Journal of International Health and Nursing
2024 Volume1,Issue1

A Comprehensive Review of Paxlovid: Composition, Mechanism, Clinical Research, and Adverse Reactions in the Treatment of COVID-19

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Article Info

Accepted: 19 November 2024

Keywords:

COVID-19
SARS-CoV-2
Paxlovid treatment
Adverse reactions

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Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become an unprecedented public health crisis. Paxlovid, a small molecule oral drug produced by Pfizer, has been licensed in several countries and territories for the treatment of COVID-19. Due to its short time to market, clinical research on Paxlovid is still ongoing and is a hot spot in medical and pharmaceutical research. This article reviews the latest research on Paxlovid within about one year after its launch from the aspects of its composition and structure, mechanism of action, clinical research, and adverse reactions. It aims to enable clinicians to use Paxlovid more reasonably in the process of daily treatment and management of patients, and provide more research directions for researchers on Paxlovid.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first discovered in Wuhan, China in December 2019 and declared a

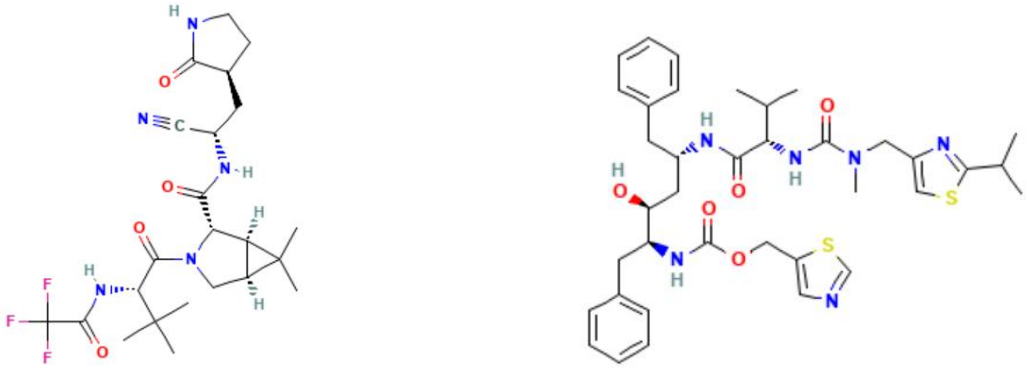
pandemic by the World Health Organization (WHO) on March 11,2020, has become a major global public health problem[1]. At present, the number of SARS-CoV-2 infections worldwide continues to increase, because the recently emerged Omicron virulent strain has increased its transmission capacity compared with previous virulent strains[2]. On December 22, 2021, the U.S. Food and Drug Administration (FDA) issued the Emergency Use Authorization (EUA) for nirmatrelvir, a research antiviral drug co-packaged with HIV-1 protease inhibitor Paxlovid-Pfizer, for oral treatment of mild or moderate COVID-19 outpatients over 12 years of age who weigh more than 40 kg and are at high risk of progression to severe disease[3]. After the United States, the regulatory authorities of the United Kingdom, Germany, Canada, Japan, China and other countries and regions have passed the license of this drug. Early in November 2021, Pfizer said that Paxlovid reduced the risk of hospitalization and death by 89 % in patients with COVID-19[4], which undoubtedly brings good news to patients suffering from COVID-19.

Paxlovid can inhibit SARS-CoV-2 main protease through Nirmatrelvir component, thereby inhibiting virus replication[5]. As a small molecule oral novel coronavirus pneumonia treatment drug, Paxlovid has the advantages of less drug resistance, convenient medication, and short-term mass production for emergency supply[6]. However, due to the urgency of Paxlovid 's time to market, we have to pay attention to reports of adverse reactions to Paxlovid. There have also been reports of a rebound in COVID-19 in some patients after Paxlovid treatment, raising concerns among patients and clinicians[7]. Due to the scattered research on Paxlovid in the academic community and the lack of systematic exposition, this paper systematically introduces the treatment of COVID-19 by Paxlovid from the aspects of Paxlovid 's mechanism of action, drug interaction, the latest progress of clinical research and adverse reactions, in order to provide important reference value for clinicians to treat and manage COVID-19 patients and prevent adverse reactions.

