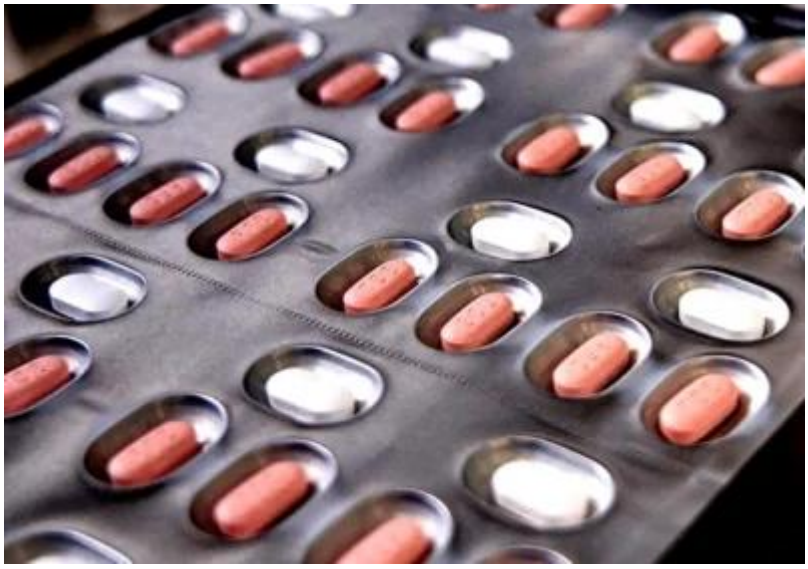
The oral combination medication used to treat coronavirus disease 2019 (COVID-19) nirmatrelvir-ritonavir (N-R) consists of nirmatrelvir, a protease inhibitor targeting the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) main protease, and ritonavir, a cytochrome P450 (CYP) 3A inhibitor. This medication is indicated for the treatment of mild to moderate COVID-19 patients aged 12 years and older. In this study, the authors from the United States and South Africa investigated the frequency and duration of the virologic rebound phenomenon in COVID-19 outpatients treated with nirmatrelvir-ritonavir (N-R).

The virologic rebound (VR) phenomenon is characterized by the recurrence of symptoms and reversion to SARS-CoV-2 test positivity. The biological mechanisms of VR are unknown.



About the study

Participants and data for this analysis came from a prospective observational Post-Vaccination Viral Characteristics Study that enrolled people with acute COVID-19 to assess quantitative viral load, viral culture, and symptom data. Individuals were included if they met the following criteria at the time of their first positive COVID-19 test: they were outpatients and enrolled within 5 days of their first diagnostic test for COVID-19, they had not received antiviral therapies other than N-R in the previous 14 days or monoclonal antibodies in the previous 90 days, and they had not completed N-R therapy at the time of

enrollment.

Participants were divided into two cohorts. 72 participants who initiated treatment with N-R within 5 days after testing positive for COVID-19 were included in the N-R group. The no-therapy group included 55 participants who did not start any COVID-19 treatment within 5 days of their first positive result. Participants in both cohorts were vaccinated against SARS-CoV-2.

Eligible participants received N-R therapy for five days and were followed for at least two weeks until either two consecutive negative polymerase chain reaction (PCR) results or detection of VR. The primary outcome was VR, detected within 20 days of the participant's first positive COVID-19 diagnostic test. VR was defined as either a positive SARS-CoV-2 viral culture after a prior negative result or if the VR event met the viral load criteria.

Results

Participants who received N-R were older (median age, 57 *versus* 39 years), had received more COVID-19 vaccinations (median, 4 versus 3), and were more frequently diagnosed with immunosuppression than untreated participants.

VR was found in 20.8% (16 patients out of 72 participants who received N-R) and in only one person (1.8%) of 55 participants from the no-therapy group. All 16 VR events (100%) met a positive SARS-CoV-2 viral culture result, and 12 (75%) met the viral load criteria. Only N-R use was associated with VR in multivariable models. Furthermore, the VR phenomenon was associated with a prolongated shedding of replication-competent viruses.

VR was more common among those who started therapy within two days of symptom onset (26.3%) than among those who started therapy more than two days after symptom onset (0%). VR remained more common in the N-R therapy group after stratification according to demographic and clinical characteristics, such as vaccination and immunosuppression status.

Conclusion

This study demonstrated that virologic rebound was found in approximately 21% of COVID-19 outpatients treated with nirmatrelvir-ritonavir and 2% of those not taking therapy. Furthermore, virologic rebound was associated with a substantially prolongated

shedding of replication-competent viruses.

The authors stated that future works should investigate the mechanisms of VR and risk factors for VR associated with N-R, the association between VR and long COVID-19 syndrome, and whether delays in initiating N-R or longer courses of N-R can prevent VR in high-risk individuals.

This article was published in Annals of Internal Medicine.

Journal Reference

Edelstein GE, Boucau J, Uddin R et al. SARS-CoV-2 Virologic Rebound With Nirmatrelvir–Ritonavir Therapy. Annals of Internal Medicine, 14 November 2023. (Open Access) https://www.acpjournals.org/doi/full/10.7326/M23-1756