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Remdesivir: a strategy to face the COVID-19 virus

Remdesivir: uma estratégia de enfrentamento ao vírus da COVID-19

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ABSTRACT
In December 2019, a new type of coronavirus was found to have emerged and the World Health Organization declared a state of public health emergency. In view of this, Remdesivir has been identified in many countries as a possible candidate for the treatment of Sars-Cov-2. Given these assumptions, this paper aims to highlight the current evidence on the mechanism of action of this drug in cells infected with COVID-19 through a literature review. Remdesivir is defined as a nucleoside analog prodrug substituted with 10-cyano. Its main function is to inhibit viral replication by competing with endogenous nucleotides for viral RNA incorporation. In a randomized double-blind study, intravenous Remdesivir had no efficacy on time to clinical improvement, mortality, or time to viral clearance in patients with severe COVID-19. In another study patients who received Remdesivir had a 10-day faster recovery compared to those who received placebo. It is concluded that one study was able to satisfactorily demonstrate the use of Remdesivir in patients with COVID-19, as patients had a short recovery time compared to placebo. However, more studies are needed to prove the efficacy of the drug to combat coronavirus.

KEYWORDS: Coronavirus, medicine, drug reuse.

1 INTRODUCTION

In December 2019, in the city of Wuhan, belonging to Hubei Province, located in China, a new type of coronavirus was found to have emerged: Sars-Cov-2. In late January 2020, the World Health Organization (WHO) declared a state of public health emergency of international importance. To combat the transmission of the virus and the contagion of the disease among humans, a series of measures have been indicated and adopted, such as social isolation and *lockdown* (CDC, 2022; HUI, 2017; PARK, 2020; WU et al., 2020).

In the absence of a cure for this new virus, the world's healthcare systems have collapsed. In the quest to find a solution, researchers focused on drastic measures to understand, monitor, and control the replication and spread of the virus and to seek timely and cost-effective therapeutic strategies in order to suggest promising treatment for hospitalized patients and those in critical states (LOU; SUN; RAO 2014; FDA, 2020).

Scientists found that Remdesivir (GS-5734) could be promising in the treatment of Sars-Cov-2 (COVID-19), as it is an antiviral/antimalarial that was originally developed for the treatment of Ebola virus and targets viral proteins that block the viral replication machinery and consequently inhibit polymerase. According to Warren et al. (2016), Remdesivir was not yet approved, but even so, on May 1, 2020 it was the first to receive *Food and Drug Administration* (FDA) clearance for emergency use, a fact that demonstrates the importance of having more studies on this drug.

Given these theoretical assumptions, this paper aims to highlight the current evidence on the mechanism of action of this drug in cells infected by COVID-19 and its therapeutic performances against the new coronavirus SARS-CoV-2.

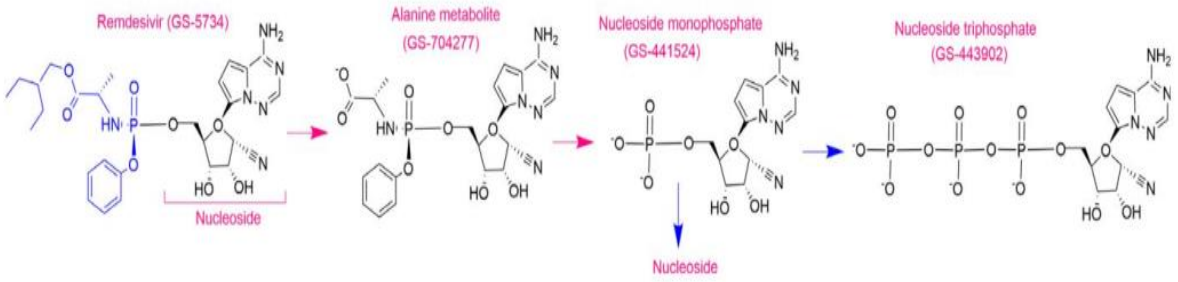
2 METHODOLOGY

This work is a literature review in the Scielo, PubMed and Lilacs article databases. For the search the following terms and key words were used: Remdesivir, COVID-19, Pharmacology and Efficacy. After reading the titles and abstracts of the articles found, as a selection criterion were used articles that contained relations between Remdesivir and efficacy in the application against COVID-19.

