Pfizer's inventive Nirmatrelvir/Ritonavir (PaxlovidTM): Another arrow in the quiver against SARS-CoV-2.

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Abstract

SARS-CoV-2 was a devastating global pandemic that swept the globe in late 2019, claiming the lives of an estimated 4 million people. Amidst challenging times, we are remembering Martin Luther King Jr.'s remark, "Mankind must put an end to war or war will put an end to mankind." In that sense, scientists are repurposing drugs meticulously to curb the nCOVID-19. New antiviral drugs on the other hand are being developed at unparallel rates. Among those Pfizer's inventive Nirmatrelvir/Ritonavir (PaxlovidTM), which inhibits the main protease (Mpro) of SARS-CoV-2, 3CL protease, will be another arrow in the quiver to mount resistance towards SARS-CoV-2. In patients treated with nirmatrelvir/ritonavir within five days of symptom onset, COVID-19-related hospitalizations and mortality were dramatically reduced. Paxlovid's high oral availability, allows it to be used in both hospitalized and outpatient patients. In this brief review, we presented pharmacokinetic, preclinical, and clinical evidence on Paxlovids for the treatment of moderate nCOVID-19.

Keywords: SARS-CoV-2, Paxlovid.

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Introduction

Coronavirus illness 2019 (COVID-19) has created a worldwide outbreak spread via respiratory infection caused by coronavirus 2 (severe acute respiratory syndrome) (SARS-CoV-2).[1,2,3]COVID-19 can produce a wide range of symptoms, often from no symptoms to severe hypoxia, multiorgan or respiratory failure, and even death.Out of 272 million confirmed cases, the SARS-CoV-2 pandemic has claimed the lives of 5.5 million individuals by the end of December 2021[4].SARS-structural CoV-2 proteins include spike glycoproteins (S), tiny envelope glycoproteins

(E), glycoprotein membranes (M), nucleocapsids (N), and various auxiliary proteins.[5]In the fight against the COVID-19 pandemic, vaccines are regarded to be the most significant and effective strategy. Remdesivir, molnupiravir, and nirmatrelvir/ritonavir are only a few of the new medications being studied or authorised to address COVID-19.Remdesivir is the sole FDA-approved antiviral medication for the treatment of SARS-CoV-2 infection (RDV; GS-5734). RDV, on either hand, must be administered intravenously, restricting its clinical application to patients with severe conditions who need to be admitted to the hospital.[6] In a phase III study enrolling non-hospitalized adults with mild to moderate COVID-19 and expelling at least one risk factor for severe disease within five days of symptom onset, the RNA-dependent RNA polymerase inhibitor Molnupiravir showed 30% efficacy in reducing hospitalisation or death compared to the placebo group[7]. The most hopeful of these new medications is the oral version of nirmatrelvir/ritonavir, which decreases the risk of hospitalisation or death by 89 percent.[8]It is projected that nirmatrelvir/ritonavir will alter the path of the COVID-19 pandemic.[9]

Emergency Use Authorization(EUA)

AEUA is a US Food and Drug Administration authorization for the emergency use of an unapproved product or the unapproved use of an approved product (i.e., drug, biological product, or device) in the United States under certain conditions, such as when the Secretary of Health and Human Services (HHS) declares a public health emergency that threatens national security or the health and security of US citizens living abroad (s).

On December 22, 2021, the U.S. Food and Drug Administration approved Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) as an emergency use authorization (EUA) for the treatment of mild-to-moderate coronavirus illness (COVID-19) in adults and paediatric patients (12 years of age and older weighing at least 40 kilos or approximately 88 pounds) with positive results of direct SARS-CoV-2. Paxlovid is only accessible by prescription and should be started as soon as possible following a COVID-19 diagnosis and within five days of symptom onset.

Paxlovid is made up of nirmatrelvir, which suppresses a SARS-CoV-2 protein and prevents the virus from reproducing, and ritonavir, which reduces nirmatrelvir's breakdown and allows it to stay in the body for longer at greater concentrations. Paxlovid is given in the form of three pills (two nirmatrelvir tablets and one ritonavir tablet) taken orally twice daily for five days, for a total of 30 tablets. Paxlovid should not be used for more than five days in a row.

