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. This study enrolled people with acute COVID-19 to assess quantitative viral load, viral culture, and symptom data. Included criteria were as follows: outpatients were enrolled within five days of their first positive COVID-19 test, they had not received antiviral therapies other than N-R in the previous 14 days or monoclonal antibodies in the last 90 days, and they had not completed N-R therapy at the time of enrollment.

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

Eligible participants received N-R therapy for five days. They were followed for at least two

weeks until either two consecutive negative polymerase chain reaction (PCR) results or the 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 the VR event that 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 of 72 participants who received N-R) and 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 the use of N-R 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 clinical characteristics, such as vaccination status or immunosuppression.

Conclusion

This study demonstrated that virologic rebound was found in 21% of COVID-19 outpatients treated with nirmatrelvir-ritonavir and 2% of those from the no-therapy group. 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, the risk factors for VR associated with N-R, and the association between VR and long COVID-19 syndrome. Also, it would be significant to explore whether a delay in initiating N-R or a longer course of N-R can prevent VR in high-risk individuals.

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