Open Forum Infectious Diseases

BRIEF REPORT

Successful Treatment of Prolonged Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Patients With Immunodeficiency With Extended Nirmatrelvir/Ritonavir: Case Series

Madison Breeden,[1] Samuel L. Aitken,[2,3] Ji Hoon Baang,[1] Misty Gravelin,[4] Daniel R. Kaul,[1] Adam S. Lauring,[1] Lindsay A. Petty,[1] and Kevin S. Gregg[1]

[1]Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, USA, [2]Department of Pharmacy, University of Michigan, Ann Arbor, Michigan, USA, [3]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, Ann Arbor, Michigan, USA, and [4]Michigan Institute for Clinical and Health Research, University of Michigan, Ann Arbor, Michigan, USA

Immunocompromised patients with B-cell deficiencies are at risk for prolonged symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. We describe 4 patients treated for B-cell malignancies with B-cell-depleting therapies who developed persistent SARS-CoV-2 infection and had resolution of symptoms following an extended course of nirmatrelvir/ritonavir.

Keywords. SARS-CoV-2; immunodeficiency; prolonged infection.

Patients with B-cell depletion are vulnerable to prolonged, symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as humoral immunity is critical in facilitating viral clearance [1–3]. The Food and Drug Administration (FDA) authorized a 5-day course of nirmatrelvir/ritonavir for mild-to-moderate coronavirus disease 2019 (COVID-19) under Emergency Use Authorization (EUA) [4–7]. One case report has described successful treatment utilizing a longer course of both nirmatrelvir/ritonavir and remdesivir in a patient with B-cell acute lymphoblastic leukemia (ALL) and prolonged SARS-CoV-2 infection [8]. Thus, there are limited data on treatment strategies for patients with B-cell depletion and prolonged infection with SARS-CoV-2, which represents an important gap in current knowledge. particularly as monoclonal antibodies are ineffective against currently circulating SARS-CoV-2 variants [9]. We describe 4 cases of patients with prolonged, symptomatic SARS-CoV-2 infection with underlying lymphoma or B-cell ALL and receipt of B-cell depleting therapies successfully treated with extended courses of nirmatrelvir/ritonavir, alone or in combination with remdesivir. As off-label use is not permitted for drugs under EUA, all patients were treated through the FDA emergency use, single-patient investigational new drug approval pathway. Written informed consent was obtained for all cases.

CASE 1

Case 1 is a 79-year-old woman with follicular lymphoma diagnosed 7 years prior to SARS-CoV-2 infection treated with lenalidomide, rituximab, zandelisib, and the investigational therapy epcoritamab in the past 2 years, but with ongoing active disease. The patient had received 3 Moderna SARS-CoV-2 vaccine doses, the last dose 1 year prior to diagnosis of SARS-CoV-2 infection. The patient's first positive SARS-CoV-2 polymerase chain reaction (PCR) test was performed due to cough, shortness of breath, and fatigue; she was treated with molnupiravir. She had received prophylactic tixagevimab/cilgavimab 2 months prior. Symptoms persisted, and she was admitted to the hospital 6 weeks later with persistent positive SARS-CoV-2 PCR results. Absolute lymphocyte count at the time of hospitalization was 0.7 K/μL (reference range, 1.2–4.0 K/μL). She did not require supplemental oxygen, and computed tomographic (CT) chest imaging revealed ground glass opacities and multilobar consolidation. Treatment included 10 days of remdesivir.

Symptoms persisted, and the patient continued to have positive tests with cycle threshold (Ct) values of 20–25 six months after initial diagnosis. SARS-CoV-2 whole genome sequencing (WGS) revealed lineage BA.1.1 throughout her course. Chest radiography remained abnormal during this time. She never required supplemental oxygen. The patient was treated with a 21-day course of nirmatrelvir/ritonavir. Her respiratory symptoms and fatigue resolved, and SARS-CoV-2 PCR was negative 8 days posttreatment. One month posttreatment, she continued to have no respiratory symptoms, and day 28 SARS-CoV-2 PCR remained negative. Three months posttreatment, she continued to have no fevers or respiratory symptoms and SARS-CoV-2 PCR remained negative.