3 RESULTS AND DISCUSSION

Remdesivir (previously GS-5734) (Figure 1) is defined as a monophosphoramidate prodrug of a 10-cyano substituted nucleoside analog (GS-441524). Its main function is to inhibit viral replication by competing with endogenous nucleotides for viral RNA incorporation via RNA-dependent RNA polymerase (RdRp). The RdRp nonstructural protein (nsp12) is intensely conserved in coronaviruses, making it an attractive target for broad-spectrum antiviral drugs. Upon entry into cells, GS-5734 undergoes rapid metabolic conversion by intracellular kinases to its active nucleoside triphosphate metabolite (GS-443902); a rate-limiting step for activation of nucleoside analogues and the generation of nucleoside monophosphate (SIEGEL et al., 2017).

Figure 1. Chemical structure of Remdesivir and its metabolites (JORGENSEN, et al., 2020).



Nucleoside phosphoramidates are monophosphate biosomers and therefore are able to bypass this rate-limiting step, but need to be administered as prodrugs to mask the charged phosphonate group and allow rapid entry into cells. The negative charge of Redemsivir is characterized by 2-ethylbutyl and L-alanine groups that are rapidly removed by intracellular esterases that exhibit high non-structural RdRp (divergent RNA-dependent RNA polymerases) selectivity when compared to human polymerases (SIEGEL et al., 2017).

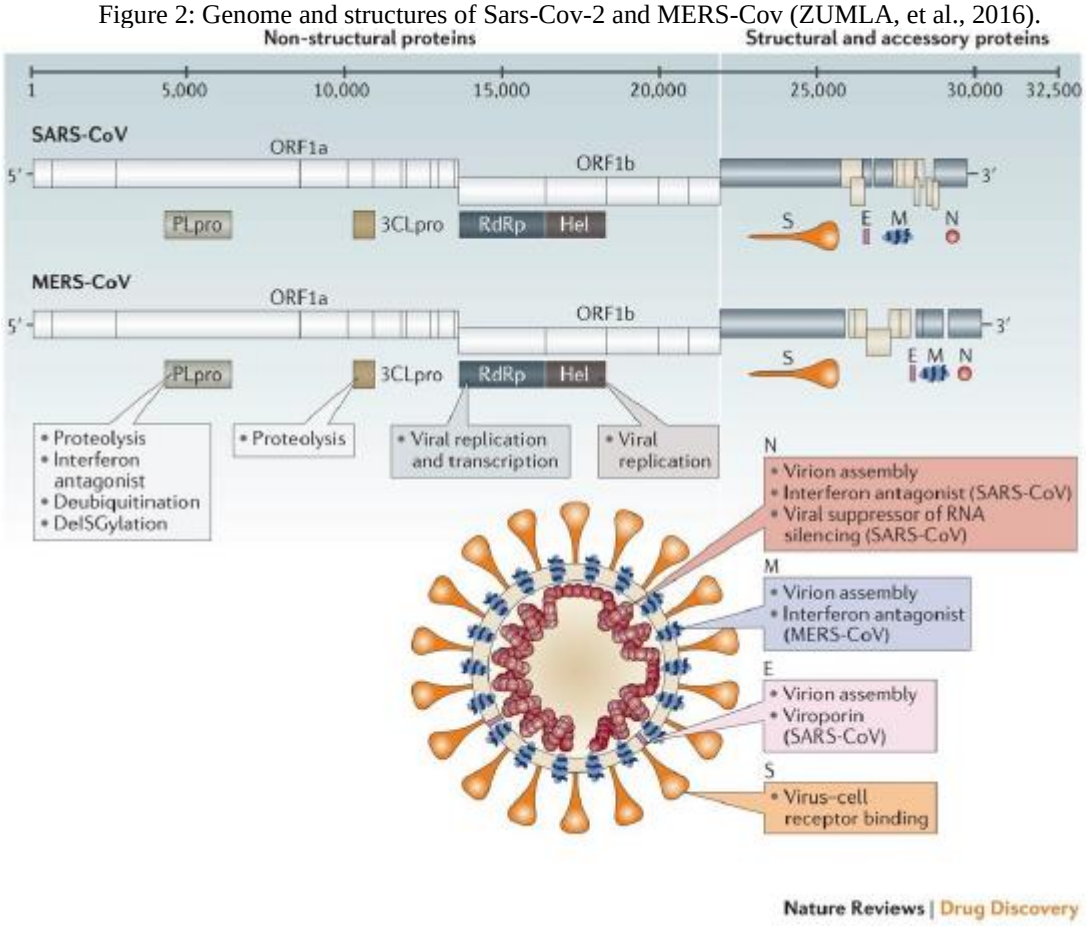
The triphosphate form of the inhibitor (RDV-TP) is used as a substrate and competes with its natural counterpart ATP; incorporation of the nucleotide analog was significantly more efficient. Once added to the growing RNA chain, the inhibitor does not cause immediate chain termination. The presence of the 3'-hydroxyl group allows the addition of three more nucleotides until RNA synthesis is stopped at the i+3 position. Therefore, the main possible mechanism of action is late RNA chain termination (GORDON et al., 2020).