2. **Molecular Structure and Physicochemical Properties of Drugs**

Paxlovid-Pfizer is a co-packaged mixed drug, mainly composed of Nirmatrelvir and Ritonavir. Among them, the active ingredient that plays an antiviral role is Nirmatrelvir, and Ritonavir plays an auxiliary role in Nirmatrelvir. The molecular formula of Nirmatrelvir is C23H32F3N5O4 (molecular weight:499.5), which is a azabicyclohexane[8] (Fig.1A). The molecular formula of Ritonavir is C37H48N6O5S2 (molecular weight:720.9), which is a L-valine derivative (Fig.1B),

easily soluble in methanol, ethanol and isopropanol, and can be used to treat AIDS[9].



(A) (B)

Figure1 The structures of Nirmatrelvir molecule (A) and Ritonavir molecule (B).

3. Mechanism of Action of Paxlovid

The coronavirus SARS-CoV-2 that causes COVID-19 and the virus SARS-CoV that causes severe acute respiratory distress syndrome and the virus MERS-CoV that causes Middle East respiratory syndrome belong to the Betacoronavirus genus (the Coronaviridae family). They can encode two proteases : papain-like protease (PLpro , also known as nsp3) and main protease (also known as 3CLpro or nsp5). These two proteases are involved in the division of the virus 's polyprotein [10], thereby promoting the proliferation of coronavirus. Among them, Mpro is a residual protease of 306 with a catalytic binary protease of histidine and cysteine, while the activated Mpro is a dimer that plays an important role in the polyprotein processing of the virus and is a more manageable therapeutic target[11-12]. In addition, studies have shown that Mpro from SARS-CoV-1 and SARS-CoV-2 has good general sequence identity. Mpro can isolate the polyprotein of the virus at 11 sites. Nirmatrelvir and its precursor drug PF-07304814 (two dipeptidyl inhibitors) can act as inhibitors of Mpro, inhibiting the processing of polyprotein by Mpro, thereby inhibiting the proliferation of coronavirus. Another major component of Paxlovid can effectively reduce the metabolism of Nirmatrelvir in the body, reduce the first-pass elimination of Nirmatrelvir, and maintain the concentration of Nirmatrelvir in human body.

4. Paxlovid recent Clinical correlated Research

Paxlovid has been proved by a large-sample randomized double-blind controlled trial[13] as early as a few months ago that Paxlovid can effectively reduce the risk of patients developing severe COVID-19 in the treatment of symptomatic, unvaccinated and unhospitalized patients, and the

drug has no obvious safety problems. At present, the latest research on Paxlovid focuses on the following aspects:

(1)The feasibility study of Paxlovid in the treatment of special age patients (children, the elderly) ;

(2)A case report of Paxlovid treatment of SARS-CoV-2 infected patients with specific underlying diseases;

(3)Interaction between Paxlovid and other drugs[14];

(4) Adverse reactions such as drug resistance and reinfection of Paxlovid in the treatment of COVID-19. This part will focus on the feasibility study of Paxlovid in the treatment of patients with special age groups and the case reports of Paxlovid in the treatment of patients with specific underlying diseases and infected with SARS-CoV-2. The adverse reactions will be introduced in the corresponding parts later in this article.

