid-19.

Obtained from B-cells of convalescent patients following Covid-19 infection, Evusheld is a mixture of two long-acting antibodies, tixagevimab and cilgavimab that bind to different, non-overlapping sites on the spike protein of the virus.

- The product is only authorized for those individuals who are not currently infected with the Covid-19 virus and who have not recently been exposed to an individual infected with Covid-19.
- The authorization also requires that individuals either have moderate to severely compromised immune systems due to a medical condition or due to taking immunosuppressive medications or treatments and therein may not mount an adequate immune response to Covid-19 vaccination.

The PROVENT Trial

(I cannot find this trial in a peer-reviewed journal. These data are from an AstraZeneca "[Fact Sheet](#).")

Methods: All subjects were either ≥ 60 years of age, had a pre-specified co-morbidity (obesity, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, immune-compromised state, or previous history of severe or serious adverse event after receiving any approved vaccine), or were at increased risk of Covid-19 infection due to their living situation or occupation. **Subjects could not have previously received a Covid-19 vaccine.** Subjects received a single dose (administered as two IM injections) of Evusheld or placebo. The baseline demographics were balanced across the Evusheld and placebo arms. The median age was 57 years, 46% of subjects were female, 73% were White, 3% were Asian 17% were Black/African American, and 15% were Hispanic/Latino. Of the 5,197 subjects, 78% had baseline co-morbidities or characteristics associated with an increased risk for severe Covid-19 including obesity (42%), diabetes (14%), cardiovascular disease (8%), cancer, including a history of cancer (7%), chronic obstructive pulmonary disease (5%), chronic kidney disease (5%), chronic liver disease (5%) and immunosuppressive medications (3%).

For the primary endpoint, a subject was defined as a Covid-19 case if their first case of Covid-19-PCR-positive symptomatic illness occurred after drug administration and prior to day 183. The primary analysis included 5,172 subjects who were Covid-19 PCR-negative at baseline of which 3,441 received Evusheld and 1,731 received placebo.

Results:

| | Number of participants | Number of symptomatic infections (%) |
|----------|------------------------|--------------------------------------|
| Evusheld | 3,441 | 8 (0.2%) |
| Placebo | 1,731 | 17 (1.0%) |

The NNT to prevent one symptomatic Covid-19 infection was 125. Among subjects who received Evusheld, there were no severe/critical Covid-19 events compared to one participant in the placebo group.

Adverse Effects: The treatment was well tolerated, and adverse events were balanced across both groups occurring in 35% and 34% of drug and placebo participants. A total of 2.4% and 2.1% of participants experienced injection site reactions in their Evusheld and placebo arms respectively. In the PROVENT Trial, there was a higher rate of cardiovascular serious adverse events, including myocardial infarction and cardiac failure in participants who received Evusheld compared with placebo; a causal relationship between the treatment and these events has not been established.



MY TAKE

- Although the NNT to prevent one symptomatic Covid-19 infection seems high at 125, the 7 million targeted immune-compromised Americans are indeed a worthy vulnerable population to attempt to protect.
- The PROVENT Trial shows protection through six months and AstraZeneca promises data that suggest protection for up to a year.
- The cost at ~\$1000 a dose is less expensive than some of the other Covid-19 monoclonal treatments.
- AstraZeneca has ongoing trials studying Evusheld's role in asymptomatic individuals exposed to Covid-19 and in hospitalized patients with severe Covid-19.
- AstraZeneca has agreed to supply the US government with 700,000 doses of Evusheld for ~\$700,000,000, approximately 1/10 of the population who would qualify for this drug based on current indications. It is not clear when additional doses will be available.

Coffee Consumption and Tachyarrhythmias: More Dogma Laid to Rest

Full disclosure:

- 1) I am a coffee snob.
- 2) I have been known to engage in confirmation bias.

The American College of Cardiology/American Heart Association guidelines (Circulation. 2018; 138[130]) that suggest that avoiding caffeine diminishes the risk for arrhythmias are based on a small observational study (J Chronic Dis. 1980; 933; 20: 67-72) from 1980. More recent studies have not shown an association between caffeine consumption and arrhythmias.

This prospective cohort study (JAMA Int Med. Sep 2021) utilized the UK Biobank data involving 386,258 Brits, 40-69 years of age, who had previously responded to questionnaires, undergone physical exams and provided biological samples. They also studied the genetic variants associated with caffeine metabolism in an attempt to eliminate this as a variable. The authors followed this group (mean age 58, 52% female) over 4.5 years.

Results:

- A total of 16,369 participants developed an arrhythmia. Atrial fib: 12,811; supraventricular tachycardias: 909; premature ventricular contractions: 632; premature atrial complexes: 97; unspecified arrhythmias: 610.
- Those who consumed more than the daily median amount of coffee (2 cups) were more likely to be older, white and male.
- After adjustment for demographic characteristics, comorbid conditions and lifestyle habits, each additional cup of coffee consumed was associated with a 3% lower risk of arrhythmia.
- This association was not significantly modified by genetic variants that affect caffeine metabolism. Those participants with genetic variants associated with slower caffeine metabolism did consume less coffee.



MY TAKE ↘

Boy! Do I like this study. I have found the ultimate coffee science. I will search no more! Sure, I recognize that the coffee consumption in the study is self-reported and that the type of coffee—espresso or not— was not delineated and that the coffee consumption reported at the beginning of the study was assumed to stay constant and yeah the study only lasted for 4+ years.

And to celebrate this quintessential study, I offer you some of my favorite coffee aphorisms:



Aphorisms about Coffee

“

A cup of coffee with a friend is happiness tasted
and time well spent.

- unknown

”



“

Coffee should be black as Hell, strong as death
and sweet as love.

- unknown

”

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