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Letter to the Editor

COVID-19 and the Functionality of Antivirals: The Day After Tomorrow

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From the start of the COVID-19 pandemic, various types of medicines have been proposed to be effective against SARS-CoV-2. However, only a small number of them have been officially approved or authorized to be used under conditional terms against SARS-CoV-2, based on the severity of the disease.

Remdesivir was the first agent that received emergency use authorization for the treatment of children and adults with COVID-19 requiring hospitalization and was later proposed to be effective in mild to moderate cases.[1-3] Molnupiravir and nirmatrelvir are considered to be efficient in reducing the risk of progression of the disease in nonhospitalized adult patients.[4,5] Several monoclonal antibodies, namely bamlanivimab plus etesevimab, casirivimab plus imdevimab, sotrovimab, levilimab, and tixagevimab–cilgavimab, have also shown clinical efficacy in reducing COVID-19 progression in mild-to-moderate ambulatory patients.[6-10] Along with antivirals, corticosteroids have been recommended to be used in cases requiring hospitalization.[11] Guidance from the National Health Service (England), the UK Medicines and Healthcare products Regulatory Agency (MHRA alerts CEM/CMO/2022/006 and CEM/CMO/2022/001), and the US National Institutes of Health recommend the use of some of the agents outlined above,[12] which could lead to their increased usage.

With the emergence of new SARS-CoV-2 variants, some therapeutical antiviral agents seem to have lost their initial efficacy due to viral resistance.[13-16] Furthermore, a recent study indicates that remdesivir has only a minor effect in reducing the mortality of hospitalized COVID-19 patients.[17] The fact that remdesivir and other antivirals may be used in combination with corticosteroids, which are known to suppress the immune system, in the treatment of COVID-19 is concerning since extended use of corticosteroids and overusage of antivirals may provide the optimum environment for the virus to replicate and the chance of viral mutation and potential antiviral resistance is higher. Moreover, long-term use of antivirals in certain cases, including immunocompromised patients, may result in the same phenomenon.[18]

New SARS-CoV-2 variants or viral diseases with similar pathogenesis to SARS-CoV-2 may emerge in the future. Antivirals that are clinically effective against COVID-19 may be useful agents for treating current or future diseases caused by coronaviruses, but their irrational use, especially along with corticosteroids, could lead to viral resistance and obsolete drugs, as with what has been seen with adamantanes and H3N2 influenza.[19] Key stakeholders in healthcare settings have to remain vigilant and strict antimicrobial stewardship programs should be conducted to prevent the development of further resistance to these valuable agents. Furthermore, since no reliable data are available on the use of corticosteroids in mild-to-moderate COVID-19 outpatients, their safety and efficacy in these cases need to be established through a well-designed

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randomized controlled trial. Moreover, the harms and benefits of using antivirals in specific populations at risk of severe COVID-19, including those with weakened immune systems, need further elaboration, ideally via a randomized controlled trial.

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