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Remdesivir in COVID-19: A critical review of pharmacology, pre-clinical and clinical studies

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ABSTRACT

Background & aims: Remdesivir is a broad spectrum anti-viral drug that has shown to inhibit SARS-CoV-2, *in vitro* and *in vivo*. In absence of any effective treatment for SARS-CoV-2 infection (COVID-19), remdesivir has been tried for a compassionate use in severe COVID-19. Newer randomized controlled studies that have recently become available, showed a mixed result. We aimed to systematically search the literature to understand the pharmacology and clinical effects of remdesivir in patients with COVID-19.

Methods: We systematically searched the PubMed, ClinicalTrial.Org and MedRxiv database up till May 5, 2020 using specific key words such as "Remdesivir" or 'GS-5734″ AND "COVID-19" or "SARS-CoV-2" and retrieved all the article published in English language, that have reported the pharmacology and the clinical outcomes of remdesivir in patients with COVID-19.

Results: Initial compassionate use of remdesivir has shown a fairly good result, but difficult to quantify, in the absence of control arm. While the very first double-blind, placebo-controlled, randomized trial conducted in Wuhan, did not find any significant benefit compared to the control, the preliminary result of another similar multi-country trial has shown a significant faster time to recovery but without any difference in mortality.

Conclusions: Remdesivir has shown a mixed result in patients with COVID-19 with an acceptable side effect. However, jury is still out while awaiting the results from the forthcoming trials.

1. Introduction

Remdesivir (initially named GS-5734) is an adenosine analogue that has a broad-spectrum antiviral activity against several viruses such as respiratory syncytial virus, Nipah virus, Ebola virus (EBOV), Middle East respiratory syndrome (MERS-CoV), and Severe Acute respiratory Syndrome Coronavirus-1 (SARS-CoV-1) [1–3]. Pharmacologically, remdesivir has been designed to efficiently deliver the monophosphate nucleoside analogue GS-441524 into cells. Inside the cells, the GS-441524 monophosphate undergoes rapid conversion to the pharmacologically active nucleoside triphosphate form GS-443902. Nucleoside triphosphate GS-443902 acts as an analogue of adenosine triphosphate (ATP) and competes with the natural ATP substrate to selectively inhibit viral RNA-dependent RNA polymerase (RdRp). The primary mechanism of inhibition is the incorporation of the nucleoside triphosphate GS-443902 into nascent RNA chains by viral RdRp, causing delayed RNA chain termination during the process of viral replication [4]. In summary, remdesivir is a prodrug and inhibits viral RNA polymerases, when intracellularly metabolized to an ATP analogue.

In vivo efficacy against EBOV in non-human primates led to its inclusion in clinical studies for the treatment of acute Ebola virus disease (EVD). It should be noted however, that the efficacy *in vitro* or in animal studies does not inevitably predict outcomes in humans. Interestingly, in a randomized controlled trial (RCT) named The Pamoja Tulinde Maisha (PALM, NCT03719586) conducted in 681 patients of acute EBV, remdesivir was found to be less effective than other monoclonal antibodies, while the mortality was 53% (significantly worse) with remdesivir, compared to 35% with the most active antibody MAB114. Authors alluded these

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differences due to more sicker patients in the remdesivir arm [5]. Another double-blind phase II RCT study named Partnership for Research on Ebola Virus in Liberia IV (PREVAIL IV, NCT02818582) conducted in chronic carriers of EVD (n = 38) has been recently completed, although the full results are still not available in literature [6].

With regards to the coronaviruses, remdesivir has been shown to inhibit all the animal and human coronaviruses *in vitro* including MERS-CoV and SARS-CoV-1 [2,7,8]. It has shown antiviral effect and clinical benefit in animal models of SARS-CoV-1 and MERS-CoV infections [2,9–11]. Interestingly, remdesivir was found to be superior to combined interferon beta plus lopinavir–ritonavir regime in the murine models of MERS-CoV infections [9].

Fortunately, remdesivir effectively inhibited SARS-CoV-2 infected Vero cells *in vitro* study [12]. Early administration of remdesivir showed a significant reduction in viral load in bronchoalveolar lavage compared to the vehicle and also decreased the pulmonary infiltrates in SARS-CoV-2 infection of rhesus macaque model. Thus, it demonstrated both antiviral as well as the clinical effects [13]. Moreover, remdesivir was found to be a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells [14]. These outcomes encouraged its use in patients with SARS-CoV-2 infection (COVID-19), in the absence of any effective treatment.

