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PAST, PRESENT AND FUTURE OF REMDESIVIR—OVERVIEW OF A MOST POPULAR ANTIVIRAL IN RECENT TIMES

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ABSTRACT

Recent international epidemics of coronavirus-associated illnesses underscore the urgent medical and public health need for vaccine development and regulatory body approved therapies. In particular, the current coronavirus disease 2019 (COVID-19) pandemic has quickly intensified interest in developing treatment options to mitigate impact on human life. Remdesivir (GS-5734™) is a broad-spectrum antiviral drug that is now being tested as a potential treatment for COVID-19 in international, multi-site clinical trials. Currently available evidence about the antiviral effects of remdesivir against to accumulate before the clinical trials are concluded. It is imperative for public health practitioners and the One Health community to stay up to date on the most promising potential therapeutic options that are under investigation. Thus, the purpose of this review is to synthesize the knowledge to date about remdesivir as a therapeutic option for coronaviruses, with a special focus on information relevant to the One Health community

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Among the myriad infectious disease threats humans face from bacteria, prions, parasites, protozoa, fungi, ectoparasites,and viruses, it is viral infections that arguably constitute the biggest pandemic threat in the modern era. The replication rates and transmissibility of viruses are two major factors that underlie this threat. However, at least one additional factor plays an essential role: the lack of 'broad-spectrum' antiviral agents. Indeed, while bacteria can still cause substantial epidemics in parts of the world where access to clean water and/ or antimicrobials is limited, the pandemic threats posed by bacteria, such as from the plague-causing Yersinia pestis, has been substantially diminished in the antibiotic era [1]. For viruses that pose epidemic risks, on the other hand, current therapeutic options are more limited. Viruses, by their obligate parasitical nature, must use host cell machinery for many functions. Thus, antiviral strategies must be directed at the virus specifically with care to avoid interfering with host cellular function. As such, the number of clear targets per virus may be limited. By contrast, bacterial protein synthesis, for example, occurs via ribosomes that belong to the bacteria and are disparate enough from human ribosomes in identity that specific antibiotics can be deployed to target only bacterial protein synthesis. This unique feature of viruses, which derives from their very nature, serves to delimit antiviral therapies in a manner not applicable to antibacterial therapies. Additionally, other characteristics of viruses serve as obstacles to broad-spectrum antiviral agents. These include differences between RNA and DNA viruses, vastly different virally encoded proteins across viral families, single or double strand genomic structure, cytoplasmic or nuclear replications cycles, and degree of reliance on host proteins. The existing armamentarium of antiviral drugs is rapidly expanding and now covers several viral families.However, very few existing antiviral agents have spectrums of activity that even slightly measure up to the spectrum of penicillin or sulfa, the first anti-bacterial agents discovered. The paucity of true broad-spectrum antiviral agents leaves a major chasm in preparedness for viral infectious disease emergencies. The current antiviral discovery process and strategy is driven by an overarching aim of finding treatments for specific individual viruses of concern and not against viral families, let alone larger groupings of viruses akin to grampositiven or gram-negative spectrum antibacterial agents. When an emerging infectious disease or pandemic strikes, if it is of bacterial or fungal origin it could be almost assured that clinicians, microbiologists, and pharmacologists could craft an effective regimen from amongst existing antimicrobials. By contrast, nearly every novel viral epidemic of regional or global importance has been characterized by the common refrain that supportive care is the mainstay of therapy with drug trials coming, for the most part, post-outbreak. If we look back into the history of pandemics in last 100 yrs the notorius bugs those have affected the whole world severely belongs to the group of viruses. So development of antiviral drugs and their uses in those pandemics times were always a major concern in treatment aspect.

Remdesivir is an investigational monophosphoramidate prodrug of an adenosine analog that was developed by Gilead Sciences, Inc. in response to the Ebola outbreak in WestAfrica from 2014 to 2016. As a nucleoside analog, remdesivir acts as a RNA-dependent RNA polymerase (RdRp) inhibitor, targeting the viral genome replication process. After the host metabolizes remdesivir into active nucleoside triphosphate (NTP), the metabolite competes with adenosine triphosphate (ATP; the natural nucleotide normally used in this process) for incorporation into the nascent RNA strand.[2] The incorporation of this substitute into the new strand results in premature termination of RNA synthesis, halting the growth of the RNA strand after a few more nucleotides are added. Once remdesivir added into the growing chain (i position), it cannot cause an immediate stop. On

the contrary, it will continue to extend three more nucleotides down to stop the strand at (i + 3) position.[3] This drug is widely distributed in the body with a predominant accumulation in

bladder, kidneys, liver, prostate gland, salivary gland (mandibular), pancreas,Seminal vesicle, epididymis and testes. Half life of the drug is 0.84-1.04 hr.It gets elimintated majorly by renal route (63%) and too some extent by billiary excretion (27.8%).It poorly crosses blood-brain barrier. Remdesivir is at least partially metabolized by the cytochrome P450 enzymes CYP2C8, CYP2D6, and

