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Can Remdesivir Treat Covid-19 Effectively in Hospitalized Pregnancies? : A Literature Review

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Abstract :

The current Coronavirus Disease 2019 (COVID-19) pandemic is an international public health problem. It caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in Wuhan, China, in December 2019. Since that time, the number of cases worldwide continues to increase exponentially in the last few months. There is limited case reporting the impact on women affected by coronaviruses (CoV) during pregnancy. In women affected by SARS and MERS, the case fatality rate appeared higher in women affected in pregnancy compared with non-pregnant women. The complete lack of specific treatment forced clinicians to use old drugs, chosen for their efficacy against similar viruses or their in vitro activity. Clinical trials are not often conducted among pregnant patients for safety reasons and this means that drugs that may be effective in the general population cannot be used for pregnant women due to the lack of knowledge of side effects in this category of people. We aimed to provide a literature review on the putative effectiveness and safety of available treatments for COVID-19 in pregnant women. We reviewed all the available literature concerning remdesivir as an experimental antiviral that has been used in the treatment of COVID-19 especially in particular condition like pregnancy and whether a safety remdesivir had been demonstrated by clinical studies (i.e. including studies on other infectious diseases). Mechanism of action, pharmacokinetics, efficacy, safety, and possible side effects with remdesivir during pregnancy were included in our review.

Keywords*: Remdesivir, Antiviral, RdRp inhibitor, Covid-19, pregnancy*

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), began in Wuhan, China in December 2019. The initial cases were linked to exposures in a seafood market in Wuhan [1,2]. The World Health Organization declared the outbreak a pandemic on March 11, 2020. Since that time, the number of cases worldwide continues to increase exponentially, including in Indonesia, with the number of cases in Indonesia now surpassing all other countries worldwide. No treatment or vaccination is currently approved for SARS-CoV-2. It is recommended to implement quarantine, social distancing, and infection-control measures to prevent disease spread and to provide supportive care for those who become ill. With the number of critically ill patients overwhelming hospitals in cities across the nation, clinicians are looking to investigational antiviral agents for possible added benefit over supportive care alone. Ongoing clinical trials of investigational treatments for SARS-CoV-2 will likely not be completed until after the peak of this pandemic in many countries. Remdesivir (Gilead Sciences, Inc.) is an investigational antiviral which displays potent in vitro activity against SARS-CoV-2. It is not currently FDA-approved to treat or prevent any diseases, including COVID-19. It has shown promise in pre-clinical models as well as in case series, with clinical trials ongoing in multiple countries [3,2].

As of May 1, 2020, remdesivir, manufactured by Gilead, is authorized for emergency use by the US Food and Drug Administration (FDA) for the treatment of suspected or laboratory-confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalized with severe disease [3,4,5]. Severe COVID-19 is defined as patients with an oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO), a heart-lung bypass machine, in an in-hospital setting intravenously, and in doses described in the authorized Fact Sheet [3,6].

Although most infections are self-limited, about 15% of infected adults develop severe pneumonia that requires treatment with supplemental oxygen and an additional 5% progress to critical illness with hypoxaemic respiratory failure, acute respiratory distress syndrome, and multiorgan failure that necessitates ventilatory support, often for several weeks [7]. At least half of patients with coronavirus disease 2019 (COVID-19) requiring invasive mechanical ventilation have died in hospital and the associated burden on health-care systems, especially intensive care units, has been overwhelming in several affected countries [8,9,10].

Pregnancy is a state of partial immune suppression that makes pregnant women more vulnerable to viral infections, and the morbidity is higher even with seasonal influenza. Therefore, the COVID- 19 pandemic may have serious consequences for pregnant women [11]. In this respect, the pandemic caused by SARS-CoV-1 registered a 25% percentage of fatality rate among pregnant women[12]. Although most human coronavirus infections are mild, the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) epidemics of the past two decades were especially grave, with approximately a third of infected pregnant women dying from the illness [13,14].

