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PAXLOVID AGAINST COVID-19: MECHANISMS, EFFICACY, AND CLINICAL OUTCOME

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ABSTRACT

As of the 7th of July 2024, 775,754,322 confirmed cases of COVID-19, including 7,053,902 deaths worldwide, had been reported to the WHO (World Health Organization). Nevertheless, untill the 15th of July 2024, a total of 13,578,710,228 vaccine doses had been administered, with almost no country spared from COVID-19 attacks. The pathophysiology of this virus is complicated, and several symptoms require a deep understanding of the actual mechanisms. It is unclear why some patients develop severe symptoms while others do not, although literature suggests a role for vitamin D. Vitamin D plays a crucial role in the infection or in ameliorating the severity of symptoms. The mechanism of action of vitamin D and vitamin D deficiency (VDD) is well understood. VDD is associated with increased hospitalization of severely ill patients and increased levels of COVID-19-caused mortality.

Recent studies suggest that vitamin D levels and genetic variations in the vitamin D receptor (VDR) gene significantly impact the severity and outcomes of COVID-19, especially in the infections caused by Delta and Omicron variants. Furthermore, VDD causes immune system dysregulation upon infection with SARS-CoV-2, indicating that vitamin D sufficiency is crucial in fighting against COVID-19 infection. The therapeutic effect of vitamin D raises interest in its potential role as a prophylactic and treatment adjunct. We evaluate the immunomodulatory effects of vitamin D and its ability to enhance the efficacy of new antiviral drugs like molnupiravir and paxlovid against SARS-CoV-2. This review discusses the role of vitamin D sufficiency and VDD in COVID-19 initiation and progression, emphasizing the molecular mechanisms by which vitamin D exerts its actions as a proactive step for the next pandemic. However, there is still no clear evidence of vitamin D's impact on prevention and treatment, leading to contradictory findings. Therefore, large-scale randomized trials are required to reach a definitive conclusion.

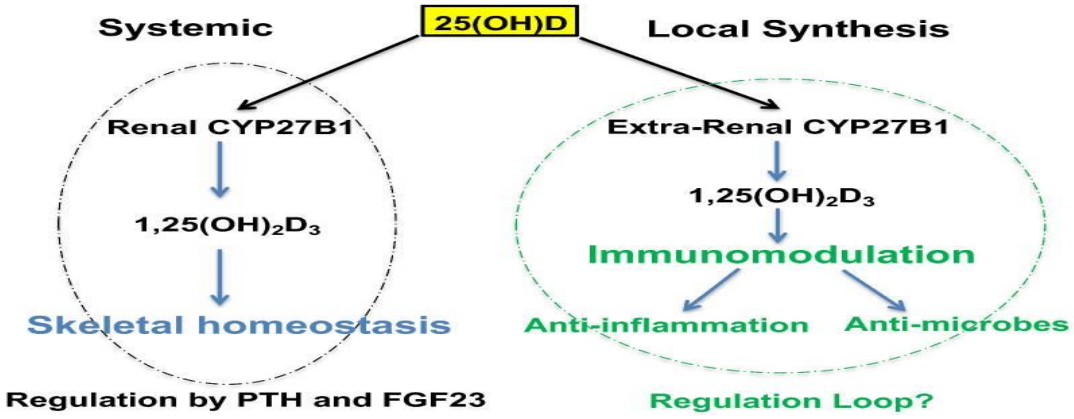
KEYWORDS: COVID-19; SARS-CoV-2; clinical trials; immunomodulation; respiratory infections; vitamin D. COVID-19; COVID-19 variants; SARS-CoV-2; Vitamin D; Vitamin D deficiency.

BACKGROUND

COVID-19 is an infectious disease caused by SARS-CoV-2, a newly discovered coronavirus that primarily spreads between people during close contact and through respiratory droplets when infected individuals cough, sneeze, or talk . Furthermore, infection might occur from the touching of a contaminated surface and subsequent contact with the face . SARS-CoV-2 is an enveloped and single positive-stranded RNA virus (~ 30 kb in length) with a nucleocapsid, which undergoes endocytosis or membrane fusion to enter the infected cells and can cause respiratory, enteric, hepatic, and neurological diseases in different species including humans . Mechanistically, SARS-CoV-2 has spike (S) glycoproteins comprised of two functional subunits called the S1 protein which binds to the host cell receptor and the S2 protein which promotes fusion of the viral and cellular membranes . Angiotensin Converting Enzyme II Receptor (ACE2) has been identified as a functional receptor for SARS-CoV-2 entry into the cell , and ACE2 expression is high in the lung, heart, ileum, kidney and bladder . At this time, there are no specific vaccines or treatments for COVID-19, and older adults with underlying comorbidities are at higher risk for severe illness .

