Remdesivir – Current evidence & perspective in management of COVID-19 infection

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ABSTRACT

Coronavirus infection or COVID 19 was first reported in December 2019 in Wuhan, China, and has rapidly spread to more than 200 countries. The pandemic has also taken a toll of over 2.2 million. But the elusive search for an effective antidote is still on. Pending multiple and robust randomized controlled studies, some drugs are being used globally based on *in-vitro* studies, *in -vivo* evidence, observational studies, and small nonrandomized studies. Remdesivir is a nucleotide analog. It inhibits viral RNA-dependent RNA polymerase enzyme. Several studies have hitherto demonstrated the promising in-vitro and in-vivo antiviral activities of the molecule against severe acute respiratory syndrome coronavirus (SARS-CoV-1) and the Middle East respiratory syndrome coronavirus (MERS-CoV) strains. It has now exhibited potential *in vitro* activity against SARS-CoV-2 strains too. Based on pivotal studies, remdesivir is now being used to treat moderate to severe patients through emergency use authorizations and other access programs around the world. This review aims to summarize the evidence and clinical trials of remdesivir as a potential therapeutic option for COVID-19.

Keywords: Coronavirus, pneumonia, remdesivir, severe disease, simple study

Introduction

Coronavirus disease is by far the largest pandemic of the century. Within a short span of 6 months, it has spread to over 200 countries of the world. Concomitantly, it has afflicted more than 100 million people across the globe and killed over 2.2 million people.[1] Despite active and aggressive research across the globe, till now we do not have a possible cure for the COVID-19 infection. Many potential candidates are in the fray including chloroquine, hydroxychloroquine, ritonavir, plasma therapy, corticosteroids, and interleukin hormones.[2] Remdesivir is a new potential treatment for hospitalized patients with moderate to severe 19 COVID-19 infections. The drug inhibits viral RNA

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polymer with proven efficacy against the Ebola virus and Middle East respiratory syndrome (MERS) virus.[3] With success in many small but pivotal studies, the drug has emerged as a new ray of hope for the infection. In this review, we analyze the trials, mechanisms, doses, and recommendations for the new drug.

Methods

We systematically searched the PubMed and Clinical trials. org database up till January 25, 2021, using the several specific keywords "COVID 19" and "Remdesivir " or "SARS COV 2 "etc. and retrieved all the articles published in the English language that reported efficacy, safety, clinical outcome, and pharmacology with the remdesivir in patients with COVID-19. We compiled all the data and narrated the past, present, and future of remdesivir in the context of COVID-19.

Coronavirus pandemic – An update

Coronaviruses are single-stranded RNA viruses belonging to the

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Coronaviridae family. The initial reports of the infection came from Wuhan, Hubei province, People's Republic of China in late December 2019.[4] After that, the virus has spread fast across the globe and was declared a pandemic by the WHO on the 10th of March 2020.[5] Currently, the virus has spread across more than 190 countries involving up to 11 million people. The fatality from the virus has gone beyond 500,000 and in many countries, the case fatality ratio is more than 10%. But we are yet to have a potential cure for the infection. There are many potential candidates in the fray including chloroquine, hydroxychloroquine, ritonavir/lopinavir, plasma therapy, corticosteroids, and interleukin hormones. Many of these drugs have demonstrated antiviral activity previously and are hence being tried against this novel virus.

Remdesivir – The drug

Remdesivir (GS-5734™) is an experimental antiviral drug developed by Gilead Life Sciences. The drug is active primarily against RNA viruses and has proven prior efficacy against Ebola and MERS-CoV viruses.[6,7] It is a nucleotide prodrug and after metabolism the active forms and becomes ATP analog. The active analog inhibits RNA-dependent RNA polymerase, inhibiting viral replication through premature termination of RNA transcription in a broad range of viruses including severe acute respiratory syndrome coronavirus (SARS-CoV) 1. The drug has also shown *in vitro* activity against SARS-CoV-2 in airway epithelial cells.[8] The safety of the drug was established in studies for Ebola virus treatment. The half-life of the drug is 20 h permitting a once-daily dosing. As the prodrug is hydrolyzed in the gastrointestinal tract, oral administration is precluded.