Basing on recent studies, there is no evidence that COVID-19 impairs pregnant women more than the general population and the clinical course of COVID- 19 during pregnancy appeared to be less serious compared to SARS and MERS, with a fatality rate of 0, 18, and 25%, respectively [15]. The treatment of COVID-19 during pregnancy is a major problem for clinicians due to the potential adverse fetal and neonatal effects of different drugs. For example, Ribavirin, one of the most used antiviral against SARS-CoV-2, is contraindicated in pregnancy due to well-known teratogenic effects [12,16]. The Monitored Emergency Use of Unregistered Interventions (MEURI) framework from the WHO should guide the ethical use of non-licensed drugs in pregnancy during pandemics. Recent studies have identified remdesivir as strong candidate drugs for the treatment of COVID-19[13]. Phase 3 clinical trials are now ongoing to evaluate the safety and antiviral activity of remdesivir in patients with mild to moderate or severe SARS-CoV-2 infection in the United States and China and it seems to be safe for the use in human pregnancies, as shown in trials conducted in Ebola and Marburg virus disease [12,17].

Besides, the paucity of data about the effectiveness and safety of antiviral drugs during pregnancy is a challenge for clinicians because of the elusive biological behavior of viruses. Viruses mutate constantly as a part of their life cycle, and it is, therefore, difficult to develop curative drugs [12]. So far, no drugs, monoclonal antibodies, or vaccines have been approved to treat human infections due to coronaviruses. Several pre-existing and potential drug candidates, including remdesivir, has been considered.

Because of the urgency of the COVID-19 outbreak and the uncertainties about its management during pregnancy, we aimed to provide a literature review on the putative effectiveness and safety of remdesivir which exhibits promising in vitro antiviral activity and preliminary clinical experiences for COVID-19 in pregnant women.

METHODS

A literature review was conducted by searching PubMed, BMCs, MedRxiv, and Elsevier databases from January until June 2020. The keywords for initial data bank searches included using a combination of the following keywords: "Remdesivir", "COVID-19,""SARS-CoV-2," "pregnancy," and "RdRP inhibitor." We limited our investigation to English-language journals. For our study purpose, we analyzed only remdesivir with a putative effect on COVID-19 whose safe assumption during pregnancy had been demonstrated by clinical studies (i.e. including studies on other infectious diseases). Whether remdesivir contraindicated, probable mechanism of action, pharmacokinetics, effectivity, and possible adverse effects with remdesivir during pregnancy were included in our review.

DISCUSSION

Remdesivir (GS-5734), the phosphoramidate prodrug of an adenosine C‑nucleoside, has a structure similar to tenofovir alafenamide, which is a nucleotide analog of adenosine 5-monophosphate with antiviral activity against hepatitis B virus and human immunodeficiency virus. It was developed by Gilead Science Inc. and has not been licensed or approved anywhere for now. The chemical formula of remdesivir with a molecular mass of 602.6 is C27H35N6O8P. In several human cell lines, remdesivir can be effectively metabolized to active nucleoside triphosphate [18,19]. Remdesivir has broadspectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS- CoV]) and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses. Remdesivir appears to have a favorable clinical safety profile, as reported based on experience in approximately 500 persons, including healthy volunteers and patients treated for acute Ebola virus infection, and supported by our data (on file and shared with the World Health Organization [WHO])[19].

