Rapid Relapse of Symptomatic Omicron SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir

Michael Charness (michael.charness@va.gov)
VA Boston Healthcare System
Kalpana Gupta
VA Boston Healthcare System
Gary Stack
VA Connecticut Healthcare System
Judith Strymish
VA Boston Healthcare System
Eleanor Adams
National Basketball Association
David Lindy
Columbia University Vagelos College of Physicians and Surgeons
Hiroshi Mohri
Columbia University Vagelos College of Physicians and Surgeons
David Ho (dh2994@cumc.columbia.edu)
Columbia University Vagelos College of Physicians and Surgeons

Case Report

Keywords: COVID-19, SARS-CoV-2, Nirmatrelvir, relapse, rebound

Posted Date: May 23rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1588371/v3

Abstract

We describe relapse of COVID-19 symptoms and SARS-CoV-2 viral load following nirmatrelvir/ritonavir (NM/R) in 10 non-immunocompromised patients aged 31 to 71-years-old. Most patients improved rapidly after treatment with NM/R and had negative antigen or PCR tests prior to relapse on Days 9-12 of their illness. Relapse symptoms were described most frequently as cold symptoms, though some patients experiencing a recurrence of fatigue and headache. All relapses resolved without additional antiviral treatment. Viral load during relapse was comparable to levels during initial infection. Sequencing in three patients indicated that relapse was not due to a treatment-emergent mutation or infection with a different viral strain. One symptomatic and one presymptomatic patient transmitted SARS-CoV-2 to family members during relapse. The presence of high viral load and the occurrence of two transmission events suggest that patients with relapse should isolate until antigen testing is negative.

Full Text

Nirmatrelvir is a SARS-CoV-2 main protease (M^{pro}) inhibitor that blocks replication of SARS-CoV-2 and markedly reduces disease severity in unvaccinated individuals at risk for progression of COVID-19 [1]. Here we report a relapse of symptoms along with viral rebound after the completion of early nirmatrelvir/ritonavir (NM/R) treatment in three well-documented cases plus seven presumptive cases.

A 71-year-old male (71M) with intermittent asthma developed rhinorrhea, sore throat, coryza, asthma, cough, fatigue, malaise, chills, and fever of 38.4^{o}C on Day 0; antigen test (BinaxNow, Abbott Laboratories) was positive. Oral NM/R was started at 3 PM on Day 0 and continued every 12 hours through the morning of Day 5. He took three doses of inhaled fluticasone 440 µg twice daily and occasional inhaled albuterol from the evening of Day 0 through Day 1. Symptoms improved rapidly with only mild rhinorrhea and asthma on Day 1 and complete resolution of symptoms from Day 2 through Day 8. On Day 9, while still isolating, he developed typical cold symptoms with rhinorrhea, sore throat, coryza, and asthma; symptoms peaked on Day 10 and resolved by Day 12.

Nasal quantitative reverse-transcriptase polymerase chain reaction (PCR) cycle threshold (Ct) and antigen testing fluctuated in parallel with symptoms with two distinct peaks of viral load and symptoms on Day 1 and Day 9 (Table). Antigen test turned negative on Day 16 and remained negative on Day 35. Respiratory pathogen screen (Biofire RP2.1) on Day 10 was positive for SARS-CoV-2 and negative for 21 other respiratory viruses. Viral genome sequencing (Ion Torrent Genexus Integrated Sequencer, ThermoFisher Scientific) demonstrated sequence identity for the omicron BA.1.20 subvariant from Day 1 through Day 11. A P132H mutation in nsp5 was present throughout; this mutation is found in 98% of BA.1.20 sequences and is not likely to influence nirmatrelvir binding to M^{pro} [2]. A heterozygous I273T mutation in nsp6 (I3842T of ORF1ab) identified on Day 1 became homozygous between Day 3 and Day 5. Serum anti-spike IgG was positive (>25,000 absolute units per ml) on Day 13, and anti-nucleocapsid IgG was 0.51 on Day 14 and 1.93 on Day 21 (considered positive when index is >1.4).

A 69-year-old male (69M) experienced cold symptoms and had a positive antigen test on Day 0 through Day 3, including a positive PCR test. A 5-day course of NM/R was begun on Day 1, and symptoms resolved on Day 4. From Day 4 to Day 9, daily antigen tests were negative along with two negative PCR tests. Mild symptoms recurred on Day 10, when a viral rebound was documented by both antigen and PCR tests (Table). The recurrence of symptoms and virus lasted only three days. A 50-year-old female member of 69M's household (50F) experienced a similar pattern of recurrent symptoms and virus rebound after complete resolution of symptoms and detectable virus following treatment with NM/R (Table). Viral sequencing of samples taken from 69M and 50F identified the omicron BA.2.9 subvariant as the culprit. Other than the P132H mutation, which is also common in BA2.9, no mutation in the nsp5 gene was noted at onset (Day 1-2) and relapse (Day 9-10).