CYP3A4.[4] Blood plasma concentrations of remdesivir are expected to decrease if it is administered

together with cytochrome P450 inducers such as rifampicin, carbamazepine, phenobarbital,

phenytoin, primidone, and St John's wort.[5]

The therapeutic efficacy of remdesivir was first described in an animal model against Ebola among infected rhesus monkeys in which once-daily dosing resulted in suppression of viral replication and protection from lethal disease.[6] Besides, in a mouse model of SARS-CoV infection, prophylactic and early therapeutic dosing of remdesivir effectively decreased the viral load in the lungs and improved pulmonary function.[7] Efficacy studies in mice showed that remdesivir had therapeutic efficacy against Severe Acute Respiratory Syndrome (SARS)-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) in Ces1c−/− mice.[8] Efficacy of this drug was tested against Nipah virus Bangladesh genotype in African green monkeys which showed in contrast to control animals, which all succumbed to the infection, all remsdesivir-treated animals survived the lethal challenge and

mild respiratory signs were observed in two of four treated animals, whereas all control animals developed severe respiratory disease signs.[9]

In 2016, remdesivir (GS-5734) was reported to be active against Ebola virus in multiple human cell types, including primary macrophages and human endothelial cells, with low half-maximal effective concentration (EC 50) values of 0.06–0.14 μM [10] . In addition, remdesivir was reported to exhibit antiviral activity in vitro against Marburg virus [10] , Paramyxoviridae (such as parainfluenza type 3 virus, Nipah virus, Hendra virus, and measles and mumps viruses) and Pneumoviridae (such as respiratory syncytial virus) [11]

Early clinical experience of remdesivir therapy in a female nurse from Scotland with Ebola meningoencephalitis, which was supported by the detection of Ebola virus RNA in plasma and cerebrospinal fluid, its first use for Ebola virus infection in humans, was reported in 2016. She was successfully treated with highdose corticosteroids and 14 days of remdesivir therapy (once-daily

infusion of 150 mg over 2 h for 2 days, and then daily 225 mg for another 12 days). No serious clinical or biochemical events occurred except a transient rise of serum amylase level. [12] Remdesivir was rapidly pushed through clinical trials due to the West African Ebola virus epidemic of 2013–2016, eventually being used in people with the disease. Preliminary results were promising; it was used in the emergency setting during the Kivu Ebola epidemic that started in 2018, along with further clinical trials, until August 2019, when Congolese health officials announced that it was significantly less effective than monoclonal antibody treatments such as mAb114 and REGN-EB3. The trials, however, established its safety profile.[13,14.15,16,17,18,19]. Phase II clinical trials were conducted in Ebola virus-infected patients.In clinical trials of anti-Ebola drugs, the fatality rate of patients in the experimental group using remdesivir was 53%, and the efficacy was significantly worse than that of the two monoclonal antibodies MAb114 (fatality rate 35%) and REGN-EB3 (fatality rate 33%) [20]. The 53% fatality rate was not significantly different from the average 50%

fatality rate of Ebola virus infection, and as a result, phase II clinical trials were stopped.

Between Feb 6, 2020, and March 12, 2020 a randomised, double-blind, placebo-controlled, multicentre trial at ten hospitals in Hubei, China was conducted with adults patients of age≥18 years admitted to hospital with laboratory-confirmed SARS-CoV-2 infection, with an interval from symptom onset to enrolment 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 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. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids.The primary endpoint was time to clinical improvement up to day 28, defined as the time (in days) from randomisation to the point of a decline of two levels on a six-point ordinal scale of clinical status (from 1=discharged to 6=death) or discharged alive from hospital, whichever came first. In this study of adult patients admitted to hospital for severe COVID-19, remdesivir was not associated with statistically significant clinical benefits. But this study was limited by insufficient power to detect assumed differences in clinical outcomes, initiation of treatment quite late in COVID-19, and the absence of data on infectious virus recovery or on possible emergence of reduced susceptibility to remdesivir.[21] On 17 March 2020, the drug was provisionally approved for use for COVID-19 patients in a serious condition as a result of the outbreak in the Czech Republic. On 23 March 2020, Gilead voluntarily suspended access for compassionate use

(excepting cases of critically ill children and pregnant women), for reasons related to supply, citing the need to continue to provide the agent for testing in clinical trials. The first report of a remdesivir-treated patient with COVID- 19 in the United States was a 35-year-old male in Snohomish