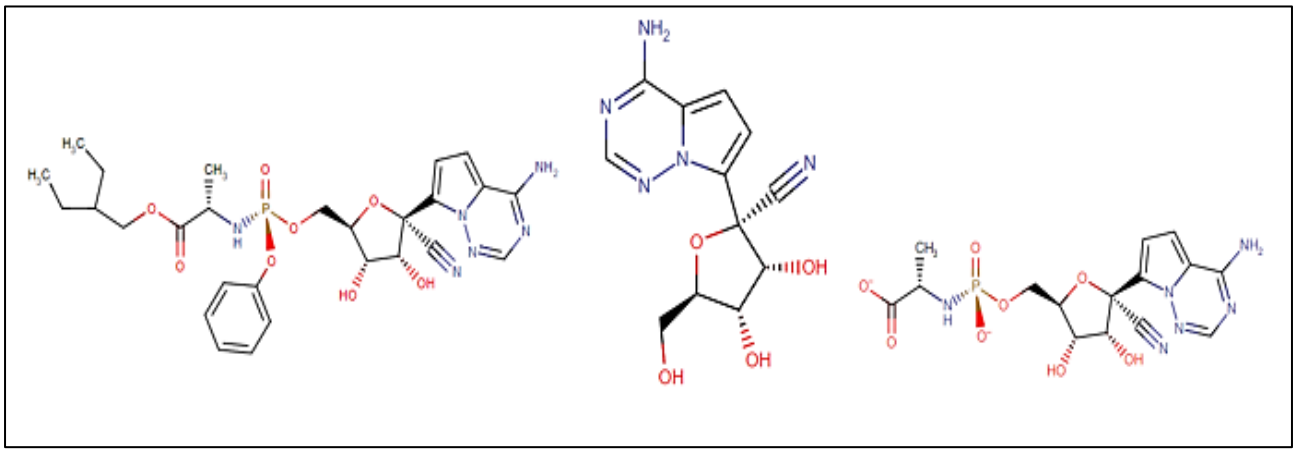

Figure 1. Chemical structure of remdesivir (a), its precursors (b) and metabolites (c)

(Source : https://www.drugbank.ca/drugs/DB14761)

Table 1. Recommended Dosage Form and Dosage in Pediatric Patients

Bodyweight	Recommended dosage form	Loading dose (on Day 1)	Maintenance dose (from Day 2)
3.5 kg to less than 40 kg	Remdesivir Lyophilized Powder for Injection Only	5 mg/kg	2.5 mg/kg
40 kg and higher	Remdesivir Lyophilized Powder for Injection or Remdesivir Injection	200 mg	100 mg

(Source : Administration USF& D. Frequently Asked Questions on the Emergency Use Authorization for Remdesivir for Certain Hospitalized COVID-19 Patients. 2020;1–2. Available from: https://www.fda.gov/media/137574)

Recommended Dosage in Adult Patients

- The recommended dosage in adults is a single loading dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg from Day 2 via IV infusion.
- For patients requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 10 days.
- For patients not requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).
- Administer remdesivir via IV infusion in a total volume of up to 250 mL 0.9% sodium chloride over 30 to 120 minutes

Recommended Dosage in Pediatric Patients

For pediatric patients weighing 3.5 kg to less than 40 kg, the dose should be calculated using the mg/kg dose according to the patient's weight. Table 1 below provides the recommended dosage and dosage form in pediatric patients.

Pharmacokinetic of Remdesivir

In a rhesus monkey model infected with MERS-CoV, treating with remdesivir 24 hours before infection can completely prevent symptoms caused by MERS-CoV, strongly inhibit viral replications in the respiratory tract, and prevent the formation of pulmonary lesions. Administering remdesivir 12 hours after infection provides clear clinical benefits, reducing clinical symptoms, lung virus replication, and lung lesions. Pharmacokinetic experiments in cynomolgus monkeys showed the first-pass effect of oral remdesivir resulted in a low bioavailability of the drug. Intramuscular injection of 3 mg/kg had a 50% survival rate compared with the control group. Administering intravenously at a dose of 10 mg/kg, remdesivir rapidly decomposed into the original drug (nucleoside phosphate) in rhesus monkeys. Within two hours, remdesivir quickly distributed in peripheral blood mononuclear cells (PBMCs), and soon afterward activated to nucleoside triphosphate to reach a peak, with a survival rate of 100% [20, 21].

As for pharmacokinetic studies in vivo, after the intravenous infusion of the remdesivir solution formulation at a single dose of 3 to 225 mg for two hours, it showed dose-linear pharmacokinetics. Intravenous infusion of 150 mg of a remdesivir solution repeated one hour per day showed a linear pharmacokinetics over 14 days. After intravenously injecting 75 and 150 mg of remdesivir solution formulations over two hours, the pharmacokinetic profile was similar to that of a lyophilized formulation. Intravenous infusion of 75 mg of drug over 30 minutes provides similar levels of parent drug exposure to the same dose over two hours. After the intravenous infusion, remdesivir will enter the cellular metabolism to form active GS-443902 (Figure 1C), but the frequencies of PBMCs exposure of GS-443902 are higher than those of intravenous infusion of remdesivir 150 mg within two hours. Studies in PBMCs show that the half-life of GS-443902 is more than 35hours. In the case of daily administration, the active substance of the drug GS-443902 will accumulate in vivo. As a result, in large-scale clinical trials, after the first dose of 200 mg is administered, the subsequent dose is adjusted to 100 mg to ensure the proper blood concentration in vivo. Intravenous infusions in previous phase I clinical trials have good safety and pharmacokinetic properties. Also, no cytotoxicity, hepatorenal toxicity, or no serious adverse reactions related to metering have been observed in climbing experiments. Subjects were tolerant in studies that repeated 150 mg intravenously daily for 7 to 14 days. Remdesivir did not show any renal injuries in a multi-dose study [20, 4, 22].