CASE 2

Case 2 is a 72-year-old man with diffuse large B-cell lymphoma diagnosed 4 years prior to SARS-CoV-2 infection. He received chimeric antigen receptor T-cell therapy 1 year prior with

Received 14 February 2023; editorial decision 03 April 2023; accepted 04 April 2023; published online 6 April 2023

Correspondence: Kevin Gregg, MD, Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, 1500 E Medical Center Dr, F4156 University Hospital South, Ann Arbor, MI 48109 (kvngregg@med.umich.edu).

Open Forum Infectious Diseases®

https://doi.org/10.1093/ofid/ofad189

complete response. The patient had received 2 Moderna SARS-CoV-2 vaccine doses, the most recent dose 18 months prior to SARS-CoV-2 diagnosis.

The patient received prophylactic tixagevimab/cilgavimab 3 months prior to diagnosis. He had fevers and cough and subsequent positive rapid COVID-19 antigen test. He received a 5-day course of nirmatrelvir/ritonavir with mild symptomatic improvement. One month later, he was admitted as his symptoms progressed and he had new hypoxia on home pulse oximetry. Multifocal ground glass opacities were noted on chest CT. SARS-CoV-2 PCR was positive with Ct value of 27.5. Absolute lymphocyte count at the time of diagnosis was 0.1 K/μL (reference range, 1.2–4.0 K/μL). The patient received remdesivir for 10 days followed by nirmatrelvir/ritonavir for 20 days starting on day 7 of remdesivir treatment. The patient's symptoms improved slowly with treatment and no further need for oxygen upon discharge. He had a negative PCR on day 3 of nirmatrelvir/ritonavir and improving cough without fevers, hypoxia, or shortness of breath at the end of his prolonged course. No specimens were available for SARS-CoV-2 sequencing and lineage determination. At 2-month follow-up, all respiratory symptoms had resolved.

CASE 3

Case 3 is a 72-year-old man with a history of stage IV mantle cell lymphoma initially diagnosed 2 years prior to SARS-CoV-2 diagnosis. Previous treatments included venetoclax, lenalidomide, and rituximab; he was on lenalidomide at the time of SARS-CoV-2 diagnosis. The patient had received 2 Pfizer SARS-CoV-2 vaccinations, the last dose 18 months prior to diagnosis of SARS-CoV-2 infection.

The patient received prophylactic tixagevimab/cilgavimab 5 months prior. He developed shortness of breath and night sweats and tested positive for SARS-CoV-2 by PCR. Symptoms continued, and he was admitted 2 months later with Ct value of 28.4. Absolute lymphocyte count was 0.3 K/μL (reference range, 1.2–4.0 K/μL). He received bebtelovimab but symptoms continued. He was readmitted 1 month later with new hypoxia, hemoptysis, and increased multifocal ground glass opacities on chest CT. SARS-CoV-2 PCR was positive on bronchoalveolar lavage (BAL) with Ct value of 15. SARS-CoV-2 WGS from both nares and BAL fluid revealed the BA.5.2.1 sequence, which was the same sequence identified from prior hospitalization. He received 10 days of remdesivir with resolution of fever but ongoing hypoxia, night sweats, and cough. After treatment with remdesivir, the patient received 15 days of nirmatrelvir/ritonavir with resolution of all symptoms. Repeat SARS-CoV-2 PCR testing was not obtained. Patient was seen in follow-up 2 months after completion of nirmatrelvir/ritonavir and reported resolution of all symptoms.

CASE 4

Case 4 is a 60-year-old woman with a history of multiple myeloma who underwent an autologous stem cell transplant 5 years prior to SARS-CoV-2 diagnosis and subsequently developed B-cell ALL 1 year prior to SARS-CoV-2 diagnosis. She achieved remission following induction chemotherapy with cyclophosphamide, daunorubicin, vincristine, prednisone, rituximab, and peg-asparaginase and received ongoing maintenance therapy with rituximab.