A preliminary report (April 29, 2020) from an interim analysis of an ongoing double-blind RCT recently suggested that remdesivir had a 31% faster time to recovery, compared to the placebo ($p < 0.001$), in patients with COVID-19 [15]. United State Food Drug Administration (US FDA) urgently gave the Emergency Use Authorization (EUA) permission for remdesivir in COVID-19 on May 1, 2020. The current EUA have permitted the use of remdesivir only to treat adults and children with suspected or laboratory confirmed COVID-19 and severe disease defined as SpO2 $\leq$ 94% on room air, requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) in an in-patient hospital setting [16]. Historically, this would be the third time USFDA has given any drug to have a EUA in human, in the absence of approved indication, pending the results from a large robust trial. Interestingly, earlier on March 30, 2020, FDA also gave EUA to chloroquine and hydroxychloroquine in the treatment of COVID-19, in the absence of approved indication [17]. In the past, an investigational neuraminidase inhibitor - peramivir was given EUA by the FDA for severely ill patients with H1N1 influenza, during the 2009–2010 outbreak. Although later, RCT failed to show any benefit of peramivir, compared with the placebo, in severely ill hospitalized patients with influenza. Nonetheless, peramivir has been approved only for uncomplicated influenza, since 2014. It should be noted that the compassionate use of remdesivir in patients with severe COVID-19 requiring mechanical ventilation got approval by European Medical Agency on April 3, 2020.

Nevertheless, this prompted us to conduct a systematic search of remdesivir to understand its pharmacology, safety and efficacy in patients with COVID-19.

2. Methods

We systematically searched the PubMed, ClinicalTrial.Org and MedRxiv database up till May 5, 2020 using the several specific key words "Remdesivir" or "GS-5734" AND "COVID-19" or "SARS-COV-2" etc. and retrieved all the articles published in English language that reported pharmacology and any clinical outcome with the remdesivir in patients with COVID-19. In addition, we also searched the ClinicalTrial.Org for the ongoing trials with remdesivir in COVID-19. We compiled all the data chronologically and narrated the past, present and future of remdesivir in the context of COVID-19.

3. Results

Remdesivir is the most promising repurposed candidate drug that has shown a consistent inhibitory effect both *in vitro* and *in vivo* against SARS-CoV-1, MERS-CoV and SARS-CoV-2. The overview of all the randomized trials that have been completed or currently ongoing with the remdesivir in COVID-19 are compiled in Table 1.

3.1. Efficacy of remdesivir in COVID-19

3.1.1. Efficacy in case studies

The "compassionate use" of remdesivir and purported benefit in patients with COVID-19 have been reported in some of the case series, over the last couple of months. The first high-profile single case report from Washington, USA that was published in New England Journal of Medicine (NEJM) got attention about remdesivir [18]. This patient received the first dose of remdesivir on hospital Day 7 (illness Day 11) on a compassionate ground, when progressively found to develop severe pneumonia (clinically and chest X-ray-wise), despite receiving parenteral vancomycin (Day 6 only) and cefepime (Day 6 and 7). Interestingly, the patient recovered significantly on hospital Day 8 (illness Day 12) clinically, with no requirement of supplemental oxygen (SpO2 improved to 96% from 94% on an ambient air). Unfortunately, no further details of remdesivir with regards to the dose and duration were made available. Another case series of 28 severe COVID-19 patient (50% of total cases eventually died) from Seattle USA, published in NEJM, Bhatraju et al. [19] also reported that 7 patients had received remdesivir, however the outcome in these patients on remdesivir was not reported.

Grein et al. [20] in a data of 53 patients from the 9 countries, who received a 1 to 10-day course of remdesivir as a compassionate use, reported clinical improvement in 68% (95% confidence interval [CI], 40–80%) even with a single dose, at a median follow up of 18 days with only 15% showed worsening; despite inclusion of severe (57% on mechanical ventilator) and critical (8% on ECMO) patients with COVID-19. Interestingly, improvement was seen in 100% of patients with mild (receiving no supplemental or low-flow oxygen) and 71% patients with moderate (receiving high-flow supplemental oxygen) COVID-19 at the baseline. Clinical improvement was defined as live discharge from the hospital, a decrease of at least 2 points from baseline on a modified ordinal six-point scale or both. The six-point scale consists of – 1. not hospitalized; 2. hospitalized, not requiring supplemental oxygen; 3. hospitalized, requiring supplemental oxygen; 4. hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5. hospitalized, requiring invasive mechanical ventilation, ECMO, or both; and 6. death. However, several limitations question the validity of the result, as also noted by the authors that include small size, short duration of follow-up, potential missing data including the lack of information on eight of the patients initially treated with remdesivir, lack of randomization and absence of control group.

