MEDICAL SCIENCE MONITOR

EDITORIAL

e-ISSN 1643-3750
© Med Sci Monit, 2022; 28: e938532
DOI: 10.12659/MSM.938532

Received: 2022.09.29
Accepted: 2022.09.29
Available online: 2022.09.30
Published: 2022.10.01

Editorial: Rebound COVID-19 and Cessation of Antiviral Treatment for SARS-CoV-2 with Paxlovid and Molnupiravir

Dinah V. Parums, MD PhD

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, USA

e-mail: dinah.v.parums@isi-science.com

Conflict of interest: None declared

Abstract One of the most recently described clinical associations with SARS-CoV-2 infection is rebound COVID-19, which occurs between five and eight days following the cessation of antiviral treatment. Most case reports of rebound COVID-19 have been associated with cessation of treatment with the combined oral antiviral agent nirmatrelvir/ritonavir (Paxlovid). On 24 May 2022, the US Centers for Disease Control and Prevention (CDC) issued a Health Alert Network (HAN) Health Advisory update for patients, healthcare providers, and public health departments on COVID-19 rebound or recurrence of COVID-19. However, population data from the US showed no significant differences in the risk of developing rebound COVID-19 between patients treated with Paxlovid and Molnupiravir. The mechanisms of rebound COVID-19 remain unclear but may involve the development of resistance to the antiviral drug, impaired immunity to the virus, or insufficient drug dosing. A further explanation may be the persistence of a high viral load of SARS-CoV-2 in individuals who are no longer symptomatic. This Editorial aims to provide an update on what is known about rebound COVID-19 and the current public health implications.

Keywords: **Rebound Infection • Paxlovid • Molnupiravir • SARS-CoV-2 • COVID-19 • Editorial**

It has been almost three years since the first cases of COVID-19 due to infection with SARS-CoV-2 were identified in China [1]. The spread of the SARS-CoV-2 virus rapidly resulted in a pandemic with patient mortality and acute and chronic consequences of COVID-19 [2]. As of 26 September 2022, 615 million cases of COVID-19 have been reported, and global mortality from COVID-19 currently stands at 6.54 million [3]. The development of vaccines to prevent SARS-CoV-2 has occurred with astonishing rapidity and now aims to match the rapid development of variants and subvariants of SARS-CoV-2, including the Omicron variant [4,5].

Developed countries have benefitted from the availability of vaccines. For example, as of 26 September 2022, 80% of the population of the US had received both primary and booster SARS-CoV-2 vaccines [6]. Because vaccines provide limited duration and degree of immune protection, antiviral agents are now available, particularly in developed countries [7]. Social restrictions and infection control measures have been reduced in many countries, where there may be a false belief that the COVID-19 pandemic is now over [8]. However, SARS-CoV-2 is now endemic worldwide, and the pathogenesis and mechanisms of spread and persistence continue to provide new challenges for patient management [9].

One of the most recently described clinical associations with SARS-CoV-2 infection is rebound COVID-19, which follows the cessation of antiviral treatment with symptoms recurring at five and eight days [10]. Most case reports of rebound COVID-19 are associated with cessation of treatment with the combined oral antiviral agent nirmatrelvir/ritonavir (Paxlovid) (Pfizer, New York, NY, USA) [10]. Because antiviral agents are available mainly in developed countries, cases of rebound COVID-19 have been reported primarily in the US and Europe [10]. Rebound COVID-19 was brought to world attention following the recent diagnosis and treatment of COVID-19 in the current US President, who experienced rebound COVID-19 following completion of a course of Paxlovid [11], but who also recently expressed the opinion that the COVID-19 pandemic is over [12]. Currently, the US Centers for Disease Control and Prevention (CDC) reports that an average of 4,000 patients are hospitalized each day, and 400 deaths per day from COVID-19 [12,13]. Global data and data from the US do not currently support that the COVID-19 pandemic is over [3,13].

Paxlovid tablets contain the dual antiviral agents nirmatrelvir and ritonavir [14]. On 22 December 2021, Paxlovid received Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA) for the treatment of adults and pediatric patients >12 years of age with a diagnosis of SARS-CoV-2 infection, mild to moderate COVID-19 not requiring hospitalization, and one or more risk factors for progression to severe disease [15]. The EUA for Paxlovid recommends that treatment

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

commences within five days of the onset of symptoms [15]. Regulatory approval of Paxlovid was based on an interim analysis of the Phase 2/3 Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) randomized, double-blind trial (NCT04960202) [16]. The EPIC-HR trial included nonhospitalized adult patients with COVID-19 at high risk of progressing to severe illness [16]. Interim data analysis showed an 89% reduction in the risk of COVID-19-related hospitalization or death from any cause compared with placebo in patients treated within three days of the onset of symptoms [16].

