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Editorial: Current Status of Oral Antiviral Drug Treatments for SARS-CoV-2 Infection in Non-Hospitalized Patients

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Abstract On 4th November 2021, the first oral antiviral drug for COVID-19, molnupiravir (Lagevrio®), received full regulatory approval from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK. Molnupiravir is an orally bioavailable antiviral drug for use at home when a SARS-CoV-2 test is positive. On 22nd December 2022, the FDA granted emergency use authorization (EUA) for the oral antiviral drug, nirmatrelvir/ritonavir (Paxlovid®) for adults and children with mild and moderate COVID-19 at increased risk of progression to severe COVID-19. These regulatory drug approvals come at a crucial time when new variants of concern of the SARS-CoV-2 virus are spreading rapidly. Although the FDA approved remdesivir (Veklury®) on 22nd October 2020 for use in adults and children for the treatment of COVID-19 requiring hospitalization, its use has been limited by the requirement for intravenous administration in a healthcare facility. The four FDA-approved therapeutic neutralizing monoclonal antibodies, imdevimab, bamlanivimab, etesevimab, and casirivimab are costly and also require medically-supervised intravenous administration. The availability of effective, low-cost oral antiviral drugs available in a community setting that can be used at an early stage of SARS-CoV-2 infection is now a priority in controlling COVID-19. An increasing number of repurposed antiviral drugs are currently under investigation or in the early stages of regulatory approval. This Editorial aims to present an update on the current status of orally bioavailable antiviral drug treatments for SARS-CoV-2 infection.

Keywords: Molnupiravir • Nirmatrelvir • Ritonavir • SARS-CoV-2 • COVID-19 • Editorial

Since January 2020, the COVID pandemic due to infection with SARS-CoV-2 has placed increasing demand on global healthcare resources and continues to cause mortality with emerging long-term effects on morbidity. Although understanding the structure and pathogenesis of the SARS-CoV-2 virus and genotype analysis have resulted in vaccine and infection surveillance programs, there are still some gaps in understanding this novel pathogen [1]. The origin of SARS-CoV-2 is still unclear, and the virulence of new circulating viral variants and the effectiveness of current vaccines to these emerging variants is still unclear [1]. SARS-CoV-2 variants with novel mutations in the spike (S) protein may have increased virus transmission and reinfection and reduced protection from neutralizing antibodies and vaccines [2]. From December 2020, the World Health Organization (WHO) variants of concern (VOC) have included the alpha variant, B.1.1.7 (first identified in the UK), the beta variant, B.1.351 (first identified in South Africa), the gamma variant, P.1 (first identified in Brazil), and the delta variant, B.1.617.2 (first identified in India) [2]. On 26th November 2021, the WHO named another VOC, the omicron variant of SARS-CoV-2, B.1.1.529, first described in South Africa and Botswana [3]. There are several reasons for the rapid spread of this viral variant. The omicron variant has more than 30 mutations in the amino acids in the viral S protein, 15 of them located in the receptor-binding domain (RBD), which is involved in viral-cell interactions mediated by the angiotensin-converting enzyme 2 (ACE-2) receptor [3]. The number of S protein mutations in the omicron variant of SARS-CoV-2 raises concerns about possible immune escape from the effects of current vaccines [3].

COVID-19 is now a global endemic disease that requires multiple approaches for control at an individual and population level. The past two years have shown that although public health and infection control measures can be effective at a local or national level, they have not prevented pandemic COVID-19 [4]. In the past year, increasing numbers of breakthrough SARS-CoV-2 infections have indicated that vaccines alone are not sufficient [6]. Clinical trials have supported treatments for hospitalized patients with severe COVID-19, including dexamethasone [6]. Drug development programs are essential in identifying individual antiviral drug treatments and combination therapies for SARS-CoV-2 infection, including repurposed drugs [7]. It is increasingly important to identify low-cost and available antiviral agents that can be given in the community and at an early stage of SARS-CoV-2 infection.

