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REVIEW ARTICLE

Paxlovid's Double-Edged Sword: Treating COVID-19 and the Risk of Viral Load Rebound

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Coronavirus disease 19 (COVID-19) is an infectious respiratory illness caused by SARS-CoV-2 virus that has caused more than 3 million deaths since its emergence as a public health emergency in January 2020 [1]. Through emergency efforts, pharmaceutical companies such as Pfizer, Moderna, and Johnson and Johnson were able to create vaccinations to reduce hospitalizations and death related to COVID-19. Until 2021, social distancing combined with N-95 masks and the primary series of vaccination were some of the only recommendations provided by the CDC to limit the risk of contracting COVID-19. At that time there were no available options for treatment once infected, that is until the development of nirmatrelvir/ritonavir (Paxlovid; Pfizer Labs) [2].

Nirmatrelvir/ritonavir is an oral antiretroviral containing both nirmatrelvir, a SARS-CoV-2 main protease inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir/ritonavir is approved for treatment of mild-moderate COVID-19 in adults at high risk for progression to severe COVID-19, including hospitalization or death. Nirmatrelvir is responsible for the inhibition of viral replication while the ritonavir component acts as a pharmacokinetic enhancer with no true activity against SARS-CoV-2. In the EPIC-HR trial initiated by Pfizer in July 2021, nirmatrelvir/ritonavir was shown to reduce hospitalizations in high-risk patients by 6.32% with an overall incident rate of 0.77% compared to 7.01% incident rate in the placebo group ($p < 0.001$). Although nirmatrelvir/ritonavir has only been FDA approved since 2023, more than 11 million prescriptions have been dispensed since its emergency use approval in late 2021 [3]. Some patients treated with nirmatrelvir/ritonavir report resolution of symptoms within approximately 2-4 days after initiation, however recent reports show that some patients experience a so called "rebound" effect of COVID-19 symptoms including persistent fatigue, brain fog, loss of smell or taste, and chest pain [4].

Cases of viral load rebound (VLR) post COVID-19 treatment first originated in early 2022, specifically in patients receiving nirmatrelvir/ritonavir described as a viral load fluctuation combined with typical COVID symptoms. In May of 2022, the CDC issued an official health advisory acknowledging the potential for "rebound COVID-19" in patients who completed a five-day course of nirmatrelvir/ritonavir treatment [5]. Typically, VLR occurs after completing a five-day course of nirmatrelvir/ritonavir, either as a brief reemergence of COVID-19 symptoms or positive test results after a previous negative result. More recent reports show that patients can have both recurrence of symptoms (symptomatic rebound) and a negative test result or a positive test result without symptoms (asymptomatic rebound). Since then, retrospective studies and observational data have been used to assess the correlation between nirmatrelvir/ritonavir use and VLR.

One particular single-center, investigator-blinded, randomized clinical trial compared the incidence of VLR and symptom rebound after a 5-day treatment course with VV116, a new oral remdesivir derivative and RNA-dependent RNA polymerase inhibitor, or nirmatrelvir/ritonavir during 60 days of follow-up after randomization [6]. Participants were enrolled from December 2022 to January 2023 and included those with mild-moderate

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COVID-19 who were at least 18 years or older and had first positive test result within 5 days of drug initiation. The primary outcome was to assess the occurrence of VLR in either of the two groups, VV116 and nirmatrelvir/ritonavir. Results showed that 20% of patients in the VV116 group and 21.7% of patients in the nirmatrelvir/ritonavir group had VLR after treatment completion, however there was no significant difference between the treatment groups in terms of rebound rate ($p = 0.70$) [6]. In addition, results showed that sustained symptom rebound occurred in 11.9% of patients in the VV116 group and 12.9% in the nirmatrelvir/ritonavir group ($p = 0.78$) [6]. Overall, the study was unable to determine if nirmatrelvir/ritonavir treatment was the main source of VLR or if outside factors such as vaccination status, age, or stage of illness impacted results.