On 24 May 2022, the CDC issued a Health Alert Network (HAN) Health Advisory update for patients, healthcare providers, and public health departments on COVID-19 rebound or recurrence of COVID-19 following cessation of Paxlovid [17]. COVID-19 rebound has been reported to occur between 2 and 8 days after initial clinical recovery [10,17,18]. COVID-19 rebound is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having a negative test [10,17,18]. In some patients, brief symptoms may return as part of the natural history of SARS-CoV-2 infection, independent of treatment or vaccination status [10,17]. Also, patients with rebound COVID-19 associated with Paxlovid usually have a mild form of the disease [10,17]. The US CDC does not recommend the additional use of Paxlovid or other treatments for SARS-CoV-2 when rebound COVID-19 is suspected or diagnosed [10,17]. The risk of transmission during rebound COVID-19 can be managed by isolation, wearing a mask, and repeat SARS-CoV-2 testing [10,17]. Currently, the (HAN) Health Advisory update relates to rebound COVID-19 following cessation of Paxlovid [17].

However, rebound COVID-19 is not unique to patients treated with Paxlovid but also follows treatment with Molnupiravir [18]. Molnupiravir (Merck & Co., Rahway, NJ, USA; Ridgeback Biotherapeutics LP, Miami, FL, USA) was granted EUA by the FDA on 23 December 2021 for adults >18 years of age for the treatment of mild-to-moderate COVID-19 at increased risk for progression to severe COVID-19, including hospitalization or death [19]. Regulatory approval of Molnupiravir was based on a phase 3 trial on the efficacy and safety of molnupiravir treatment within 5 days after the onset of signs or symptoms of COVID-19 in nonhospitalized, unvaccinated adults with mild-to-moderate illness and at least one risk factor for severe COVID-19 (NCT04575597) [20]. The results showed that early treatment with Molnupiravir reduced the risk of hospitalization or death in unvaccinated, at-risk adults with COVID-19 [20].

A retrospective study of the electronic health records of 92 million US patients, including 13,644 patients ≥18 years of age who contracted COVID-19 during six months from 1 January 2022, was recently published [18]. The study included 11,270 patients with COVID-19 treated with Paxlovid and 2,374 patients with COVID-19 treated with Molnupiravir within five days of diagnosis [18]. The study evaluated COVID-19 rebound rates at 7 days and 30 days regarding SARS-CoV-2 infection, COVID-19 symptoms, and hospitalizations for COVID-19 [18]. After Paxlovid treatment, the 7-day and 30-day COVID-19 rebound rates were 3.53% and 5.40% for SARS-CoV-2 infection, 2.31% and 5.87% for symptoms of COVID-19, and 0.44% and 0.77% for hospitalizations due to COVID-19 [18]. After Molnupiravir treatment, the 7-day and 30-day COVID-19 rebound rates were 5.86% and 8.59% for SARS-CoV-2 infection, 3.75% and 8.21% for symptoms of COVID-19, and 0.84% and 1.39% for hospitalizations due to COVID-19 [18]. Propensity score matching analysis showed no significant differences in the risk of developing rebound COVID-19 between COVID-19 patients treated with Paxlovid and COVID-19 patients treated with Molnupiravir [18]. This US population study also showed that the rates of COVID-19 rebound increased with time following treatment and were increased in patients with comorbidities [18]. These initial findings from a large US population study help to clarify that, despite recent media attention given to an association with Paxlovid, rebound COVID-19 is also associated with treatment with Molnupiravir and may occur following other antiviral treatments for COVID-19.

The mechanisms of rebound COVID-19 remain unclear but may involve the development of resistance to the antiviral drug, impaired immunity to the virus, or insufficient drug dosing. A further explanation may be the persistence of a high viral load of SARS-CoV-2 in individuals who are no longer symptomatic, irrespective of antiviral treatment. This latter explanation is supported by studies showing the presence of culturable SARS-CoV-2 virus in nasal swabs for up to 2 weeks after symptomatic COVID-19 [21]. This finding has future implications for viral surveillance and isolation of treated patients, with revision of current public health guidelines.