Paxlovids' Efficacy in Preventing Severe CoVID-19 Death

According to Pfizer's experimental treatment, using paxlovid (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) reduces the risk of hospitalisation or death by 89 percent (onset of symptoms within 3 days) and 88 percent (5 days of symptoms) as compared to the placebo group.[14]The EPIC-HR study enrolled 2246 participants and discovered that 0.7 percent of people who underwent (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) were hospitalised through Day 28 following randomization (5/697 hospitalised, no deaths), compared to 6.5 percent of patients who received placebo and were hospitalised or died (44/682 hospitalised, 9 deaths).As per the company, the comparative risk reduction in patients 65 and older was 94 percent; 1.1 percent of people who underwent (nirmatrelvir [PF-07321332] tablets and ritonavir tablets) were hospitalised through Day 28 (1/94 hospitalised with no deaths), compared to 16.3 percent of patients who received placebo (16/98 hospitalised with 6 deaths), with high statistical significance ($p \leq 0.01$). There were no fatalities recorded in the whole trial group of Paxlovid patients until Day 28, compared to 12 (1.2 percent) deaths among placebo participants. [15]

The issuing of an EUA is not the same as FDA approval.When deciding whether to issue an EUA, the FDA considers all available scientific information and carefully weighs any known

or possible dangers against any known or potential benefits of the product.Based on an evaluation of the available scientific information, the FDA decided that it is reasonable to assume Paxlovid may be helpful in the treatment of mild-to-moderate COVID-19 in permitted patients.The agency has also assessed that the current and prospective advantages of Paxlovid exceed the known and possible hazards of the medication when used under the terms and conditions of the authorization. Paxlovid has no appropriate, authorised, or available alternatives for the treatment ofCOVID-19[10].https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19

Ritonavir Enhanced Nirmatrelvir Preclinical Aspects

According to in vitro research, nirmatrelvir has stronger anti-SARS-COV-2 action. SARS-CoV-2 viral proliferation was suppressed in differentiated normal human bronchial epithelial cells treated for three days with varied doses of nirmatrelvir with no evident cytotoxicity. Nirmatrelvir has minimal in vitro cytotoxicity, demonstrating that it is a safe medication. In vitro investigations revealed that CYP3A4 was important in the breakdown of nirmatrelvir, implying that co-treatment with the powerful CYP3A4 inactivator, ritonavir, might increase blood concentrations of nirmatrelvir.[8] Ritonavir improves the pharmacokinetic action of the majority of HIV inhibitors (e.g., darunavir and lopinavir) that are metabolised by CYP3A4.[11] Thus, ritonavir and nirmatrelvir were combined to boost treatment effectiveness.Leist et al. developed a widely used mouse model of SARS-CoV-2 infection. In a summary, 10-week-old BALB/c mice were intranasally infected with SARS-CoV-2 MA10, which concluded in a 10% decrease in body weight. This model mimics the illness spectrum and host immune responses of COVID-19, such as elevated T-helper (Th)-1 cytokines and failure of surfactant expression and pulmonary function in connection with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), demonstrated a dose-dependent upsurge in mortality and morbidity over the course of 14 days with SARS-CoV-2 MA10 (ARDS).[12]

Mice were protected from weight loss after infection with SARS-CoV-2 MA10 when given nirmatrelvir at 300 and 1000 mg/kg dosages twice daily.Furthermore, nirmatrelvir significantly decreased SARS-CoV-2 MA10 pulmonary virus levels in mice.Furthermore, mice given nirmatrelvir showed decreased inflammation in their perivascular tissues, and also their bronchial and bronchiolar epithelia.The good antiviral action of nirmatrelvir in these animals makes it a suitable option for additional clinical studies to test its potential for treating SARS-CoV-2 infection. [13]

Drug Information

PAXLOVID is a combination of nirmatrelvir and ritonavir pills.Nirmatrelvir is the main protease (Mpro) inhibitor for SARS-CoV-2, while ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor.