3.1.2. Efficacy in randomized trials

In the first double-blind, placebo-controlled, randomized trial (DBRCT) conducted with remdesivir versus placebo (n = 236) in severe COVID-19 patients, Wang et al. [21] found no significant difference in primary outcome of time to clinical improvement within 28-days either in intention-to-treat analysis (median 21.0 days in remdesivir vs. 23 days in placebo arm; hazard ratio [HR] 1.23; 95% CI, 0.87–1.75, favoring remdesivir) or in the per-protocol analysis (median 21.0 days in remdesivir vs. 23 days in placebo arm; HR 1.27, 95% CI; 0.89–1.80, favoring remdesivir). Clinical improvement was defined as a two-point improvement on a 6-point ordinal

Table 1
Randomized studies of remdesivir in COVID-19 (as of May 5, 2020).

Trial name, number	Country	Title	Trial type	N	Arms	Primary outcome	Expected Results
NCT04252664 [23]	China	Trial of remdesivir in adults with mild and moderate COVID-19	DBRCT	308	Remdesivir vs. PBO	Time to Clinical recovery (TTCR). TTCR is defined as the time (in hours) from initiation of study treatment (active or placebo) until normalization of fever (<37 °C), respiratory rate (≤24/minute on room air), and oxygen saturation (>94% on room air), and alleviation of cough (mild or absent), sustained for at least 72 h, or live hospital discharge, whichever comes first.	April 2020
NCT04257656 [21]	China	Trial of remdesivir in adults with severe COVID-19	DBRCT	237	Remdesivir vs. PBO	Time to Clinical Improvement (TTCI). The primary endpoint is time to clinical improvement (censored at Day 28), defined as the time (in days) from randomization of study treatment (remdesivir or placebo) until a decline of two categories on a six-category ordinal scale of clinical status (1 =discharged; 6 = death) or live discharge from hospital. Six-category ordinal scale: 6. Death; 5. ICU, requiring ECMO and/or IMV; 4. ICU/ hospitalization, requiring NIV/HFNC therapy; 3. Hospitalization, requiring supplemental oxygen (but not NIV/HFNC); 2. Hospitalization, not requiring supplemental oxygen; 1. Hospital discharge or meet discharge criteria (discharge criteria are defined as clinical recovery, i.e. fever, respiratory rate, oxygen saturation return to normal, and cough relief)	Published
ACTT Trial NCT04280705 [15]	NIAID, USA	Adaptive COVID-19 Treatment Trial (ACTT)	DBRCT	572 (800)	Remdesivir vs. PBO	Time to recovery – Day of recovery is defined as the first day on which the subject satisfies one of the following three categories from the ordinal scale: 1)	April 2023, Interim report presented but not published

(*continued on next page*)

Table 1 (*continued*)

Trial name, number	Country	Title	Trial type	N	Arms	Primary outcome	Expected Results
						Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities.	
SIMPLE trial NCT04292730 [25]	Multi-country, Gilead Science	Safety and antiviral activity of remdesivir in participants with moderate COVID-19	OLRCT	600 (expanded to 1600)	Remdesivir 5-days vs. Remdesivir 10-days vs. SOC	The Odds Ratio for Improvement on a 7-point Ordinal Scale on Day 11. Each day, the worst score from the previous day will be recorded. The scale is as follows: 1. Death 2. Hospitalized, on invasive mechanical ventilation or ECMO 3. Hospitalized, on non-invasive ventilation or high flow oxygen devices 4. Hospitalized, requiring low flow supplemental oxygen 5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise) 6. Hospitalized, not requiring supplemental oxygen - no longer required ongoing medical care (other than per protocol Remdesivir administration 7. Not hospitalized.	May 2020
SIMPLE trial NCT04292899 [24]	Multi-country, Gilead Science	Safety and antiviral activity of remdesivir in participants with severe COVID-19	OLRT	397 (expanded to 6000 patients including on IMV)	Remdesivir 5-days vs. Remdesivir 10-days, in addition to SOC	The Odds Ratio for Improvement on a 7-point Ordinal Scale on Day 14. Each day, the worst score from the previous day will be recorded (as previous one)	Top line results out (Unpublished)
DisCoVeRy, EudraCT 2020-000936-23 NCT04315948 [27]	INSERM, France	Multi-centre, adaptive, randomized trial of the safety and efficacy of treatments of COVID-19 in hospitalized adults	OLRCT	3100	Remdesivir vs. Lopinavir/ Ritonavir + IFNb vs. HCQ vs. PBO	Clinical status for improvement on a 7-point Ordinal Scale on day 15: 1. Not hospitalized, no limitations on activities 2.Not hospitalized, limitation on activities 3. hospitalized, note requiring oxygen 4. hospitalized requiring oxygen 5. hospitalized requiring non-invasive ventilation or high flow oxygen devices 6. hospitalized on invasive	March 2023