Remdesivir – The initial experience

A small study (n = 53) of compassionate use of the drug in severe COVID -19 had shown significant improvement in oxygen requirement and improved extubation rates on mechanical ventilation.[9] This study had provided the basis for further studies on the drug. But, a subsequent study of 237 patients had failed to show clinical improvement compared to the placebo.[10] However, patients with symptoms less than 10 days, showed clinical improvement with the drug. Serious adverse events (respiratory distress or failure), however, were higher in the study prompting trial discontinuation. The trial had also failed to meet its enrollment target and hence was underpowered. The results of the study can be best called inconclusive, and the results fueled the need for more data.

SIMPLE study

It was a phase 3 multicenter trial of the drug in 180 sites across the world. About 397 patients hospitalized with COVID-19 pneumonia were randomized to remdesivir with standard therapy (5 day and 10-day regimens) versus standard of care.[11] A 7-point ordinal score was used to assess the improvement in clinical status which was the primary endpoint. Safety of the drug was the key secondary outcome. The patients who underwent the 5-day regimen were significantly more likely to have clinical improvement compared to the standard group (OR-1.56; P = 0.017) as were the patients in the 10-day arm, but results did not meet statistical significance (OR- 1.31; P = 0.18). More than 75% of patients in the 5 day regimen had more 1 point improvement in the ordinal scale while 76% in the 10-day regimens had improvement. Compared to this in the standard of care group, only 66% had some improvement in the ordinal scale. No significant side effects were observed during this study. Nausea, diarrhea, and headaches were seen in more than 5% of the study population. The study was funded by Gilead Life Sciences.

Adaptive COVID-19 Treatment *Trial* (ACTT-1) study

The study also endeavored to find the role of the drug in COVID-19 infection. About, 1063 patients hospitalized with COVID-19 respiratory infection were randomized to the drug or placebo.[12] The time to recovery was significantly shortened in the remdesivir arm (11 days versus 15 days; P < 0.001). Mortality at 14 days (Kaplan Meier estimates) was significantly lower in the remdesivir arm (7.1% vs. 11.9%). Interestingly, adverse effects were not different from the placebo arms attesting to the safety of the drug. The study was principally funded by the National Institute of allergy and Infectious Diseases (NIAID) and the National Institute of Health (NIH) lending more credibility and free of commercial bias. Table 1 gives a brief of the three major trials of the drug.

ACTT1 trial final report showed that remdesivir is superior to placebo in hospitalized patients with COVID-19 pneumonia. It reduces the time to recovery. Remdesivir group had a shorter time to recovery than patients in the placebo group (median, 10 days, as compared with 15 days). It also prevents progression to more severe respiratory disease, lower evidence of severe adverse events, and lower incidence of oxygen use who were not on oxygen.[13]

The National Institute of Allergy and Infectious Diseases (NIAID) has recently published data on the combination of barcitinib and remdesivir versus monotherapy with remdesivir in the ACTT-2 study (NCT04401579). ACTT-2 trial showed that barcitinib plus remdesivir is superior to remdesivir alone in patients with COVID-19 pneumonia those receiving high flow oxygen or noninvasive ventilation. The combination therapy reduces recovery time and showed improvement in clinical status.[14] The drug was also a part of the international collaboration launched by the World Health Organization -WHO SOLIDARITY trial. The trial enrolled 11,330 patients from 30 countries and showed that remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had no benefit in overall mortality, initiation of ventilation, and duration of hospital stay in patients with COVID-19.[15]

