Omicron Therapeutics

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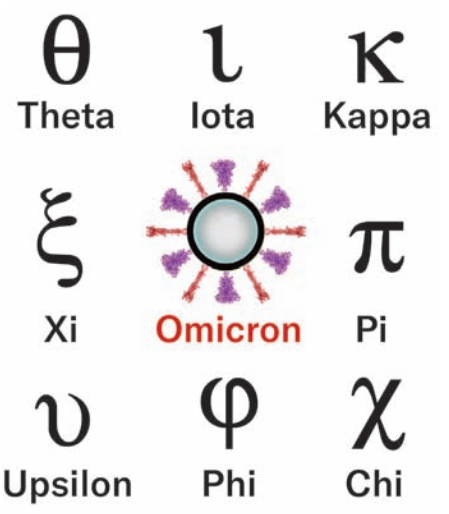
The unwelcome emergence of the Omicron SARS-CoV-2 variant of concern in late November 2021 presaged yet another phase of the ongoing COVID-19 pandemic. This was expected. Last July, Rella and colleagues predicted that failure to decrease transmission rates through lags in vaccination and relaxation of non-pharmaceutical interventions would likely lead to the emergence of resistant strains (*Sci Rep* 2021;11:15729). It happened. Omicron is the anticipated highly immune-evading variant sweeping through vaccinated and unvaccinated populations worldwide. The CDC has suspended its monitoring of SARS-CoV-2 variants because of the Christmas holiday (Yuletide greetings from the CDC). However, as of December 18, the most recent update, Omicron accounted for 73% of new cases in the United States. Omicron currently accounts for over 90% of the cases in the U.K. (asamonitor.pub/3pzY8Bd). It likely accounts for even more in the U.S. We will find out in the new year.

Because of the high level of immune escape in Omicron, on December 23 the NIH updated its treatment guidelines for Omicron (asamonitor.pub/3lnSgXg; asamonitor.pub/3mEbuun). Quoting the guidelines, drugs that are expected to be effective for outpatient management are:

- **Sotrovimab** (Xevudy) 500 mg I.V. as a single infusion administered as soon as possible and within 10 days of symptom onset; or
- **Remdesivir** (Veklury) 200 mg I.V. on day one, then 100 mg once daily on days two and three, initiated as soon as possible and within seven days of symptom onset.
- Use of **tixagevimab plus cilgavimab** (Evusheld) as pre-exposure prophylaxis for severely immunocompromised individuals over moderately immunocompromised individuals.

It is important to note that these are guidelines for patients who are not hospitalized. The challenge for sotrovimab and remdesivir is to identify patients at sufficiently high risk of clinical progression to institute the required intravenous therapy as outpatients. The combination of tixagevimab plus cilgavimab is administered intramuscularly but is only indicated for a very narrow population.



The NIH guidelines also mention the recent Food and Drug Administration Emergency Use Authorization (EUA) of ritonavir-boosted nirmatrelvir (Paxlovid) from Pfizer, and molnupiravir (Lagevrio) from Merck. The NIH guidelines simply note that these drugs are approved but that they have not yet had time to incorporate them into the treatment guidelines.

The NIH notes that two monoclonal antibody cocktails that were effective against prior variants of concern, bamlanivimab plus etesevimab (from Lilly) and casirivimab plus imdevimab (REGEN-COV from Regeneron) have markedly reduced efficacy against Omicron. This has been discussed in detail in Nature News (*Nature* December 2021).

The NIH did not change its recommendations for inpatient therapy, which continues to include remdesivir, dexamethasone, baricitinib, sarilumab, tocilizumab, and tofacitinib (Table A of the current guidelines).

