Innovations for remdesivir to remain in the game against COVID-19

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Remdesivir is an antiviral drug approved for emergency use against COVID-19 in several countries. Remdesivir is a nucleotide analogue prodrug that perturbs viral replication by inhibiting the RNA-directed RNA polymerase (RdRp).

Remdesivir, also commercially named Veklury®, is an inhibitor of RNA-directed RNA polymerase (RdRp) with a broad *in vitro* activity against several viral infections (1,2,3). It is a prodrug that needs to be biochemically converted into an alanine metabolite and then into a monophosphate drug. Thereafter, it needs to be transformed into a nucleoside triphosphate derivative, which is dephosphorylated into the cells to become the active molecule (GS-441524). This last metabolite mimics the adenosine nucleotide in the RNA stripe and blocks the production of RdRp (2,3).

In August 2018, remdesivir was evaluated for the treatment of the Ebola virus (EBOV) in humans in a randomly assigned 1:1:1:1 ratio clinical trial in comparison with three monoclonal antibody treatments. The remdesivir group achieved the lowest mortality reduction, 51.3%, compared with 35.1% for the MAB114 group,

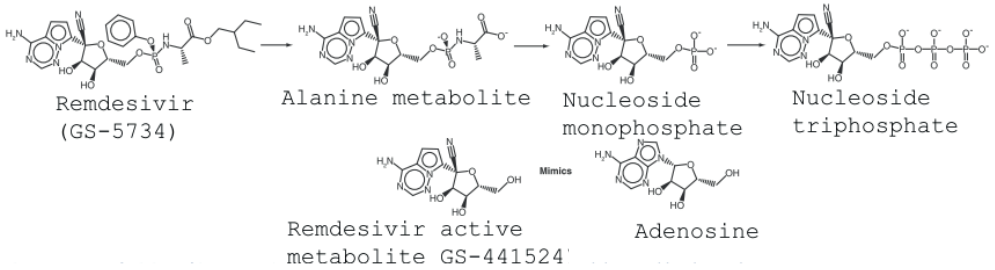

Figure 1. Remdesivir and its metabolites in the human body. Figure adaptation from Viveiros Rosa & Santos, 2022 (3).

33.5% for the REGN-EB3 group and 49.7% for the ZMapp group (4). However, remdesivir was granted an orphan drug designation for the treatment of EBOV in the USA and the EU (5).

The compound has also been evaluated in preclinical studies for a putative treatment of infections caused by severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) (5). Such a demonstration of *in vitro* activity against other coronavirus inspired new clinical trials in patients with the coronavirus disease COVID-19, an infection caused by severe acute respiratory syndrome-2 (SARS-CoV-2), which has caused 577.36 million confirmed cases and 6.4 million confirmed deaths around the world (6).

According to actualised data from the United States (US) National Institute of Health (NIH) (7,8), intravenous therapy with remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in high-risk, hospitalised or non-hospitalised patients aged over 12 years and weighing more than 40 kg. A Day-1 attacking dose of 200 mg is used, followed by a 100 mg dose for the subsequent days. For hospitalised cases, a five-day course of treatment should be given, while treatment should be given for only three days in non-hospitalised patients, initiated within seven days of the onset of symptoms. For paediatric patients weighing 3.5-40 kg or aged less than 12 years, whether hospitalised or not, there is also an FDA-approved possibility of treatment (7,8).

Gottlieb *et al*. (2022) pointed out that treatment of non-hospitalised patients within 7 days of symptoms reduced the risk of hospitalisation and death by 87% (9). On the other hand, Heil *et al*. (2022) (10) argued that, whilst representing the most promising of any remdesivir study, this last clinical trial (9) still has some limitations, such as the exclusion of vaccinated patients for the trial and the lack of difference in viral load between the non-treated/treated groups.

With regard to hospitalised patients, other authors have already pointed out that remdesivir treatment for COVID-19 has not shown to be effective in preventing the first outcomes of death and mechanical ventilation (1,3,11), but could be useful in reducing secondary outcomes, such as hospitalisation days and adverse events.

