**New COVID pills? What is coming down the horizon?**

Recent press releases have lauded the breakthrough advancement of new oral treatments for SARS-CoV2 infections: **molnupravir** from Merck and **paxlovid** from Pfizer. Both Merck and Pfizer have applied to the FDA for emergency use authorization as treatments for mild-to-moderate COVID-19. Below is a what is known about these agents.

**What is molnupravir?**

Molnupravir is a novel antiviral medication that works by disrupting viral replication by inserting itself into the viral RNA polymerase. This result is the creation of nonviable virus mutations that in essence kills the virus (referred to as viral error catastrophe or lethal mutagenesis). Molnupravir itself is a prodrug of the nucleoside analogue, β-D-N 4-Hydroxycytidine 5'-triphosphate (also called EIDD-1931).

Molnupravir has previously been studied as a possible treatment for other viruses. *In vitro* experiments have demonstrated efficacy against a number of viruses including influenza and Ebola.

On October 1, 2021, Merck announced that molnupravir lowered the chance of hospitalization or death by about 50% in COVID-19 patients at risk for severe disease when treated within five days of onset.

**What is paxlovid?**

Paxlovid is a 3C-like protease inhibitor, that is involved in the replication of the SARS-CoV2 virus. While the mechanism of action is akin to protease inhibitors used in the management of HIV, 3C-like proteases are more specific to coronaviruses. Paxlovid is given with another protease inhibitor, ritonavir. While ritonavir by itself is not an effective protease inhibitor, it decreases the metabolism of paxlovid, in effect "boosting" its effect in the body.

In the press release, the clinical trial for paxlovid showed that it reduced the chance of hospitalization or death by 89% in COVID-19 patients at risk for severe illness when given within three days of the onset of symptoms and by 85% when given within five days of onset.

**Which one is better?**

It is difficult to say at this time. While the reported numbers suggest that paxlovid may be more effective, this is based on the limited data released by both companies. Clinical trial data have not been official peer reviewed.

**How will these medications impact on current treatment guidelines?**

It is expected that these oral medications will provide another tool in our arsenal for treating persons with mild-to-moderate COVID-19 disease in the outpatient setting. Both medications have been successful in managing persons early in their disease – within five days of symptom onset.

No clinical data on the use of either molnupravir or paxlovid is available for hospitalized patients. Neither drug is expected to be approved for use in hospitalized patients.

Current guidelines recommend the use of monoclonal antibodies (mAbs) for the treatment of persons with early mild-to-moderate disease (casirivimab-imdevimab, bamlanivimab-etesevimab, sotrovimab). While the FDA has approved the use of mAbs in persons with up to ten days of symptoms, the most benefit is seen when given within five days of symptom onset. The use of mAbs has been limited by logistical challenges as they are recommended as intravenous infusions when treating COVID-19 disease. The issues that have limited the widespread use of mAbs is circumvented with these oral therapies. Note that there are no head-to-head studies comparing either molnupravir or paxlovid to any of the COVID mAbs.

The pharmacologic characteristics of the drugs will also likely factor into who may be preferred candidates for each agent. The broader antiviral effects of molnupravir may be more beneficial if we experience an outbreak of both COVID-19 and influenza. Paxlovid is given with ritonavir, which is well known to interact with a lot of medications including statins and immune suppressants.

**How will these medications be distributed once they receive FDA emergency use authorization?**

The United States government has contracted with both companies to purchase millions of doses upon receiving emergency use authorization. Specific distribution details have not yet been delineated.

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