The typical coronavirus (CoV) genome is a single-stranded, non-segmented RNA genome of approximately 26 to 32 kb. (Figure 2). It contains 5'-methylated caps and 3'-polyadenylated tails and is arranged in the order of 5', replicase genes, genes encoding structural proteins (spike glycoprotein (S), envelope protein (E), membrane protein (M) and nucleocapsid

protein (N)), polyadenylated tail and then the 3' end. The open reading frame 1a/b of the partially overlapping 5' terminus (ORF1a/b) is within the 5' two-thirds of the CoV genome and encodes the large replicase polyprotein 1a (pp1a) and pp1ab (GORDON et al., 2020).

These polyproteins are cleaved by papain-like cysteine protease (PLpro) and serine protease type 3C (3CLpro) to produce nonstructural proteins, including RNA-dependent RNA polymerase (RdRp) and helicase (Hel), which are important enzymes involved in CoV transcription and replication. The one-third 3' of the CoV genome encodes structural proteins (S, E, M and N), which are essential for virus-cell-receptor binding and assembly of the virion, and other non-structural proteins and accessory proteins that may have immunomodulatory effects 297 (PEIRIS, SM, GUAN et al., 2004).

Figure 2: Genome and structures of Sars-Cov-2 and MERS-Cov (ZUMLA, et al., 2016).



Coronaviruses (CoVs) enter the host cell via the endosomal pathway and/or the non-endosomal cell surface pathway. The entry of CoVs into endosomal cells is facilitated by low pH and pH-dependent endosomal cysteine protease cathepsins. CoVs then dissimulate intracellularly to release the nucleocapsid and viral RNA into the cytoplasm for translation of ORF1a/b into the large replicase polyprotein 1a (pp1a) and pp1ab and for replication of the genomic RNA. The

full-length positive strand genomic RNA is transcribed to form a full-length negative strand template for synthesis of new genomic RNAs and overlapping subgenomic negative strand templates. The subgenomic mRNAs are then synthesized and translated to produce the structural and accessory proteins. The helical nucleocapsid formed by assembly of the nucleocapsid protein (N) and genomic RNA interacts with the other structural proteins to form the assembled virion, which is then released by exocytosis into the extracellular compartment (Figure 3) (ZUMLA, et al., 2016).

