



Cautious Optimism and Considerations for Health Providers and Patients: Oral Antiviral for Early Treatment of High-Risk Patients and Vaccines for Prevention of COVID-19

On December 22, 2021, the US Food and Drug Administration (FDA) granted an Emergency Use Authorization (EUA) for the first oral antiviral, a pill containing 2 protease inhibitors, nirmatrelvir and ritonavir (Paxlovid, Pfizer), for the early treatment of coronavirus disease 2019 (COVID-19).¹ This drug was approved for adults 18 years of age and older with acute COVID-19 as well as having a prespecified risk factor for progression to severe disease or 60 years of age or older regardless of chronic medical conditions. The pivotal trial enrolled high-risk newly infected patients who had neither received a COVID-19 vaccine nor had been previously infected. The prespecified primary outcome was hospitalization due to COVID-19 or death from any cause during 28 days of follow-up. Among 2085 randomized subjects, the primary outcome occurred in 0.8% of 1039 who received the active drug (1 death) and 7.8% of 1046 given placebo (10 deaths), a highly significant 88% reduction.¹

The following day, the FDA issued another EUA for a novel viral RNA polymerase inhibitor, molnupiravir

(Merck/Ridgeback Biotherapeutics). In January 2022, advisers to the FDA debated the benefits and risks. First, the benefit is far lower than for nirmatrelvir and ritonavir, and second, risks include the possibility of mutations that might make the virus more dangerous or transmissible.² In a randomized trial in 1408 randomized subjects, the primary outcome occurred in 6.8% among 709 assigned to molnupiravir and 9.7% of 699 given a placebo, a significant but, much lower, 30% reduction. The advisory committee was split on molnupiravir, with a 13-10 vote approving the drug.³

We express optimism to health providers regarding the potentially large clinical and public health impacts of their judicious prescription of the new oral antiviral drugs to prevent progression of early COVID-19 in high-risk patients, as well as their wider use of vaccines to prevent severe and fatal COVID-19 infections.

With respect to early preemptive antiviral therapy, the new oral antiviral drugs are projected to cost approximately \$500 and can be taken at home.^{1,3} To preserve antiviral efficacy for as long as possible, these drugs must be prescribed judiciously by health care providers. This implies that the oral antiviral drug should be prescribed to patients with symptoms of COVID-19 within 5 days as well as proof of a positive standardized diagnostic test. These drugs should not be prescribed for either worried uninfected patients or immunized infected patients at low risk of progression to severe disease. Health care providers should be aware that their unrestricted widespread prescription and prolonged use will likely accelerate the emergence and rapid spread of variants highly resistant to these promising drugs, as occurred with amantadine and rimantadine for influenza⁴ and following the introduction and widespread single-drug use of zidovudine (AZT) for HIV infection.⁵

In regard to the enormous importance of vaccination for prevention, on December 27, 2021, unvaccinated patients had 10 times the risk of becoming infected and 20 times the risk of death from COVID-19, compared with the fully

Funding: None.

Conflicts of Interest: JC, DGM report none. CHH reports that serving as an independent scientist in an advisory role to investigators and sponsors as chair of data monitoring committees for Amgen, British Heart Foundation, Cadila, Canadian Institutes of Health Research, DalCor, and Regeneron; to the Collaborative Institutional Training Initiative (CITI), legal counsel for Pfizer, the US Food and Drug Administration, and UpToDate; receives royalties for authorship or editorship of 3 textbooks and as coinventor on patents for inflammatory markers and cardiovascular disease that are held by Brigham and Women's Hospital; has an investment management relationship with the West-Bacon Group within Truist Investment Services, which has discretionary investment authority; and does not own any common or preferred stock in any pharmaceutical or medical device company.

Authorship: All authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to Jennifer Caceres, Senior Associate Dean for Student Affairs and Admissions, Charles E. Schmidt College of Medicine, Florida Atlantic University, 777 Glades Road Bldg. 71 Suite: 120, Boca Raton, FL, 33431.