Mode of Action of Remdesivir: an analog nucleotide inhibitor of RNA-dependent RNA polymerases

1) SARS-CoV-2 enters target cells by binding the S protein to the ACE2 receptor on the cell surface; 2) Remdesivir, the nucleotide analogues, act as RdRp inhibitors, can provide a scheme for blocking RNA replication; 3) Once remdesivir added into the growing chain (I position), is 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; 4) Remdesivir triphosphate cannot be removed by nsp14-ExoN [20].

Remdesivir is a prodrug. Its active analog enters and accumulates in cells, inhibiting viral RdRp4 and stopping viral replication. Coronaviruses have an enzyme (exoribonuclease) that corrects errors in the RNA sequence, potentially limiting the effects of analogs, but remdesivir can evade this proofreading. In the laboratory, viral mutation can lead to resistance to remdesivir, but the mutant viruses are less infective [23, 19].

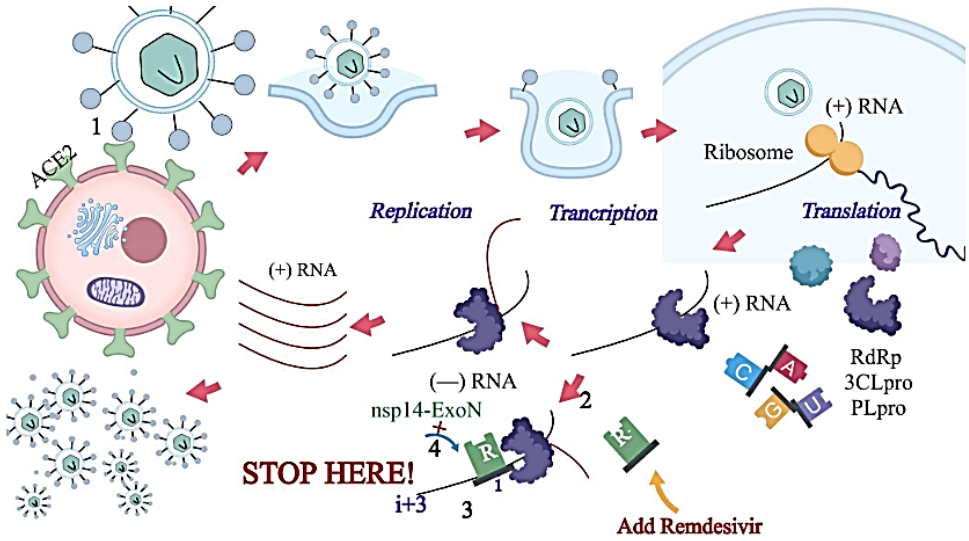

Figure 2. SARS-COV-2 invasion process and how remdesivir works

(Source : www.sciencedirect.com. Cao, et al. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. *Travel Medicine and Infectious Disease*, 2020, 101647)

As a nucleoside analog, remdesivir acts targeting the viral genome replication process [12, 24]. The RdRp is the protein complex CoVs use to replicate their RNA-based genomes. After the host metabolizes remdesivir into active NTP, the metabolite competes with adenosine triphosphate (ATP; the natural nucleotide normally used in this process) for incorporation into the nascent RNA strand. 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. Although CoVs have a proofreading process that can detect and remove other nucleoside analogs, rendering them resistant to many of these drugs, remdesivir seems to outpace this viral proofreading activity, thus maintaining antiviral activity [24, 25]. Remdesivir acts by reducing viral replication within the host cells and improving MERS/CoV induced lung damage as demonstrated in non-human primates. Remdesivir reduced the severity of disease, virus replication, and damage to the lungs when administered as pre-exposure prophylaxis and treatment in rhesus macaques [12, 26].

Before this authorization, the use was approved only in the context of compassionate use protocols (child < 18 years and pregnant women) or in subjects enrolled in clinical trials, therefore it is not classified in any FDA toxicity category [5]. The dosage currently proposed is a single iv 200-mg loading dose, followed by 100-mg daily infusion for 9 d. At these dosages remdesivir does not appear to cause harmful side effects on the liver or kidney, however, treatment should not be started in patients with a glomerular filtration fraction less than 30 l/min and in those with alanine aminotransferase level >5 times the upper limit of normal [12, 27].