A phase 2-3, double-blind, randomized, controlled trial, similar to the EPIC-HR trial mentioned earlier, was performed to evaluate the risk of VLR with nirmatrelvir/ritonavir treatment. The study included 2246 unvaccinated symptomatic patients at high risk for progression to severe COVID-19 within 5 days after symptom onset. The primary outcome of the study was to assess the viral load measurement at baseline and at least once after completing nirmatrelvir/ritonavir treatment. Recurrence of COVID-19 was defined according to prespecified criteria for VLR: A half-log increase in viral load on day 10 or day 14. Nasopharyngeal swab samples were collected on the first day of enrollment which was used to establish baseline and then on days 3, 5, 10, and 14. From baseline through day 14, VLR occurred in 23/990 patients in the nirmatrelvir/ritonavir group (2.3%) and 17/980 in the placebo group (1.7%) with no clear statistical difference between the two groups [7]. Additionally, a meta-analysis performed in 2022 evaluated the onset and duration of VLR. Among 22 patients from three studies who received nirmatrelvir/ritonavir treatment, median time to negative test results was 6 days after initial positive test and the median time to viral rebound was 9 days with resolution of symptoms occurring at 16 days after initial diagnosis [8].

Although retrospective and observational data have not been able to link clinical significance to VLR in patients who have completed a five-day course of nirmatrelvir/ritonavir, studies are still ongoing as the definition of “rebound” continues to evolve. A majority of studies involving nirmatrelvir/ritonavir include one very important limitation in relation to prospective data specifically in identifying when a patient initially tests positive for COVID-19. Initial positive test results are difficult to detect in part to individual patient presentation indicating that patients included in the study may have in fact been experiencing VLR effect resulting in a type II error. Certain risk factors that may put patients at a higher risk of experiencing rebound effects include older age, lack of vaccination against COVID-19, and comorbidities such as diabetes, heart disease, kidney disease, or cancer. Some researchers have concluded that rebound occurs not necessarily due to antiviral treatment, but more so because of a host-mounted immune response to infection during the course of illness.

The conversation of VLR has sparked a discussion as to whether or not other COVID-19 treatment agents are associated with a surge in symptoms and if so, how do those agents compare with the rebound effect of nirmatrelvir/ritonavir. Data from a recent trial completed in June 2022 comparing rebound effects between Molnupiravir and nirmatrelvir/ritonavir is in the process of being published [9]. It is important to note that at this point in time there is no consistent association between nirmatrelvir/ritonavir treatment and rebound symptoms. Per National Institutes of Health COVID-19 Treatment Guidelines, rebound should not deter providers from prescribing antiviral treatments when indicated to reduce morbidity and mortality from COVID-19 [10].

References

1. World Health Organization (2021) The true death toll of COVID-19: Estimating global excess mortality.
2. (2019) PAXLOVIDTM (nirmatrelvir tablets; ritonavir tablets) For Patients.
3. News P (2023) COVID pill Paxlovid gets full FDA approval after over a year of pandemic emergency use. PBS News.
4. Nania R (2022) Most Common Symptoms of Long COVID. AARP.
5. Smith DJ, Lambrou A, Patel P (2023) SARS-CoV-2 rebound with and without use of COVID-19 oral antivirals. MMWR Morb Mortal Wkly Rep 72: 1357-1364.
6. Yang Z, Xu Y, Zheng R, Ye L, Lv G, et al. (2024) COVID-19 rebound after VV116 vs Nirmatrelvir-Ritonavir treatment: A randomized clinical trial. JAMA Netw Open 7: e241765.
7. Anderson AS, Caubel P, Rusnak JM, EPIC-HR Trial Investigators (2022) Nirmatrelvir-Ritonavir and viral load rebound in Covid-19. N Engl J Med 387: 1047-1049.
8. Samuels FMD (2022) What Is paxlovid rebound, and how common is it? Scientific American.
9. Wang L, Berger NA, Davis PB, Kaelber DC, Volkow ND, et al. (2022) COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022.
10. CDC (2022) This Is an Official CDC HEALTH ADVISORY.