Molnupiravir and paxlovid – how much is genomic and protein destabilization harmful to SARS-CoV-2 survival and resistance?

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Since the outbreak of the pandemic caused by the SARS-CoV-2 coronavirus, challenge is the word that has moved world science with regard to the epidemiological control and pharmacotherapy of the disease. For science, with regard to future challenges, the aggressiveness of early pneumonia cases and their treatment is giving way to the possibility of the emergence of increasingly virulent and dangerous strains that could be resistant to vaccines. The development of antiviral therapies for cases of established infections and transmission blocking is necessary for cases in which the vaccine does not prevent severe disease and for populations that do not have adequate access to preventive immunotherapy (either to monoclonal antibodies approved for emergency use or to vaccination; Teixeira and Santos 2021). In this context, Merck and Pfizer have potential antiviral candidates in advanced clinical trials and that are already being evaluated by regulatory agencies such as the FDA and EMA.

The outbreak caused by the coronavirus known as SARS-CoV-1 in 2002 motivated research aimed at developing antivirals capable of fighting the disease caused by this virus. Merck had a preclinical candidate until then called EIDD-2801, just as Pfizer also had a preclinical candidate until then called PF-07321332. With the control of the outbreak, the research was discontinued and the prototypes became 'freezer compounds' (Cully 2021). The COVID-19 pandemic has rekindled interest in continuing tests related to the two preclinical candidates mentioned above. Merck currently has a proposal for a broad-spectrum antiviral called Molnupiravir (EIDD-2801) which has the registered name SID 440285862 in PATENTSCOPE (WIPO) (SHEAHAN et al., 2020) and Pfizer has a proposal for an extremely selective antiviral for SARS-CoV-2 called Paxlovid (PF-07321332) (OWEN et al., 2021).

Molnupiravir is a broad-spectrum, direct-acting antiviral (active against SARS-CoV-1, SARS-CoV-2, MERS-CoV and influenza), classified as a prodrug

of the ribonucleoside analogue β-DN4-hydroxycytidine (NHC) (Figure 1). NHC is rapidly converted in plasma to the active form 5'-triphosphate (MTP) by host kinases (PAINTER et al., 2021). Kabinger et al. (2021) reported that MTP can be used by the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 as a substrate instead of CTP (cytidine triphosphate) or UTP (uracil triphosphate). First, RdRp is likely to promote the incorporation of M (Molnupiravir) rather than C or U in the synthesis of positive-strand genomic RNA (+gRNA) – which serves as a template for the synthesis of negative-strand genomic RNA (–gRNA) and subgenomic RNA (–sgRNA). In a second step, the –gRNA containing M can be used as a template for the synthesis of +gRNA or positive-stranded subgenomic mRNA (+sgmRNA). Therefore, the +gRNA products may mutate and not support the formation of functional and infectious viruses according to the 'error catastrophe' model (TOOTS et al., 2020) (Figure 3).

Paxlovid is composed of the protease inhibitor PF-07321332 (designed specifically for the protease SARS-CoV-2-3CL) (Figure 2) and ritonavir (used in HIV therapy). The function of ritonavir is to increase the efficacy of an orally administered protease inhibitor by preventing PF-07321332 from being rapidly metabolized by liver enzymes, thus maintaining adequate circulating PF-07321332 concentrations for viral deactivation (Couzin-Frankel 2021). PF-07321332 acts by inhibiting viral proteolysis mediated by the SARS-CoV-2-3CL protease, responsible for the cleavage of precursor proteins into structural proteins and enzymes that act on viral replication and maturation (AHMAD et al., 2021) (Figure 3).