Possible side effects of remdesivir are:

• Infusion-related reactions. Infusion-related reactions have been seen during a remdesivir infusion or around the time remdesivir was given. Signs and symptoms of infusion-related reactions may include: low blood pressure, nausea, vomiting, sweating, and shivering.

• Increases in levels of liver enzymes, seen in abnormal liver blood tests. Increases in levels of liver enzymes have been seen in people who have received remdesivir, which may be a sign of inflammation or damage to cells in the liver.

These are not all the possible side effects of remdesivir. Remdesivir is still being studied so it is possible that all of the risks are not known at this time [3].

Clinical Trials and Successful cases of Remdesivir in treating COVID-19

In vitro (laboratory) testing of remdesivir demonstrated it is active against SARS-CoV-2 (the virus causing COVID-19). Preliminary results from a Phase 3, placebo-controlled clinical trial of remdesivir by the National Institute for Allergy and Infectious Diseases suggested that patients taking remdesivir experienced faster time to recovery as compared to patients taking a placebo. This trial included a sizeable proportion of patients who were receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO) at baseline. Based on these findings, the Fact Sheet for Health Care Providers details a 10-day treatment course for patients receiving mechanical ventilation or ECMO [3]. Patients who receive a 5-day treatment course but do not demonstrate clinical improvement are eligible to continue to receive remdesivir for an additional 5 days. The safety and efficacy of remdesivir for the treatment of COVID-19 are being evaluated in multiple ongoing clinical trials [3, 27].

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. In this study, the time to clinical improvement for 50 percent of patients was 10 days in the 5-day treatment group and 11 days in the 10-day treatment group.

More than half of patients in both treatment groups were discharged from the hospital by Day 14 (5-day: 60.0%, n=120/200 vs.10-day: 52.3% n=103/197; p=0.14). At Day 14, 64.5 percent (n=129/200) of patients in the 5-day treatment group and 53.8 percent (n=106/197) of patients in the 10-day treatment group achieved clinical recovery. Clinical outcomes varied by geography. Outside of Italy, the overall mortality rate at Day 14 was 7 percent (n=23/320) across both treatment groups, with 64 percent (n=205/320) of patients experiencing clinical improvement at Day 14 and 61 percent (n=196/320) of patients discharged from the hospital [3, 27].

Remdesivir was generally well-tolerated in both the 5-day and 10-day treatment groups. The most common adverse events occurring in more than 10 percent of patients in either group were nausea (5-day: 10.0%, n=20/200 vs. 10-day: 8.6%, n=17/197) and acute respiratory failure (5-day: 6.0%, n=12/200 vs. 10-day: 10.7%, n= 21/197). Grade 3 or higher liver enzyme (ALT) elevations occurred in 7.3 percent (n=28/385) of patients, with 3.0 percent (n=12/397) of patients discontinuing remdesivir treatment due to elevated liver tests [3, 27, 28].
Key efficacy and safety results from the study are included in the table below.

Gilead initiated two randomized, open-label, multi-center Phase 3 clinical trials for remdesivir, the SIMPLE studies, in countries with a 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 (USA), China, France, Germany, Hong Kong, Italy, Japan, Korea, Netherlands, Singapore, Spain, Sweden, Switzerland, Taiwan and United Kingdom (UK) [3].

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 National Institute of Allergy and Infectious Diseases (NIAID) released the results of its trial using remdesivir for COVID-19 patients. They studied the effects of the drug on patients who were already infected with COVID-19 to see whether it helped them recover faster and improve their survival rate [3].

Adult patients hospitalized with COVID-19 were given daily injections of remdesivir. They were found to recover four days faster, an improvement of 31%, when compared with other patients who only received standard care and placebo (29). The results also indicated that more patients survived the infection with remdesivir treatment, with the death rate dropping from 11.6% to 8%. But we need to treat the results of this trial with caution; for the moment they are only preliminary [3].

In the end, the study only collected data on 237 patients, compared with 1,063 patients in the NIAID trial. The authors acknowledge further study is needed in more seriously ill patients and with a larger sample size. Currently, there are more than a dozen other clinical trials of remdesivir and COVID-19 being undertaken throughout the world. We need to await the data to know for sure whether the drug is as effective as we need it to be [3, 30].