Seven additional examples of relapsing viral replication and symptoms were identified, including two family members of 71M (Table). The 10 patients ranged in age from 31 to 71-years-old and included 6 males and 4 females. All patients were fully vaccinated and had received at least one mRNA booster dose 2 weeks to 6 months prior to infection. None were immunocompromised, and only one took inhaled steroids briefly during NM/R treatment. NM/R was begun on Days 0-2 (median Day 1), and symptoms improved or resolved 1-6 days (median 3 days) after initiation of treatment. Relapse symptoms began between 3 and 8 days (median 5 days) after the completion of treatment with NM/R on Days 9-12 (median Day 10) and lasted between 3 and 10 days (median 4 days). Relapse symptoms were described most frequently as cold symptoms, though some patients experiencing a recurrence of fatigue and headache. Relapse symptoms were milder than presenting symptoms in 7 of 10 cases, and fever was not reported. No patient required urgent care, emergency room, or hospital care during initial or relapse symptoms, and all patients recovered without additional antiviral treatment. Antigen tests during relapse became strongly positive on Days 9-13 (median Day 10) and remained so for at least 2 to 7 days (median 6 days; not measured daily) until as late as Day 18, well past the recommended period for isolation.

There were two instances of transmission during relapse. Patient 63M had close contact with two family members during 3 days of relapse, and both family members became symptomatic and tested positive for COVID-19 within 3 days of the initial relapse exposure. Patient 67M had close contact with a 6-month-old male family member for 15 to 30 minutes while presymptomatic on Day 12; he became symptomatic 8-10 hours later and had a positive antigen test the following day. The infant became symptomatic with a positive antigen test 3 days later, and his parents became symptomatic with positive antigen tests after an additional 2-3 days. Neither the infant nor his parents had other close contacts during this time. Our finding of high viral load and transmission during relapse and the report of viral culture from a nasal sample obtained during relapse [4] suggest that patients with relapse should isolate until antigen testing is negative. In our case series, testing was triggered by the recrudescence of symptoms; it remains unknown whether or how often asymptomatic relapse occurs.

Rapid relapse of COVID-19 symptoms followed the completion of early, effective treatment with NM/R. Sequencing in three patients indicated that relapse was not due to a treatment-emergent mutation or infection with a different viral strain. Although this was a convenience sample, it is noteworthy that 5 of

10 cases occurred within two families, suggesting that relapse following NM/R treatment is not rare. In contrast, Ct values below 30 were not detected between Day 11 and Day 15 in National Basketball Association personnel (including team operations staff, gameday staff, and other vendors) with the SARS-CoV-2 omicron variant who were diagnosed during frequent surveillance and did not receive NM/R [3]. Similarly, from December 14, 2021 to March 1, 2022, an omicron predominant period, relapse did not occur among nearly 1,000 NBA-related personnel who were diagnosed with COVID-19 and untreated with NM/R (unpublished data). Further work is required to determine the etiology, frequency, duration, and spectrum of rebound symptoms and the relation to NM/R treatment.

The VA Boston IRB determined this was quality improvement work not requiring further review. Some of the cases were part of an observational cohort study that was approved by the IRB of Columbia University Medical Center.

References

1. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med 2022. DOI: 10.1056/NEJMoa2118542.

2. Sacco MD, Hu Y, Gongora MV, et al. The P132H mutation in the main protease of Omicron SARS-CoV-2 decreases thermal stability without compromising catalysis or small-molecule drug inhibition. Cell Res 2022;32(5):498-500. DOI: 10.1038/s41422-022-00640-y.

3. Hay JA, Kissler SM, Fauver JR, et al. Viral dynamics and duration of PCR positivity of the SARS-CoV-2 Omicron variant. medRxiv 2022. DOI: 10.1101/2022.01.13.22269257.

4. Carlin AF, Clark AE, Chaillon A, et al. Virological and immunological characterization of COVID-19 recrudescence after nirmatrelvir/ritonavir treatment. Research Square 2022. DOI: 10.21203/rs.3.rs-1662783/v1.

Tables

Table 1 is in the supplementary files section.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ResearchSquareTablev352222.docx