4.1 Paxlovid 's treatment of children with COVID-19

In order to analyze the feasibility, safety and efficacy of Paxlovid in the treatment of children aged 6-14 with SARS-CoV-2 infection, Gangfeng Yan and Jianguo Zhou et al.conducted a cohort study[15]. The researchers recruited 5 children with underlying diseases (1 male and 4 females) who received Paxlovid treatment between April 7 and May 26,2022 and 30 age-matched children with underlying diseases who did not receive Paxlovid treatment as controls. The underlying diseases were mainly congenital heart disease, cerebral palsy, Down 's syndrome, and leukemia. The treatment time of the Paxlovid treatment group was 5 days. During the treatment of Paxlovid, one patient developed diarrhea on the second day and no symptoms disappeared after one day. One patient had elevated liver drug enzymes in the laboratory. There were no other adverse reactions such as allergic reactions and muscle pain. This experiment suggests that Paxlovid is feasible and effective in the treatment of SARS-CoV-2 infected children aged 6-14 years, but it still needs a larger sample study to determine the safety of the treatment regimen.

4.2 Paxlovid in the treatment of elderly patients infected with SARS-CoV-2 omicron variants

Compared with other SARS-CoV-2 strains, omicron variants had lower severity and mortality[16-17]. However, omicron variants have unique immunological characteristics and can lead to extensive immune escape of existing neutralizing antibodies[18-20]. Due to the lack of studies on the efficacy of Paxlovid in elderly patients with SARS-CoV-2 omicron variants infection, Weijie Zhong et al.conducted a non-randomized trial[21] to evaluate the safety and

efficacy of Paxlovid in the treatment of elderly patients with omicron variants infection. The researchers recruited 142 patients with omicron variants infection in Shanghai, China, including 36 patients who did not receive Paxlovid treatment as the control group and 106 patients as the Paxlovid treatment group. The Paxlovid treatment group received 300 mg of Nirmatrelvir and 100 mg of Ritonavir daily for 5 days, and the control group received standard care for COVID-19. Taking the virus clearance time as the standard, the study found that the Paxlovid group had a shorter virus clearance time than the control group. Paxlovid has a significant effect on the treatment of elderly patients infected with omicron variants. It is worth noting that 28 patients in the Paxlovid treatment group reported oral bitterness. The specific mechanism of this phenomenon is unknown and should be paid attention to in subsequent research and treatment.

4.3 Paxlovid in the treatment of kidney transplant recipients infected with SARS-CoV-2

Since ritonavir in Paxlovid has an inhibitory effect on cytochrome (CYP) P450-3A and β -glycoprotein, calcineurin inhibitors (CNIs) have significant potential harmful interactions. In order to find evidence that Paxlovid treats kidney transplant recipients (KTRs) infected with SARS-CoV-2 and providing data on the management, safety and efficacy of Paxlovid in the treatment of SARS-CoV-2 infection, Arnaud Devresse et al.conducted a single-center retrospective study[22], which retrospectively included all KTRs actually treated from April 28,2022 to June 3,2022. Before the first use of nirmatrelvir or ritonavir, the researchers implemented a standardized management program for all KTRs suspected of being infected with SARS-CoV-2. After that, the anti-metabolite drugs were discontinued for 7 days, and the steroid dose remained unchanged. Paxlovid was prescribed twice a day for 5 days. Standard biological monitoring was performed during and after Paxlovid treatment, and the patient was finally reassessed clinically at the outpatient clinic. Clinical results Paxlovid was well tolerated without discontinuation. There was no acute rejection confirmed by clinical biopsy during the study period. Two patients were hospitalized for graft acute pyelonephritis, and were rapidly relieved on D11 (patient 4) and D2 (patient 7) using antibiotics (intravenous ceftriaxone, followed by oral ciprofloxacin). No patient died during the study period, and no patient developed viral pneumonia. However, 2 patients had early recurrence of COVID-19 symptoms (patients 1 and 4) and the increase of viral load. The symptoms of both patients subsided rapidly within a few days without further intervention, and then PCR tests were negative on D26 (patient 1) and D35 (patient 4). Paxlovid can prevent severe COVID-19. In fact, none of the patients in the trial required

hospitalization for viral pneumonia and none died. In addition, the viral load of D7 in all patients decreased significantly. During the study period, Paxlovid could be used to infect KTRs of SARS-CoV-2.