Nirmatrelvir

The nirmatrelvir chemically designated as (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6dimethyl-3-azabicyclohexane-2-carboxamide]. It has thechemical formula of $C_{23}H_{32}F_3N_5O_4$ and a atomic weight of 499.54.Nirmatrelvir is a peptidomimetic blocker of SARS-CoV-2 Mpro, also known as 3C-like protease (3CLpro) or nsp5 protease.SARS-CoV-2 Mpro inhibition makes it incapable of digesting polyprotein precursors, halting viral replication.

Nirmatrelvir is marketed as a film-coated tablet for immediate release. Each tablet includes 150 mg nirmatrelvir along with colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate as inactive components.The film coating contains the following ingredients: iron oxide red, hydroxy propyl methylcellulose, titanium dioxide and polyethylene glycol.

Ritonavir

Ritonavir molecular name is 10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1 methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)]. Its chemical formula is $C_{37}H_{48}N_6O_5S_2$, and its atomic weight is 720.95.Ritonavir is an HIV-1 protease inhibitor, however, it does not affect SARS-CoV-2 Mpro.Ritonavir blocks the CYP3A-mediated metabolism of nirmatrelvir, leading to higher nirmatrelvir plasma concentrations.

Ritonavir is available in the form of film-coated tablets. Each pill includes 100 mg ritonavir as well as the inactive components listed below:sorbitan monolaurate, anhydrous dibasic calcium phosphate, colloidal silicon dioxide, sodium stearyl fumarate, andcopovidone. The following components may be present in the film coating:polyethylene glycol, colloidal silicon dioxide, titanium dioxide, colloidal anhydrous silica, hydroxypropyl cellulose, hypromellose, polysorbate 80, and talc.

Paxlovid's potential side effects[18]

Symptoms include a loss of taste, diarrhoea, elevated blood pressure, and muscular pains. Taking Paxlovid alongside certain other medications may result in potentially serious drug interactions. Paxlovid use in persons with uncontrolled or undetected HIV-1 infection may result in HIV-1 treatment resistance. Because ritonavir can cause liver damage, Paxlovid should be used with caution in individuals who have a history of liver illness, abnormal liver enzymes, or liver inflammation[19].

Allergic reactions-Hives, difficulty swallowing or breathing, puffiness of the mouth, lips, or face, throat discomfort, hoarseness, pruritus.

Liver Problems-Appetite loss, yellowing of the skin and whites of the eyes, black urine, pale faeces, itchy skin, stomach ache.

Resistance to HIV medicines-If a person has an untreated HIV infection, PAXALOVID may cause some HIV medications to fail in the future.

Drug Interactions

Lurasidone, simvastatin, ergotamine, Alfuzosin, midazolam, phenobarbital, St. John's Wort (hypericum perforatum), propoxyphene, Ranolazine, methylergonovine, sildenafil (Revatio) for pulmonary arterial hypertension (PAH), Lovastatin, propafenone, Pethidine, Triazolam, flecainide, Carbamazepine, phenytoin, Amiodarone, quinidine, Dihydroergotamine, Colchicine, clozapine, pimozide, Apalutamide, Rifampin, dronedarone.

Contraindications

Paxlovid is contraindicated with certain drugs that are highly dependent on those enzymes for metabolism and for which elevated concentrations of certain drugs are associated with serious and/or life-threatening reactions because it works in part by inhibiting a group of enzymes that break down certain drugs. Paxlovid is also contraindicated in combination with drugs that strongly induce those same enzymes, resulting in the faster breakdown of nirmatrelvir or ritonavir, because lower concentrations of nirmatrelvir or ritonavir may be associated with potentially losing virologic response and developing viral resistance. Because the effects of such drugs persist after withdrawal, Paxlovid cannot be begun immediately after discontinuation.