E-mail address: jcaceres3@health.fau.edu

vaccinated who had also received a booster. This implies that the risk of death from COVID-19 among patients receiving 2 doses and a booster is no higher than that from influenza. Moreover, the unvaccinated had 5 times the risk of becoming infected and 14 times the risk of death from COVID-19, compared with those who were vaccinated but had not received a booster.⁶

In the United States, fortunately, health care providers are the most trusted professionals by the general public, especially for reliable information about COVID-19.⁷ Health care providers already have and will continue to play a crucial role in reducing preventable morbidity and mortality from COVID-19. Today, their powerful advocacy of more widespread vaccinations is crucial to the primary prevention of COVID-19. In addition, they are now able to add to their armamentarium against COVID-19 their judicious prescription of the new antiviral drugs for high-risk, newly infected patients as soon as possible following their diagnosis, or within 5 days of the onset of symptoms.¹ In the prescription of oral antivirals, health care providers will need to inform their patients and monitor their side effects, which include renal, hepatic, and adverse interactions with other widely prescribed and used drugs.¹ Access will be an issue for several months, but it is encouraging that the US government has already bought 10 million courses of treatment from Pfizer for \$5 billion.¹

As of February 1, 2022, the omicron variant accounts for >99% of all US cases. Omicron was, not surprisingly, first detected in South Africa and the United Kingdom, a tribute to their robust genomic surveillance of COVID-19. Notably, the United Kingdom leads the world in genomic surveillance and South Africa is in the top 10, whereas the U.S. is ranked 43rd. It is clear that omicron is far more transmissible but also less virulent than the delta variant. The United States needs to conduct far greater genomic surveillance to detect emerging variants as early as possible, especially variants that are even more resistant to the first-generation vaccines and that might be more virulent to more effectively target preventive efforts, particularly new adaptive vaccines.⁸

In summary, health care providers must remain cognizant that achieving much higher vaccination rates is essential to prevent, mitigate, and control the US epidemic and the worldwide pandemic and to stem the continued ravaging of health care systems around the world. Failure to greatly reduce the incidence of active COVID-19 in the United States and worldwide will predictably accelerate the emergence and spread of vaccine-resistant and more virulent strains associated with greater transmissibility, giving life to the specter of global deaths from COVID-19 surpassing the number of deaths from the great influenza pandemic of 1918, which has already occurred in the United States, and complete devastation of health care systems and collapse of national economies. Health providers and political

leaders must unite to urgently address “vaccine misinformation” and eliminate “vaccine hesitancy,” which are fueling the current epidemic of COVID-19 in the United States, primarily among the unvaccinated.⁹

ACKNOWLEDGEMENT

We dedicate this manuscript to the memory of our valued mentor, colleague, and dear friend, Donald B. Louria, MD (1928-2001).

Jennifer Caceres, MD^a

Dennis G. Maki, MD^b

Charles H. Hennekens, MD, DrPH^a

^aCharles E. Schmidt College of
Medicine, Florida Atlantic Univer-
sity, Boca Raton, Fla

^bCOVID-19 Intensive Care Unit,
University of Wisconsin School of
Medicine and Public Health,
Madison

References

1. FDA News Release. Coronavirus (COVID-19) update: FDA authorizes first oral antiviral for treatment of COVID-19. <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19>. Accessed February 2, 2022.
2. The COVID-19 Treatment Guidelines Panel. Statement on therapies for high-risk, nonhospitalized patients with mild to moderate COVID-19. Available at: <https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/>. Accessed February 2, 2022.
3. FDA News Release. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment of COVID-19 in certain adults. Available at: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19>. Accessed February 2, 2022.
4. Centers for Disease Control and Prevention (CDC). Influenza antiviral drug resistance. Available at: <https://www.cdc.gov/flu/treatment/antiviralresistance.htm>. Accessed February 2, 2022.
5. Wainberg MA, Brenner BG, Turner D. Changing patterns in the selection of viral mutations among patients receiving nucleoside and nucleotide drug combinations directed against human immunodeficiency virus type 1 reverse transcriptase. *Antimicrob Agents Chemother* 2005;49(5):1671–8. <https://doi.org/10.1128/AAC.49.5.1671-1678.2005>.
6. Centers for Disease Control and Prevention. COVID data tracker. Cases and deaths by vaccination status. Available at: <https://covid.cdc.gov/covid-data-tracker/#datatracker-home>. Accessed February 2, 2022.
7. Hamel L, Kirzinger A, Muñana C, et al. *KFF COVID-19 Vaccine Monitor December 2020*. Kaiser Family Foundation. Available at: <https://www.kff.org/coronavirus-covid-19/report/kff-covid-19-vaccine-monitor-december-2020/>. Accessed February 2, 2022.
8. Robishaw JD, Alter SM, Solano JJ, et al. Genomic surveillance to combat COVID-19: challenges and opportunities. *Lancet-Microbe* 2021;2:e481–4.
9. Loomba S, de Figueiredo A, Piatek SJ, et al. Measuring the impact of COVID-19 vaccine misinformation on vaccination intent in the UK and USA. *Nat Hum Behav* 2021;5:337–48. <https://doi.org/10.1038/s41562-021-01056-1>.