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SHORT COMMUNICATION

Nirmatrelvir–remdesivir association for non-hospitalized adults with COVID-19, point of view

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Abstract

The efforts of the scientific world directed to identifying new antiviral drugs and therapies effective against SARS-CoV-2 continue. New oral antivirals against SARS-CoV-2 such as paxlovid have recently authorized. Evidence shows that these antivirals have good efficacy in reducing the risk of hospitalization in COVID-19 positive patients. Remdesivir is an authorized antiviral for the treatment of SARS-CoV-2 infection. To date, there are still few data in the literature on the safety profile and the risk of generating antiviral-resistant SARS-CoV-2 drug variants. In this manuscript we describe the evidence in the literature on the monotherapy use of paxlovid and monotherapy use of remdesivir, and the scientific hypothesis of using nirmatrelvir and remdesivir in association with the aim of increasing treatment efficacy, reducing the risk of adverse reactions and generating antiviral drug-resistant variants.

Keywords COVID-19 · Sars-CoV-2 · Drugs · Antivirals

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

SARS-CoV-2 infection and associated coronavirus disease 2019 (COVID-19) continue to threaten global health. Coronavirus disease (COVID-19) strikes in a variety of ways. Most people have mild or moderate symptoms such as mild fever, cough, weakness, and recover without the need for hospitalization. A very small percentage may present with severe symptoms such as respiratory distress syndrome, and require hospitalization (Hu et al. 2021). To date, COVID-19 disease has caused about 6 Mln deaths (https://covid19.who.int/). People with special characteristics such as advanced age or in polypathology are at high risk for severe COVID-19 (Takagi 2021; Kim et al. 2021). From the beginning of the first infections to the present, the virus has demonstrated high human-to-human transmissibility and high ability to mutate. The main SARS-CoV-2 variants responsible for the strongest epidemic waves have been Alpha, Beta, Gamma and Omicron variant strains (Mistry et al. 2022). Efforts by the scientific world to identify increasingly safe and effective drug treatments continue unabated (Vitiello et al. 2021, 2022; Vitiello and Ferrara 2021). There is an increasing need to identify treatments that can prevent progression of infection to more severe disease, hospitalization and death; shorten clinical recovery time; and reduce transmission rates. For non-hospitalized patients with mild to moderate COVID-19, treatment options include new oral antivirals such as Paxlovid.

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Paxlovid and remdesivir for adults with COVID-19

The first pharmacological therapeutic agents used for SARS-CoV-2 infection were drugs mostly used off-label, and aimed at managing severe COVID-19 symptoms without any activity against virus replication (Vitiello and Ferrara 2021; Vitiello et al. 2021). The cornerstone of COVID-19 therapy was the use of SARS-CoV-2 vaccines, particularly those with mRNA methodology, which enabled large-scale, safe vaccines with high prophylactic efficacy against SARS-CoV-2 in a short period of time (Kostoff et al. 2020; Vitiello et al. 2021). However, an important weapon to combat SARS-CoV-2 infection is antiviral agents (Şimşek-Yavuz and Komsuoğlu Çelikyurt 2021; Wen et al. 2022). Recently, a new oral antiviral against SARS-Cov-2 has been approved for home treatment, paxlovid. The new oral antiviral paxlovid consists of two active drugs: nirmatrelvir (PF-07321332), which acts by inhibiting viral replication the virus protease (Fig. 1), and ritonavir, an antiretroviral indicated for the treatment of HIV, used to slow the metabolism of nirmatrelvir. Paxlovid is authorized in 150 mg nirmatrelvir tablets co-packaged with 100 mg ritonavir tablets. Paxlovid demonstrated an 89% reduction in hospitalizations for COVID-19 and a significant reduction in mortality, in pre-registration clinical trials, when administered within 5 days of onset of first symptoms. Paxlovid was granted emergency use authorization (EUA) in December 2021 as a therapy for non-hospitalized patients with COVID-19 infection. A recent phase 2–3, double-blind, randomized, controlled trial showed that patients treated within 3 days of symptom onset with paxlovid had the lowest incidence of COVID-19-related hospitalization or death by day 28 compared with the placebo group. The study recruited 2246 patients; 1120 patients received nirmatrelvir plus ritonavir (nirmatrelvir group) and 1126 received placebo (placebo group) showing that treatment of symptomatic COVID-19 with nirmatrelvir plus ritonavir resulted in an 89% lower risk of progression to severe COVID-19 than the risk with placebo, with no particular safety issues related to drug administration (Hammond et al. 2022).

