Paxlovid: antiviral combination for the treatment of COVID-19

STEVE CHAPLIN

Paxlovid (nirmatrelvir/ritonavir) is an oral antiviral combination for the treatment of COVID-19 in adults at risk of progression to severe disease. This article summarises its indications, interactions and efficacy.

KEY POINTS

- Paxlovid is an antiviral combination of nirmatrelvir and ritonavir, supplied as separate tablets taken together
- It is licensed for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progression to severe disease
- The recommended dose is nirmatrelvir two 150mg tablets plus ritonavir one 100mg tablet twice daily for five days
- There is a relatively high risk of clinically significant drug interactions
- In an interim analysis of a phase 2/3 trial in people with mild to moderate COVID-19 who were treated within five days of symptom onset, Paxlovid significantly reduced the risk of hospital admission for COVID-19 or death from any cause (1.0% with Paxlovid *vs* 6.7% with placebo)
- The corresponding figures for those treated within three days of symptom onset were 0.8% with Paxlovid *vs* 7.0% with placebo
- There were no deaths in the Paxlovid group and 10 deaths in the placebo group
- Paxlovid reduced viral load after five days compared with placebo, the effect being greater in those who were seronegative or had a high viral load at baseline, and in those treated within three days of symptom onset
- The most common adverse effects were diarrhoea, vomiting and dysgeusia

The primary strategy in the management of COVID-19 is prevention by vaccination. NICE has published rapid guidance on treatment in the community and in patients admitted to hospital, recommending a range of interventions depending on severity and serology status that includes physiological support and intensive care, corticosteroids, the antivirals remdesivir (Veklury) and molnupiravir (Lagevrio), neutralising monoclonal antibodies, and the anti-interleukin-6 monoclonal antibodies tocilizumab and sarilumab.[1] This guidance is being constantly reviewed and updated.

Remdesivir was the first oral antiviral to be approved for the treatment of COVID-19 in June 2020. It has a NICE conditional recommendation for use in patients aged 12 years and over (weighing at least 40kg) with COVID-19 pneumonia who are in hospital and need low-flow supplemental oxygen. In February 2022, NICE gave remdesivir a conditional recommendation for patients aged 12 years and over with COVID-19 who do not need supplemental oxygen, are within seven days of symptom onset, and are thought to be at high risk of progression to severe COVID-19.[1]

The oral antiviral molnupiravir was licensed in November 2021 for the treatment of mild to moderate COVID-19 in adults who have tested positive for SARS-CoV-2 and who have at least one risk factor for severe illness. Mild to moderate disease is defined as 'non-severe', meaning the absence of any criteria for severe or critical COVID-19. An interim analysis of the MOVe-OUT trial in this patient group showed that a five-day course of molnupiravir given within five days of symptom onset reduced the rate of all-cause hospital admission or death within 29 days (7.3% *vs* 14.1% with placebo).[2-4] In the subsequently published analysis of all participants who underwent randomisation (n=1433), the figures were adjusted to 6.8% with molnupiravir *vs* 9.7% with placebo; nine deaths occurred in the placebo group and one in the molnupiravir group up to day 29.[5]

NICE also gave molnupiravir a condi-

tional recommendation in February 2022 for the treatment of adults with COVID-19 who do not need supplemental oxygen for COVID-19, are within five days of symptom onset and are thought to be at high risk of progression to severe COVID-19.[1] It should not be offered to children or pregnant women.

Paxlovid is a new oral antiviral combination for the treatment of COVID-19 that was approved in the UK at the end of December 2021. At the time of writing, NICE guidance on the use of Paxlovid for COVID-19 is still awaited.

Indication and administration

Paxlovid is a product comprising two oral antiviral drugs, nirmatrelvir (also known as PF-07321332) and ritonavir, that must be taken together. It is licensed for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progression to severe disease. Nirmatrelvir is a coronavirus 3C-like protease inhibitor that blocks replication of SARS-CoV-2. Ritonavir has no direct activity against the SARS-CoV-2 virus but prolongs the activity of nirmatrelvir by inhibiting its metabolism by hepatic CYP3A enzymes. This is similar to the use of ritonavir as part of combined therapy in the treatment of HIV.