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The current recommendation from the US National Institutes for Health (NIH) has identified remdesivir as the only antiviral agent currently approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 [8]. On 22nd October 2020, the US FDA approved remdesivir (Veklury®) for use in adults and children, 12 years of age and older, for the treatment of COVID-19 requiring hospitalization [9]. Full FDA approval followed emergency use authorization (EUA) on 1st May 2020, and expanded authorization on 28th August 2021 [9]. Full FDA approval was based mainly on the findings from the Adaptive COVID-19 Treatment Trial (ACTT-1), sponsored by the National Institute of Allergy and Infectious Diseases (NIAID) [10]. However, remdesivir must be administered intravenously or by injection, which requires treatment in a hospital or a healthcare facility.

According to current NIH guidelines, there is insufficient evidence to support the use of ivermectin, lopinavir/ritonavir, and other viral protease inhibitors in hospitalized patients with COVID-19 [8]. There is no supportive evidence for systemic treatment with interferons or nitazoxanide in hospitalized patients with COVID-19 [8]. Also, there is insufficient evidence for chloroquine, hydroxychloroquine, and/or azithromycin in non-hospitalized patients or hospitalized patients with COVID-19 [8]. At this time of increasing global infection rates, outbreaks of new SARS-CoV-2 variants, incomplete vaccination programs, and limited hospital access, there is still a need for accessible and effective oral antiviral drugs that can treat SARS-CoV-2 infection at an early stage.

On 4th November 2021, the first oral antiviral for COVID-19, molnupiravir (Lagevrio®), received regulatory approval from the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK [11]. Molnupiravir was developed at Emory University by Drug Innovation Ventures, which was acquired by Ridgeback Biotherapeutics (Miami, FL, USA) in partnership with Merck (Kenilworth, NJ, USA) [12]. Regulatory approval was given for patients at risk of severe COVID-19 who are positive for SARS-CoV-2 infection following lateral flow testing of a nasopharyngeal swab [11]. Molnupiravir is a prodrug of beta-d-N4-hydroxycytidine (EIDD-1931) and was formerly known as EIDD-2801 [12]. Molnupiravir acts as an inhibitor of RNA-dependent RNA polymerase and was previously developed to treat influenza [12]. The mechanism of action is by increasing the frequency of viral RNA mutations to impair the replication of SARS-CoV-2 by a two-step mutagenesis mechanism, which may explain its broad-spectrum antiviral activity [13,14]. The potential activity of molnupiravir as an antiviral prophylactic against SARS-CoV-2 was first shown in vitro in human airway epithelial cells and in vivo as it blocked SARS-CoV-2 transmission in ferrets [15,16]. Two phase I clinical trials (NCT04392219 and NCT04746183) supported the safety and tolerability of molnupiravir [17,18]. Two phase 2 clinical trials (NCT04405739 and NCT04405570) showed that five days of oral molnupiravir therapy effectively eliminated nasopharyngeal SARS-CoV-2 in patients with early COVID-19 [19,20]. The recent approval of molnupiravir was based on a phase 2-3 clinical trial (NCT04575597), which showed that molnupiravir significantly reduced the risk of hospitalization or death in adults with mild or moderate COVID-19 [21]. This phase 3 randomized, double-blind, controlled trial evaluated the efficacy and safety of molnupiravir given within five days after the onset of signs or symptoms in unvaccinated and non-hospitalized adults with mild or moderate SARS-CoV-2 infection and at least one risk factor for developing severe COVID-19 (age >60 years, diabetes, obesity, or cardiovascular disease) [21]. The 1,433 study participants were randomly assigned to receive 800 mg of molnupiravir as four tablets twice daily or placebo twice daily for five days [21]. The primary efficacy endpoint was the incidence of hospitalization or death on day 29 [21]. The primary safety endpoint used was the incidence of adverse events [21]. The study findings showed that in high-risk, unvaccinated adults with mild or moderate COVID-19, early treatment with molnupiravir significantly reduced the risk of hospitalization or death [21]. In this trial, treatment with molnupiravir began within 72 hours after the onset of symptoms in 50% of patients [21]. In patients with available sequence data, molnupiravir was active against the three predominant variants of SARS-CoV-2 in the UK at the time of the trial, including the delta and gamma variants [21].

