EDITORIAL

Treating Acute Covid-19 — Final Chapters Still Unwritten

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Nirmatrelvir–ritonavir (Paxlovid [Pfizer]) is used as first-line therapy for nonhospitalized persons with Covid-19[1] on the basis of the results of the Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients (EPIC-HR) trial, which showed that this medication reduced the risk of hospitalization or death by 88%.[2] The EPIC-HR trial enrolled adults who had not received a SARS-CoV-2 vaccine and who were at high risk for progression to severe Covid-19. Given those results, the question arose as to whether nirmatrelvir–ritonavir conferred a benefit in persons who had been vaccinated or who did not have risk factors for severe disease.

The manufacturer-sponsored Evaluation of Protease Inhibition for Covid-19 in Standard-Risk Patients (EPIC-SR) trial, the results of which are reported in this issue of the *Journal*[3] sought to answer these questions. Participants had symptom onset within 5 days before randomization and either were fully vaccinated and had risk factors for severe disease or were unvaccinated (or had not received a Covid-19 vaccine within the previous year) and had no risk factors. Participants received nirmatrelvir–ritonavir or placebo for 5 days.

The trial enrolled nearly 1300 persons: 57% had been vaccinated against Covid-19, and 50% had a risk factor for severe disease. The participants' median age was 42 years, and only 5% were 65 years of age or older. Other than obesity, smoking, and hypertension, risk factors for severe Covid-19 were uncommon; for example, less than 2% of the participants had heart or lung disease. In this relatively low-risk population, the time to sustained alleviation of symptoms (the primary end point) was similar in the nirmatrelvir–ritonavir group and the placebo group (median, 12 and 13 days, respectively). Although fewer participants were hospitalized for Covid-19 or died from any cause in the nirmatrelvir–ritonavir group than in the placebo group (5 of 654 [0.8%] vs. 10 of 634 [1.6%], with the only death occurring in the placebo group), the difference was not significant. Of note, 6.3% of the participants in the placebo group in the EPIC-HR trial (which enrolled unvaccinated adults with risk factors) were hospitalized or died, which highlights the substantially lower risk of Covid-19 progression among the participants in the EPIC-SR trial.

What can we conclude from these two trials about nirmatrelvir–ritonavir for the treatment of Covid-19? Clearly, the benefit observed among unvaccinated high-risk persons does not extend to those at lower risk for severe Covid-19. This result supports guidelines that recommend nirmatrelvir–ritonavir only for persons who are at high risk for disease progression.[4,5]

What about treating people who have risk factors for severe Covid-19 but have received SARS-CoV-2 vaccines? Some observational studies suggest that treating vaccinated persons is beneficial,[6] but these studies are not definitive because of possible residual confounding. The EPIC-SR trial did not show evidence for benefit but enrolled only a small percentage of persons at the highest risk for progression — older persons, those who are immunocompromised, and those with serious coexisting conditions (e.g., heart or lung disease) — who constitute most of the patients hospitalized with Covid-19. As with many medical interventions, there is likely to be a gradient of benefit for nirmatrelvir–ritonavir, with the patients at highest risk for progression most likely to derive the greatest benefit. Thus, it appears reasonable to recommend nirmatrelvir–ritonavir primarily for the treatment of Covid-19 in older patients (particularly those ≥65 years of age), those who are immunocompromised, and those who have conditions that substantially increase the risk of severe Covid-19, regardless of previous vaccination or infection status.

The EPIC-SR trial, like the EPIC-HR trial, showed that symptom and viral rebound were not statistically associated with the use of nirmatrelvir–ritonavir. By contrast, some observational studies that defined rebound differently (and included more frequent sampling) have suggested an association.[7] What is common to all such studies, however, is that rebound is generally brief and mild. Therefore, concerns about rebound should not be a reason to withhold nirmatrelvir–ritonavir in those who may benefit. Trials of different treatment durations for acute Covid-19 and of a second course in those who have rebound are under way (ClinicalTrials.gov numbers, NCT05567952 and NCT05438602).

The results of the EPIC-SR trial point toward the need for additional studies of Covid-19 treatment. Because nirmatrelvir–ritonavir interacts with certain drugs (which lowers its benefit–risk ratio in patients who take those medications), the development of treatments with fewer drug interactions remains a high priority. Because progression to severe Covid-19 is uncommon among most infected people, studies assessing the effect that medications have on the risk of hospitalization would have to be quite large; therefore, trials should focus on the alleviation of symptoms — an end point frequently used in influenza treatment trials. In the EPIC-SR trial, nirmatrelvir–ritonavir did not hasten symptom alleviation, but antivirals that have been approved or authorized in countries outside the United States (ritonavir-boosted simnotrelvir, ensitrelvir, and mindeudesivir) have shown clinical benefit.[8-10] The disparate results between the EPIC-SR trial and studies supporting the use of other medications may be related to differences in timing (e.g., studies showing benefit initiated treatment within 72 hours after symptom onset), participant characteristics, how symptom amelioration was assessed, SARS-CoV-2 variants (although small-molecule drugs, like nirmatrelvir–ritonavir, that target viral enzymes are expected to be active against all of the variants detected so far), or the antiviral potency of the medications. Going forward, we should adopt more standardized trial designs, inclusion criteria, and end points to facilitate comparisons of results.

In addition, given broad population immunity to SARS-CoV-2 from widespread infection and vaccination, we need a deeper understanding of who remains at greatest risk, as well as better tools to predict the likelihood that severe Covid-19 will develop in a given patient. The Centers for Disease Control and Prevention lists disparate conditions that confer risk, but we should adopt a tiered approach in order to target treatment to those whose illness is most likely to progress. Severely immunocompromised persons are among the populations at highest risk for severe Covid-19; we need trials that evaluate different treatment durations and combination therapies as compared with monotherapies to understand how best to treat such patients. Finally, we should require longer-term follow-up of participants in trials to determine whether the treatment of acute infection prevents post–Covid-19 conditions. Although we have learned an amazing amount about SARS-CoV-2 therapy, the final chapters on treating Covid-19 are yet to be written.

NOTES

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

SUPPLEMENTARY MATERIAL

Disclosure Forms (nejme2402224_disclosures.pdf)

DOWNLOAD 153.67 KB

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