A study using real population-based data to evaluate the efficacy of paxlovid considered a total of 180,351 eligible patients considered of which 4737 (2.6%) were treated with paxlovid and 135,482 (75.1%) had adequate COVID-19 vaccination status, which in the omicron era and in real-world settings paxlovid is highly effective in reducing the risk of severe COVID-19 or mortality. In addition, it appears that paxlovid is highly effective in elderly and immunosuppressed patients (Najjar-Debbiny et al. 2022). Remdesivir is indicated for the treatment of coronavirus disease 2019

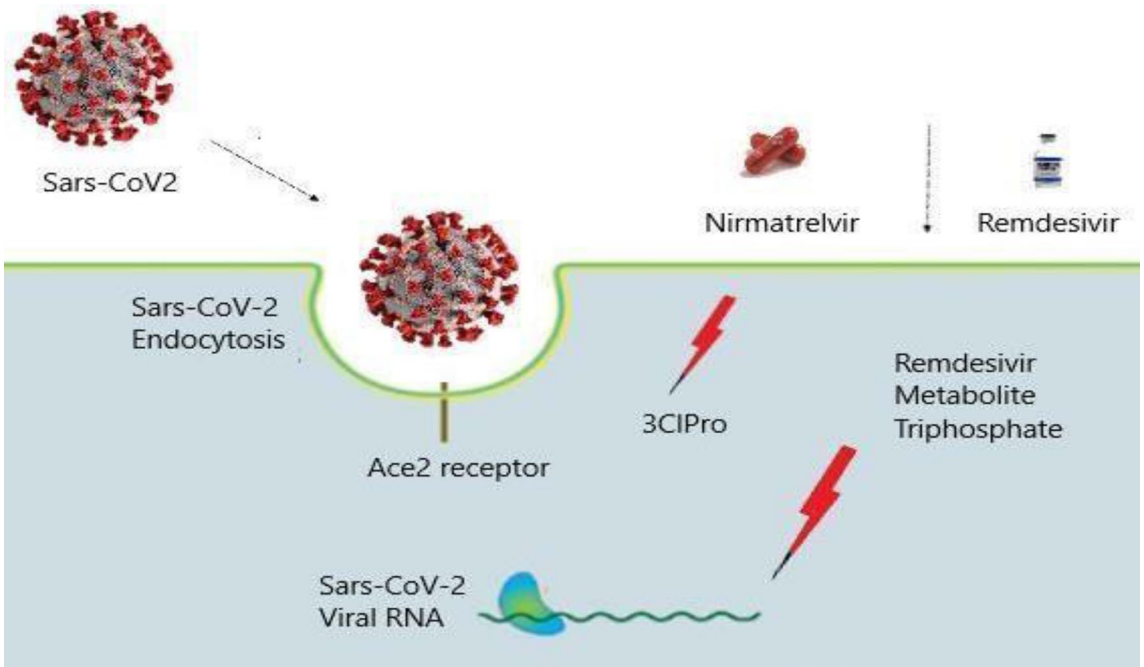

Fig. 1 Nirmatrelvir is a peptidomimetic inhibitor of the major protease (Mpro) of SARS-CoV-2, also known as 3C-like protease (3CLpro) or nsp5 protease. Mpro inhibition of SARS-CoV-2 renders the protein unable to process polyprotein precursors, which results in prevention of viral replication. Remdesivir is metabolized in host cells to form the active nucleoside triphosphate metabolite that acts as an adenosine triphosphate (ATP) analog and competes with the natural ATP substrate for incorporation into nascent RNA chains by the RNA-dependent RNA-polymerase of SARS-CoV-2, causing delayed chain termination during viral RNA replication

(COVID-19) in adults and adolescents (aged 12–18 years, weighing at least 40 kg) (Young et al. 2021; Vitiello et al. 2021). Remdesivir is administered intravenously with a single loading dose of 200 mg, from day 2 onward 100 mg administered once daily. The total duration of treatment should be at least 5 days and should not exceed 10 days. Remdesivir is a nucleotide analog of adenosine that is metabolized in host cells to form the pharmacologically active metabolite nucleoside triphosphate. Remdesivir acts as an adenosine triphosphate (ATP) analog and competes with the natural ATP substrate for incorporation into nascent RNA chains by the RNA-dependent RNA-polymerase of SARS-CoV-2, causing delayed chain termination during viral RNA replication (Fig. 1).

