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Review Article

Safety and Efficacy of Paxlovid in COVID-19 Treatment: A Rapid Review

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Abstract

Context: In the first stage of viral replication, COVID-19 may cause a remarkable inflammatory response in patients. Paxlovid is an oral antivirus medicine that functions through the inhibition of one of the essential enzymes to viral replication, called protease. The present study intends to help policymakers decide on using Paxlovid in COVID-19 treatment.

Evidence Acquisition: This rapid review searched databases including Cochrane, PubMed, and Google Scholar by the end of July 2022. The inclusion criteria were randomized clinical trials investigating the safety and effectiveness of Paxlovid oral medicine at different doses in COVID-19 patients, compared with placebo or other routine care methods.

Results: Based on the results (from three studies meeting the inclusion criteria), Paxlovid has no serious side effects, but when used, the patients must be checked for renal and hepatic failure, as well as drug interactions. Patients treated with this medicine within five days after the symptom onset were hospitalized, with 1% (6/607) in the Paxlovid group and 6.7% (41/612) in the placebo group. Also, no fatalities were reported in the Paxlovid group until day 28, while 10 (1.6%) patients died in the placebo group.

Conclusions: Paxlovid is very effective in outpatient treatment and comes in a combination pack containing nirmatrelvir 150 mg and ritonavir 100 mg film-coated tablets, to be taken twice daily for five days after the symptom onset in adults and children (over 12 years old and a minimum weight of 40 kg) who have mild to moderate symptoms of COVID-19 in order to prevent severe disease, which may lead to hospitalization and death. However, there is high uncertainty about the possibility of drug interactions.

Keywords: Paxlovid; Rapid Review; COVID-19; Pandemic; Health Technology Assessment

1. Context

Coronaviruses comprise a large family of viruses that range from the common cold virus to the ones causing more severe diseases such as SARS, MERS, and COVID-19. So far, seven human-transmitted coronaviruses have been discovered. The latest one is severe respiratory coronavirus syndrome. The first case of COVID-19 was reported in December 2019 in Wuhan, China (1).

In the first stage of viral replication, COVID-19 may cause a remarkable inflammatory response in patients. This inflammation can lead to harsh consequences, including hospitalization, the need for mechanical ventilation, and death. However, treatments that target SARS-CoV-2 proliferation may improve outcomes if they have been taken into action prior to the inflammatory stage of COVID-19 (2).

As proven, the early treatment of COVID-19 patients with mild symptoms can reduce the number of patients with severe conditions who need hospitalization or ICU admission (3). Paxlovid is an oral antivirus treatment inhibiting SARS-CoV-2 protease (an essential enzyme for replication of coronavirus) that can be prescribed right after symptom onset or the awareness of exposure to the virus. This potentially helps patients prevent severe diseases that can lead to hospitalization and death (3).

Paxlovid is a new antivirus combination pack containing nirmatrelvir 150 mg and ritonavir 100 mg film-coated tablets (2). In the treatment regimen, two pink nirmatrelvir tablets and one white ritonavir tablet (three tablets in total) must be taken simultaneously, once in the morning and once in the evening for five days (i.e., six tablets per day) (2).

The FDA issued an emergency use authorization for Pax-

lovid on December 22, 2021. This medicine can be used for adults and children (over 12 years old with a minimum weight of 40 kg) with mild to moderate symptoms of COVID-19 (these patients must be at high risk for progression to severe conditions, including hospitalization and death). Paxlovid must be prescribed within the first five days of symptom onset (4).

Older age groups, people who have not been vaccinated or whose vaccines are not getting updated, and those at the highest risk are on the priority list for this medicine. Those infected with the virus should start treatment within the first five days after symptom onset. Paxlovid can be prescribed to treat COVID-19 in adults who do not need supplemental oxygen but are endangered to progress into the severe phase (5).

Paxlovid is preferably prescribed to patients with mild COVID-19 who are at higher risk for severe disease or its complications (2), including: People with immunodeficiency disorders, regardless of their vaccination status; unvaccinated people over 50 or with severe underlying diseases.

Another oral antiviral medication suggested for COVID-19 treatment is molnupiravir (development codes MK-4482 and EIDD-2801), which functions by inhibiting the replication of RNA viruses, including coronavirus (SARS-CoV-2), using the "copy error" technique. 2).

Hence, this article intends to help policymakers decide on using this medicine by reviewing available evidence related to Paxlovid.

2. Evidence Acquisition

This study was a rapid review of evidence and health technology assessment reports, which was conducted in five stages: (1) searching the electronic library on Cochrane, PubMed, and Google Scholar databases using a proper approach to searching related keywords (Paxlovid, nirmatrelvir/ritonavir, HTA, systematic review); (2) screening the retrieved reports by identifying appropriate inclusion and exclusion criteria; (3) extracting data from studies using an organized data extraction form; (4) analyzing data thematically.

The inclusion criteria were randomized clinical trials investigating the safety and efficacy of Paxlovid oral medicine at different doses in the population of COVID-19 patients, compared with placebo or other routine care methods. The clinical trial findings were completed by horizontal scanning reports and other published reports in this field.

3. Results

Searching the mentioned databases on July 19, 2022, we found one BMJ news report, one technology technical report, one rapid review of health technology assessment, and one systematic review. Also, three registered clinical trials were found by reviewing the clinical trials website (clinicaltrials.gov) (Tables 1-2).

In order to identify the ongoing local clinical trials, the website of (www.irct.ir) was also searched, but no relevant study was found in this regard. (Tables 1-2).