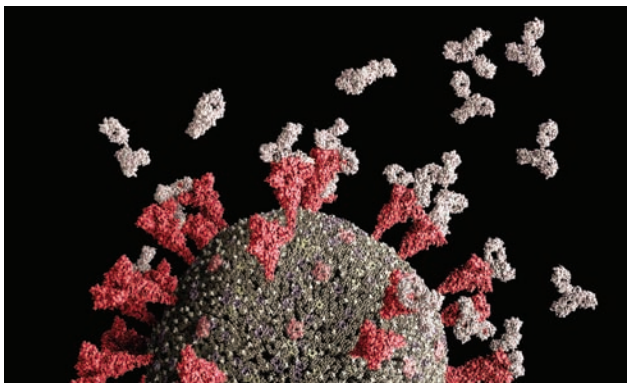
Remdesivir

The recommendation of early intravenous remdesivir for outpatient treatment is based on the PINETREE study published last week in the *New England Journal of Medicine* (*N Engl J Med* December 2021). The study randomized 562 patients with risk factors for disease progression to receiving either placebo or remdesivir (200 mg on day one and 100 mg on days two and three) by intravenous infusion. Treatment was started within seven days of symptom onset. Remdesivir reduced the risk of hospitalization by 87%. This study is the basis of the NIH recommendation for remdesivir in patients at risk for severe disease (e.g., the very elderly, immunocompromised, or those with underlying medical conditions). However, it has been noted that a three-day course of intravenous administration poses a considerable logistical challenge (*N Engl J Med* December 2021).

Remdesivir targets the viral RNA-dependent RNA polymerase responsible for SARS-CoV-2 reproduction. As noted by Gilead, the Omicron variant does not have any novel mutations in this gene (asamonitor.pub/3ezx7rf). Thus, remdesivir is expected to have normal activity against SARS-CoV-2.

Sotrovimab

Sotrovimab is an antibody that targets a highly conserved epitope in the receptor binding domain of the spike protein. In May 2021, the FDA authorized sotrovimab (Xevudy) for treatment of adults with mild to moderate COVID-19 (e.g., hospitalized or requiring oxygen) at risk of progression to severe disease or death. In a randomized trial of 583 patients, sotrovimab given within five days of symptom onset reduced progression to severe disease or death by 85% (*N Engl J Med* 2021;385:1941-50).



Unique among the monoclonal antibodies, there is only modestly reduced binding of sotrovimab to the Omicron spike protein (*bioRxiv* December 2021; *medRxiv* December 2021). The FDA's recent re-issue of the EUA for sotrovimab noted that no change was expected with the efficacy against Omicron (asamonitor.pub/3HjWWb3).

Since sotrovimab is marketed as a single antibody treatment, rather than a cocktail of two treatments, it may be more prone to induce resistant mutations. This was observed in roughly a quarter of the subjects in the COMET-ICE study (*N Engl J Med* 2021;385:1941-50), where novel mutations at position 340 conferred a nearly 100-fold loss of efficacy (asamonitor.pub/3mFsC2B). A study in Australia found that nine of 50 patients treated with sotrovimab developed these mutations (*medRxiv* December 2021). Animal models confirmed this finding (*bioRxiv* December 2021).

As with remdesivir, sotrovimab must be administered using an intravenous infusion over 30 minutes. In many settings this may prove impractical. Also, supplies of sotrovimab are limited. Hospitals in New York recently reported that they have completely run out of the drug (asamonitor.pub/32KsA2j).

Tixagevimab plus cilgavimab

The monoclonal cocktail of tixagevimab and cilgavimab combines two antibodies directed against the SARS-CoV-2 spike protein (*medRxiv* September 2021). The combination did not meet its primary endpoint in an (unpublished) study of patients exposed to SARS-CoV-2 (asamonitor.pub/3FBoJmN). However, another (unpublished) study demonstrated efficacy preventing infection pre-exposure in high-risk subjects (asamonitor.pub/315tje6). On this basis, Evusheld was authorized by the FDA on December 8, 2021, for "*pre-exposure prophylaxis of coronavirus disease 2019 (COVID-19) in adults and pediatric individuals (12 years of age and older weighing at least 40 kg):*

- *Who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and*
- *Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments and may not mount an adequate immune response to COVID-19 vaccination or*
- *For whom vaccination with any available COVID-19 vaccine, according to the approved or authorized schedule, is not recommended due to a history of severe adverse reaction (e.g., severe allergic reaction) to a COVID-19 vaccine(s) and/or COVID-19 vaccine component(s).*"

The combination of tixagevimab and cilgavimab is about 70-fold less potent against Omicron than against the ancestral variant (*medRxiv* December 2021). That's not great efficacy, but it is the only monoclonal antibody other than sotrovimab that retains any activity at all.