FIGURE 1

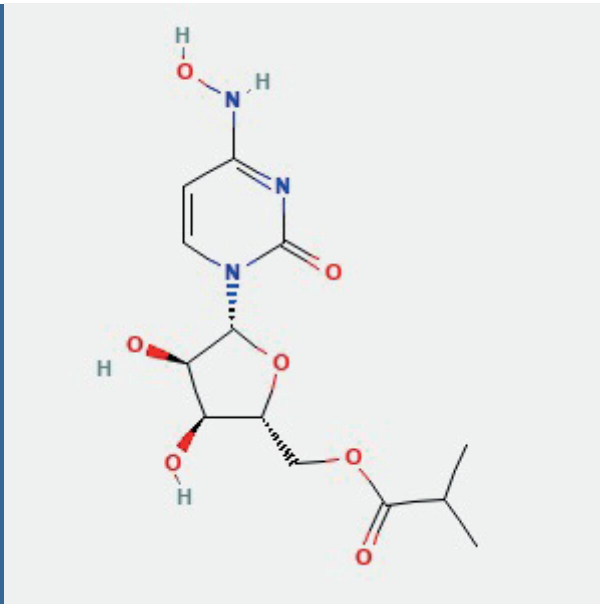

Figure 1. Chemical Structure Molnupiravir - IUPAC Name [(2R, 3S, 4R, 5R) -3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1-yl]oxolan-2-yl] methyl 2-methylpropanoate (Extracted from PubChem CID 145996610).

FIGURE 2

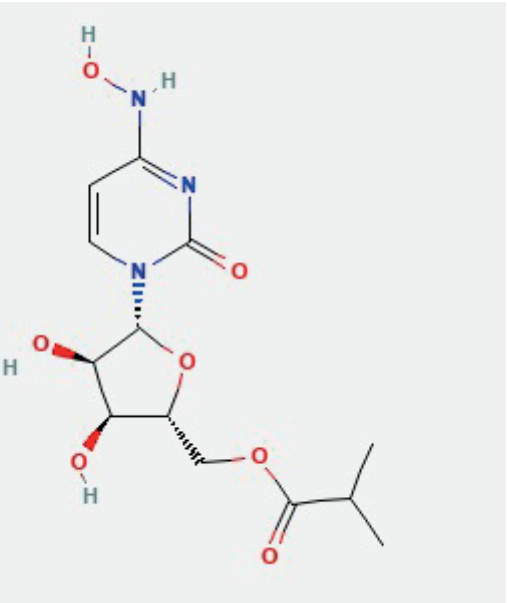

Figure 2. Chemical Structure Paxlovid - IUPAC Name (1 R , 2 S , 5 S) - N - [(1 S) -1-cyano-2 - [(3 S) -2-oxopyrrolidin-3-yl] ethyl] -3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide (Extracted from PubChem CID 155903259).

FIGURE 3

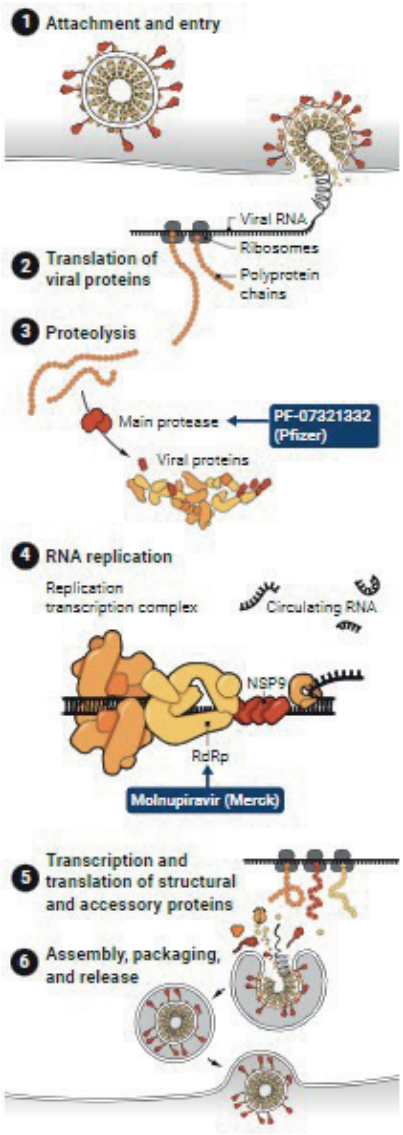

Figure 3. Molnupiravir and Paxlovid Mechanism of Action. (Extracted from Couzin-Frankel)

