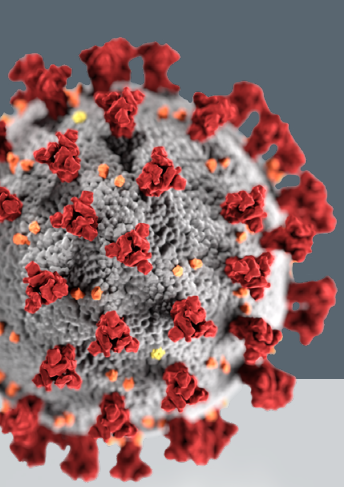

BOLETIM RAMB
COVID-19

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Use of remdesivir for patients with Covid-19: a review article

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RAMB
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

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Associação Médica Brasileira

Em um momento em que há uma emergência mundial de saúde pública, é fundamental que o conhecimento científico gerado durante a pandemia chegue rapidamente à classe médica classe médica.

Dentro desta dinâmica a Revista da Associação Médica Brasileira (Ramb) está adotando uma série de medidas a fim de acelerar o processo editorial para publicação de artigos sobre a Covid-19. A partir de hoje (14/04/2020), a AMB publicará o Boletim Ramb Covid-19, que antecipará os artigos científicos selecionados pelos editores da Ramb sobre o tema.

"Os artigos foram escritos por especialistas e selecionados dentro dos critérios da Ramb para esclarecer temas fisiopatológicos, assim como oferecer orientações de prevenção e tratamento da doença. Dessa forma, esperamos colaborar com os médicos para o melhor atendimento aos seus pacientes, com a disponibilidade mais ágil desses artigos, antes de sua publicação na Ramb", comenta Carlos Serrano Jr., editor-chefe da Ramb.

Para o diretor científico da AMB, Antonio Carlos Palandri Chagas, "neste momento ímpar vivido no mundo por conta da pandemia de Covid-19, a AMB cumpre seu papel de estar levando à comunidade científica brasileira os recentes artigos sobre os mecanismos fisiopatológicos e aspectos clínicos relevantes dessa situação que assola a saúde pública".

Carlos Serrano Jr.

Antonio Carlos Palandri Chagas

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Medical Interns and COVID-19: results of national research

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SUMMARY

The etiological agent of COVID-19, which causes severe respiratory diseases such as pneumonia and pulmonary insufficiency, has been confirmed as a new coronavirus, now known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). There is currently no authorized medication for the treatment of COVID-19. No vaccines have been authorized. Thus, this study aimed at conducting a review of the use of Remdesivir in patients with COVID-19. The following electronic databases were used MEDLINE, SCIELO, LILACS, and PUBMED. On May 1, Remdesivir received emergency use authorization from the Food and Drug Administration. Remdesivir is currently the most promising molecule in the treatment of COVID-19, taking into account its broad antiviral spectrum (considering the genetic sequences of the virus, it is expected to maintain activity against SARS-CoV-2). There is in vitro and in vivo information available for coronaviruses, as well as an extensive clinical safety database (from a clinical trial of the Ebola virus and in the context of the Monitored Emergency Use of Unregistered and Investigational Interventions - MEURI). Further studies are relevant as available data on the efficacy and safety of Remdesivir against SARS-nCoV-2 are limited.

KEYWORDS: *Betacoronavirus. Coronavirus Infections/therapy. Coronavirus.*

RESUMO

O agente etiológico da COVID-19, que causa doenças respiratórias graves, como pneumonia e insuficiência pulmonar, foi confirmado como um novo coronavírus, agora conhecido como coronavirus de síndrome respiratória aguda grave 2 (SARS-CoV-2). Não existem atualmente medicamentos autorizados para o tratamento de COVID-19, nem estão também autorizadas quaisquer vacinas. Assim, o estudo teve como objetivo realizar uma revisão sobre a utilização de Remdesivir em pacientes com COVID-19. As seguintes bases de dados eletrônicas foram utilizadas MEDLINE, SCIELO, LILACS e PUBMED. Em primeiro de maio, o Redemsivir recebeu autorização de uso de emergência da Food and Drug Administration. Remdesivir é presentemente a molécula promissora no tratamento da COVID-19 tendo em conta o seu largo espetro antiviral (considerando as sequências genéticas do vírus, é expectável que mantenha atividade contra o SARS-CoV-2). A informação in vitro e in vivo está disponível para os coronavírus, assim como a extensiva base de dados de segurança clínica (proveniente de ensaio clínico do vírus Ebola e no contexto do Monitored Emergency Use of Unregistered and Investigational Interventions - MEURI). A realização de novos estudos torna-se relevantes uma vez que os dados disponíveis são limitados sobre eficácia e segurança do Remdesivir contra SARS-nCoV-2.

