IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 9 Ser.9 (September. 2020), PP 25-30
www.iosrjournals.org

Investigational Antiviral Agents for SARS-COV - 2 -Remdesivir - A Critical Review of Pharmacology and Clinical Studies

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Abstract:
BACKGROUND & AIMS:
Remdesivir is a broad spectrum antiviral drug that has shown to inhibit SARS-CoV-2 invitro. In the absence of other effective treatments for COVID-19 (SARS-CoV-2) infection, remdesivir has been tried for compassionate use in the same. Many new randomised controlled studies have shown mixed results. We aimed to systematically search the literature to understand the pharmacology and clinical effects of remdesivir on COVID-19 patients.
METHODS:
We systematically searched the ClinicalTrial.org, Pubmed and MedRxiv database uptil April 30, 2020 using specific keywords such as 'Remdesivir', GS-5374 and SARS-CoV-2. We retrieved all the articles published in English language, that reported the pharmacology and clinical effects of remdesivir on patients with COVID-19.
CONCLUSION;
Remdesivir has shown mixed results. The first randomised double blind, placebo controlled trial conducted in Wuhan, did not find any significant benefit compared to control. However the study concluded that the time to recovery was significantly faster in patients treated with Remdesivir compared to controls.

Keywords;
Remdesivir, SARS-CoV-2, COVID 19, GS-5734
The current EUA guidelines permit the use of Remdesivir for severe COVID-19 patients (Table 1) in hospital settings.

Date of Submission: 12-09-2020 Date of Acceptance: 29-09-2020

METHODS:
We researched PUBMED, MedRxiv and ClinicalTrial.Org uptil April 31, 2020 using keywords 'Remdesivir' or 'GS-5734' and 'COVID-19' and retrieve all other articles published in English language . We searched for ongoing trials with remdesivir in COVID-19.

RESULTS:
Remdesivir has consistently shown promising effects in vitro and in vivo against SARS-CO-VI, MERS-COV, and SARS-CoV-2.

EFFICACY OF REMDESIVIR IN COVID-19

The compassionate use of Remdesivir and its benefits in COVID-19 have been reported. The patient who received the first dose of Remdesivir on day 7 of hospitalisation on a compassionate ground was reported in New England Journal of Medicine. The patient was given remdesivir after he developed severe pneumonia. The patient recovered significantly with no requirement of supplemental O2.

A case series of 28 severe COVID 19 patients published in NEJM also reported the use of remdesivir but the outcome was unknown.

A study on the compassionate use of remdesivir on 53 patients across 9 countries showed 68% improvement (95% confidence interval) even with a single dose. Only 15% showed worsening (which included mechanical ventilation and patients on ECMO). Interestingly 100% improvement was seen in patients with mild (no or minimum O2 support) and 71% with moderate (high flow O2) COVID 19 patients. Discharged alive from hospitals, and a reduction in 2 points from modified ordinal 6 point scale or both are considered as clinical improvement. The 6 point scale

I. Not hospitalised
II. Hospitalised
III. Hospitalised + requiring supplemental O2
IV. Hospitalised + requiring high flow nasal O2 (NIV)

V. Hospitalised + requiring invasive mechanical ventilation or ECMO or both
VI. Death

EFFICACY OF RCT

The first ever DBRCT was conducted by Wang et al with Remsdesivir vs placebo. It found no significant difference in the primary outcome of time to clinical improvement (for 28 days period). The result showed 21 days for remdesivir and 23 days for placebo. Also no significant difference in mortality was observed. The death was 14% and 15% in the placebo group.

On April 29,2020, National Institute of Allergy and Infectious Diseases (NIAID) published the result of Adaptive COVID 19 Treatment Trial. It had over 1060 patients. The study was conducted across 68 sites. Preliminary results showed the median time of recovery was 11 days compared to 15 days for people who received placebo ($p<0.001$). But the survival data with remdesivir is not statistically significant. The mortality rate in remdesivir is 8.0% compared to 11.6% for placebo group ($p<0.059$)

Another open labelled randomised phase 3 SIMPLE trial (NCT04292899) by Gilead science, the manufacturer of remdesivir compared short duration (5 days) vs long course treatment duration (10 days). The patients included had severe COVID 19 (patient with O2 requirement and pneumonia but without need for mechanical ventilation). The results showed that both 5 day and 10 day courses had similar outcome. Improvement of 2 or more points from baseline of predefined 6 point scale. The results were observed on day 14. The time clinical improvement was 10 days in 5 day course vs 11 days in 10 day course (odds ratio 0.75, 95%CI 0.51-1.12). Clinical recovery was 64% in 5 day course vs 58.3% in10 day course. Also mortality was 7% in both the groups.

A second open labelled and randomised trial is currently evaluating safety and efficacy of both 5 and 10 day regimes for remdesivir in (n=600) patients.

ADVERSE EVENTS OF REMDESIVIR ON COVID 19 PATIENTS:

The adverse reactions observed in phase I in healthy individuals (n=150) include nausea, constipation, headache and phlebitis. Laboratory investigations showed an increase in liver enzymes (transaminases) and prothrombin time. Blood sugar (random) was also mildly elevated.

