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Remdesivir effectiveness in COVID-19 and recommendations for its use

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ABSTRACT: In January 2020, a new coronavirus emerged as a serious threat to the world health. SARS-CoV-2 causes a flu-like syndrome in 90% of the cases, but 10% of the cases are characterized by a severe viral pneumonia, which may need intensive care. Currently, there are no specific antiviral treatments for CoV in humans. Attempt to treat patients with approved antivirals, such as ribavirin and lopinavir, and immunomodulators, such as corticosteroids and interferon, have failed to demonstrate effectiveness in randomized controlled trials.

Remdesivir is a small molecule monophosphoramidate prodrug of an adenosine analog. It carries out its action by inhibiting the RNA-dependent RNA-polymerase through its nucleoside component, after being activated to a triphosphate. Several *in vitro* studies demonstrated the activity of RDV against a variety of coronaviruses, including SARS-CoV-2.

Here we review remdesivir, a novel broad-range antiviral molecule, developed for use against Ebola Virus, with demonstrated *in vitro* antiviral activity against coronaviruses. We aim to summarize evidences and recommendations for its use against COVID-19.

Keywords: SARS-CoV-2, Coronavirus, Remdesivir.

BACKGROUND

Lower respiratory tract infections cause more than 4 million deaths per year. Almost 40% of them are caused by respiratory viruses[1]. Most common respiratory viruses causing severe lower respiratory tract infections are influenza A and B, adenovirus, coronavirus (HKU1, 229E, NL63, OC43), human bocavirus, human metapneumovirus, parainfluenza virus, rhinovirus and respiratory syncytial virus[2]. Less frequently, lower respiratory tract infections are caused by known and feared coronaviruses (CoV) such as SARS-CoV and MERS-CoV[2].

In January 2020, a new coronavirus emerged as a serious threat to the world health. SARS-CoV-2 causes a flu-like syndrome in 90% of the cases, but 10% of the cases are characterized by a severe viral pneumonia, which may need intensive care[3]. Moreover, this new virus quickly spread, causing the World Health Organization (WHO) to label it as "potentially pandemic". At the moment we write, WHO still has not declared a pandemic.

Currently, there are no specific antiviral treatments for CoV in humans[3]. Attempt to treat patients with approved antivirals, such as ribavirin and lopinavir, and immunomodulators, such as corticosteroids and interferon, have failed to demonstrate effectiveness in randomized controlled trials[1].

Here we review remdesivir (RDV), a novel broad-range antiviral molecule, developed for use against Ebola Virus, with demonstrated *in vitro* antiviral activity against coronaviruses. We aim to summarize evidences and recommendations for its use against COVID-19.

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DRUG CHARACTERISTICS

RDV is a small molecule monophosphoramidate prodrug of an adenosine analog[4,5]. It carries out its action by inhibiting the RNA-dependent RNA-polymerase (RdRp) through its nucleoside component, after being activated to a triphosphate (RDV-TP)[4]. RDV-TP mechanism of inhibition circumvents CoV Exonuclease (ExoN) surveillance and activity and inhibits viral RNA synthesis determining premature termination of viral RNA transcription[4]. This termination is considered delayed, opposed to immediate, as two-to-three nucleotides are added after the RDV-TP point of insertion of RDV-TP[6].

RDV is active, *in vitro*, against all the human CoVs: CoV-OC43, CoV-229E, CoV-NL63, CoV-HKU1, SARS-CoV and MERS-CoV. RdRp-targeted drugs, such as RDV, are more likely to be broadly active against past, current and future CoVs, due to the inherent genetic conservation of the CoV replicase[5].

Mutations within the F476 and V553 residues of the murine hepatitis virus (MHV)-RdRp reduce sensitivity to RDV. However, they also reduce the fitness of the virus, which replicates less than the wild-type virus. Those residues are completely preserved across CoVs[4].

RESULTS *IN VITRO*

Several *in vitro* studies demonstrated the activity of RDV against a variety of coronaviruses. In particular, Sheahan et al[5] demonstrated that in several respiratory tissue cell lines (lung, airway and bronchiolar cells), RDV shows effectiveness against CoV, and especially prevents SARS-CoV and MERS-CoV replication at low micromolar concentrations. Moreover, RDV shows no cytotoxicity at therapeutic concentrations[5].

Following this study, Agostini et al[4] showed the effectiveness of RDV in decreasing viral RNA levels of SARS-CoV and MERS-CoV at early times post-infection. They used a murine model with MHV to demonstrate that adding RDV after 10 hours post-infection in a single-cycle infection has the same effect of inhibition on viral replication than dimethyl sulfoxide (DMSO) alone[4].