The recommended dosage of Paxlovid is two 150mg tablets of nirmatrelvir plus one 100mg tablet of ritonavir taken together twice daily for five days. Treatment should start as soon as possible after a positive SARS-CoV-2 test and within five days of onset of symptoms. No dose adjustment is recommended for elderly people, or patients with mild renal impairment or mild or moderate hepatic impairment. Patients with moderate renal impairment should reduce the dosage to one tablet each of nirmatrelvir and ritonavir twice daily for five days. Paxlovid is not recommended for patients with severe renal or hepatic impairment.

Both nirmatrelvir and ritonavir are highly susceptible to drug interactions. Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious or life-threatening reactions, *eg* some antiarrhythmics, antipsychotics, statins and benzodiazepines, and ergot derivatives.

It is also contraindicated with drugs that are potent CYP3A inducers where significantly reduced plasma nirmatrelvir/ritonavir concentrations may be associated with potential loss of virological response and possible resistance, *eg* some anticonvulsants, St John's wort. There is also a risk of clinically significant interactions with a large number of other drugs, particularly those with extensive first-pass metabolism, due to the effects of Paxlovid on other hepatic enzymes. The Summary of Product Characteristics includes a full list of affected drugs;[6] possible drug interactions with ritonavir can also be checked with the University of Liverpool's online tool (https://www.hiv-druginteractions.org/checker).

Efficacy

The MHRA conditional approval of Paxlovid was based on an interim analysis of the phase 2/3 EPIC-HR trial.[7] The full study results have subsequently been published in *New England Journal of Medicine,*[8] but here we report the results of the interim analysis the approval was based on. The data are summarised in the Summary of Product Characteristics.[6]

The eligibility criteria were: non-hospitalised adults with confirmed COVID-19, onset of symptoms within five days and at least one symptom on the day of randomisation, and at least one risk factor for severe disease. Those with prior COVID-19 or who had been vaccinated were excluded. The primary endpoint was the proportion of participants admitted to hospital due to COVID-19 or dying from any cause after 28 days.

The trial included a total of 1361 participants (mean age 45 years) randomised to receive Paxlovid or placebo for five days. Just over half were male; 63% were White, 5% were Black, 48% were Hispanic or Latino and 20% were Asian. The commonest risk factors were BMI ≥25kg/m^2 (79%), tobacco use (37%), hypertension (32%), age ≥60 years (19%) and diabetes (13%); 44% of participants were seronegative at baseline. Mean viral load at baseline was 4.71 $\log_{10}$ copies/ml (higher viral load is associated with more severe illness[9] and a load of ≥5.6 $\log_{10}$ copies/ml may be associated with a significantly increased risk of death).[10]

The interim analysis included 1219 participants who had developed symptoms within the past five days. Between days 1 and 28, hospital admission or death occurred in 1.0% of those treated with Paxlovid and 6.7% of those given placebo ($p<0.0001$), a relative risk reduction of 85% . There were no deaths in the Paxlovid group and 10 deaths in the placebo group.

Outcomes after treatment with Paxlovid were similar but slightly better for the subgroup who were treated within three days of symptom onset (the primary endpoint of hospitalisation or death occurred in 0.8% with Paxlovid *vs* 7.0% with placebo; $p<0.0001$); a relative risk reduction of 89%.

Subgroup analysis of patients treated within three days of symptom onset showed that Paxlovid significantly reduced admission or death in subgroups with high (≥4 $\log_{10}$ copies/ml) or very high (≥7 $\log_{10}$ copies/ml) viral load, but not in those with lower viral load (<4 $\log_{10}$ copies/ml). It was also more effective in participants who were seronegative at baseline.

In the subgroup of participants with detectable viral load at baseline (n=572), the viral load averaged 0.93 $\log_{10}$ copies/ml lower after five days in those treated with Paxlovid than with placebo. This difference was greater in those who were seronegative or had high viral load level at baseline, or who were treated within three days of symptom onset.

Adverse effects

In the interim analysis of EPIC-HR, upon which the MHRA approval was based, Paxlovid was associated with diarrhoea (3.9% *vs* 1.9%), vomiting (1.3% *vs* 0.3%) and dysgeusia (4.8% *vs* 0.1%) more commonly than with placebo.

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Declaration of interests

None to declare.

Steve Chaplin is a medical writer specialising in therapeutics