Table 1. Ongoing Clinical Trial Studies Related to Paxlovid (clinicaltrial.gov)

No.	Title	Disease	Comparing Group	Place	Last Status
1	EPIC-HR: Study of oral PF-07321332/ritonavir compared with placebo in non-hospitalized high-risk adults with COVID-19	COVID-19	Placebo	USA	Ongoing
2	Evaluation of protease inhibition for COVID-19 in standard-risk patients (EPIC-SR).	COVID-19	Placebo	USA	Ongoing
3	A study of a potential oral treatment to prevent COVID-19 in adults who are exposed to household member(s) with a confirmed symptomatic COVID-19 infection	COVID-19	Placebo	USA	Recruiting

Table 2. Included Papers

Article	Year of Publication	Type	Reference
Regulatory approval of Paxlovid: Summary of product characteristics for Paxlovid	Jan. 11, 2022	Technical report	(5)
COVID-19: Pfizer's Paxlovid is 89% effective in patients at risk of serious illness, company reports	Nov. 08, 2021	BMJ news report	(6)
Nirmatrelvir/ritonavir (Paxlovid) what prescribers and pharmacists need to know	Jan. 25, 2022	Rapid review	(2)
Efficacy and safety of three new oral antiviral treatments (molnupiravir, fluvoxamine, and Paxlovid) for COVID-19: A meta-analysis	2022	Systematic review	(7)

3.1. Clinical Trial Studies

There are no peer-reviewed studies available for analyzing the results of this medicine except those published reports, which are only the summarized results in the BMJ news report (by the time of searching databases). However, based on unpublished data of EPIC-HR, Paxlovid has been confirmed to be used for unvaccinated and high-risk individuals before Omicron (2). It seems that FDA clinical case for emergency authorization of Paxlovid includes five studies in the first phase as well as one study in phase 2/3 clinical trial (5).

3.2. Quality of Included Clinical Trials

Since the results of clinical trials of this medicine have not been published yet, neither as preprint nor peer-review articles, it is impossible to examine their quality.

3.3. Safety

Paxlovid is contraindicated for the following patients (2):

- Having a background of remarkable clinical allergy to the active ingredients of the medicine (PF 07321332/ritonavir)
- Having a severe hepatic impairment
- Having severe renal failure
- Concomitant use with pharmaceutical products that are highly dependent on CYP3A clearance and the increase of their plasma concentration may lead to serious reactions and/or be life-threatening
- Concomitant use with pharmaceutical products, which are potent stimulants of CYP3A
- The proportion of participants experiencing unpleasant side effects was approximately the same in both receiving groups. It was 19% in the Paxlovid group and 21% in the placebo group, most of whom were mild. The possibility of observing these side effects was less in patients who received antiviral treatments (1.7% in the Paxlovid group vs. 6.6% in the placebo group) (6).

Regarding the safety of oral drugs (molnupiravir, fluvoxamine, and Paxlovid), the total OR of adverse events in the drug and placebo groups was 0.85 (95% CI, 0.72 - 1.02), exhibiting no significant difference in the incidence of adverse events between the drug group and the placebo group. This indicates that oral antiviral drugs are generally safe. The most common adverse events of the three oral antiviral drugs include nausea, diarrhea, headache, runny nose, and muscle pain (7).

3.4. Efficacy

In a randomized clinical trial, half of the participants received Paxlovid while the other half received a placebo orally every 12 hours for five days. Also, 0.8% (3/389) of those who received Paxlovid treatment within three days after symptom onset were hospitalized until 28 days later, and no deaths were observed. In comparison, 7% of patients who received a placebo were hospitalized, and seven deaths were reported ($P < 0.0001$) (6).

Patients treated within five days after symptom onset were hospitalized, with 1% (6/607) in the Paxlovid group and 6.7% (41/612) in the placebo group. In general, no fatalities were reported in the Paxlovid group until the 28th day, while 10 (1.6%) patients of the placebo group died (6).

The clinical study shows that Paxlovid can effectively reduce patients' mortality or hospitalization rates. Whether Paxlovid can effectively reduce mortality or hospitalization, the study sample size needs further expansion to obtain robust results (8).

The OR was 0.05 (95% CI, 0.00 - 0.81) in the Paxlovid group, showing substantial therapeutic effects (7) (Table 3).

Table 3. Efficacy Results of Paxlovid (7)

Study and Outcome	Intervention Group		Placebo Group	
Pfizer	Events (n)	Total (n)	Events (n)	Total (n)
Hospitalization	6	607	41	612
Death	0	607	10	612

3.5. Probable Prediction in Miscellaneous Reports

According to a report published on the New York Times website on December 14, 2021, Pfizer officials stated that this medicine could be sufficiently effective on Omicron (9).

4. Discussion

Due to the relatively limited evidence available, which mainly includes technical reviews or news reports, Paxlovid is an oral medicine that comes in a combination package containing Nirmatrelvir 150 mg and Ritonavir 100 mg film-coated tablets that should be taken twice daily for five days after the onset of symptoms in adults and children (over 12 years old with a minimum weight of 40 kg) who has mild to moderate symptoms of COVID-19 in order to prevent the progression of severe disease that may lead to hospitalization and death.

It is currently approved in Canada and the USA for treating mild-to-moderate COVID-19 in patients at high risk of disease progression. Paxlovid reduces the risk of hospitalization and/or death in patients with mild COVID-19 (6, 7, 10).

Considering the first promising results of the Paxlovid

clinical trial, it seems that this medicine, along with vaccines and non-pharmaceutical interventions, can be a light of hope in the global darkness of the COVID-19 age (8, 11). This medicine has no serious side effects, but when used, the patients must be checked for renal and hepatic failure and drug interactions (8, 11). Since the results of clinical trials of this medicine have not been published yet, neither as preprint nor peer-review articles, itis recommended that this medicine be approved after completing ongoing studies and achieving more accurate and precise evidence.

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