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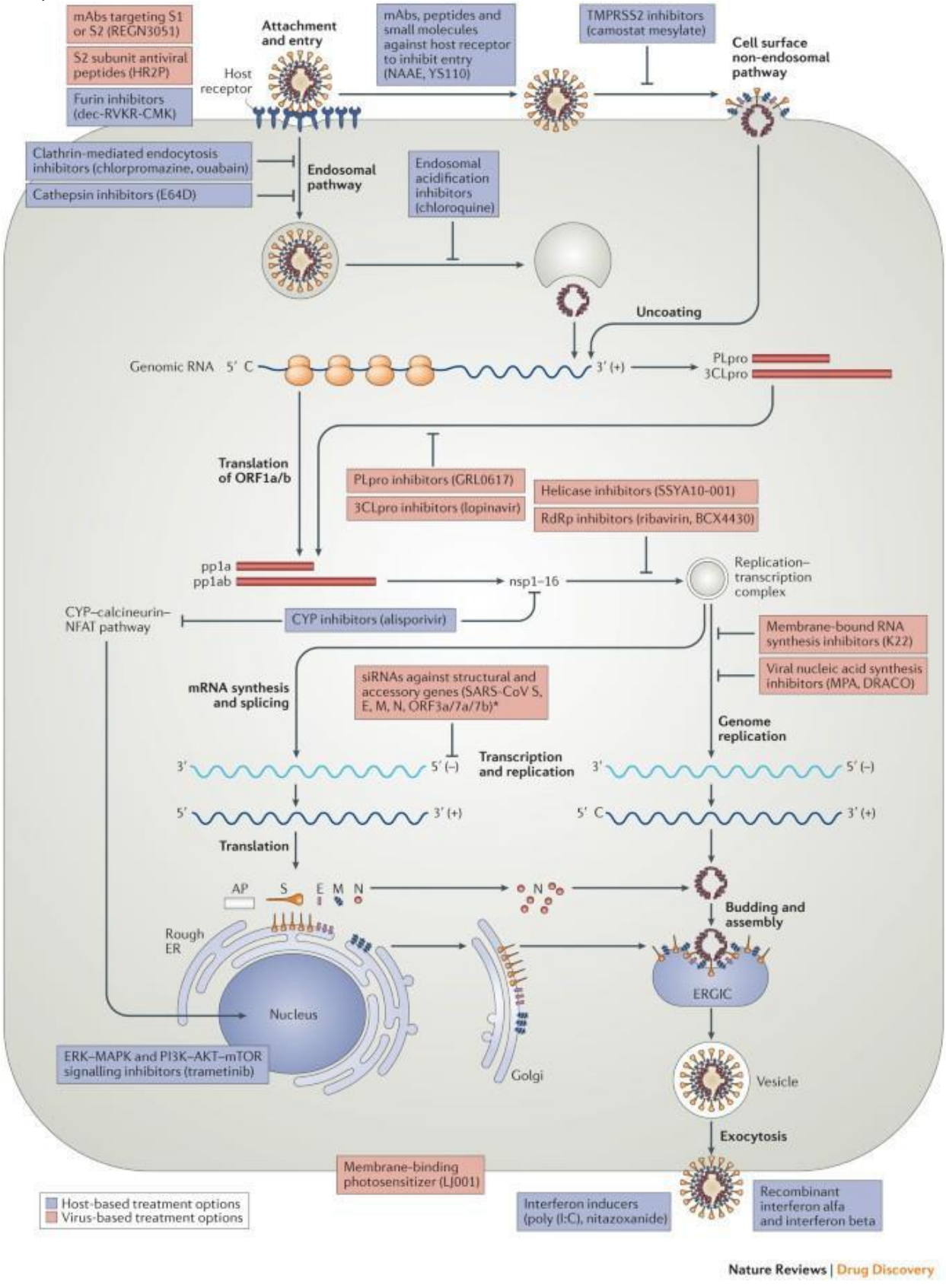
Figure 3. Virus- and host-based treatment options targeting the coronavirus replication cycle (ZUMLA, et al., 2016).



Wang et al. (2020) conducted a randomized double-blind, placebo-controlled study on 255 eligible patients in hospitals in Hubei, China, with oxygen saturation of 94% and stratified according to respiratory support level (no oxygen support, and or high flow oxygen) with symptom onset up to twelve (12) days, with radiological evidence of pneumonia. Remdesivir, was administered intravenously with single daily infusions, starting with 200mg on day 1, 100mg between days 2-10.

The study showed that intravenous Remdesivir had no efficacy on time to clinical improvement, mortality or time to virus clearance in patients with severe COVID-19, were similar to the placebo group, but there was a 5 day reduction in mean time to clinical improvement. The study did not reach the predetermined sample size because the COVID-19 outbreak was controlled in China, future studies are needed to understand its efficacy and potential (Wang et al., 2020).