Nirmatrelvir

On December 22, 2021, the FDA granted an EUA for the therapeutic combination of nirmatrelvir and ritonavir (Paxlovid)

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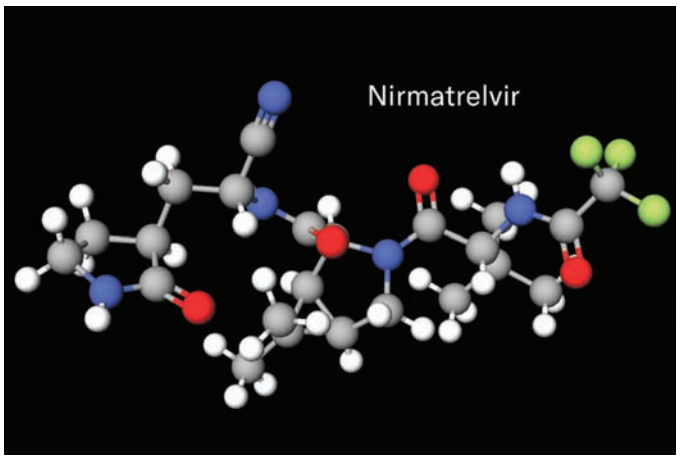
for the treatment of mild to moderate COVID-19 (asamonitor.pub/3mF1qRJ). In the EUA, the combination was granted for



adults and children 12 years of age or older weighing ~40kg or more displaying positive results from a direct COVID-19 test who are "at high risk for progression to severe COVID-19, including hospitalization or death." The FDA noted that therapy should begin as quickly as possible after diagnosis within five days of symptoms and should not last for more than five consecutive days.

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Nirmatrelvir takes advantage of the SARS-CoV-2 Achilles' heel: M^{pro}. After entry into a cell, the viral RNA is directly transcribed into a long polyprotein. This long amino acid strand spontaneously cleaves at two locations, liberating the viral enzyme M^{pro} (*Curr Opin Virol* 2021;49:36-40). M^{pro} is a protease, meaning that it cleaves other proteins. Specifically, M^{pro} cleaves the virus's polyprotein at 11 other sites, liberating the proteins that do much of the work of replication. The active site of M^{pro} is highly conserved *among all coronaviruses* (*Nature* 2020;582:289-93). This suggests that the virus has very little "wiggle room" at the active site.

In 2003, Pfizer started looking at PF-00835231, an M^{pro} inhibitor, as a therapeutic target for the original SARS-CoV. The pandemic passed before they completed their assessment. However, Pfizer continued working on M^{pro} inhibitors, eventually settling on an orally bioavailable molecule, nirmatrelvir (*Science* 2021;374:1586-93). Nirmatrelvir has demonstrated potent inhibition of M^{pro} from all coronavirus types known to infect humans, including betacoronaviruses (SARS-CoV-2, SARS-CoV-1, HKU1, OC43, and MERS-CoV), as well as alpha-coronaviruses (229E and NL63) (*Science* 2021;374:1586-93).

The (yet unpublished) pivotal Phase III trial for Paxlovid demonstrated an 89% reduced risk of hospitalization or death when taken within three days of symptom onset, and by 88% if taken within five days of symptom onset (asamonitor.pub/3z4cGvU).

Because the M^{pro} active site is so highly conserved across coronaviruses, nirmatrelvir is expected to have full activity against Omicron (*bioRxiv* November 2021). Initial studies suggest this is the case (*bioRxiv* December 2021).

Unfortunately, nirmatrelvir is rapidly metabolized by cytochrome P450 3A4 (CYP3A4). To maintain therapeutic concentrations, Pfizer combined nirmatrelvir with ritonavir to inhibit CYP3A4 metabolism. This strategy has been used with other protease inhibitors, such as darunavir and lopinavir.

