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Perspective

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Is standby therapy for Covid-19 a practical option for travellers?

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Background

Covid-19 vaccines and therapeutics developed through remarkable efforts have helped bolster public confidence to reopen the world and to restart travel.[1] Covid-19 vaccines on the World Health Organization Emergency Use Listing [Covid-19 Vaccines with WHO Emergency Use Listing. Available at: https://extranet.who.int/pqweb/vaccines/vaccinescovid-19-vaccine-eul-issued] are generally—but not always—accepted by many countries and jurisdictions. Many countries have imposed vaccine requirements for travel, which have evolved over time. The emergence of SARS-CoV-2 variants and the 'immune escape' that they exhibit have introduced concern about potential decline of protection from Covid-19 vaccines.[2]

At the same time, Covid-19 treatments and prophylaxis for ambulatory use that received Emergency Use Authorization (EUA) by the US Food and Drug Administration (FDA), conditional approval or authorization by the European Medicines Agency and similar authorizations in many other countries, have shown efficacy. The oral antivirals nirmatrelvir-ritonavir (Paxlovid™) and molnupiravir (Lagevrio™) are authorized for treatment. The intramuscular monoclonal antibody product, tixagevimab-cilgavimab (Evusheld™), is authorized for pre-exposure prophylaxis.[3–6] Among them, nirmatrelvir-ritonavir is especially widely recognized and accepted. Nirmatrelvir-ritonavir and tixagevimab-cilgavimab are particularly promising medications for travel-related considerations.

Evidence of benefit

Nirmatrelvir-ritonavir, a viral protease packaged with a cytochrome P450 3A4 inhibitor, ritonavir, to enhance nirmatrelvir concentration, has demonstrated benefit in clinical trials and in clinical experience.[3] In the EPIC-HR trial, a Phase 2–3 double-blind, randomized, controlled trial, the drug reduced the risk of progression to severe Covid-19 by 89% compared with placebo, and was associated with lower viral load.[3] Patients 65 years of age or older treated with nirmatrelvir-ritonavir January–March 2022 during the omicron wave had significantly lower rates of hospitalization and death [adjusted hazard ratio (HR) 0.27 (95% confidence interval (CI) 0.15–0.49) and 0.21 (95% CI 0.05–0.82), respectively].[7]

Molnupiravir, a ribonucleoside analogue with broad antiviral activity against RNA viruses and which inhibits RNA polymerase, has also shown positive impact.[4] In MOVe-OUT trial, a Phase 3 double-blind, randomized, placebo-controlled trial, molnupiravir-treated patients had a 31% lower rate of hospitalization or death compared with placebo; the molnupiravir group had 89% lower risk of death than the placebo group.[4] During a SARS-CoV-2 omicron BA.2 wave in Hong Kong, patients treated with nirmatrelvir-ritonavir were observed to have lower risk of all-cause mortality [HR 0.34 (0.23–0.50)], disease progression [HR 0.57 (0.45–0.72)] and need for oxygen therapy [HR 0.73 (0.54–0.97)], compared with matched controls.[8] Molnupiravir also showed lower risk for the respective parameters [HR 0.48 (0.40–0.59), 0.60 (0.52–0.69), 0.69 (0.57–0.83)].[8] However, Covid-19 treatment guidelines generally consider nirmatrelvir-ritonavir as the preferred oral agent [NIH https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/].

Tixagevimab-cilgavimab is a combination of two human monoclonal antibodies with long half-life that binds to the SARS-CoV-2 spike protein receptor-binding domain, thus neutralizing the virus.[5] The Phase 3 PROVENT trial of pre-exposure

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prophylaxis with these monoclonal antibodies found 82.8% relative risk reduction against symptomatic Covid-19 at 6 months follow-up.[5]

EUA indications

Currently, the indications of the medications under the EUA appear to be limiting. For example, the FDA EUA for nirmatrelvir-ritonavir specifies its use 'for the treatment of mild-to-moderate coronavirus disease 2019 (Covid-19) in adults and paediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe Covid-19, including hospitalization or death' [FDA https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-oral-antiviral-treatment-covid-19]. The EUA for monulpiravir specifies its indication 'for the treatment of mild-to-moderate coronavirus disease (Covid-19) in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe Covid-19, including hospitalization or death, and for whom alternative Covid-19 treatment options authorized by the FDA are not accessible or clinically appropriate' [https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-additional-oral-antiviral-treatment-covid-19-certain].

For pre-exposure prophylaxis, tixagevimab-cilgavimab is only authorized for those individuals who are not currently infected with the SARS-CoV-2 virus and who have not recently been exposed to an individual infected with SARS-CoV-2. The EUA requires that individuals either have (i) moderate to severe immune compromise resulting in suboptimal immune response to Covid-19 vaccination, or (ii) a history of severe adverse reactions to a Covid-19 vaccine or component(s) of those vaccines which precludes their Covid-19 vaccination [FDA https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-long-acting-monoclonal-antibodies-pre-exposure].

