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Nirmatrelvir, a novel medication for COVID-19 treatment

Mohammad Reza Hajian[1], Hamid Reza Jahantigh[2], Shahrzad Alimohammadi[3,4], Zahra Mojtahedi[5], Neda Kianpour[6], Majid Foroutan[7*]

[1]Nickan Research Institute, Isfahan, Iran
[2]Animal Health and Zoonosis PhD Course, Department of Veterinary Medicine, University of Bari, Bari, Italy
[3]Doctoral School of Molecular Medicine, University of Debrecen, Debrecen, Hungary
[4]Department of Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[5]School of Public Health, University of Nevada, Las Vegas, Nevada, USA
[6]Department of Biotechnology, Inland Norway University of Applied Science, Hamar, Hedmark, Norway
[7]Department of Internal Medicine, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran

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COVID-19 is a viral disease that first emerged in December 2019, Wuhan, China. In a short time, the disease spread and the world faced with a new pandemic. Since then, great effort implanted to produce effective vaccines and medications for the disease. Nirmatrelvir (PF-07321332) is a new drug developed by Pfizer, Inc for COVID-19 treatment. In this essay, we stated recent findings about Nirmatrelvir.

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News and Views

Since the emergence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in late December 2019, COVID-19 is still the most important global health issue. As of 7 March 2022, the World Health Organization (WHO) has reported almost 445 million COVID-19 cases and over 5.9 million deaths worldwide.

Up to date, great effort has been implemented in the production of effective vaccines and possible therapy against this multi-organ viral infection. Although vaccination could greatly assist the control of COVID-19 infection, the emergence of new SARS-CoV-2 variants could compromise the efficacy of the existing COVID-19 vaccines, and cause reinfection (1). This fact emphasizes the importance of producing an effective therapy.

Nirmatrelvir (PF-07321332) developed by Pfizer, Inc., is an orally administered antiviral agent inhibiting the SARS-CoV-2 3-chymotrypsin–like cysteine protease enzyme (Mpro) (2). Mpro can be a suitable antiviral target for drug development because it is essential in the viral replication cycle and has a good off-target selectivity, due to the lack of recognized human homologous (3). Nirmatrelvir is metabolized mainly through CYP3A4. Ritonavir is a CYP3A4 inhibitor that has been used as a pharmacokinetic enhancer of several protease inhibitors which used in HIV treatment (4). Thus, by combining Ritonavir and nirmatrelvir, the therapeutic concentration of nirmatrelvir can be enhanced by slowing down its metabolism in the liver and reach to the effective dose with a lower dose. *In vivo* and *in vitro* studies reveal the anti-SARS-CoV-2 activity of nirmatrelvir (2,5). The oral bioavailability and gastrointestinal absorption rate of nirmatrelvir is 50% and 95%, respectively in rats. Thus, makes it suitable for oral administration (2). These encouraging results make nirmatrelvir a promising candidate for human clinical trials.

According to a double-blind, randomized, placebo-controlled trial, nirmatrelvir/ritonavir (Paxlovid) was effective in COVID-19 patients. In this study, patients received 300 mg nirmatrelvir plus 100 mg ritonavir every 12 hours within 3 days after commencing of COVID-19 symptoms for 5 days. The relative risk reduction of COVID-19 related hospitalization or death due to any cause by day 28 among non-hospitalized high-risk adults

***Corresponding author**: Majid Foroutan, Email: dr_forotan@yahoo.com, dr_forotan@semums.ac.ir

was 89.1%. The mortality rate was zero in the group that received nirmatrelvir/ritonavir (Paxlovid) whereas 13 deaths occurred in the placebo group. Also, the viral load of SARS-CoV-2 was lower in treated patients (6).

Thereafter, on 22 December 2021, the Food and Drug Administration (FDA) announced an Emergency Use Authorization (EUA) for nirmatrelvir/ritonavir (Paxlovid) for the treatment of patients which have all the 3 following criteria: (a) mild to moderate COVID-19, (b) Less than 5 days have passed since the onset of symptoms, (c) and have a risk of progression to severe disease (7).

Studies have shown that nirmatrelvir is effective against all beta and alpha coronaviruses (2). The other positive point is that due to the nature of Mpro, SARS-CoV-2 mutant variants including Omicron remain susceptible to Mpro inhibitors like nirmatrelvir (8, 9). This has somewhat decreased the concern about the efficacy of the current vaccine and drugs on new mutant variants.

In the context of pharmacokinetics, the time of maximum drug concentration (Tmax) for a single dose of 300 mg nirmatrelvir and 150 mg ritonavir is 3.00 hours and 3.98 hours respectively. Also, the mean half-life (t1/2) for nirmatrelvir and ritonavir is 6.05 and 6.15 hours, respectively.

The main route of elimination for nirmatrelvir is renal. However, ritonavir is metabolized in the liver (7). In the moderate chronic kidney disease (CKD) patients with 30<eGFR<60 mL/min/1.73 m^2 (eGFR=estimated glomerular filtration rate) the suggested dose is 150 mg nirmatrelvir and 100 mg ritonavir twice daily. Nirmatrelvir and ritonavir is not suggested in patients with severe kidney disease (eGFR<30 mL/min/1.73 m^2) or severe liver disease (Child–Pugh class C) (7).

The most common adverse effects that occurred more often in patients who receive nirmatrelvir/ritonavir (Paxlovid) in comparison to placebo include dysgeusia, diarrhea, vomiting, hypertension, and myalgia which were not serious (6, 7). The common side effects of ritonavir are nausea, vomiting, diarrhea, changes in taste, fatigue, rash which are almost similar to nirmatrelvir/ritonavir (Paxlovid) side effects. Thus, it is not clear that these side effects are related to nirmatrelvir, ritonavir or both (10, 11). As stated before, ritonavir is a cytochrome P450-3A4 (CYP450-3A4) inhibitor. Therefore, we have to consider co-administration of ritonavir with medications that metabolized through CYP450-3A4 pathway as this could increase the drug plasma concentration.

In summary, nirmatrelvir is an orally Mpro inhibitor agent that based on studies, early administration of it in combination with ritonavir could decrease the rate of hospitalization and mortality in non-hospitalized patients with COVID-19. Higher mortality and hospitalization risk reduction, good oral bioavailability, efficacy against new mutant variants, and low non-serious adverse effects, are some of the strength points of nirmatrelvir. Also, no need for cold chain, the possibility of production on a large scale, outpatient use, and lower price in comparison with other approved drugs and vaccines, would enhance the clinical utility of nirmatrelvir (12, 13). Furthermore, nirmatrelvir is being studied and it is expected to provide more valuable clinical information in the future which would change the situation in our favor against SARS-CoV-2.

Authors' contribution

Conceptualization: MRH. Methodology: MRH and MF. Validation: ZM. Formal Analysis: MRH. Investigation: NK, SA and HRJ. Data Curation: MRH. Writing—Original Draft Preparation: MRH and MF. Writing—Review and Editing: ZM, NK and SA. Visualization: MF and ZM. Supervision: MF. Project Administration: MRH.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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