Conclusions

Rebound COVID-19 can occur following cessation of antiviral treatment with Paxlovid and Molnupiravir. These findings support that continuous patient surveillance should be undertaken not only during antiviral treatment but also up to 30 days after treatment. Further studies on COVID-19 rebound are required, and the association between drug dosing and treatment duration may lead to treatment regimens that prevent rebound infection. Further analysis of risk factors, including patient comorbidities and other treatments, might identify vulnerable patients who require changes in treatment regimens combined with regular post-treatment testing of their SARS-CoV-2 status.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

References:

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727
2. Groff D, Sun A, Ssentongo AE, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: A systematic review. JAMA Netw Open. 2021;4(10):e2128568
3. World Health Organization (WHO). Coronavirus (COVID-19) dashboard. Sept 26 2022. Available at: https://covid19.who.int
4. Gong W, Parkkila S, Wu X, Aspatwar A. SARS-CoV-2 variants and COVID-19 vaccines: Current challenges and future strategies. Int Rev Immunol. 2022;28:1-22
5. Parums DV. Editorial: World Health Organization (WHO) Variants of Concern Lineages Under Monitoring (VOC-LUM) in response to the global spread of lineages and sublineages of Omicron, or B.1.1.529, SARS-CoV-2. Med Sci Monit. 2022;28:e937676
6. Centers for Disease Control and Prevention (CDC). COVID data tracker. COVID-19 Vaccinations in the United States. September 26 2022. Available at: https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-onedose-pop-5yr
7. Parums DV. Editorial: Current status of oral antiviral drug treatments for SARS-CoV-2 infection in non-hospitalized patients. Med Sci Monit. 2022;28:e935952
8. Koelle K, Martin MA, Antia R, Lopman B, Dean NE. The changing epidemiology of SARS-CoV-2. Science. 2022;375(6585):1116-21
9. Biancolella M, Colona VL, Mehrian-Shai R, et al. COVID-19 2022 update: Transition of the pandemic to the endemic phase. Hum Genomics. 2022;16(1):19
10. Rubin R. From positive to negative to positive again – the mystery of why COVID-19 rebounds in some patients who take Paxlovid. JAMA. 2022;327(24):2380-82
11. Piettsch B. 'Rebound' coronavirus cases: What to know after Biden tests positive again. The Washington Post. July 31 2022. Available at: https://www.washingtonpost.com/health/2022/07/31/biden-covid-rebound-paxlovid-answers/
12. Stolberg SG. With 400 to 500 Americans still dying every day of COVID-19, President Biden has declared that "the pandemic is over." The New York Times. Sept 19 2022. Available at: https://www.nytimes.com/2022/09/19/us/politics/biden-covid-pandemic-over.html
13. Centers for Disease Control and Prevention (CDC). COVID data tracker. Daily updates for the United States. September 26 2022. Available at: https://covid.cdc.gov/covid-data-tracker/#datatracker-home
14. Paxlovid for treatment of COVID-19. Med Lett Drugs Ther. 2022;64(1642):9-10
15. Food and Drug Administration (FDA). News release. Coronavirus (COVID-19) update: Emergency use authorization. Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use). FDA Authorizes First Oral Antiviral for Treatment of COVID-19. December 22, 2021. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19
16. Hammond J, Leister-Tebbe H, Gardner A, et al; EPIC-HR Investigators. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med. 2022;386(15):1397-408
17. Centers for Disease Control and Prevention (CDC). CDC Health Alert Network. Health advisory. COVID-19 rebound after Paxlovid treatment. May 24 2022. Available at: https://emergency.cdc.gov/han/2022/pdf/CDC_HAN_467.pdf
18. Wang L, Berger NA, Davis PB, et al. COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022. medRxiv [Preprint]. 2022 Jun 22: 2022.06.21.22276724. doi: 10.1101/2022.06.21.22276724
19. Food and Drug Administration (FDA). News release. Coronavirus (COVID-19) update: FDA authorizes additional oral antiviral for treatment of COVID-19 in certain adults. Emergency use authorization. Molnupiravir. December 23, 2021. Available at: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain
20. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al; MOVe-OUT Study Group. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med. 2022;386(6):509-20
21. Boucau J, Uddin R, Marino C, et al Characterization of virologic rebound following nirmatrelvir-ritonavir treatment for COVID-19. Clin Infect Dis. 2022;ciac512. doi: 10.1093/cid/ciac512 [Online ahead of print]

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]