Drug Dosing

The drug is administered as an intravenous infusion. The loading

Table 1: Pivotal trials of Remdesivir use in COVID-19 infection					
Author	Study type	Patients type	Drug dose	Primary end points	Outcome
ACCT1 Trial	Double-blind, randomized, placebo-controlled trial (*n*=1063)	All in hospitalized patients 541 were assigned to the remdesivir group and 522 to the placebo group.	Remdesivir (200 mg loading dose on day 1 IV, followed by 100 mg daily for up to 9 additional days)	The time to recovery, defined by either discharge from the hospital or hospitalization for infection- control purposes only.	Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days, as compared with 15 days; rate ratio for recovery, 1.32; 95% confidence interval [CI], 1.12 to 1.55; *P*<0.001;
Wang *et al.*	Randomized, double-blind, placebo-controlled, multicenter trial (*n*=237)	All in hospitalized patients age >18 y with oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset.	Intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2-10 in single daily infusions)	Time to clinical improvement up to day 28	Remdesivir was not associated with a difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87-1·75]), not statistically significant. However, remdesivir arm had a numerically faster time to clinical improvement than the placebo arm with a symptom duration of 10 days or less (hazard ratio 1·52 [0·95-2·43])
SIMPLE trial	Randomized, open-label, phase 3 trial (*n*=397)	Hospitalized patient's Age >12 years, radiographic evidence of pulmonary infiltrates or had an oxygen saturation of 94% or less while they were breathing ambient air or were receiving supplemental oxygen.	All patients received 200 mg of and remdesivir on day 1 and 100 mg once daily on subsequent days. 5 days or 10 days regimen.	The primary endpoint was the clinical status on day 14, assessed on a 7-point ordinal scale.	65% of patients who received a 5-day course of Remdesivir showed a clinical improvement of at least 2 points on the 7-point ordinal scale at day 14, as compared with 54% of patients who received a 10-day course. The two groups had similar outcomes after adjustment for baseline clinical status
Grein *et al.*	Compassionate Use of remdesivir open-label program (*n*=61)	Hospitalized COVID-19 patients who had an oxygen saturation of 94% or less while they were breathing ambient air or who were receiving oxygen support.	10-day course of remdesivir, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days	Although there were no pre specified endpoints for this program, However, quantified clinical events, including changes in oxygen-support, NIPPV, invasive mechanical ventilation, and ECMO, hospital discharge, and serious adverse events, and death were assessed.	36 patients (68%) improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and 7 patients (13%) died; mortality was 18% (6 of 34) among patients receiving invasive ventilation and 5% (1 of 19) among those not receiving invasive ventilation.

IV - Intravenous; CI - confidence interval, NIPPV - noninvasive positive pressure ventilation, ECMO - extracorporeal membrane oxygenation

dose is 200 mg on day 1, and it is followed by a maintenance dose of 100 mg daily for the rest of the days (4 days or 9 days). Other researchers have proposed additional intrapulmonary dosing to increase the therapeutic efficacy of the molecule.[16] The primary argument provided is the inadequate pulmonary levels attained by the drug to effectively neutralize the virus. The researchers calculate that assuming an 80% drug loss in the upper airways, a proposed dose of 50 mg administered via nebulization for 30 min could be one of the fastest methods of intrapulmonary delivery, and further investigation is needed for this potential route.

Side Effect and Interaction Profile

Wang *et al.* demonstrated that rate of adverse events was almost similar in both the group (remdesivir vs placebo, 66% vs 64%).[10] Hypoalbuminemia, constipation, anemia, hypokalemia, increased aspartate aminotransferase, increased blood lipids, increased total bilirubin, nausea, and vomiting were common adverse effects in both the groups. Twenty-eight (18%) serious adverse events were reported in the remdesivir group and 20 (26%) were reported in the control group. Respiratory failure or acute respiratory distress syndrome was a serious adverse effect in the remdesivir group.

In more recent studies, common adverse events noted were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension.[11,12] The most common serious adverse events were multiple organ dysfunction syndrome, septic shock, acute kidney injury, and hypotension. These side effects were more commonly seen in patients on invasive ventilation. The major contraindications are summarized in Figure 1.