RESULTS *IN VIVO*

Experiments on animal models of SARS-CoV and MERS-CoV infection showed that prophylactic administration of RDV reduces SARS-CoV-induced lung pathology, including denuding bronchiolitis, perivascular accumulation of inflammatory infiltrates, intra-alveolar edema associated with diffuse alveolar damage as compared to vehicle-treated animals[4,7]. Therapeutic administration is effective, although suffering from a "window period" of effectiveness. After this window timeframe, RDV is only effective in reducing SARS-CoV titers but has little to none effect on disease severity[4].

Supposedly, as the time from onset of the symptoms to the peak viral load in lung cells is longer in humans than in mice and non-human primates, the timespan during which administering the drug offers some benefit to the patient is longer and estimated around one week[7].

REMDESIVIR *VS.* OTHER EXPERIMENTAL REGIMENS IN MERS-CoV

Several studies demonstrated the effectiveness of the antiretroviral drug combination lopinavir/ritonavir (LPV/r) in association with interferon (IFN)-a against SARS-CoV and of IFN-b against MERS-CoV.

A recent study by Sheahan et al[8] showed that RDV has a superior therapeutic efficacy against MERS-CoV than LPV, ritonavir and LPV/r. As a matter of fact, although all the drugs show some effect in decreasing viral replication, RDV acts at lower concentrations (EC_{50} = 0.09 μL) than the drugs previously mentioned[8]. However, it is correct to remember that although RDV acts at a lower concentration on viral replication, RDV and LPV/r show a comparable effect in improving the pulmonary function[8].

COVID-19 TREATMENT

Currently, guidelines on COVID-19 treatment endorsed by the Chinese Center for Disease Control and Prevention (CDC) suggest to treat with active symptomatic support, which is considered the mainstay, and to use experimental treatments with either LPV/r 400/100 mg bis in die (bid) in association with IFN-a 5 millions of international units (MIU) bid or RDV in accordance with the manufacturer's indications[3].

RDV is currently reserved for compassionate use in patients affected by a severe form of pneumonia, requiring mechanical ventilation but not inotropes for circulation support.

Recently, two new drugs with proven *in vitro* efficacy entered clinical trials to demonstrate their effectiveness in reducing the severity of the pulmonary disease. The first one is camostat mesylate, a serine protease inhibitor used in some cancers and other viral infections[9]. As a matter of fact, it has been demonstrated that SARS-CoV-2 cell entry depends on angiotensin converting enzyme 2 (ACE-2) and exploits a serine protease, TMPRSS2, as co-receptor. *In vitro*, camostat mesylate is able to inhibit the action of TMPRSS2, thus reducing the virus entry into the lung cells, and ultimately decreasing the severity of the damage[9].

The second drug, tocilizumab, is an interleukin (IL)-6 inhibitor clinically used for the treatment of several rheumatic diseases, such as rheumatic arthritis and giant cell arteritis[10]. Recently, the Chinese Food and Drug Administration (FDA) approved it for use in the treatment of SARS-CoV-2[10]. As a matter of fact, IL-6 dramatically increases in the most severe forms of COronaVIrus

Disease (COVID)-19, determining a cytokine storm that impairs the immune response and worsen the prognosis of the patient[10]. Although already approved for the treatment of extremely severe cases of COVID-19, tocilizumab entered a clinical trial which is expected to give the preliminary results on effectiveness during the first week of May[10].

REMDESIVIR *VS.* SARS-COV-2

The use of RDV against SARS-CoV-2 was at first based on knowledge of its effectiveness against SARS-CoV and MERS-CoV[3]. The drug has been shown to have a safety track record and it is effective against other viruses than CoV[11]. Although clinical trials are necessary to prove its effectiveness, RDV has been reportedly and successfully used in the first US case of COVID-19[12].

REMDESIVIR *VS.* OTHER EXPERIMENTAL REGIMENS IN SARS-COV-2

In a recent study, Wang et al[13] show the *in vitro* efficacy of RDV against SARS-CoV-2. Moreover, they tested a series of antivirals against the virus. Ribavirin, penciclovir and favirapir were shown to reduce intracellular viral load only at high concentrations, therefore they are not the best treatment for the disease when alternatives are available[13].

Nafamostat, nitazoxanide and RDV were proven effective against SARS-CoV-2 at low-micromolar concentrations[13]. In particular, Wang et al[13] recommend further evaluation of nitazoxamide, an antiprotozoal agent.

In addition to prove RDV effectiveness against SARS-CoV-2, Wang et al[13] showed that chloroquine inhibits viral replication both at entry and post-entry stages.

CONCLUSIONS

RDV is an interesting drug in the case of a CoV infection, especially in treatment of those CoV causing severe lung damage. It has been demonstrated to be effective *in vitro* against SARS-CoV-2, but more studies are required to prove its clinical effectiveness. Although its use is burdened by a window timeframe of action which can be missed, it cannot be denied that it is currently the most effective drug available against SARS-CoV-2.

Its use in various combinations with camostat mesylate and tocilizumab should be tested.

Conflict of Interest:
The authors declare they do not have any conflict of interest

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