4.4 Efficacy of Paxlovid in patients with acute kidney injury who developed COVID-19

Studies have shown that acute kidney injury (AKI) patients with COVID-19 have worse outcomes and higher risks than patients without acute kidney injury[23]. In order to study the efficacy of Paxlovid in patients with AKI and evaluate the efficacy of Paxlovid in improving the prognosis of patients with AKI, HongCai et al.conducted a retrospective observational study[24] on AKI patients aged 18 to 103 who developed COVID-19 in Shanghai from April 7,2022 to June 21,2022. There were 104 people in the final analysis sample (mean age 76.14 ± 13.47). Among them, 61 patients received Paxlovid treatment. Compared with patients who did not receive Paxlovid treatment, patients who received Paxlovid had a lower incidence of pulmonary infection (60.6 % vs 81.4 %, P = 0.031), shorter hospital stay (18.15 ± 6.85 vs 22.70 ± 11.91 d, P = 0.015) and virus elimination time (9.00 [6.00-11.00] vs 17.00 [11.00-22.50] days, P < 0.001). CVD-related mortality, Charlson comorbidity index and baseline estimated glomerular filtration rate were similar in the non-Paxlovid group and the Paxlovid group. The results of this study showed that the virus elimination time of AKI patients treated with Paxlovid was short. The efficacy of Paxlovid in patients with stage II and III AKI was better than that in patients who did not receive Paxlovid.

5. Study of adverse reactions of Paxlovid

The most common adverse reactions of Paxlovid were taste disorder, diarrhea, hypertension and myalgia[25]. At present, researchers have observed another adverse reaction of Paxlovid : Paxlovid may have long-term side effects on the musculoskeletal system. Through a series of cell biology and molecular biology experiments, researchers found that Paxlovid significantly inhibited matrix protein secretion in a concentration-dependent manner, and further verified the effect of Paxlovid on cartilage differentiation by qRT-PCR and Western blotting. Through further KEGG pathway enrichment analysis and GSEA results, it was speculated that the mechanism of Paxlovid 's effect on cartilage differentiation may trigger endoplasmic reticulum stress and destroy redox homeostasis and induce ferroptosis, thereby inducing DNA damage, hindering cartilage differentiation and accelerating osteoarthritis[26].

The resistance of SARS-CoV-2 virus to Paxlovid caused by mutation is also a research hotspot. Naturally occurring mutations of SARS-CoV-2 main protease confers drug resistance to nirmatrelvir. The emergence of SARS-CoV-2 variant with Mpro mutation has sounded the alarm of potential drug resistance. In a recent study[27], researchers identified 100 naturally occurring Mpro mutations at the nirmatrelvir binding site, including 20 mutants including S144M / F / A / G / Y, M165T, E166G, H172Q / F and Q192T / S / L / A / I / P / H / V / W / C / F, which showed comparable enzyme activity to the wild type and resistance to the nirmatrelvir component in Paxlovid.

6. Discussion

As an oral new drug for the treatment of COVID-19, Paxlovid can effectively reduce the risk of hospitalization or death in patients with COVID-19. According to the existing research, Paxlovid has good curative effect in patients with different age groups and different basic diseases. The popularity of Paxlovid may be of great significance in the ' post-epidemic era ' in China and even the world to control the spread of SARS-CoV-2 virus, especially the Omicron strain, and alleviate the symptoms of patients. With the deepening of pharmacological and clinical research on Paxlovid, the interaction between Paxlovid and other drugs is gradually clear : rifampicin, carbamazepine, phenobarbital and other drugs will reduce the serum concentration of Nirmatrelvir and Ritonavir, so they cannot be combined with Paxlovid[28]. In addition, the rebound phenomenon after the use of Paxlovid in the treatment of COVID-19 has attracted the attention of epidemiologists and clinicians[29], but the related mechanism remains to be studied.

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