van Kampen et al. (2021) demonstrated a direct relationship between SARS-CoV-2 RNA levels, infectious virus isolation and hospitalization rates. Later, Cox et al. (2021), in animal specimens, found a direct association between viral RNA levels and transmission rate. Aiming to address these issues, the clinical study 'A Safety, Tolerability and Efficacy of Molnupiravir (EIDD-2801) to Eliminate Infectious Virus Detection in Persons With COVID-19' (NCT04405570) showed promising results, being characterized as a phase IIa, multicentre, double-blind, placebo-controlled and randomized trial. Molnupiravir reduced viral shedding time in nasopharyngeal smears and decreased SARS-CoV-2 replication rates and viral pathogenesis. After 5 days, the virus was not isolated from any participant who received 400 or 800 mg of Molnupiravir, against 11.1% of those who received placebo (FISCHER et al. 2021).

The EPIC-HR clinical trial (NCT04960202) is an ongoing interventional study aimed at proving the efficacy and safety of oral administration of PF-07321332/ritonavir (Paxlovid) compared to placebo in asymptomatic non-hospitalized adult individuals at increased risk of progression to severe disease. EPIC-HR is classified as a randomized, double-blind, placebo-controlled trial. In an interim analysis of Paxlovid outcomes, in 1,219 patients, the treatment reduced hospitalization or death by 89% when given within 3 days of symptom onset (CULLY 2021).

On November 4, 2021, Molnupiravir (Merck & Co.) was approved in the UK on the grounds of halving the risk of hospitalization. A day later, Pfizer announced that its drug, Paxlovid, reduced hospitalizations by 89% (LEDFORD 2021). However, weeks later, the drugmaker Merck reported that its antiviral pill works far less effectively than the preliminary data suggested. In an official statement, Merck announced that Molnupiravir reduced the risk of hospitalization and death by 30% rather than 50%. The results update announced by Merck demonstrates that in the real world, controlled environment idealizations are not always reproducible. Other concerns regarding the mutagenic effects of Molnupiravir were reported by Zhou et al. (2021); their findings showed that the antiviral can cause mutations in human DNA.

Although the proposals for both antiviral pills show promising results regarding their monotherapy, an important aspect must be taken into account: viral resistance. The eminent viral resistance in treatments based on monotherapy is responsible for treatments consisting of combinations of antivirals in diseases such as hepatitis C and HIV (LEDFORD 2021). Although the proposed treatment duration is 5 days, the mutations arising from the treatments can serve as a selection mechanism for more aggressive strains instead of inactivating the virus. According to infectologist Douglas Richman – a specialist in infectious diseases at the University of California at San Diego – this risk is even more worrying in immunocompromised populations, since in these populations the infection can last longer, providing real opportunities for the emergence of resistance (LEDFORD 2021).

Couzin-Frankel (2021) reported that the combination of antivirals may be the key to early treatment against COVID-19. The risks of mutations related to the machinery of protein production and genetic material can compromise the positive results obtained related to vaccines and monoclonal antibodies in emergency use, producing more aggressive and lethal viruses. The most worrying new strains, Delta and Omicron, are represented by more infectious viruses that have mutations mainly in the spike protein that so far are not resistant to the immunological therapies in use worldwide (CULLY 2021).

The proposal of antiviral pills capable of being administered, distributed and stored in a less complicated manner than monoclonal antibodies (intravenous administration in a hospital environment) and vaccines is tempting, mainly for populations with lower purchasing power and technological development; however, investigations must be more in-depth so that the mutations generated by antivirals are attested to be actually inactivating for the virus and not a way to generate more aggressive viruses. The companies Merck and Pfizer present proposals for more affordable prices for antivirals for the poorest populations in countries with lower purchasing power. However, the need for early diagnosis that determines the applicability of the antivirals Molnupiravir and Paxlovid could be a limiting factor for pharmacotherapy, especially in poorer populations. Studies involving Paxlovid and Molnupiravir continue and evaluate different ethnicities and vaccinated and unvaccinated populations that may impact the preliminary results.

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