Despite doubts over the clinical evidence of remdesivir's clinical applicability for COVID-19 treatment, Gilead Sciences reported $27.3 billion in year-end revenue for 2021, anchored by sales of its COVID-19 therapeutic medicine, which hit revenues of $5.6 billion in 2021, almost double the 2020 revenues for the same drug. Gilead said that although hospitalisation rates will fall in 2022, it is still projecting $2 billion in sales this year (12). A specialised website is forecasting predicted sales revenues of between $1.59 – 2.13 billion for Veklury® from 2023 up to 2026 (13).

In fact, the emergence of other oral antiviral drugs threatens the choice of intravenous remdesivir as a treatment in non-hospitalised patients. Molnupiravir (Lagevrio®) and the nirmatrelvir–ritonavir combination (Paxlovid®) are already approved for COVID-19 treatment in several countries (14). Furthermore, a recent repurposing of Azvudine for COVID-19, with approval from the Chinese sanitary agency, expands the portfolio of oral pills against SARS-CoV-2 infection (15).

It is important to note that the first patent application of remdesivir was applied by Gilead Pharmaceuticals in 2008, disclosing a Markush formula with several molecules as an RdRp inhibitor for the hepatitis C virus (HCV), although another patent applied in 2018, with new formulations containing a type of cyclodextrin, extends the exclusivity protection for the injectable remdesivir formulations in the USA (3,16) and maybe in other countries up to 2038.

Additionally, as a solution to sustain remdesivir prescriptions for COVID-19, inhalation formulations are also being developed by Chinese (3,15) and US pharmaceutical companies (17). In addition, after a licensing agreement with Gilead Sciences, the Indian pharmaceutical company Jubilant Generics (Yeshwantpur) has started additional studies with an oral remdesivir composition and a phase I clinical trial (18) is testing a sublingual tablet comprising 100 mg remdesivir, which is to be compared with the injectable drug.

A deuterated compound derived from remdesivir, named VV-116, showed promising results in *in vitro* studies, showing oral bioavailability almost 50% higher than the non-deuterated derivative, and also demonstrated an antiviral effect in mice (3). A phase III trial, sponsored by Shanghai Junshi Bioscience (Shangai, China), comparing the effectiveness and safety of VV-116 with the clinical use of Paxlovid® for COVID-19 treatment, demonstrated a faster relief of symptoms, but no detailed data has yet been released (15).

A Phase I trial sponsored by Copycat Sciences LLC (Boston, Massachusetts, US) evaluated the safety, tolerability and pharmacokinetics of an oral formulation of the remdesivir active metabolite GS-441524 in one healthy human volunteer (19). This study was completed in August 2021, but no published results could be retrieved. Recently, Copycat Sciences LLC applied for a patent (20) for oral formulations containing prodrugs of GS-441524, which is still pending analysis.

Two clinical trials sponsored by the Indian pharmaceutical industries Cipla Ltd (Mumbai) and Lupin Ltd Research (Mumbai) (21,22) are evaluating the bioavailability of a remdesivir oral solution (100 mg/5mL) in healthy adult males, for oral dose optimisation and assessment of bioequivalence with the injectable drug. A patent applied by Lupin Ltd (23) reveals several oral capsule formulations comprising polyethylene glycol as a vehicle, a macrogolglycerol ricinoleate compound as a solubilising agent, and the drug remdesivir.

On the other hand, with the current evidence available for intravenous remdesivir, with no survival benefit and with the unit price of $520 per vial (3,24,25), it is hard to believe that such treatment for 5 or 10 days could be affordable in the health systems of developing and poor countries. In India, for example, some licensing agreements were made to produce intravenous remdesivir and the Indian Government made serious interventions to reduce the price per vial (25). Considering all these innovations, reducing the dose and/or transforming the drug into an oral pill, improving patient outcomes, can also facilitate access in countries that currently do not have remdesivir in their treatment protocols for COVID-19.

Together, all this information indicates that not only has remdesivir been redirected to remain in the market for different viral infections (EBOV and SARS-CoV-2), but it has also been constantly studied specifically for COVID-19, to enable it to be prescribed to a larger range of ages, weight, and disease severity. Remdesivir or one of its derivatives may also soon be marketed in oral formulations, enhancing the arsenal for COVID-19 treatment, which already has several vaccines available, to combat a disease that has caused millions of deaths.

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