							mechanical ventilation or ECMO 7. death	
NCT04321616 [28]	Oslo, Norway	The efficacy of different anti-viral drugs in COVID-19 infected patients	OLRCT	700	Remdesivir vs. HCQ vs. SOC	All cause in-hospital mortality		November 2020

IMV, invasive mechanical ventilation; NIV, non-invasive mechanical ventilation; HFNC, High-flow nasal cannula, SOC- standard of care, DBRCT-double blind randomized controlled trial, OLRT-open label randomized trial, OLRCT-open label randomized controlled trial, PBO- placebo, ECMO- Extracorporeal Membrane Oxygenation.

scale (as mentioned above in study by Grein et al.). Moreover, no significant difference in 28-day mortality observed between the remdesivir and placebo (14% death in remdesivir vs. 13% in placebo group; Δ 1.1%, 95% CI, −8.1 to 10.3%) group. No difference in viral load exhibited between the two arms. Neither any difference in outcome was observed in patient receiving remdesivir early (within 10 days of illness) or late (after 10 days of illness). It should be noted that this trial was stopped early after recruiting 236 patients due to the lack of eligible patient in Wuhan, although it was powered for the inclusion of 453 patients. This early stop may have made this a statistically underpowered trial to have any conclusive result. Nevertheless, it was calculated that even if 453 patients would have been recruited, this trial could not have demonstrated any benefit [22]. Collectively, this suggest that despite an available result from a double-blind, placebo-controlled trial, we still do not know the benefit or futility of remdesivir, compared to the placebo in patients with severe COVID-19. Another DBRCT of remdesivir in mild to moderate COVID-19 patients (n = 308) conducted in China is expected anytime soon [23].

Meanwhile on April 29, 2020, National Institute of Allergy and Infectious Diseases (NIAID), announced an interim result of a randomized, controlled trial named ACTT (Adaptive COVID-19 Treatment Trial) involving 1063 patients (NCT04280705) that started on Feb 21, 2020 and closed on April 19, 2020 for new enrollments. This study was conducted at 68 sites (47 in USA and 21 in Europe and Asia) and sponsored by NIAID, the part of the National Institutes of Health. Preliminary results indicate that the median time to recovery was 11 days for patients treated with remdesivir compared to 15 days for those who received placebo, thereby suggesting that patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p < 0.001$). However, the survival benefit with remdesivir was not statistically significant compared to the control, since remdesivir group had a mortality rate of 8.0% compared to 11.6% for the placebo group ($p = 0.059$) [15].

Interestingly, on the same day (April 29, 2020), the Gilead science, manufacturers of remdesivir also announced the top line results from an open-label, randomized, phase 3, SIMPLE trial (NCT04292899) that compared the clinical improvement (primary objective) of 5-days (short-course) versus 10-days (long-course) treatment duration of remdesivir (n = 397) in hospitalized patients with severe (evidence of pneumonia and reduced oxygen levels, that did not require mechanical ventilation) COVID-19, in addition to the standard of care, in 15 countries. Secondary objectives included rates of adverse events and additional measures of clinical response in both treatment groups. Clinical improvement was defined as an improvement of two or more points from baseline on a predefined seven-point scale (vide Table 1). The study showed 10-days course had similar outcome, compared to 5-days course (Odds Ratio [OR] 0.75, 95% CI 0.51–1.12) assessed on Day 14, without any new safety signals. Interestingly, 5-days course faired similar although more impressive to 10-days course of remdesivir. The time to clinical improvement for 50% of patients was 10 day vs. 11 day in the 5-days vs. 10-days treatment group, respectively. Patients discharged from the hospital by Day 14 was 60.0% vs. 52.3%, in 5-days vs. 10-days groups, respectively ($p = 0.14$). Clinical recovery at Day 14 was 64.5% vs. 58.3% in 5-days vs. 10-days group, respectively. Interestingly, the overall mortality rate in 320 patients on Day 14 was only 7% in both treatment groups but outside of Italy. An exploratory analysis of this study suggested a larger benefit, if remdesivir was initiated early within 10 days of symptoms. Pooled data from both the arm found that at Day 14, 62% vs. 49% got discharged from the hospital, if remdesivir was started within 10 days vs. after 10 days of symptoms, respectively [24].