Vitamin D might aid in preventing SARS-CoV-2 infection through immunomodulation

Overview of vitamin D Renal and Extra-renal metabolism and regulation (Fig. 1)



Inclusion and exclusion criteria

The study included all confirmed COVID-19 patients who were diagnosed by RT-PCR and met the criteria of moderate and severe criteria [WHO/National guidelines]. We excluded: (1) suspected cases without RT-PCR confirmation, (2) patients with missing critical data (e.g., baseline CT imaging or laboratory results), (3) inadequate blood samples (< 5 mL) or samples failing quality control (hemolysis index > 50 mg/dL or visible clotting), and (4) individuals with contraindications to essential procedures (e.g., contrast allergy).

MECHANISM OF ACTION

Paxlovid is a mixture of the antiviral capsules ritonavirus and nimmatrelvir.

1. Nirmovirus:

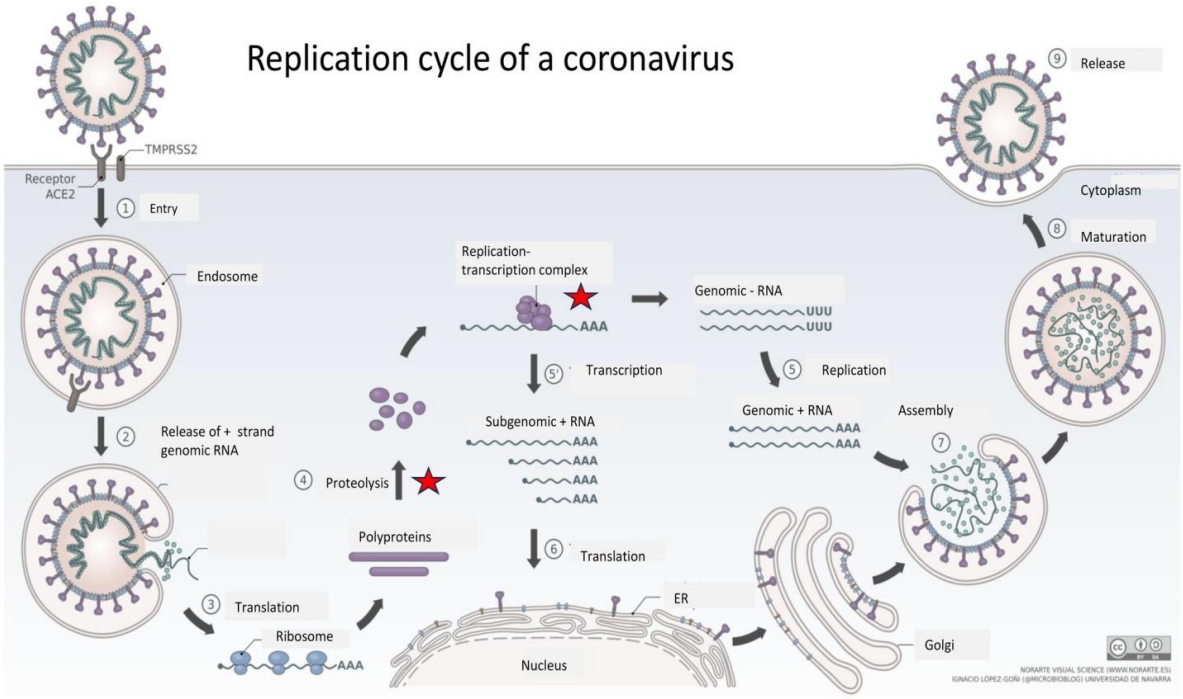
The main active ingredient is this protease inhibitor, nirmovirus. Its function depends on selectively concentrating on the main protease (Mpro), sometimes called the SARS-CoV-2 3CL protease, an enzyme essential for viral replication. The 3CL protease breaks down viral polyproteinsinto preferred components for viral meeting and replication. By blocking this protease, nimatrelvir prevents the virus from processing these polyproteins, therefore lowering its ability to replicate

1. Ritonavir is essential to increase the effectiveness of Nirmatrelvir regardless of whether it has little effect on SARS-CoV-2.

