



London

lang.kathj26@gmail.com

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COVID UNKNOWNNS

How do we best use Paxlovid and other covid antivirals?

Paxlovid “rebound” is a growing concern—as is resistance generally to existing covid antivirals. With covid still a risk to vulnerable groups, what does current research make of Paxlovid’s place in our treatment options? **Katharine Lang** reports

Katharine Lang *freelance journalist*

Paxlovid (nirmatrelvir-ritonavir) is one of many oral antivirals that have been tested against SARS-CoV-2. Several showed promise in early trials, but few of them realised that potential. The two that have stayed the course are Merck’s Lagevrio (molnupiravir) and Pfizer’s Paxlovid. An overview of two observational studies suggests that, in clinical use, Paxlovid is more effective, although that commentary didn’t look at the safety of either drug.¹

The UK’s Medicines and Healthcare Products Regulatory Agency granted conditional market authorisation for Paxlovid in December 2021 after it was found to be “safe and effective at reducing the risk of hospitalisation and death in unvaccinated people with mild to moderate covid-19 infection who are at an increased risk of developing severe disease.”²

Paxlovid is a combination of nirmatrelvir, which inhibits the main protease of SARS-CoV-2 to stop the virus replicating, and ritonavir, which slows the metabolism of nirmatrelvir to prolong its antiviral activity.³ Patients take two nirmatrelvir 150 mg tablets and one ritonavir 100 mg tablet twice daily for five days, starting within five days of symptoms showing.

How effective is it?

In a phase 2-3 trial, Pfizer reported that Paxlovid reduced the risk of hospital admission and death in unvaccinated people at risk of severe covid-19 from 7% to 0.8%.² For this level of efficacy the drug had to be given within three days of symptoms starting.

After the emergence of the omicron variant, this benefit was reduced. A press release by Pfizer advised that Paxlovid still reduced the rate of hospital admission or death by 44% when compared with no antiviral treatment,⁴ on the basis of a large scale population based study.⁵ A real world study carried out from March to August 2022,⁶ when the omicron variant was circulating, found that treatment with Paxlovid resulted in a reduction in 28 day all cause hospital admission, all cause mortality, and visits to the emergency department.

Alex Richter, professor in clinical immunology and director of the Clinical Immunology Service at the University of Birmingham, says that some questions still need to be answered. “Paxlovid is successful at reducing risk of hospitalisation in immune vulnerable and elderly people,” she says. “We don’t know what the right treatment course is for patients, and there’s

no guidance on retreatment if ‘wear-off’ occurs and the virus fails to clear.”

Concerns have been raised about this “wear-off” or “rebound” with Paxlovid, where symptoms have reappeared and lateral flow tests have become newly positive after patients responded to the five day treatment.⁷

Janet Scott, consultant in infectious disease and research medicine at NHS Highland, believes that we may need to rethink the length of treatment. She says, “The worst thing you can do with a virus is to treat it but not treat it enough or not treat it properly, because then you select out resistant subtypes, and then if you haven’t actually killed it all off they then replicate.

“If I have a patient with a nasty [bacterial] bone and joint infection, I treat for 12 weeks. Maybe we aren’t treating for long enough.”

Is Paxlovid the best antiviral against covid-19?

Currently, yes, says Richter. “At this stage, this is the best available antiviral for use in the community. Molnupiravir is also available but is thought not to be as effective, and there is some evidence that this drug enhances mutation of the virus,” she says.⁸

The big advantage of both treatments is that they are taken as oral tablets. Other antivirals, such as remdesivir, are administered intravenously, so they can be given only in a healthcare setting.

Paxlovid’s two advantages over the only other oral antiviral, molnupiravir, are higher efficacy rates in clinical trials and observational studies⁹ and less potential to cause mutations.¹⁰ But there are some issues.

Who should not take Paxlovid?

Nirmatrelvir is the antiviral in Paxlovid that destroys SARS-CoV-2.¹¹ To increase its efficacy it’s given in combination with ritonavir, which slows down the metabolism of nirmatrelvir, to keep it working for longer.

And therein lies the problem. As a protease inhibitor, ritonavir prevents the liver from breaking down nirmatrelvir. But many of the vulnerable people who need an antiviral for covid are taking several other medicines—and ritonavir stops the liver breaking those down, too. These include anticoagulants, anticonvulsants, corticosteroids, pethidine,

amiodarone, flecainide, colchicine, clozapine, lovastatin, simvastatin, sildenafil, and midazolam.¹² Anyone taking these drugs should not be given Paxlovid. Richter adds that Paxlovid shouldn't be given to patients with significant hepatic impairment or renal impairment, and it can be given to people with moderate renal impairment only at a reduced dose.

Paxlovid is contraindicated with medicinal products that are highly dependent on CYP3A (an enzyme vital for drug metabolism by the liver¹³) for clearance and for which elevated plasma concentrations are associated with serious or life threatening reactions. It's also contraindicated with medicinal products that are potent CYP3A inducers where significantly reduced plasma nirmatrelvir-ritonavir concentrations may be associated with the potential for loss of virologic response and possible resistance.

Stephen Griffin, virologist at the University of Leeds, says that ritonavir was part of the reason Paxlovid isn't licensed for under 18s. "There's such a huge raft of interactions between ritonavir and other drugs, because it acts on the liver to stop it degrading things," he says, "That is a real concern going forward for many clinically vulnerable people."

Who's eligible for Paxlovid—and can they get it?

Paxlovid is available only to people at the highest risk.¹⁴ These are vulnerable groups at risk of escalating to severe covid-19 who might benefit from Paxlovid, says Scott. "However, people who think they should be on the list may not be," she explains. "If you are on methotrexate for rheumatoid arthritis you are not eligible; if you are on it for interstitial lung disease, you will get Paxlovid. It's the lung disease, not the methotrexate, that makes you eligible."

Richter is concerned, however, that Paxlovid and other antivirals are soon going to be harder to obtain. "Individuals who detect their covid infection early are still eligible for Paxlovid in the community, although there is no clarity on how these treatments will be delivered by the integrated care boards when the CMDUs [covid medicines delivery units] close at the end of June," she told *The BMJ* shortly before that deadline.¹⁵ "There is real concern that a mechanism for early treatment will not be consistently in place across the UK to enable equity of access to treatment and communication to patients to enable them to instigate access care."

Griffin says, "The list of people who can have Paxlovid is quite restrictive," although he adds that prescriptions moving from CMDUs to GPs may help flexibility over who can have it. "But if you overuse it, you run the risk of resistance," he warns. "In the long run, we need to be really careful to watch for resistance."

What if SARS-CoV-2 becomes resistant to Paxlovid?

The National Institute for Health and Care Excellence (NICE) has recommended against using remdesivir in the community—which worries Griffin, because we are "basically left with [just] Paxlovid." He adds, "We know that there are transmitted variants that are inherently resistant to nirmatrelvir. NICE has said that we're going to be left with just Paxlovid, with sotrovimab as a fallback if Paxlovid doesn't work. But sotrovimab doesn't work against many of the new variants."

Scott is equally frustrated. "Paxlovid is there to stop these patients getting into hospital in the first place, but it's not 100% effective," she says. "Some of these patients are still coming into hospital despite having Paxlovid, so then what do we do?"

Griffin expresses frustration that combination treatments are not yet being trialled. "There's a great scope for combining those drugs, potentially with remdesivir or molnupiravir," he says. "We could

combine drugs, but none of the companies are doing it. There's no incentive for them to do it because everything is being pared down.

"The long term outlook, I think, is quite troubling. We need drug combinations."

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