Goldman et al. (2020) conducted an open randomized multicenter phase 3 study, there were 408 critically ill patients with COVID-19 screened for eligibility, hospitalized patients with confirmed SARS-COV2 infection, with oxygen saturation of 94% or less while breathing on room air and radiological evidence of severe pneumonia. Patients were randomly assigned in a 1:1 ratio to receive intravenous Remdesivir for 5 days or 10 days, at a dose of 200mg on day 1 and 100mg on the remaining days.

No significant difference in efficacy was found between the 5 to 10 days of Remdesivir groups. After adjusting for baseline imbalances in disease severity, the results were similar as measured by several endpoints: clinical status on day 14, time to clinical improvement, recovery, and death from any cause. However, these results cannot be extrapolated to critically ill patients on mechanical ventilation, since few of the patients in the study were on mechanical ventilation before starting Remdesivir treatment. Without placebo control, however, the magnitude of the benefit cannot be determined (Goldman et al., 2020).

Spinner et al. (2020) presented a randomized, open-label trial of hospitalized patients with confirmed coronavirus 2 (SARS-CoV-2) infection of severe acute respiratory syndrome and COVID-19-moderate pneumonia (pulmonary infiltrates and room air oxygen saturation > 94%). Of the 612 patients who consented and were screened for eligibility, 596 were randomized and 584 started the study: 193 started a 10-day course of Remdesivir, 191 patients started a 5-day course of Remdesivir, and 200 continued standard treatment.

Beigel et al. (2020) conducted a randomized, double-blind, multicenter placebo-controlled study with patients randomly chosen from multiple sites; with intravenous Remdesivir

in adults hospitalized with COVID-19, the starting dose used was 200mg on the first day and on the others 100mg for 9 days or until they were discharged or died. They used a sample of 1,062 people. Those who required mechanical ventilation, supplemental oxygen, and if the measured oxygen saturation was 94% or less while breathing on room air, or if they had tachypnea, were considered to be in critical condition.

Patients who received Remdesivir had 10 days faster recovery compared to those who received placebo who had recovery in 15 days. In the severe disease stratum (957 patients), the average recovery time was 11 days compared to 18 days. The benefit of Remdesivir was greatest when administered early in the disease, although the benefit persisted in most analyses of symptom duration. With regard to mortality, the Remdesivir group showed significant compared to the placebo group estimates for day 29 were 11.4% and 15.2% in the group without Remdesivir, respectively. The differences in mortality between the groups varied considerably according to initial severity (Beigel et al., 2020).

Patients in the Remdesivir group had shorter time to discharge, the initial length of stay was shorter in the Remdesivir group than in the placebo group. Among the 913 patients who received oxygen at enrollment, those in the Remdesivir group continued to receive oxygen for fewer days than patients in the placebo group, and the incidence of new oxygen use among patients who did not go on oxygen at enrollment was lower in the Remdesivir group than in the placebo group. For the 193 patients who received noninvasive ventilation or high-flow oxygen at enrollment, the average duration of use of these interventions was 6 days in the Remdesivir and placebo groups. Among the 573 patients who were not on noninvasive ventilation, high-flow oxygen, invasive ventilation, or Extracorporeal Membrane Oxygenation (ECMO) therapy at the start of the study, the incidence of new noninvasive ventilation or high-flow oxygen use was lower in the Remdesivir group than in the placebo group. Among the 285 patients who were on mechanical ventilation or ECMO at enrollment, patients in the Remdesivir group received these interventions for fewer subsequent days than those in the placebo group (Beigel et al., 2020).

5 CONCLUSION

Remdesivir was first created for the Ebola Virus, but treatment was discontinued due to the high rate of side effects in patients. However, in 2020 it returned as a protagonist for the treatment of COVID-19. The first studies did not demonstrate its effectiveness, some of them not completed due to the control of the outbreak, limitation of protocols, viral load not evaluated, open studies and methods that interfered with the final result of the work.

However, one study was able to satisfactorily demonstrate the use of Remdesivir in patients with COVID-19. It showed a short recovery time compared to placebo, an average of 10 to 15 days, the hospitalization and discharge time had significant results with an average of 12 to 17 days, and mortality showed relevant data from 11.4% to 15.2%, i.e. Remdesivir was effective in COVID-19.

Therefore, further studies on the drug are needed to ensure safety and quality of life for patients who use it.

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