PALAVRAS-CHAVE: *Betacoronavirus. Infecções por Coronavirus/terapia. Coronavírus.*

INTRODUCTION

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is a newly-emerging human infectious coronavirus, originating in Wuhan, China, that has been spreading rapidly in China and other countries since December 2019[1]. SARS-CoV-2 is a β-coronavirus, which is an enveloped non-segmented positive-sense RNA virus (subgenus sarbecovirus, Orthocoronavirinae subfamily)[2].

The World Health Organization (WHO) named this novel coronavirus disease COVID-19, and there have been confirmed cases in 189 countries or territories outside China, including Japan, the United States of America, Italy, Iran, and Brasil[3]. In Brasil, 52,771 deaths have been caused by COVID-19 and there have been 1,151,479 confirmed cases of the disease recorded nationwide as of June, 23th, 2020[4].

The clinical features of COVID-19 are varied, ranging from an asymptomatic state to acute respiratory distress syndrome and multi-organ dysfunction. The common clinical features include fever (not in all cases), cough, sore throat, headache, fatigue, myalgia, and breathlessness. Conjunctivitis (pink eye) has also been described[5].

There is no evidence from randomized clinical trials (RCTs) that any potential therapy improves outcomes in patients with suspected or confirmed COVID-19. This review summarizes current evidence on the use of Remdesivir for COVID-19 and provides a summary of the current clinical experience and treatment guidelines for this epidemic Novel Coronavirus.

METHODS

A literature search was performed in a Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed (1966 to January 2020), available through the following link: https://www.ncbi.nlm.nih.gov/pubmed/; Scientific Electronic Library Online (SCIELO), available at https://www.scielo.org/ and Literatura Latino Americana e do Caribe em Ciências da Saúde (LILACS), available through the following link: https://bvsalud.org/, using the following terms: 2019-nCoV, COVID-19, SARS-CoV-2, Coronavirus and Treatment, to find articles published from January 5 to April 30, 2020. Moreover, we used the findings of literature retrieved by searching authoritative texts and manual searches in WHO reports. We checked the reference lists of all studies identified by the above methods. Studies were excluded if old data was used, if the topics were inappropriate or not pertinent to the purpose of the study.

Use of Antiviral Remdesivir

The Food and Drug Administration (FDA), the agency that regulates medicines in the United States, has approved the use of Antiviral Remdesivir (GS-5734™) (Figure 1) in the treatment of severe cases of COVID-19, the disease caused by the new coronavirus (Sars-CoV-2)[6]. The drug, from drugmaker Gilead, was originally developed to fight Ebola, but with no success[7].

Remdesivir (also GS-5734) is a monophosphoramidate prodrug of an adenosine analog that has a broad antiviral spectrum including filoviruses, paramyxoviruses, pneumoviruses, and coronaviruses. Remdesivir is a prodrug that is metabolized into its active form GS-441524, an adenine nucleotide analog that interferes with the activity of viral RNA polymerase and promotes evasion of proofreading by viral exoribonuclease, leading to inhibition of viral RNA synthesis. Remdesivir acts early in infection and decreases viral RNA levels in a dose-dependent manner that parallels impairment of viral load *in vitro*[8].

Remdesivir has demonstrated *in vitro* and *in vivo* activity in animal models against the viral pathogens that cause MERS and SARS, which are coronaviruses structurally similar to SARS-CoV-2, the coronavirus that causes COVID-19[9,10].