Potential novel self-treatment and prophylactic strategies

Although the number of Covid-19 cases at most travel destinations has decreased, it remains a threat and travellers are sensitized to the need for information on and protection from destination specific health risks. Wearing good quality masks and self-monitoring with rapid tests will continue to be important measures in preventing exposure to Covid-19 and limiting its transmission. Additional attractive possible strategies to protect travellers from severe Covid-19 include the prescribing of oral antiviral medication as standby treatment or the administration of monoclonal antibodies as pre-exposure prophylaxis for travellers at high risk of developing severe disease.[1]

Travel medicine as a distinct medical discipline arose in response to the need for accurate, reliable and up to date information on health risks in travel. The pre-travel consultation is the bedrock of this effort and during the consultation, advice on the risk of enteric disease, respiratory disease, vector-borne disease, environmental risks, and trauma and injury consumes much of the consultation.

A unique aspect of travel medicine is the fact that after the pre-travel clinic visit, the traveller is on their own at their destination and must rely on the recollection of the advice provided during the consultation as their provider is not readily available by virtue of distance, change in time zones and remoteness of the destination, among other factors. As a result, travel medicine practitioners often provide travellers with prescription medications for self-treatment. The most prescribed are antibiotics for the self-treatment of severe travellers' diarrhoea.[9] In some cases, stand-by or self-treatment for malaria may be provided as well. In addition, self-treatment for influenza with oseltamivir or baloxavir has also been utilized.

The question has been raised: should antiviral medications (such as nirmatrelvir-ritonavir) be prescribed for travellers for self-treatment if they develop SARS-CoV-2 infection while travelling? The general medical community seems to be divided on this, with many if not most medical practitioners refusing to prescribe unless the diagnosis of Covid-19 has been made, in following the EUA specification. The problem with this approach is as follows: by the time someone is at their destination it may be difficult if not impossible to access anti-viral medications for Covid-19.

Because nirmatrelvir-ritonavir is the preferred oral antiviral treatment for Covid-19, travellers may query how to access the drug if they become infected during travel. The pre-travel consultation is the perfect time to review the appropriate use of nirmatrelvir-ritonavir and review potential drug–drug interactions. We are in favour of providing a self-treatment prescription for nirmatrelvir-ritonavir with certain caveats. Travellers should carry Covid-19 self-test kits to aid in the diagnosis. Once a diagnosis of Covid-19 is made, the traveller should be instructed to contact the provider either by phone, e-mail or text and discuss the diagnosis, their symptoms and whether they should start nirmatrelvir-ritonavir. Clearly, implementing such communication and instruction during travel will face many difficulties. Hence, a more feasible alternative strategy is to carefully educate the traveller on performing and interpreting a rapid test, and on the appropriate way to take the oral treatment if the test is positive, including potential side effects.

At the same time, travellers with any immune compromise should be recommended to consider tixagevimab-cilgavimab before international travel. The pre-exposure prophylaxis should be administered a minimum of 2 weeks after a Covid-19 vaccine (or any time before a Covid-19 vaccine). It can be administered near departure and can provide up to 6 months of protection. In the US, this medication appears to be under recognized and underutilized. Assuming that the medication supply remains plentiful and that it continues to protect against future variants, potentially tixagevimab-cilgavimab may be considered for travellers who have significant comorbidities that increase their risk for severe Covid-19. However, the recommendations for standby treatment and re-exposure prophylaxis will depend on their effectiveness against new variants.

Potential pitfalls and concerns

The prescription of nirmatrelvir-ritonavir for self-treatment carries with it the burden of care of the traveller from afar. Presumably by reviewing the potential for drug–drug interactions in advance, this may reduce the hesitation in recommending self-treatment. However, if we are to assume travellers will attempt to contact their physician before starting the medication, what happens if the traveller does not respond to therapy, becomes sicker and requires additional intervention? Does

the practitioner have the responsibility and means to manage from afar? The development of resistance to antiviral medications also looms in the background, as the medication becomes widely used.

Another theoretical concern is the impact of dispensing of thousands of treatment courses of antiviral medication to individuals who are not yet sick with Covid-19 and may never be. Does this deplete the supply for those who are in actual need of the medication for a confirmed Covid-19 diagnosis or is there enough supply to meet this more important need?

Finally, health inequities have been demonstrated throughout the pandemic. Would the application of these medications for travel lead to further inequities? To date the pandemic response has provided these medications free to all. Should these medications incur out-of-pocket costs in the future, inequities may increase.

Conclusion

Advances in diagnosis, treatment, and prevention of Covid-19 have contributed to restarting travel, including the use of oral antivirals and pre-exposure prophylaxis. To protect travellers from severe Covid-19 illness abroad, nirmatrelvir-ritonavir, molnupiravir and tixagevimab-cilgavimab have particularly promising applications. The individual traveller's risk for severe Covid-19 disease if they were infected, as well as their limited access to appropriate medical care, can help to shape a standby treatment and/or pre-exposure prophylaxis plan. To evaluate drug effectiveness and monitor for resistance, surveillance for new variants and their drug sensitivities will continue to be critical. Finally, expert consensus and innovative research are warranted to assess the 'standby treatment for Covid-19' strategy.

Author contribution

The authors contributed equally to this work.

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