The patient had received 4 Moderna SARS-CoV-2 vaccines, the most recent dose 2 months prior to diagnosis of SARS-CoV-2 infection. The patient received 2 doses of tixagevimab/cilgavimab, 8

Table 1. Description of Patient Characteristics, Severe Acute Respiratory Syndrome Coronavirus 2 Variant Type and Treatments, and Response to Extended Nirmatrelvir/Ritonavir

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Demographics				
Age	79 y	72 y	72 y	60 y
Ethnicity	Non-Hispanic	Non-Hispanic	Non-Hispanic	Non-Hispanic
Sex	Female	Male	Male	Female
Underlying condition	Follicular lymphoma	Diffuse large B-cell lymphoma	Mantle cell lymphoma	B-cell ALL
Duration of SARS-CoV-2 positivity	8 mo	1.5 mo	3 mo	2 mo
Duration of symptoms	8 mo	2 mo	4 mo	3 mo
SARS-CoV-2 variant type	BA.1.1	NA	BA.5.2.1	BF.28
SARS-CoV-2 treatments (total)				
Remdesivir	Yes	Yes	Yes	Yes
Nirmatrelvir/ritonavir (standard course)	No	Yes	No	Yes
Molnupiravir	Yes	No	No	No
Bebtelovimab	No	No	Yes	Yes
SARS-CoV-2 treatments (at the time of extended nirmatrelvir/ritonavir administration)	Remdesivir	Remdesivir	Remdesivir	Remdesivir, bebtelovimab
Extended nirmatrelvir/ritonavir duration	21 d	20 d	15 d	21 d
Response to nirmatrelvir/ritonavir	Clinical, virologic	Clinical, virologic	Clinical	Clinical, radiologic

Abbreviations: ALL, acute lymphoblastic leukemia; NA, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

and 5 months prior to diagnosis. She developed congestion, cough, chills, and fever and had a positive SARS-CoV-2 PCR result. Patient received 5 days of nirmatrelvir/ritonavir with initial improvement but developed recurrent fatigue and fevers. The patient had a SARS-CoV-2 PCR-positive result 1 month later. Symptoms continued, and she received a 7-day course of remdesivir without significant improvement in cough, congestion, fevers, and lack of appetite. CT chest at the time was notable for bilateral airspace opacities. Two months after initial diagnosis, absolute lymphocyte count was 0.6 K/μL (reference range, 1.2–4.0 K/μL), and SARS-CoV-2 WGS revealed persistent BF.28 sequence. Given ongoing symptoms and persistent positivity, she received 7 days of remdesivir and bebtelovimab once, followed by a 20-day course of nirmatrelvir/ritonavir with complete resolution of symptoms and improvement in bilateral opacities on chest CT. Patient had sustained resolution of symptoms 1 month after completion of nirmatrelvir/ritonavir and negative SARS-CoV-2 PCR 3 months following completion.

DISCUSSION

We present 4 cases of patients with B-cell malignancy receiving B-cell-depleting therapies with documented lymphocytopenia who experienced prolonged symptomatic infection with SARS-CoV-2 and clinical cure following extended-course nirmatrelvir/ritonavir (Table 1). The length of treatment with nirmatrelvir/ritonavir was informed by the severity of symptoms, duration of infection, and Ct value, but was ultimately determined by the treating clinician. In all cases, an extensive workup for other infections was negative. All 4 patients tolerated the therapy without any significant adverse events or drug–drug interactions. WGS revealed persistence of the infecting lineage in 3 of the 4 cases, strongly suggesting that prolonged positivity was related to chronic infection rather than episodes of reinfection; no mutations were identified. In the 2 cases where test-of-cure PCR was performed, the SARS-CoV-2 PCR was negative despite persistent positive tests prior to nirmatrelvir/ritonavir. The resolution of patient symptoms in all cases coincident with extended nirmatrelvir/ritonavir treatment in the presence of persistence following prior therapy suggests that this was an important factor in treatment. These cases add to and expand upon a previously published case report of clearance of SARS-CoV-2 following extended remdesivir and nirmatrelvir/ritonavir treatment in a patient with B-cell ALL and prolonged symptoms of SARS-CoV-2 infection [8].