A separate study on compassionate use of remdesivir in patients with COVID 19 by Green et al included hypotension, rashes, diarrhoea, renal impairment and elevated liver enzymes. Severe adverse events were noted in 23% which included septic shock, acute kidney injury and multi organ failure. Almost 60% had at least one of the above mentioned adverse events. Nausea was the most common adverse event noted in various trials occurring in more than 10% patients of both groups. Around 8% showed elevated liver enzymes.

EFFECT ON RENAL SYSTEM:

Caution is advised in using remdesivir in healthy individuals. 100mg remdesivir solution (lyophilised) has SBECD (Sulfo Butyl Ether beta Cycle Dextrin). A dose monitoring of GFR is required, especially in patients with renal impairment. Remdesivir is to be discontinued if GFR falls >50% from baseline. As of now, no dose modification is recommended for patients with mild and moderate renal impairment.

EFFECT ON HEPATIC SYSTEM:

The effect of remdesivir on hepatic system was substantial. Patients on remdesivir had moderate to severe liver dysfunction and failure. Remdesivir is metabolised in liver. It is rapidly hydrolysed. As of now, there is no dose modification for mild to moderate hepatic failure. But for patients with more than 5 times alanine transferase remdesivir is contraindicated.

REMDESIVIR ON PREGNANCY AND LACTATION:

A non clinical reproductive toxicity study was conducted in which no adverse effect on embryo metal development in pregnancy was observed. But at systematically toxic doses, embryonic toxicity was observed. Remdesivir has not been studied in pregnant and lactating women.

REMDESIVIR ON PAEDIATRIC POPULATION:

In Palm study of acute Ebola virus disease, 26% children received remdesivir without any notable side effects. In COVID 19, there is no study on remdesivir in paediatric population.

DRUG INTERACTIONS:

Remdesivir is a potent inducer of liver enzymes (CYP1A2, CYP2B6, CYP3A4). This happens when remdesivir is exposed to hepatocytes. This is considered to be the reason behind transient elevation of transaminases.

FORMULA AND DOSING:

Remdesivir is available for injection as 100mg solid (preservative free) to be reconstituted with 19 ml of sterile water. It can be diluted with 0.9% saline prior to iv administration. Storage properties is under 30 degree celsius. 100 mg vial remdesivir injection 5mg/ml is stored (refrigerated) at 5-8 degree celsius after dilution with 0.9% saline. Shelf life is 4 hours at room temperature or 24 hours at 2-8 degree celsius.

FDA recommended dose is 200mg in in 0.9%saline bolus dose over 60 minutes on day 1 followed by 100mg iv diluted in 0.9% saline given over 60 minutes for next 4 days/ 9 days depending on short or long course therapy.

DISCUSSION:

Remdesivir is a broad spectrum antiviral agent. It has shown significant inhibition of the virus invitro and invivo. Studies clearly showed advantage of using remdesivir at an early stage to be more effective. Also remdesivir showed significant reduction in viral load from BAL. the FDA has currently approved remdesivir for severe COVID 19 in both adults and children. Regarding the outcome, the drug is still in a stage of equipoise. The safety profile is also incompletely profiled by COVID 19. Nevertheless, proper pharmacovigilance is required while administering the drug. Also concomitant use of vasopressors is not a contraindication for the use of remdesivir.

CONCLUSION:

Remdesivir appears to have optimal safety profile as concluded by many randomised control trials. But its efficacy in the treatment of COVID 19 has a mixed outcome. Further trials are expected to shed more light on its efficacy and safety profile. Future trials are also expected to show its cost effectiveness.

DECLARATION OF COMPETING INTEREST:

Nothing to declare by all the authors.

FUNDING:

No funding

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	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	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.	Published

						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)	
ACTT Trial NCT04280705	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) 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.	April 2023, Interim report presented but not published
SIMPLE trial NCT04292730	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	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	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-	March 2023

						invasive ventilation or high flow oxygen devices 6. hospitalized on invasive mechanical ventilation or ECMO 7. death	
NCT04321616	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.

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	Cost of therapy in USD
	SARS-CoV-1	MERS-CoV	SARS-CoV-2	EC50 (μM) SARS-CoV-2	SARS-CoV-1	MERS-CoV	SARS-CoV-2	RCT (Benefit – Y/N)	Non-RCT (Benefit – Y/N)		
Remdesivir/GS-5734	+++	+++	+++	1.76	+++	+++	+++	Wang et al. – N ACTT – Y SIMPLE - Y	Holshue et al. – Y Grein et al. – Y	200 mg IV then 100 mg OD X 2-10D	>5000
Hydroxy-chloroquine	+/−	Not studied	+++	0.73	Not studied	Not studied	Not studied	Chen – Y Jun et al. – N Tang et al. – N	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	400 mg then 400 mg 12 h later, then 200 mg BID X 4D	4.1
Chloroquine	+++	++	++	5.47	+/−	Not studied	Not studied	CloroCovid – N	Gao et al. – Y Huang et al. – Y	600 mg then 300 mg 12 h later, then 300 mg BID X 4D	6.6
Lopinavir/Ritonavir	+/−	–	Not studied	Not studied	Not studied	+/−	Not studied	Cao et al. – N	Jun et al. – N	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, EC50: effective concentration to inhibit 50%.

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XXXXXXXX, et. al. "Investigational Antiviral Agents for SARS-COV - 2 -Remdesivir - A Critical Review of Pharmacology and Clinical Studies." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(9), 2020, pp. 25-30.