EDITORIAL

The Potential of Intentional Drug Development

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At the start of the Covid-19 pandemic more than 2 years ago, hopes were high for rapid interventions that could lessen the severity of disease and save lives. Several approved and investigational drugs had some in vitro activity against the causative virus, SARS-CoV-2. Many repurposed medications were quickly enlisted but ultimately did not have meaningful clinical activity against Covid. Two investigational agents, remdesivir and molnupiravir, eventually showed some clinical efficacy. But both have considerable drawbacks; remdesivir is available only as a parenteral formulation, and molnupiravir has only a modest effect. Studies of these drugs, along with monoclonal antibodies, did make one point clear: intervention with antiviral agents is possible, but only early in the course of disease.[1]

Investigators now report in the *Journal* the first small-molecule antiviral agent designed specifically to inhibit SARS-CoV-2.[2] The active component, nirmatrelvir, is an inhibitor of the SARS-CoV-2 3-chymotrypsin–like cysteine protease enzyme, one of two essential proteases encoded by the virus. Protease inhibitors have a record of success in treating viral infections that dates from their introduction for the treatment of HIV. Like the antiretroviral medications, nirmatrelvir is rapidly metabolized by cytochrome P450 3A4 (CYP3A4) and is therefore administered together with a low dose of the potent inhibitor of that enzyme, ritonavir. Nirmatrelvir blocks viral replication in vitro at low concentrations and, when given with ritonavir, achieves effective plasma levels.

In this phase 3 randomized, controlled trial, nirmatrelvir plus ritonavir or placebo was administered to unvaccinated outpatients who were infected with SARS-CoV-2, were at high risk for progression to severe disease, and had symptom onset within 5 days before randomization. The primary outcome was a composite of progression to hospitalization for Covid-19 and death from any cause through day 28 in patients whose first dose was administered within 3 days after symptom onset and who had not received monoclonal antibody therapy. The trial was designed to include about 3000 patients, but it was terminated at the time of a planned interim analysis by the data monitoring committee because the efficacy end point had been reached. This report includes all enrolled patients — those who had reached the interim analysis point and those subsequently enrolled who had not yet reached the day 28 assessment, a total of 2246 patients split between the nirmatrelvir and placebo groups.

Nirmatrelvir plus ritonavir was associated with mild dysgeusia and diarrhea, but no particularly troubling safety concerns were identified. Treatment with the drug had a substantial effect on the primary outcome. In the final analysis population, which largely mirrored that of the interim analysis, 5 of 697 (0.72%) in the nirmatrelvir group were hospitalized or died, as compared with 44 of 682 (6.45%) in the placebo group. There were no deaths in the nirmatrelvir group and 9 in the placebo group. This effectiveness held up in a secondary analysis that included all participants whose first dose occurred within 5 days after symptom onset, with 8 of 1039 (0.77%) who received nirmatrelvir plus ritonavir and 66 of 1046 (6.31%) who received placebo reaching the composite end point. That the results

from the interim analysis were consistent with those of the final analysis is reassuring; it has not been the case for every Covid-19 trial.[3]

The results are clear, but nonetheless it is worth considering the difference between absolute and relative risk reduction. Although the relative risk reductions were large and similar across most subgroups (at about 89%), those at lower risk had a very small absolute benefit. For example, in patients who were SARS-CoV-2 seronegative at baseline, the absolute risk reduction was about 10 percentage points. However, in those who were SARS-CoV-2 seropositive at baseline, either because they had been infected in the past or had already undergone seroconversion from their current infection, the absolute risk reduction was about 1 percentage point. Thus, although all groups seem to have a similar relative benefit, the greatest absolute benefit is among those at highest risk.

This trial was performed between mid-July and early December 2021, a period when the delta variant was most likely responsible for the majority of infections. We do not yet know how nirmatrelvir plus ritonavir will perform as new variants, such as omicron, emerge. In vitro studies, however, suggest that the activity of nirmatrelvir is preserved across all tested viral strains.[4] We have not yet seen resistance to the new agent, but just as newer variants have evolved to be less susceptible to immune control (including control by monoclonal antibodies), it is likely that resistance to a single agent such as nirmatrelvir will become an issue.

Given that likelihood, how can we best use this effective drug? Supplies are currently constrained and are likely to remain so for some time. Who then should receive this scant resource? Here the new study provides some guidance: the absolute benefit will accrue primarily to patients at highest risk for disease progression, particularly those with multiple and serious coexisting conditions and those unable to mount sufficient immune responses. The timing of nirmatrelvir therapy is probably critical as well. Although the trial showed little difference between initiating treatment within 3 days and initiating it within 5 days after the onset of symptoms, initiating therapy much later than 5 days is very likely to be less effective. This is certainly true for other antiviral agents, such as remdesivir, which has only a small effect in hospitalized patients[5] but has a much greater effect when given early in the course of infection.[6] It will be very important to assess patients individually, since ritonavir interferes with the metabolism of many therapeutic agents, from antiseizure to immunosuppressive to anticoagulant medications. And, finally, until we have a better idea of the potential for the emergence of resistance, we need to be good stewards of this medication. By limiting its use to those most likely to benefit, we can potentially prolong its useful life.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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1. Heil EL, Kottilil S. The Goldilocks time for remdesivir — is any indication just right? N Engl J Med 2022;386:385-7.
2. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2118542.
3. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med 2022;386:509-20.
4. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of antibodies and antiviral drugs against Covid-19 omicron variant. N Engl J Med. DOI: 10.1056/NEJMc2119407.
5. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — final report. N Engl J Med 2020;383:1813-26.
6. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. N Engl J Med 2022;386:305-15.

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