Patients with B-cell depletion are at risk for prolonged infection with SARS-CoV-2 and are no longer protected by tixagevimab/cilgavimab [9]. Short courses of antivirals, including nirmatrelvir/ritonavir, remdesivir, and molnupiravir, may not be effective in this population. While studies of longer duration are ongoing for early disease and strategies for passive immunity in immunocompromised hosts have been proposed [10], we are not aware of any ongoing studies in patients with B-cell depletion and persistent infection with SARS-CoV-2.

In summary, extended-course nirmatrelvir/ritonavir appears to be a potential treatment option for this vulnerable population, assuming no prohibitive drug interactions are present. In these cases, access under EUA presents a barrier to extended treatment with nirmatrelvir/ritonavir, as the off-label use requires the same FDA and institutional review board approval as the clinical use of an investigational drug under the FDA Expanded Access regulations. Within a single institution, treatment length was variable as there are no standard criteria to assist clinicians in determining appropriate duration, thus highlighting the need for investigation into a standard treatment course. Future studies should evaluate long-term outcomes in patients with B-cell depletion and evaluate the optimal duration of therapy.

Notes

Acknowledgments. The authors acknowledge Jason Smith from the Michigan Department of Health and Human Services. The authors also acknowledge Andrew Smith, PharmD, Lauren Quiroga, PharmD, and all of the pharmacists and technicians from University of Michigan Investigational Pharmacy Services who facilitated this process.

Patient consent. This study was reviewed by the Institutional Review Board at the University of Michigan and determined to be exempt. It was determined this was secondary research for which consent was not required.

Potential conflicts of interest. S. L. A. serves on an AstraZeneca advisory board. D. R. K. is a funded investigator for Gilead, AstraZeneca, Janssen, Nobelpharma, and Takeda. A. S. L. receives fees from Roche for service on steering committee for study of influenza antivirals. K. S. G. is principal investigator on trials for Pfizer and Ansun Pharmaceuticals. All other authors report no potential conflicts.

References

1. Jones JM, Faruqi AJ, Sullivan JK, et al. COVID-19 outcomes in patients undergoing B cell depletion therapy and those with humoral immunodeficiency states: a scoping review. Pathog Immun **2021**; 6:76–103.
2. Baang JH, Smith C, Mirabelli C, et al. Prolonged severe acute respiratory syndrome coronavirus 2 replication in an immunocompromised patient. J Infect Dis **2021**; 223:23–7.
3. Horiuchi H, Sasaki H, Miyazaki K, Miyata N, Yoshimura Y, Tachikawa N. Recovery from severe persistent COVID-19 without evidence of an anti-SARS-CoV-2 antibody response in a man with mantle cell lymphoma treated with rituximab. J Infect Chemother **2022**; 28:329–32.
4. Centers for Disease Control and Prevention. COVID-19 treatments and medications. **2022**. Available at: www.cdc.gov/coronavirus/2019-ncov/your-health/treatments-for-severe-illness.html. Accessed 16 January 2023.
5. National Institutes of Health. Ritonavir-boosted nirmatrelvir (Paxlovid). **2022**. Available at: https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibodyproducts/ritonavir-boosted-nirmatrelvir–paxlovid-/. Accessed 16 January 2023.
6. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med **2022**; 386:1397–408.
7. Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 in a large U.S. health system: a population-based cohort study. Ann Intern Med **2023**; 176:77–84.
8. Ford, ES, Simmons W, Karmarkar EN, et al. Successful treatment of prolonged, severe coronavirus disease 2019 lower respiratory tract disease in a B-cell acute lymphoblastic leukemia patient with an extended course of remdesivir and nirmatrelvir/ritonavir. Clin Infect Dis **2023**; 76:926–9.
9. US Food and Drug Administration Center for Drug Evaluation and Research. Latest FDA updates for Evusheld. **2023**. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-releases-important-information-about-risk-covid-19-due-certain-variants-not-neutralized-evusheld. Accessed 16 January 2023.
10. Dioverti V, Salto-Alejandre S, Haidar G. Immunocompromised patients with protracted COVID-19: a review of "long persisters." Curr Transplant Rep **2022**; 9:209–18.