A second randomized, open-label SIMPLE trial (NCT04292730) is currently evaluating the safety and efficacy of 5-day and 10-days

Table 2
Remdesivir and its comparison to other repurposed candidate drugs for COVID-19.

Drug	*In vitro* studies*				*In vivo* studies*			Clinical studies in COVID-19 (as of May 5, 2020)		Dosage in SARS-CoV-2 being given in DISCOVERY trial [27]	Cost of therapy in USD
	SARS-CoV-1	MERS-CoV	SARS-CoV-2	EC_{50} (μM) SARS-CoV-2	SARS-CoV-1	MERS-CoV	SARS-CoV-2	RCT (Benefit – Y/N)	Non-RCT (Benefit – Y/N)		
Remdesivir/GS-5734 [2,3,7–11]*	+++	+++	+++	1.76	+++	+++	+++	Wang et al. – N ACTT – Y SIMPLE - Y [15,21,24]	Holshue et al. – Y Grein et al. – Y [18,20]	200 mg IV then 100 mg OD X 2-10D	>5000
Hydroxy-chloroquine [29,30]*	+/–	Not studied	+++	0.73	Not studied	Not studied	Not studied	Chen – Y Jun et al. – N Tang et al. – N [39,41,42]	Gautret et al. – Y Barbosa et al. – N Mahevas et al. – N Magagnoli et al. – N Molina et al. – N Gautret et al. – Y Million et al. – Y Geleris et al. – N [40,43–49]	400 mg then 400 mg 12 h later, then 200 mg BID X 4D	4.1
Chloroquine [31–34]*	+++	++	++	5.47	+/–	Not studied	Not studied	CloroCovid – N [51]	Gao et al. – Y Huang et al. – Y [50,52]	600 mg then 300 mg 12 h later, then 300 mg BID X 4D	6.6
Lopinavir/Ritonavir [35–38]*	+/–	–	Not studied	Not studied	Not studied	+/–	Not studied	Cao et al. – N [54]	Jun et al. – N [53]	400 mg/100 mg every 12 h. X 14D	215 (brand), 61 (generic)

+++: highest inhibitory effect, ++: moderate inhibitory effect, +/–: inconclusive, some study shown inhibition while other shown no inhibition, Y: yes, N: no, OD: once daily, BID; twice daily, D: days, USD: US dollar, RCT: randomized controlled trial, EC_{50}: effective concentration to inhibit 50%.

regime of remdesivir (n = 600) in patients with moderate COVID-19, compared to the standard of care and is expected at the end of May 2020 [25]. Other randomized trials that are currently undergoing has been summarized in Table 1 [26–28].

These are the currently available efficacy studies with remdesivir as of now. A comparative pre-clinical, clinical, and cost analysis of 4 repurposed drug such as remdesivir, hydroxychloroquine, chloroquine and lopinavir/ritonavir have been summarized in Table 2 [29–54].

3.2. Safety of remdesivir in COVID-19 studies

Adverse event (≤5%) observed in 4 Phase-1, blinded-studies (GS-US-399-1812, 1954, 4231, 5505) conducted with remdesivir (n = 138) in healthy individuals include phlebitis, constipation, headache, ecchymosis, nausea and pain in the extremities. The laboratory abnormalities observed during the phase-1 trials include transient increase in liver enzymes, prothrombin time and blood sugar in <5% of subjects [4]. While no additional safety information was collected in PALM and PREVAIL IV studies during EVD, one patient died from hypotension and cardiac arrest at the time of the loading dose on Day 1 in PALM study (n = 681), although the death could not be distinguished from underlying EVD and one of the patients was withdrawn from remdesivir therapy due to the adverse event in PREVAIL IV trial (n = 38) [4–6].

The common adverse event noted during compassionate use of remdesivir in patients with COVID-19 by Grein et al. include rash, diarrhea, hypotension, abnormal liver function and renal impairment. Serious adverse events (acute kidney injury, septic shock, multi-organ failure) was noted in 23%, while 60% had at least one adverse event and 8% discontinued due to various side effect of remdesivir [20]. Adverse events were similar in remdesivir (66%) and control arm (64%) in study of Wang et al. [21]. Although serious adverse events reported in 18% vs. 26% in remdesivir vs. control arm respectively; more patients from the remdesivir group discontinued remdesivir (12%), compared to the control arm (5%) either because of adverse events or serious adverse events (notably, 5% in remdesivir group had acute respiratory distress syndrome or respiratory failure). The most common adverse events noted in SIMPLE trial occurring in more than 10% of patients in either group were nausea (10.0% vs. 8.6%, 5-days vs. 10-days group, respectively) and acute respiratory failure (6.0% vs.10.7%, 5-days vs. 10-days group, respectively). Grade 3 or higher liver enzyme elevations occurred in 7.3% of patients, while 5% in 5-days arm and 10% in 10-days arm had to withdraw from remdesivir due to severe adverse events [24].