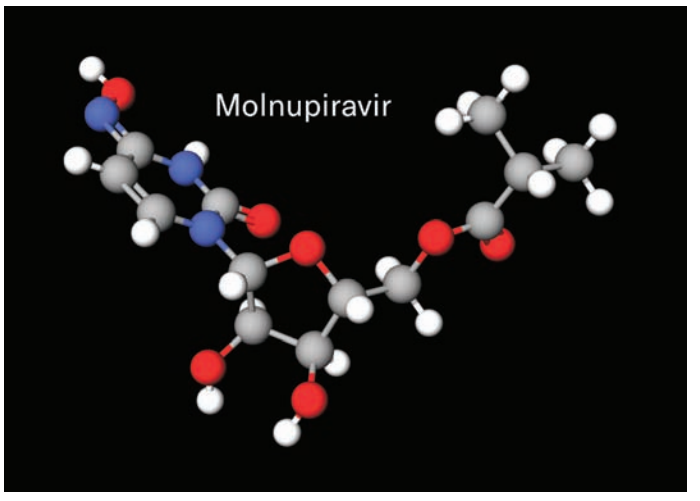
Since ritonavir was included specifically to inhibit CYP3A4, the FDA package insert contains the usual warning about pharmacokinetic interactions. Specifically, the FDA mentions reduced clearance and therefore increased concentrations of alfuzosin, meperidine, piroxicam, propoxyphene, ranolazine, amiodarone, dronedarone, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, clozapine, dihydroergotamine, ergotamine, methylergonovine, lovastatin, simvastatin, sildenafil, triazolam, and midazolam (asamonitor.pub/314DnE6).

These anticipated pharmacokinetic implications have generated hyperbolic headlines (asamonitor.pub/3pw9upH). The risks are likely overblown, because Paxlovid is only supposed to be taken for five days in patients at risk for progression to severe disease. A briefly elevated concentration of simvastatin is unlikely to be consequential, although that might not be the case for sildenafil. I might cut back on the midazolam for an emergency anesthetic in a patient with COVID-19 on Paxlovid.

The FDA also notes that Paxlovid may be ineffective in patients on CPY3A4 inducers, including apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, and St. John's Wort because of increased metabolism. OK… however, if I (SLS) had COVID-19 and was at high risk of severe disease, and had been taking a CYP3A4 inhibitor, I'd just take a bigger dose of Paxlovid. Seriously.

Molnupiravir

On December 23, 2021, one day after the EUA was issued for Paxlovid, the FDA granted an EUA for the antiviral molnupiravir in adults who have positive results for COVID-19 direct testing and are "at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate"



(asamonitor.pub/3ey57nS). As with Paxlovid, molnupiravir should be administered as quickly as possible after positive results and within five days of symptoms. The FDA did not approve molnupiravir for patients younger than 18 years, as it "may affect bone and cartilage growth." Molnupiravir is not approved for the pre- or post-exposure prevention of COVID-19. Additionally, since no treatment benefit was noted in those patients receiving molnupiravir post-hospitalization, authorization was not granted for therapy initiation in hospitalized patients.

Molnupiravir is a prodrug for the ribonucleoside analog β-d-N^4-hydroxycytidine (NHC) (*medRxiv* June 2021). Molnupiravir is converted *in vivo* into the active analog, NHC triphosphate. NHC triphosphate is a competitive substrate for viral RNA-dependent RNA polymerase, similar to the mechanism of remdesivir. However, remdesivir works by inserting nucleotides that halt RNA synthesis. Molnupiravir exerts its antiviral effects by introducing mutations during RNA replication (*Nat Struct Mol Biol* 2021;28:740-6; *Nat Struct Mol Biol* 2021;28:706-8). The fact that molnupiravir is mutagenic caused concern during the FDA review (*BMJ* 2021;375:n2984). First there was concern about mutagenesis in patients. This is one of the reasons it was not approved during pregnancy, in lactating women, and in children. There was also concern about mutagenesis in the coronavirus genome and whether that could accelerate resistance or infectivity. Quoting the FDA briefing document, "*there are potential safety concerns pertaining to molnupiravir, including embryofetal toxicity, bone and cartilage toxicity, and mutagenicity, as well as evidence that molnupiravir may increase the rate of changes in the viral spike protein, which, in theory, could enhance SARS-CoV-2 spike protein evolution*" (asamonitor.pub/3FD2rkO).

The efficacy of molnupiravir also proved to be disappointing. An interim analysis of a pivotal trial demonstrated an efficacy of nearly 50% in reducing hospital admissions (*N Engl J Med* December 2021). Subsequent results submitted to the FDA suggested that efficacy was closer to 30% (*Nature* December 2021).

The good news for molnupiravir is that, like nirmatrelvir, it is expected to retain full activity against Omicron. As Fischer and colleagues recently summarized in *Science Translational Medicine*, "*these data suggest that the emergence of future SARS-CoV-2 variants of concern is unlikely to diminish the antiviral activity of molnupiravir as the target of its antiviral activity has a diminished capacity for change compared to Spike protein*" (*Sci Transl Med* December 2021).

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