Coadministration of remdesivir is not recommended with chloroquine or hydroxychloroquine by the United States Food and Drug Administration (FDA). Based on *in vitro* data, chloroquine

Figure 1: Key features of remdesivir use in COVID-19 infection. [*ECMO -Extracorporeal membrane oxygenation; *HCQS- Hydroxychloroquine]

demonstrated an antagonistic effect on the intracellular metabolic activation and antiviral activity of remdesivir.

Remdesivir vis-à-vis Hydroxychloroquine Economics and Beyond

Gilead Life Sciences has priced remdesivir at $2,340 per patient for developed nations. Gilead will charge $3,120 per course, or $520 per vial for the U.S. patients with insurance, which is a 33% increase over the $390 per vial it will charge governments of developed countries and the U.S. patients in government health care programs. An analysis by the Institute of Clinical and Economic Review (ICER) has estimated that the drug becomes cost-effective at 4460$ per treatment course. The researchers used cost-effectiveness modeling and assumed 50,000$ for per quality-adjusted life-years gained with drug use.[17] The drug was originally developed by an American firm Gilead and has been recently launched in India by generic drug makers such as Cipla, Hetero, and Mylan and priced, at less than 5,000 ($66) per 100 mg vial. Hydroxychloroquine (HCQS) is available freely across the globe at a price of less than 1$ per tablet. Clinicians are also familiar with the use of the drug for the past 2decades. However, the drug has not shown unequivocal benefits as shown by remdesivir in large randomized trials. Initial data was encouraging with small trials, but later larger trials failed to replicate these findings.[18] But, because of low cost, good safety record, and widespread availability the drug is still on the recommendation of various guidelines. However, data has now emerged regarding the toxicity of the drug in combination with azithromycin – another combination that had initially positive reviews.[19] Hence, HCQS should be used alone rather than in combination with azithromycin. Again, because of the corrected QT interval (QTc) interval prolonging behavior of HCQS, it is best avoided in patients with baseline QTc prolongation.[20] More recently, hydroxychloroquine has been removed from the World Health Organization's phase III/IV SOLIDARITY trial for COVID-19. The trial initially planned for the evaluation of four investigational therapies that are lopinavir/ritonavir, remdesivir, and HCQS. Owing

to the futility of HCQS in reducing mortality, the steering committee recommended discontinuation of the HCQS arm which the WHO has accepted.[21]

Although not backed by rigorous clinical data, it would be safe to propose HCQS and remdesivir as complementary approaches in COVID-19. The former is best utilized in mild to moderate cases avoiding the cardiotoxic side effects in severe cases. Remdesivir is recommended in only moderate to severe cases as trials have generally included hospitalized patients only as the drug has to be administered intravenously and can have side effects which should be managed in an in-patient setting.

Recommendations

Remdesivir has been approved for emergency use in severely-ill patients in the United States, India, and South Korea. The drug is currently approved in Japan for the treatment of moderate to severe COVID-19.[22] The United States Food and drug administration (USFDA) has also granted emergency use approval to the drug after the success of SIMPLE and ACTT-1 studies.[23] The Drug Controlled General of India (DCGI) has also approved restricted emergency use of the drug for severely ill COVID-19 patients on the 1st of June.[24] The key features of remdesivir are shown in Figure 2. The major guideline recommendations are summarized in Table 2.[25-28]

Future Directions

Further trials of the drug are being conducted to evaluate the molecule in the management of COVID-19. Gilead Life Sciences is conducting another SIMPLE trial in patients with moderate COVID-19 disease (NCT04292730) and CARAVAN Study in children suffering from the disease (NCT04431453). REMDACTA is another trial utilizing remdesivir with toclizumab combination for severe COVID-19 19 infections (NCT04409262). Remdesivir is also a part of the multicountry and multisite DISCOVERY trial by the Institut National de la Santé et de la Recherche Médicale (INSERM) Institute (France) which is enrolling COVID-19 patients with respiratory symptoms (NCT04315948). Phase Ia clinical trial of an inhaled version of remdesivir to treat COVID-19 patients in the outpatient setting is undergoing via Gillead Lifesciences.