County, Washington who received treatment on hospital day 7 (illness day 11) due to developing pneumonia and persistent fevers . The patient experienced clinical improvement and

negativity of oropharyngeal swab on hospital day 8, although nasopharyngeal swab remained positive. No adverse events to remdesivir were reported for the patient, which is consistent

with previous case reports of use in other viruses. Among the first 12 patients confirmed by the CDC to have COVID-19 in the United States, 3 were treated with remdesivir via compassionate use protocol . All patients reportedtransient gastrointestinal symptoms and aminotransferase elevation inspite of reported to be recovering. On April 29 2020, Gilead Sciences, Inc. announced topline results from the open-label, Phase 3 SIMPLE trial evaluating 5-day and 10-day dosing durations of the investigational antiviral remdesivir in hospitalized patients with severe manifestations of COVID-19 disease. The study demonstrated that patients receiving a 10-day treatment course of remdesivir achieved similar improvement in clinical status compared with those taking a 5-day treatment course (Odds Ratio: 0.75 [95% CI 0.51 – 1.12] on Day 14). No new safety signals were identified with remdesivir across either treatment group. These study results complement data from the placebo-controlled study of remdesivir known as the Adaptive COVID-19 Treatment Trial, or ACTT conducted by the National Institute for Allergy and Infectious Diseases and help to determine the optimal duration of treatment with remdesivir. On 1 May 2020, the U.S. Food and Drug Administration granted Gilead Emergency Use Authorization of remdesivir to be distributed and used by licensed health care providers to treat adults and children hospitalized with severe COVID-19. Gilead will supply remdesivir to authorized distributors, or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as

directed by the U.S. Government, in collaboration with state and local government authorities, as needed.[22]

Gilead initiated two randomized, open-label, multi-center Phase 3 clinical trials for remdesivir, the SIMPLE studies, in countries with high prevalence of COVID-19 infection.The first SIMPLE trial is evaluating the safety and efficacy of 5-day and 10-day dosing regimens of remdesivir in hospitalized patients with severe manifestations of COVID-19. The initial phase of the study randomized 397 patients in a 1:1 ratio to receive remdesivir 200 mg on the first day, followed by remdesivir 100 mg each day until day 5 or 10, administered intravenously, in addition to standard of care. An expansion phase of the study was recently added and will enroll an additional 5,600 patients, including patients on mechanical ventilation. The study is being conducted at 180 trial sites around the world, including sites in the United States, China, France, Germany, Hong Kong, Italy, Japan, Korea, the Netherlands, Singapore, Spain, Sweden, Switz erland, Taiwan and the United Kingdom. A second SIMPLE trial is evaluating the safety and efficacy of 5-day and 10-day dosing durations of remdesivir administered intravenously in patients with moderate manifestations of COVID-19, compared with standard of care. The results from the first 600 patients of this study are expected at the end of May.

Currently Nine trials(Table-1) on Remdesivir are ongoing to evaluate its safety and efficacy in the treatment of Covid 19. While previous studies on remdesivir are promising, formal clinical evaluation is strongly warranted. In general, there are many reasons why favorable preclinical data can fail to translate directly into human clinical trial results, such as inadvertent use of irrelevant models, inability to achieve effective serum drug concentrations in patients, or the occurrence of unanticipated severe adverse events among patients.Therefore, postulating on expected results of the trials is extremely challenging. Results of the clinical trials currently underway will provide crucial information about whether remdesivir represents a viable treatment option for COVID-19 . If the trial findings are ultimately positive, it will be imperative to ensure that the drug is produced on a commercial scale capable of meeting the demand generated by both the current pandemic and future outbreaks. Such a change in production may also allow for the added benefit of the drug becoming more available for agricultural and veterinary use for relevant indications. Whatever the progress of the clinical trials is, we are expecting that the clinical trials of remdesivir, a starring drug, would bring outstanding breakthroughs to the treatment of COVID-19, or more promisingly, other virus infection in the future.

Table 1— List of Ongoing trials on Remdesivir in the treatment of COVID-19

Clinical trial ID (Registry)	Intervention	Size	Randomised	Blinded	Status	Country of origin (pharma sponsor)
NCT04302766 (ClinicalTrials.gov)	Arm A: remdesivir	Unspecified	Unspecified	Unspecified	Available	USA
NCT04292899 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: standard treatment	400	Yes	No	Recruiting	USA and Asia
NCT04292730 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: standard treatment	600	Yes	No	Recruiting	USA and Asia
NCT04280705 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo	394	Yes	Double	Recruiting	USA and South Korea
2020-000841-15 (EU-CTR)	Arm A: remdesivir Arm B: standard treatment	400	Yes	No	Recruiting	Worldwide
2020-000842-32 (EU-CTR)	) Arm A: remdesivir Arm B: standard treatment	600	Yes	No	Recruiting	Worldwide
NCT04252664 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo	308	Yes	Quadruple	Recruiting	China

NCT04257656 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: placebo	453	Yes	Quadruple	Recruiting	China
NCT04315948 (ClinicalTrials.gov)	Arm A: remdesivir Arm B: lopinavir/ritonavir Arm C: lopinavir/ritonavir and interferon beta 1a Arm D: hydroxychloroquine Arm E: standard treatment	3100	Yes	No	Recruiting	France

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