3.2.1. Renal safety

Although no evidence of nephrotoxicity was noted in healthy subjects, some caution is required while using remdesivir. A 150-mg dose of the remdesivir solution and lyophilized formulations of remdesivir contains 9.0 and 4.5 g, of sulfo-butyl-ether β-cyclodextrin-sodium (SBECD), respectively (maximum recommended daily dose is approximately 250 mg/kg, based on EMA safety review). SBECD is used in the formulation as a solubilizing agent due to the limited aqueous solubility of remdesivir. Since SBECD is renally cleared, subjects with moderate or severe renal impairment may have SBECD exposures. A close look on eGFR is necessary while administrating remdesivir, especially in patients with known renal impairment and discontinuation is required if eGFR falls to ≥50% from baseline. Although the parent compound remdesivir has only minor renal excretion, but since urine is found to have 49% of its metabolite GS-441524, impaired renal impairment may theoretically increase plasma exposure to this metabolite. Nevertheless, given the benefit-risk ratio in patients with COVID-19, no dose

modification is currently recommended in patients with mild and moderate renal impairment, although it is contraindicated in patients with severe renal impairment (eGFR <30 ml/min). It should be noted that no specific studies have been conducted with remdesivir in patients with renal impairment [4].

3.2.2. Hepatic safety

A substantial proportion of patients with acute EVD who received remdesivir in PALM trial had moderate to severe liver and renal dysfunction, however no additional renal or hepatic function deterioration attributed to remdesivir was noted. Remdesivir is believed to be rapidly cleaved by hydrolases and thus the effect of hepatic impairment on remdesivir plasma levels is likely low. Given the benefit-risk ratio, no dose modification is currently recommended in patients with COVID-19, though it is contraindicated in patients with alanine transferase (ALT) > 5-times upper limit of normal or severe hepatic dysfunction. There are no specific studies conducted with remdesivir in patients with hepatic dysfunction [4].

3.2.3. Pregnancy, Lactation and pediatric population

In non-clinical reproductive toxicity studies, no adverse effect on embryo-fetal development in pregnant animal or male infertility were observed with remdesivir, however at a systematically toxic dose an embryonic toxicity was seen. Remdesivir has not been studied in pregnancy, lactating women and pediatric population. Interestingly, in PALM study of acute EVD, 3% of pregnant women and 26% of children received remdesivir, without any notable side effects [4].

3.2.4. Drug interaction

The potential of induction of CYP enzymes (CYP1A2, CYP2B6, and CYP3A4) following exposure of human hepatocytes to remdesivir has been seen (the reason for transient increase in liver enzymes), however, no data available currently for the drug-drug interaction [4].

3.2.5. Formulation and dosing

Remdesivir for injection, 100 mg, is a sterile, preservative-free lyophilized solid that is to be reconstituted with 19 mL of sterile water for injection and diluted into 0.9% saline prior to IV administration. Remdesivir for injection, 100 mg, vials should be stored below 30 °C until time of use. Remdesivir injection, 5 mg/mL vials should be stored at refrigerated temperatures (2 °C–8 °C) until time of use. Following dilution with 0.9% saline, the solution can be stored for up to 4 h at room temperature (20 °C–25 °C) or 24 h at refrigerated temperatures (2 °C–8 °C).

Current dose recommendation of remdesivir in COVID-19 is a bolus dose of 200 mg IV diluted in normal saline (0.9%) or 5% dextrose to be given over 60 min on Day 1, followed by 100 mg IV to be given diluted over 60 min for the next 9 days.

Interestingly, in previous two clinical studies conducted in EVD such as PALM and PREVAIL IV, the dose used for remdesivir was 200 mg IV over an hour on Day 1 as a loading dose and then 100 mg IV over 1 h daily for 4 days (in PREVAIL IV) or 9–13 days (in PALM), as a maintenance dose.

