Remdesivir as a Possible Therapeutic Option for the COVID-19

Jaffar A. Al-Tawfiq [1,2,3*], Ali H. Al-Homoud[4], and Ziad A. Memish, MD[5,6,7]

[1]Infectious Disease Unit, Specialty Internal Medicine, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia, [2]Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA; [3]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [4]Pharmacy Services Division, Johns Hopkins Aramco Healthcare, Dhahran, Saudi Arabia; [5]Director Research Center, King Saud Medical City, Ministry of Health, [6]Al-Faisal University, Riyadh, Saudi Arabia; [7]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA5

Dr. Jaffar A. Al-Tawfiq*

P.O. Box 76; Room A-428-2, Building 61, Dhahran Health Center,

Johns Hopkins Aramco Healthcare, Dhahran 31311, Saudi Arabia.

E-mail address: jaffar.tawfiq@jhah.com; jaltawfi@yahoo.com

Tel: +966-13-870-3524; Fax: +966-13-870-3790

All authors have no conflicts of interest

This is the author's manuscript of the article published in final edited form as:

Al-Tawfiq, J. A., Al-Homoud, A. H., & Memish, Z. A. (2020). Remdesivir as a possible therapeutic option for the COVID-19. Travel medicine and infectious disease. https://doi.org/10.1016/j.tmaid.2020.101615

To the editor,

In a recent review article, there were multiple preventive measures that were proposed for the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [1]. Since 2002, we had witnessed the emergence of three coronaviruses with a significant impact. These are the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), MERS-CoV and the SARS-CoV-2, the causative agent of COVID-19. SARS-CoV-2 emerged in Wuhan, China, in December 2019, and according to the World Health Organization (WHO), the global number of cases is 80239 confirmed as of February 25, 2020 [2]. However, there is no recommended therapy for any of these CoVs.

Remdesivir (with a development code GS-5734) is a broad-spectrum antiviral agent. This medication is an experimental drug and had not been licensed or approved at the time of writing this article. It was synthesized and developed by Gilead Sciences in 2017 as a treatment for Ebola virus infection. It is a monophosphoramidate prodrug and is an adenosine analog. Remdesivir is metabolizes into its active form, GS-441524, that obscures viral RNA polymerase and evades proofreading by viral exonuclease, causing a decrease in viral RNA production. The antiviral mechanism for remdesivir is a delayed chain cessation of nascent viral RNA of Ebola virus. Remdesivir showed antiviral activity against multiple variants of Ebola virus in cell-based assays [3] as well as in a rhesus monkey model of Ebola virus disease, [4]. Remdesivir was given on a compassionate-use basis to a British nurse who survived Ebola virus disease when she relapsed nine months later in the United Kingdom with meningoencephalitis [5]. In a randomized controlled trial of Ebola Virus disease therapeutics, 673 participants received one of three monoclonal antibodies (Zmapp, mAb114 or REGN-EB3) or remdesivir [6]. However, the

study was stopped as an interim analysis found that individuals who received REGN-EB3 or mAb114 had greater survival than either ZMapp or remdesivir [6].

In-vitro studies showed that remdesivir can inhibit coronavirus such as SARS-CoV and MERS-CoV replication. In an in-vitro test utilizing epithelial cell cultures of a primary human airway, remdesivir was effective against bat CoVs, prepandemic bat CoVs, and circulating contemporary human CoV in primary human lung cells [7,8]. One study showed that remdesiv and interferon beta were superior to lopinavir, ritonavir and interferon beta both *in vitro* and in MERS-CoV mouse model [9].

With the emergence of the 2019-nCoV (COVID-19), we are in a need for an effective antiviral agent to be able to halt the current outbreak. It had been suggested that remdesivir might be an option for the therapy of the COVID-19 patients [10]. In a case report, remdisivir reatment with started intravenous on day 7 in a patient with 2019-nCoV (COVID-19) [11]. Given the broad-spectrum anti-CoV activity of remdesivir demonstrated in pre-clinical studies; a randomized, controlled, double blind clinical trial is planned to evaluate the efficacy and safety of remdesivir in hospitalized patients with mild or moderate 2019-nCoV respiratory disease [12]. This clinical trial has already involved 308 hospitalized adult patients with mild and moderate 2019-nCoV respiratory disease. The participants were randomized to either placebo or remdesivir 200 mg loading dose on day 1 followed by 100 mg iv once-daily as maintenance doses for 9 days. The primary outcome was defined as the Time to Clinical recovery (TTCR), up to 28 days [12]. TTCR is defined as the time (in hours) from initiation of study treatment (active or placebo) until normalization of fever, respiratory rate, and oxygen saturation, and alleviation of cough, sustained for at least 72 hours [12]. Another ongoing phase 3 randomized, double-blind, placebo-controlled, multicenter study is evaluating the efficacy and safety of remdesivir in

452 hospitalized adult patients with severe 2019-nCoV respiratory disease [13]. Any clinical impact of remdesivir on 2019-nCoV remains unknown, until we get final results of ongoing studies.

References:

[1] Baharoon S, Memish ZA. MERS-CoV as an emerging respiratory illness: A review of prevention methods. Travel Med Infect Dis 2019;32. doi:10.1016/j.tmaid.2019.101520.

[2] World Health Organization. Situation Report-17 SITUATION IN NUMBERS total and new cases in last 24 hours 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200206-sitrep-17-ncov.pdf?sfvrsn=17f0dca_2 (accessed February 7, 2020).

[3] Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 2016;531:381–5. doi:10.1038/nature17180.

[4] Warren T, Jordan R, Lo M, Soloveva V, Ray A, Bannister R, et al. Nucleotide Prodrug GS-5734 Is a Broad-Spectrum Filovirus Inhibitor That Provides Complete Therapeutic Protection Against the Development of Ebola Virus Disease (EVD) in Infected Non-human Primates. Open Forum Infect Dis 2015;2. doi:10.1093/ofid/ofv130.02.

[5] Jacobs M, Rodger A, Bell DJ, Bhagani S, Cropley I, Filipe A, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. Lancet 2016;388:498–503. doi:10.1016/S0140-6736(16)30386-5.

[6] Mulangu S, Dodd LE, Davey RT, Mbaya OT, Proschan M, Mukadi D, et al. A

randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381:2293–303. doi:10.1056/NEJMoa1910993.

[7] Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. MBio 2018;9. doi:10.1128/mBio.00221-18.

[8] Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9. doi:10.1126/scitranslmed.aal3653.

[9] Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11. doi:10.1038/s41467-019-13940-6.

[10] Liu W, Morse JS, Lalonde T, Xu S. Learning from the Past: Possible Urgent Prevention and Treatment Options for Severe Acute Respiratory Infections Caused by 2019□nCoV. ChemBioChem 2020:cbic.202000047. doi:10.1002/cbic.202000047.

[11] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020. doi:10.1056/nejmoa2001191.

[12] Cao B. Mild/Moderate 2019-nCoV Remdesivir RCT - Full Text View - ClinicalTrials.gov 2020. https://clinicaltrials.gov/ct2/show/NCT04252664 (accessed February 13, 2020).

[13] Cao B. Severe 2019-nCoV Remdesivir RCT - Full Text View - ClinicalTrials.gov 2020. https://clinicaltrials.gov/ct2/show/NCT04257656 (accessed February 13, 2020).