Conclusion

COVID-19 infection is surging past territorial borders across the globe at a lightning pace. Hitherto, there has been no specific therapy for the infection. Hydroxychloroquine has been utilized in the initial days of the pandemic as a potential remedy. Remdesivir is an investigational antiviral drug with proven effectiveness against Ebola/MERS CoV viruses and has shown promising effects in in-vitro studies against COVID-19. After the initial success in the Compassionate use program, two large randomized trials (SIMPLE and ACTT1) both have shown significantly shortened recovery time and reduce mortality with the drug.
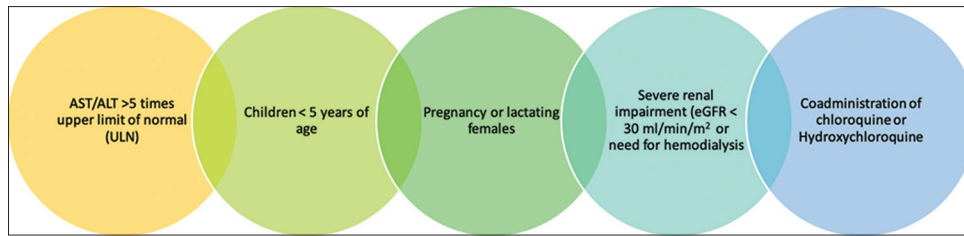
Figure 2: The major contraindications for remdesivir use in COVID-19 infections.

Table 2: Guideline recommendations on Remdesivir use in COVID-19

Guidelines	Recommendation
Government of India (MOHFW) ministry of health and family welfare[25]	Remdesivir may be considered in COVID-19 patients with moderate disease (patients on oxygen), 200 mg IV on day 1 followed by 100 mg iv daily for 5 days
WHO[26]	Recommend that the remdesivir drugs not be administered as treatment or prophylaxis for COVID-19, outside of the context of clinical trials:
NIH/CDC[27]	Remdesivir for treatment of COVID-19 in hospitalized patients with SpO_2 ≤94% on room air or those who require supplemental oxygen. The guideline recommends remdesivir for treatment of COVID-19 in patients who are on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (BI).
Infectious Diseases Society of America (IDSA) Management Guidelines[28]	Remdesivir: in severe COVID-19 patients, the guideline favors remdesivir over no antiviral treatment. In patients with severe COVID-19 who are receiving supplemental oxygen but not on mechanical ventilation or ECMO, 5 days of remdesivir therapy suggested instead of 10 days.

Remdesivir has been approved for emergency use in severely-ill patients in the United States, India, South Korea, and Japan based on contemporary clinical data. In addition, various clinical trials are ongoing to generate more data on the safety and efficacy of remdesivir for COVID-19. Remdesivir has definitely emerged as a valuable weapon for managing COIVD-19 infection.

Implication for a family physician

The COVID-19 pandemic has led to a dramatic loss of human life worldwide and presents an unprecedented challenge to the entire globe. It is difficult to differentiate symptoms of COVID-19 and influenza-like illnesses by family physicians and medical officers on the first outdoor visit. Every physician should know the management of COVID-19 pneumonia according to the severity of the disease. Family physicians are generally the first contact of any type of illness including COVID-19. Hence, they should aware of all types of management available for COVID-19 19. Remdesivir is the only available drug that consistently showed benefit in the management of moderate to severe COVID-19. This article is about a complete overview of remdesivir and a guide to a primary physician on when and how to use remdesivir.

Highlights

1. Coronavirus disease is by far the largest pandemic of the century. Within a short span of 6 months, it has spread to over 200 countries of the world.
2. Remdesivir (GS5 734) is an antiviral nucleotide analog prodrug.
3. The United States Food and drug administration (US FDA) has also granted emergency use approval of the drug for moderate to severe COVID-19 in hospitalized patients.
4. Co-administration of remdesivir is not recommended with chloroquine or hydroxychloroquine.

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Conflicts of interest

There are no conflicts of interest.

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