Remdesivir is a direct-acting nucleotide prodrug inhibitor of the SARS-CoV-2 RNA-dependent RNA-polymerase; it has potent nanomolar activity in primary human airway epithelial cells (Pizzorno et al. 2020). A phase 3 trial of remdesivir showed that both a 10-day course and a 5-day course of remdesivir shortened the recovery time in patients hospitalized with COVID-19 (Beigel et al. 2020). The clinical and therapeutic efficacy of remdesivir in hospitalized COVID-19 patients is demonstrated by several scientific evidences. However, it has yet to be demonstrated whether remdesivir, when administered in COVID-19-positive patients who are not hospitalized and at high risk of hospitalization due to concomitant diseases (diabetes, heart disease, etc.), is effective in reducing the risk of hospitalization and severe symptoms of the disease. A randomized, double-blind, placebo-controlled trial involved non-hospitalized adult patients on COVID-19 with symptom onset within the previous 7 days and who had at least one risk factor for disease progression (age $\geq$ 60 years, obesity, or certain coexisting medical conditions). A total of 562 patients were randomly assigned to receive intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) or placebo. Hospitalization or death from any COVID-19-related cause occurred in 2 patients (0.7%) in the remdesivir group and in 15 (5.3%) in the placebo group. In addition, the study showed that among non-hospitalized patients who were at high risk of COVID-19 progression, a 3-day course of remdesivir had an acceptable safety profile (Gottlieb et al. 2022).

Pharmacological medical hypotheses

RNA viruses, such as coronaviruses and retroviruses, are subject to continuous errors and thus very high-mutation capacity. So it is important to consider that every time antiretroviral therapy is used, the viral species shifts to a more or less drug-resistant form, so it is inevitable to pose this problem with the use of SARS-CoV-2 antivirals. Antiviral drugs are difficult to develop, and the risk of developing viruses that are resistant to antiviral drug treatment is always a serious concern particularly for viruses that have high mutant capacity, and especially when antiviral drugs are used in massive quantities, out of indication, as may inevitably happen during pandemics. In the early stages of the COVID-19 pandemic, as there were no commercially available antiviral drugs directed against SARS-CoV-2, several licensed antiviral drugs were used for other viruses, as well as remdesivir a drug originally designed as a therapy for Ebolavirus. Given the absence of other antivirals in the early stages of the COVID-19 pandemic, remdesivir was widely used in massive quantities in off-label prescriptions, and later in on label prescriptions (Focosi et al. 2022). SARS-CoV-2 remdesivir resistance mutations have been generated in vitro but have not been reported in patients receiving treatment with the antiviral agent. Recently, however, a case of an immunocompromized patient was demonstrated to have generated remdesivir resistance mutation during treatment of persistent SARS-CoV-2 infection (Gandhi et al. 2021). These early evidences of SARS- CoV-2 mutations resistant to antiviral drugs may sound as an early warning sign. Knowledge with the history of HIV antiretroviral treatment may help in this regard. Indeed, initially, early HIV protease inhibitors were considered very potent antivirals; however, it soon became apparent that polymorphism in the HIV-1 PR sequence, with substitutions at more than 20 amino acids in the sequence, made these inhibitors of very limited efficacy (Boden and Markowitz 1998). Viral mutations responsible for resistance to protease inhibitor drugs can result from amino acid substitutions in the active site (Chen et al. 1995). The Mpro of SARS-CoV-2 is also called 3-chymotrypsin-like protease, 3CLpro, is the active binding site for the new anti-SARS-CoV-2 antiviral, nirmatrelvir. Nirmatrelvir is a second-generation reversible covalent inhibitor of SARS-CoV-2 Mpro, which binds to the catalytic cysteine residue (C145) through its nitrile head (Vandyck and Deval 2021; Owen et al. 2021). Recent in vitro evidence has identified the earliest forms of SARS-CoV-2 viral resistance at the Mpro site (Sacco et al. 2022). Therefore, the scientific community needs to carefully monitor potential drug resistance mechanisms, especially since SARS-CoV-2 is naïve to Mpro inhibitors. Probably one solution to the problem of antiviral treatment-resistant variants could be, as in HIV antiretroviral treatment, to use pharmacological agents that act on multiple molecular targets. An interesting scientific medical hypothesis would be to use nirmatrelvir and remdesivir in combination, at lower doses than those used in monotherapy and licensed, in adult, COVID-19-positive, non-hospitalized patients. The benefits could be multiple. First, a reduction in the risk of generating forms of antiviral resistance; second, greater tolerability of therapeutic treatment, as the single drugs used at lower doses, third greater efficacy because more molecular targets are acted upon. Well-structured

clinical trials are needed to demonstrate this interesting medical-scientific hypothesis.

Conclusions

Antiviral therapy against SARS-CoV-2, the virus responsible for the current global COVID-19 pandemic, has recently seen the introduction of new agents such as nirmatrelvir, which complement the licensed antiviral remdesivir. Nirmatrelvir is used in non-hospitalized patients; remdesivir in this target population has little clinical evidence to date. However, we believe that the use of nirmatrelvir–remdesivir dual therapy administered in combination at lower dosages than monotherapy could be of benefit in avoiding the generation of drug-resistant viral forms, be of greater tolerability and clinical efficacy than monotherapy. Well-structured clinical trials could generate the clinical evidence needed to demonstrate this interesting medical-scientific hypothesis.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare that the opinions expressed are of a personal nature and do not in any way commit the responsibility of the Administrations to which they belong.

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