Paxlovid should not be used in people who have significant renal or liver damage. A lower Paxlovid dosage is required in patients with significant renal impairment. Patients with renal or liver issues should talk to their doctor about if Paxlovid is good for them.[15]

Authorized use Restrictions

1. PAXLOVID is not approved for use in individuals who require hospitalisation due to severe or critical illness due to COVID-19
2. PAXLOVID is not approved for use as a pre- or post-exposure treatment for COVID-19 prevention.
3. PAXLOVID should not be used for more than 5 days in a row.

PAXLOVID may only be given to a single patient by doctors, advanced practice registered nurses, and medical specialists who are licenced or allowed by state law to prescribe medications in the therapeutic class to which PAXLOVID belongs (i.e., anti-

infectives).PAXLOVID has not been licenced for any application, including the treatment of COVID-19.

PAXLOVID is permitted only for the period of the declaration that circumstances exist requiring the emergency use of PAXLOVID under section 564(b)(1) of the Act, 21 U.S.C.§ 360bbb-3(b)(1) unless the authorisation is terminated or withdrawn sooner.

Information on Available Alternatives for EUA Authorized Use

Veklury (remdesivir) is an FDA-approved treatment for COVID-19 in adults and paediatric patients (12 years of age or older weighing at least 40 kg) with positive direct SARS-CoV-2 viral testing, who are not hospitalised and have mild-to-moderate COVID-19, and who are at high risk of progression to severe COVID-19, including hospitalisation or death.Veklury is given as an intravenous infusion over the course of three days.Although Veklury is an approved alternative treatment for mild-to-moderate COVID-19 in adults and paediatric patients, the FDA does not consider Veklury to be an appropriate alternative to PAXLOVID for this authorised use because it may not be feasible or practical for certain patients (e.g., it requires an intravenous infusion daily for 3 days).https://www.fda.gov/emergency-preparedness-and-response/mcm-legalregulatory-and-policy-framework/emergency-use-authorization.

Effectiveness of PF-07321332 against SARS-CoV-2 Variants

Nirmatrelvir possesses antiviral activity against all known human coronaviruses, including beta- and alpha-coronaviruses (SARS-CoV-2, SARS-CoV-1, MERS-CoV, HKU1, and OC43).It also demonstrates the effect on mutant SARS-COV-2.[16]The level of nirmatrelvir inhibition against these five primary protease variations was comparable, with 5 nM inhibiting activity by 50%, 20 nM inhibiting activity by >50%, and 100 nM inhibiting the activity of protease versions of five SARS-CoV-2 lineages.The P132H mutation in nsp5 (Mpro) in the new Omicron version was detected, however, structural research reveals that it has no effect on the active site and so may not alter nirmatrelvir's antiviral effectiveness.[17]

Pharmacokinetic profile

In healthy subjects, the time to maximum drug concentration (Tmax) following a single dosage of 300 mg nirmatrelvir (2 ×150 mg tablet formulation) provided combined with a 100 mg ritonavir tablet was 3.00 h and 3.98 h, respectively, and the mean half-life (t1/2) was 6.05 h and 6.15 h, respectively.Nirmatrelvir is primarily excreted by the kidneys, whereas ritonaviris through the liver.

The prescribing information states that the individual should consult with a healthcare provider if he or she has any allergies, liver or kidney disease, are pregnant or plans to become pregnant, are breastfeeding a child, or has any serious illnesses, as well as about all the medications he or she takes, including prescription and over-the-counter medications, vitamins, and herbal supplements.Some medications may interact with PAXLOVID, resulting in significant adverse effects. Maintain a list of the medicines to show the healthcare provider and pharmacist when getting a new medicine[10]

Summary and Outlook

Paxlovid appears to be substantially more effective than any similar anti-virals in reducing the risk of hospitalization and death and shows 89% efficacy compared to the placebo group, the ongoing trials on the drug will help prevent disease transmission and plays a vital role in the future. The use of the effective oral agent nirmatrelvir/ritonavir is a ray of hope in the covid 19 pandemic.

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