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LETTER TO THE EDITOR

Sars-Cov-2 and risk of antiviral drug resistance

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Dear Editor,

The current global pandemic caused by the SARS-CoV-2 coronavirus is ongoing. To date, recorded data indicate approximately 216 million infected and 4.5 million deaths [1, 2]. A massive worldwide vaccination campaign began in January 2021; however, studies continue to investigate the most effective and safe drug therapies to manage the various stages of viral infection [3, 4]. One topic of scientific interest that needs to be highlighted is the risk of antiviral drug resistance in SARS-CoV-2. Since the onset of the pandemic, numerous pharmacological agents with antiviral properties have been investigated against SARS-CoV-2, of which only a few have demonstrated clinical efficacy. Similar to cancer cells that can develop resistance against chemotherapeutic drugs, microorganisms such as viruses can develop drug resistance [5]. The development of viral resistance to SARS-CoV-2 could be an increasing problem with long-term treatment, and in particular could be one of the causes of clinical treatment failure in some cases. Surveillance of viral resistance is necessary to choose appropriate empiric therapy and to monitor the spread of resistant virus in the population. Most viruses adapt and mutate to become resistant to antiviral therapy, and this can affect patient and disease management. The prevalence of resistance can be limited with infection control measures and appropriate antiviral treatment, especially used in combinations of multiple effective drugs directed at different targets and proteins within the virus. In this context, surveillance of the potential emergence of antiviral resistance is critical for public health during the COVID-19 pandemic. Antiviral treatments have been shown to lead to the emergence of resistance in hepatitis B virus, human immunodeficiency virus (HIV-1), hepatitis C virus (HCV), and influenza virus [5–7] and the ability to develop resistance during single-drug therapies. In support of this, in vitro experiments on SARS-CoV, the causative agent of severe acute respiratory syndrome (SARS), and a relative of SARS-CoV-2, show that specific SNPs mutations within nsp12, the major RdRp subunit, can alter the efficacy of Remdesivir. Indeed, the Nsp12:Phe480Leu substitution destabilizes the interface between the different subdomains of the protein and affects Remdesivir binding. The EC50 of Remdesivir increased from 0.01 μM to 0.06 μM in SARS-CoV cultures carrying the Nsp12:Phe480Leu or Nsp12:Val557Leu mutations. In the absence of Remdesivir, these viral mutants were found to replicate less efficiently and showed substantially reduced viability. Identifying and monitoring the transmission of potential antiviral-resistant strains is essential for disease surveillance [8]. A new research paper discusses the emergence of mutations in the SARSCoV-2 virus that allow it to escape the effects of the drug Remdesivir. The researchers found that out of 12 viral lines passaged in media containing Remdesivir at 1 μM or 2.5 μM, they showed cytopathic effects (CPE), indicating active replication of the virus in the cell. In two of the viral lineages, replication rate and amplitude showed a change, as did the concentration of Remdesivir required to achieve 50% inhibition. These lineages replicated actively in the presence of 7.5 μM Remdesivir. However, titers were lower than in culture without Remdesivir. In Vero cells, these actively replicating strains showed a twofold increase in IC50 and a nearly fourfold increase compared with the parental strain. When the same viruses were run in media not containing Remdesivir, the IC50 remained comparable to the parental strain. These experiments indicate the emergence of specific resistance mutations to Remdesivir in the presence of the drug in vitro [8]. To date, the mechanisms of antiviral resistance with SARS-CoV-2 and the point mutations are still not fully understood. Currently, the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp, encoded by nsp12-nsp7-nsp8) is being targeted by several inhibitors with a discussed clinical impact, such as Remdesivir [9]. An interesting preprint study demonstrates that in more than 56,000 SARS-CoV-2 viral genomes studied, selective negative pressure targeting nsp12 was identified, with potential antiviral escape mutations, albeit in a low percentage (only

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0.3%) of sequenced genomes. These affected key residues, such as Nsp12:Val473 and Nsp12:Arg555 [10]. Potentially, these mutations could destabilize the ligand of RdRp-targeted drugs, such as Remdesivir or Molnupiravir that have the same mechanism of RdRp inhibition. These observations may represent the starting point for a broader effort to monitor SARS-CoV-2 antiviral drug resistance. This evidence suggests the risk of developing forms of SARS-CoV-2 that are resistant to currently used antivirals and the need to use available antiviral therapies appropriately. Probably the combined use of different antivirals, with different molecular targets, and in association with immunomodulatory/anti-inflammatory agents to manage the hyperinflammatory state in the most severe stages of COVID-19, could reduce the risk of developing drug-resistant viral forms, have greater therapeutic efficacy and a lower risk of drug-related adverse reactions.

Author contributions **AV:** conceptualization, writing — original draft, methodology, writing — original draft.

Availability of data and materials Full availability of data and materials.

Declarations

Ethical approval Not applicable.

Conflict of interest The author declares no competing interests.

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