Ritonavir greatly blocks the cytochrome P450 3A4 (CYP3A4) enzyme, which the liver uses to process nirmatrelvir. Ritonavir increases the antiviral interest of nirmatrelvir by delaying its degradation and prolonging the time of therapeutic tiers within the body

GRAPHICAL ABSTRACT

The target sites of COVID-19 antivirals discussed in the present opinion paper, namely the RNA dependent RNA polymerase Nsp12 and of the main viral protease Nsp5, are indicated by a red star in the overview of the replication cycle of coronavirus SARS-CoV-2.



SARS-CoV-2 has become yesterday's news, ranking in public risk perception with flu or even common cold. Mortality and hospitalisation data indeed showed a drastic reduction. In January 2021, at the peak of the COVID-19 epidemic in the US, 26,000 COVID-19 deaths were counted nationally per week. This was a staggering figure when compared to the 58,000 US soldiers killed during the entire Vietnam war which traumatised the US society for years. During the 2024 summer wave of SARS-CoV-2 infection which deviated from recent declining trends, the death count in the US was 600 per week. This trend was also seen in hospitalizations.

DISCUSSION

The persistent global public health challenge posed by SARS-CoV-2 underscores an urgent need for novel antiviral strategies beyond existing vaccines and therapeutics . In this study, we aimed to identify new chemical scaffolds with potent anti-SARS-CoV-2 activity by screening a series of PZP and TZP derivatives, building upon prior molecular docking and dynamics insights and their established antimalarial properties . Our findings reveal that PZPs

and TZPs represent a promising class of compounds with significant inhibitory activity against SARS-CoV-2 in vitro, offering a new avenue for antiviral drug discovery.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Coronavirus disease 2019
PPS2	Pyrazolopyridine–sulfonamide compound 2
PZP	Pyrazolopyrimidine
TZP	Triazolopyrimidine
IC50	Inhibitory concentration 50%
CC50	Cytotoxic concentration 50%
ToA	Time of addition assay
FDA	Food and Drug Administration
RNA	Ribonucleic acid
DMSO	Dimethyl sulfoxide
RDV	Remdesivir
NMV	Nirmatrelvir
FBS	Fetal bovine serum
PCR	Polymerase chain reaction
BSL3	Biosafety level 3
WHO	World Health Organization

TREATMENT

Standard treatments (including dexamethasone, tocilizumab, baricitinib, and remdesivir) were widely used in Korea in accordance with clinical guidelines. Several domestic studies have evaluated their effectiveness.

In severe cases, dexamethasone combined with immunomodulators improved recovery rates without increasing infectious complications or impairing antiviral immune responses. While dexamethasone 6 mg/day remains the standard of care, a nationwide matched cohort study using health insurance data (January 2020–June 2021) compared high-dose versus standard-dose corticosteroids in adults with severe-to-critical COVID-19 requiring supplemental oxygen. High-dose therapy was associated with higher 28- and 90-day mortality, as well as a

trend toward increased COVID-19–associated pulmonary aspergillosis (aHR, 2.97; 95% CI, 0.94–9.43).

The use of ECMO has also been reported. A multicenter study of 19 critically ill patients treated with ECMO in six hospitals in Daegu (February–April 2020) demonstrated a mortality rate of 58%, with many survivors requiring prolonged mechanical ventilation because of delayed lung recovery. Another multicenter registry analysis compared 72 patients treated with ECMO to 390 patients managed with mechanical ventilation alone.Among those with arterial partial pressure of oxygen/fraction of inspired oxygen < 80 or arterial partial pressure of carbon dioxide ≥ 60 mmHg, ECMO initiated within seven days of mechanical ventilation significantly reduced mortality (HR, 0.56; 95% CI, 0.36–0.96) and risk of pulmonary fibrosis (HR, 0.30; 95% CI, 0.11–0.70). The greatest benefit was observed in patients younger than 70 years, with fewer comorbidities, prior prone positioning, and driving pressure ≥ 15 cmH_2O.