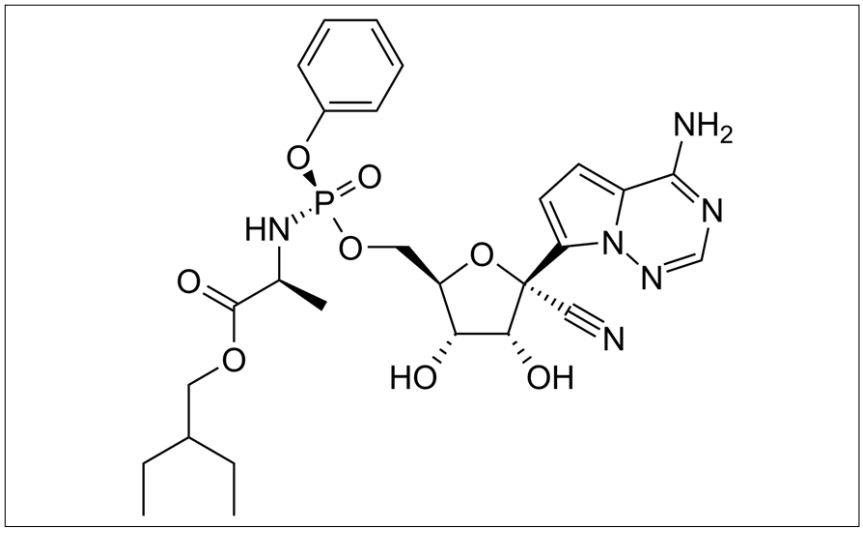
Concerning its metabolism, it has been shown that, upon intravenous (IV) administration of a 10 mg/kg dose in Rhesus Monkeys, Remdesivir exhibited a short plasma half-life (t1=2 = 0.39 h) with rapid systemic elimination followed by the appearance of transient systemic levels of a key intracellular intermediate alanine metabolite and more persistent levels of GS-441524 (detectable for over 24h in plasma)[11].

Regarding the clinical use of Remdesivir, the results were published by Grein et al.[9], in which patients received a 10-day course of Remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days of the treatment. It was observed, at the end of the follow-up, that of the 61 patients who received at least one dose of Remdesivir, data from 8 could not be analyzed (including 7 patients with no post-treatment data and 1 with a dosing error). Of the 53 patients whose data were analyzed, 22 were in the United States, 22 in Europe or Canada, and 9 were in Japan. At baseline, 30 patients (57%) were receiving mechanical ventilation and 4 (8%) were receiving extracorporeal membrane oxygenation.

During a median follow-up of 18 days, 36 patients (68%) had an improvement in oxygen-support class, and 17 of 30 patients (57%) receiving mechanical ventilation were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 out of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation. In this cohort of patients hospitalized for severe Covid-19 who were treated with compassionate-use Remdesivir, clinical improvement was observed in 36 of 53 patients (68%). Measuring the efficacy of this approach will require ongoing, randomized, placebo-controlled trials of Remdesivir therapy.

In another published study, eligible patients were adults (aged ≥18 years) admitted to the hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to the moment of enrollment of 12 days or less, oxygen saturation of 94% or less on room air, or a ratio of arterial oxygen partial pressure to fractional inspired

FIGURE 1. CHEMICAL STRUCTURE OF REMDESIVIR.



oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia. Patients were randomly assigned in a 2:1 ratio to intravenous Remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) or the same volume of placebo infusions for 10 days. 237 patients were enrolled and randomly assigned to a treatment group (158 to Remdesivir and 79 to placebo); One patient in the placebo group who withdrew after randomization was not included in the ITT population.

Remdesivir use was not associated with any difference in the time for clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]). Although not statistically significant, patients receiving Remdesivir had a numerically faster time to clinical improvement than those receiving placebo, among patients with symptom duration of 10 days or less (hazard ratio 1·52 [0·95–2·43]). In this study of adult patients admitted to hospital for severe COVID-19, Remdesivir was not associated with statistically significant clinical benefits. However, the numerical reduction in the time for clinical improvement in those treated earlier requires confirmation in larger studies[10]. At least 23 studies on Remdesivir are currently listed on various trial registers, intending to study 23,500 patients, but fewer than a quarter are double-blind, and some are uncontrolled observational studies.

CONCLUSION

Thusly the studies demonstrated that intravenous doses of Remdesivir were adequately tolerated in patients; this medication was not utilized in patients seriously infected by COVID-19, necessitating control clinical trials. Because of this, more scientific information is needed to reach conclusions about Remdesivir, its benefits, and in what situations it should be used.

Conflicts of Interest

The authors declare that there are no conflicts of interest that may have influenced this work.

Authors' Contributions

TCPA, ARVSC, MLCF, PCPA, and RNSF performed searches in the databases. TJMR, CFSR, FTB, and FWSR selected the articles that would be included in the research. FWSR corrected the writing in English. All authors performed the other parts of the research in an equal way. All authors have reviewed and approved the final text of this article and are responsible for its content. ■

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