Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COMMENTARY

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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 molnupriavir and 9.7% of 699 given a placebo, a significant but, much lower, 30% reduction. The advisory committee was split on molnupriavir, 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 influenza[4] 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

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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]

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