4. Discussion

Remdesivir is an anti-viral agent that has shown a significant inhibitory effect *in vitro* and *in vivo* studies against SARS-CoV-2 and appears to be ahead to other repurposed drug being tried for the treatment of COVID-19. Table 2 summarize the comparison of results from both pre-clinical and clinical studies of these 4 repurposed candidate drugs. Animal studies clearly hinted that early administration of remdesivir was more effective like in other acute viral diseases. From this point of view, treating patients those already have respiratory failure, may not represent the optimal use of remdesivir. However, since viral shedding in COVID-19 and intensive care admission tends to be more protracted, even late administration could be useful. In this regard, FDA has currently authorized remdesivir only in severe COVID-19 in both adults and children. With regards to the outcome of remdesivir in COVID-19, while one RCT found no benefit, preliminary results from other RCT have shown some benefit. Therefore, the overall outcome with remdesivir is perhaps in a stage of clinical equipoise at this point of time. The safety profile of remdesivir in COVID-19 is incompletely characterized in COVID-19. While the safety data from the previous use during acute EVD suggest no specific alarm, COVID-19 differs profoundly in its clinical characteristics from EVD. Nevertheless, hitherto no safety findings allows remdesivir to be used in COVID-19, under a proper pharmacovigilance. Special attention should be given for disproportionate rise in ALT or decrease in GFR, during the treatment with remdesivir. The current contraindication of starting remdesivir with concomitant vasopressors use is primarily based on this being an indication of end organ failure. In contrast, once a patient initiates treatment with remdesivir, subsequent use of vasopressors is not a reason for discontinuation of remdesivir. Moreover, the use of vasopressor at low/medium doses for inotropic support due to the use of sedation and paralytics while on the ventilator is allowed.

5. Conclusion

Remdesivir appears to have optimal safety profile although its efficacy in the treatment of COVID-19 appears to have a mixed outcome at the moment. Jury is still out and future trials should further enlighten its cost-effectiveness, in particular when the results of head-to-head trial with other low-cost repurposed drugs is available.

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Declaration of competing interest

Nothing to declare by all the authors.

References

[1] Lo MK, Jordan R, Arvey A, et al. GS-5734 and its parent nucleoside analog inhibit filo-, pneumo-, and paramyxoviruses. Sci Rep 2017;7:43395.
[2] Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9:eaal3653.
[3] 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. https://doi.org/10.1128/mBio.00221-18.
[4] Summary on compassionate use remdesivir Gilead. https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf (Accessed May 5, 2020).
[5] Mulangu S, Dodd LE, Davey Jr RT, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381:2293–303.
[6] GS-5734 to assess the antiviral activity, longer-term clearance of Ebola virus, and safety in male Ebola survivors with evidence of Ebola virus persistence in semen. https://clinicaltrials.gov/ct2/show/NCT02818582.
[7] Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 2016;531:381–5.
[8] Brown AJ, Won JJ, Graham RL, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antivir Res 2019;169:104541.
[9] Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222.
[10] de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir

(GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci USA 2020;117:6771–6.
[11] Gordon CJ, Tchesnokov EP, Feng JY, Porter DP, Gotte M. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. J Biol Chem 2020:013056. jbc.AC120.
[12] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res Published Online First 4 February 2020. https://doi.org/10.1038/s41422-020-0282-0.
[13] Williamson BN, Feldmann F, Schwarz B, et al. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. bioRxiv 2020. https://doi.org/10.1101/2020.04.15.043166. published online April 22, (preprint).
[14] Pizzorno A, Padey B, Julien T, et al. Characterization and treatment of SARS-CoV-2 in nasal and bronchial human airway epithelia. bioRxiv 2020. https://doi.org/10.1101/2020.03.31.017889. published online April 2, (preprint).
[15] NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19 (April 29, 2020), https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19.
[16] FDA emergency use authorization for remdisivir. https://www.fda.gov/media/137564/download (Accessed May 5, 2020).
[17] Wilson KC, Chotirmall SH, Bai C, Rello J. COVID-19: interim guidance on management pending empirical evidence. April 3, https://www.thoracic.org/covid/covid-19-guidance.pdf. 2020.
[18] Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929–36.
[19] Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region—case series. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2004500. published online March 30.
[20] Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2007016. published online April 10.
[21] Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020. https://doi.org/10.1016/S0140-6736(20)31022-9. published online April 29.
[22] Norrie JD. Remdesivir for COVID-19: challenges of underpowered studies. Published Online April 29, https://doi.org/10.1016/S0140-6736(20)31023-0; 2020.
[23] A trial of remdesivir in adults with mild and moderate COVID-19. https://clinicaltrials.gov/ct2/show/NCT04252664.
[24] Gilead announces results from phase 3 trial of investigational antiviral remdesivir in patients with severe COVID-19. https://www.gilead.com/news-and-press/press-room/press-releases/2020/4/gilead-announces-results-from-phase-3-trial-of-investigational-antiviral-remdesivir-in-patients-with-severe-covid-19.
[25] Study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with moderate coronavirus disease (COVID-19) compared to standard of care treatment. https://clinicaltrials.gov/ct2/show/NCT04292730.
[26] A trial of remdesivir in adults with mild and moderate COVID-19. https://clinicaltrials.gov/ct2/show/NCT04252664.
[27] Trial of treatments for COVID-19 in hospitalized adults (DisCoVeRy). https://clinicaltrials.gov/ct2/show/NCT04315948.
[28] The efficacy of different anti-viral drugs in COVID 19 infected patients. https://clinicaltrials.gov/ct2/show/NCT04321616.
[29] Biot C, Daher W, Chavain N, et al. Design and synthesis of hydroxychloroquine derivatives with antimalarial and antiviral activities. J Med Chem 2006;49:2845–9.
[30] Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis Published Online First 9 March 2020. https://doi.org/10.1093/cid/ciaa237.
[31] Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69.
[32] Keyaerts E, Vijgen L, Maes P, Neyts J, Van Ranst M. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 2004;323:264–8.
[33] de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. Antimicrob Agents Chemother 2014;58:4875–84.
[34] Barnard DL, Day CW, Bailey K, et al. Evaluation of immunomodulators, interferons and known in vitro SARS-CoV inhibitors for inhibition of SARS-cov replication in BALB/c mice. Antiviral Chem Chemother 2006;17:275–84.
[35] Chen F, Chan K, Jiang Y, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. J Clin Virol 2004;31:69–75.
[36] Yamamoto N, Yang R, Yoshinaka Y, et al. HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. Biochem Biophys Res Commun 2004;318:719–25.
[37] Chu CM, Cheng VCC, Hung IFN, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax 2004;59:252–6.
[38] Chan JFW, Chan KH, Kao RYT, et al. Broad-spectrum antivirals for the emerging Middle East respiratory syndrome coronavirus. J Infect 2013;67:606–16.
[39] Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Version 2 medRxiv 2020. https://doi.org/10.1101/2020.03.22.20040758. 03.22.20040758. [Preprint.].
[40] Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020:105949. https://doi.org/10.1016/j.ijantimicag.2020.105949.32205204.
[41] Jun C, Danping L, Li L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci) 2020. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03.
[42] Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. doi: https://doi.org/10.1101/2020.04.10.20060558.
[43] Barbosa J, Kaitis D, Ryan F, Kim L, Xihui L. Clinical outcomes of hydroxychloroquine in hospitalized patients with COVID-19: a quasi-randomized comparative study. Biblio 2020. https://bibliovid.org/clinical-outcomes-of-hydroxychloroquine-in-hospitalized-patients-with-covid-19-a-302.
[44] Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. medRxiv 2020. 2020.04.10.20060699.
[45] Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. doi: https://doi.org/10.1101/2020.04.16.20065920.
[46] Molina JM, Delaugeree C, Goff JL, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. Med Maladies Infect 2020. https://doi.org/10.1016/j.medmal.2020.03.006.
[47] Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: an observational study. IHU Méditerranée Infection 2020;27(1).
[48] Million M, Lagier JC, Gautret O, et al. Early treatment of 1061 COVID-19 patients with hydroxychloroquine and azithromycin. Marseille: France. Bibliovid; 2020.
[49] Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with covid-19. published on May 7, 2020. DOI: 10.1056/NEJMoa2012410
[50] Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72–3. https://doi.org/10.5582/bst.2020.01047.32074550.
[51] Borba MGS, Val FFA, Sampaio VS, et al. CloroCovid-19 Team. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Open 2020;3(4):e208857. https://doi.org/10.1001/jamanetworkopen.2020.8857.
[52] Huang M, Li M, Xiao F, et al. Preliminary evidence from a multicenter 1 prospective observational study of the safety and efficacy of chloroquine for the treatment of COVID-19. medRxiv preprint doi: https://doi.org/10.1101/2020.04.26.20081059.
[53] Chen Jun, Yun Ling, Xi Xiuhong, et al. Efficacies of lopinavir/ritonavir and abidol in the treatment of novel coronavirus pneumonia. Chin J Infect Dis 2020. E008–E008.
[54] Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2001282. published online March 18.