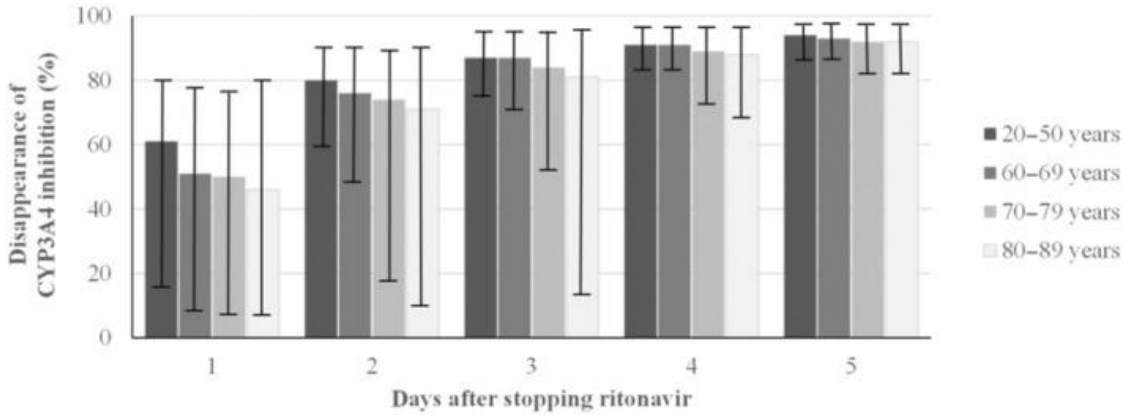
Impact of Lung Cancer TKI on Ritonavir-Boosted Nirmatrelvir

Because ritonavir-boosted nirmatrelvir is a substrate of CYP 3A4, induction or inhibition of CYP 3A4 by oral TKI can lead to a decreased or increased concentration of ritonavir-boosted nirmatrelvir. In fact, induction of ritonavir-boosted nirmatrelvir may potentially decrease its efficacy, and the concomitant use of strong CYP 3A4 inducers is contraindicated according to the emergency use authorization of the FDA. Conversely, inhibition of ritonavir-boosted nirmatrelvir can increase concentrations of the medication leading to increased risk of adverse effects (e.g., dysgeusia, diarrhea, hypertension, and myalgia)

Duration of CYP3A4 inhibitory effect after stopping ritonavir

Ritonavir irreversibly inhibits CYP3A4 leading to the loss of the enzyme. As a consequence, inhibition takes several days to reverse as it requires *de novo* enzyme synthesis to restore baseline metabolic activity. Modeling suggests that over 80% of CYP3A4 inhibition will have resolved 3 days after stopping ritonavir in young and elderly adults although significant interindividual variability should be noted.The time window for pausing drugs should also factor in the critical indication of some drugs. Real-life data for the management of the nirmatrelvir/ritonavir interaction with the narrow therapeutic index drug tacrolimus showed that pausing tacrolimus for 8 days (i.e., 5 days during nirmatrelvir/ritonavir treatment + 3 days waiting period for the disappearance of CYP3A4 inhibition) resulted in tacrolimus levels within therapeutic range in most patients. A few individuals had supratherapeutic tacrolimus

levels after re-initiating tacrolimus at day 8 due to the slower CYP3A4 inhibition disappearance. Based on these real-life data, most comedications which are paused during nirmatrelvir/ritonavir therapy can be restarted 3 days after the last dose of nirmatrelvir/ritonavir. For narrow therapeutic index drugs, it is recommended to wait at least 3 days and, if possible, up to 5 days after completing nirmatrelvir/ritonavir treatment due to the large interindividual variability in the disappearance of CYP3A4 inhibition.



CONCLUSION

Nirmatrelvir, alone or in combination with ritonavir (Paxlovid), seems to be a potent antiviral drug to treat COVID-19, but there are some unanswered questions. First, the full findings of extensive clinical studies are yet to be released. Second, keeping a careful eye on the efficacy of nirmatrelvir against new COVID-19 strains in the years to come is essential. Selection pressure on the virus can cause additional mutations to arise in the protease protein, resulting in a decline in nirmatrelvir/ritonavir effectiveness. Third, regarding the inhibitory effect of ritonavir on CYP3A4, the interactions with other drugs should be kept in mind. Despite these facts, the existing evidence from randomized trials has shown that nirmatrelvir/ritonavir is effective in treating COVID-19 with a reasonable safety profile, and with the most prominent effects of this drug being reduced chance of progression to severe disease and also death rate. Finally, further evaluation is needed to confirm nirmatrelvir/ritonavir efficacy in treatment of COVID-19 and it low manufacturing cost and easy administration make it a valuable tool in fighting COVID-19, especially for countries with a low vaccination rate.

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