There are some early lessons from this initial approval of an oral antiviral drug to treat SARS-CoV-2. The role of molnupiravir in moderate to severe COVID-19 remains unknown and awaits further clinical trials. Because the efficacy of molnupiravir, and other potential oral antiviral agents, requires early diagnosis and treatment, there may be a requirement for the development of companion diagnostic tests in addition to lateral flow testing kits. The safety profile of molnupiravir requires further evaluation, including evaluating possible mutagenic effects. Because of this concern, the molnupiravir approval in the UK does not include pregnant women, women who intend to become pregnant, or women who are breastfeeding [11]. In Oxford, UK, the Platform Randomised Trial of Treatments in the Community for Epidemic and Pandemic Illnesses (PRINCIPLE) is currently recruiting people who test positive for SARS-CoV-2 within 14 days, regardless of vaccine status, who will receive home delivery of molnupiravir tablets [22]. This example of a real-world community-based clinical trial is part of a program of ongoing studies to evaluate the safety and efficacy of accessible and cost-effective potential drug therapies for SARS-CoV-2 infection [22]. Currently, the PRINCIPLE molnupiravir trial has recruited more than 8,000 study participants [22].

Several investigational drugs have the potential to inhibit the entry of SARS-CoV-2 into the host cell via the ACE-2 receptor

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through their action on transmembrane serine protease 2 (TMPRSS2), or by blocking membrane ion channels [8]. Other investigational drugs prevent viral-cell membrane fusion, endocytosis, or inhibit the activity of SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) or RNA polymerases [8]. A recent success in the latter group is nirmatrelvir/ritonavir (Paxlovid®). On 5th November 2021, Pfizer announced the findings from an interim analysis of this second-generation orally bioavailable 3CLpro inhibitor, PF-07321332; nirmatrelvir/ritonavir (Paxlovid®) in the phase 2-3 trial, Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) (NCT04960202) [23]. EPIC-HR included non-hospitalized adult patients with COVID-19 at high risk of severe illness [23]. An interim study analysis showed significantly reduced hospitalization and mortality risk due to COVID-19 [23]. On 22nd December 2022, the FDA granted emergency use authorization (EUA) for the oral antiviral drug, nirmatrelvir/ritonavir (Paxlovid®), for adults and children with mild and moderate COVID-19 at increased risk of progression to severe COVID-19 [24]. This oral antiviral drug is given twice daily as three pills (two of nirmatrelvir and one of ritonavir) for five days, to include a total of 30 pills [24]. The FDA cautions that this drug is not recommended for patients with severe liver or renal function impairment and that recognized side effects include nausea, diarrhea, and increased blood pressure [24]. Full regulatory approval of nirmatrelvir/ritonavir (Paxlovid®) is still awaited.

The first regulatory approvals of molnupiravir and nirmatrelvir/ritonavir as the first oral antiviral drugs for COVID-19 have come at a crucial time [25]. The widespread use of remdesivir has been limited by the need for intravenous administration. The four FDA-approved therapeutic neutralizing monoclonal antibodies, imdevimab, bamlanivimab, etesevimab, and casirivimab are costly and require medically supervised intravenous administration in a hospital or other healthcare setting [25]. The availability of effective, low-cost oral antiviral drugs that can be administered in the community at an early stage of SARS-CoV-2 infection is now a priority in the control of COVID-19 [25].

Conclusions

Two years on from the start of the COVID-19 pandemic, it is clear that not only is the SARS-CoV-2 virus now an endemic pathogen, but it can rapidly mutate and develop new variants that may evade the immune response generated by current vaccines. The increasing burden on hospitals and healthcare systems is not sustainable and more control of SARS-CoV-2 infection is required at the community level, with early treatment from home. Full regulatory authorization of the orally bioavailable and repurposed oral antiviral drug, molnupiravir, and the recent FDA EUA of nirmatrelvir/ritonavir, herald the era of early treatment of SARS-CoV-2 infection to prevent severe COVID-19 and reduce hospital admissions.

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