Table 2. Efficacy and Safety Results of 5-Day RDV vs 10-Day RDV

	5-Day RDV	10-Day RDV	Baseline adjusted
	n=200	n=197	p-value[1]
Clinical Efficacy Outcomes at Day 14			
≥ 2-point improvement in ordinal scale	129 (65)	107 (54)	0.16
Clinical recovery	129 (65)	106 (54)	0.17
Discharge	120 (60)	103 (52)	0.44
Death	16 (8)	21 (11)	0.70
Safety			
Any adverse event (AE)	141 (71)	145 (74)	0.86
Grade ≥3 study drug-related AE	8 (4)	10 (5)	0.65
Study drug-related serious adverse event (SAE)	3 (2)	4 (2)	0.73
AE leading to discontinuation	9 (5)	20 (10)	0.07

[1]Adjusted for baseline clinical status
(Source : Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med [Internet]. 2020;1–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32459919)

Early data from a randomized, placebo-controlled study by the National Institutes of Health (NIH) reported that remdesivir helps to accelerate the time to recovery in severely ill patients with COVID-19. This trial showed that recovery was reduced from 15 to 11 days. Results included 1,063 patients from 68 sites (47 in the United States and 21 in European and Asian countries) are still awaiting a peer review. On 1st May 2020, few days after early data of the remdesivir trials were released by NIH, the FDA approved the emergency use (EUA) of the remdesivir for the treatment of COVID-19 in adults and children hospitalized with severe disease [31]. The dosage currently proposed is a single iv 200 mg loading dose, followed by 100 mg daily infusion for 9 d. At these dosages remdesivir does not appear to cause harmful side effects on the liver or kidney, however, treatment should not be started in patients with a glomerular filtration fraction less than 30 l/min and in those with alanine aminotransferase level >5 times the upper limit of normal [12, 32, 33].

The recent case report recorded the administration of compassionate-use remdesivir on the 35-year-old man with COVID-19 in the United States. The patient had initial symptoms of mild cough and low-grade intermittent fevers; subsequently his nasopharyngeal and oropharyngeal swabs were tested positive for SARS-CoV-2 by real-time reverse-transcriptase-polymerase-chain-reaction assay. His vital signs and respiratory status remained largely stable before the 9th day of COVID-19 except for intermittent fevers and nonproductive cough. Since from day 9, the patient began to develop atypical pneumonia, with a worsening chest radiograph, decreasing oxygen saturation values, and substantial rales in both lungs. With remdesivir administered on day 11, significant improvements in oxygen saturation values, rales, and other symptoms were observed on day 12, indicating the rapid benefit of remdesivir. Subsequently, the patient returned to be afebrile, and all symptoms had resolved except for mild cough. Besides, a recently published study revealed results of compassionate use of remdesivir for patients with severe COVID-19. In 53 patients who received at least one dose of remdesivir, 36 (68%) had clinical improvements, including changes on oxygen-support and extubation of mechanical ventilation. The mortality of the patients was 13%, which was lower than the general mortality of severe patients with COVID-19 (over 50%), as reported by the WHO [34, 35.]

Clinical Trials of Remdesivir for treating COVID-19 in hospitalized pregnancies

No adequate and well-controlled studies of remdesivir use in pregnant women have been conducted. Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryofetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose [3, 36, 37].

Chen et al. report 9 women delivering by caesarean section from 36 weeks onwards, 2 pre-term. In two women at term, fetal distress was reported. In 6 of these women with COVID-19 who delivered by caesarean section and underwent testing after delivery by caesarean section, there was no evidence of SARS-CoV 2 in amniotic fluid, cord blood neonatal throat swab or breastmilk samples. A news report of a baby with a COVID-19 infected mother testing positive at 30 hours has not been reported in scientific journals [38, 39].

Wang et al reported on one woman who underwent a caesarean section for fetal distress at 30 weeks gestation, the infant was born in good condition and samples of amniotic fluid, neonatal gastric samples, placenta and infant throat swabs were negative for SARS-CoV 2. In Chen et al, n=9, all babies were delivered after 36 weeks and were well at discharge. Zhu et al reported a cohort born at earlier gestation (from 31 weeks gestation), 6/10 babies were admitted to the NNU for respiratory support, 2 developed DIC, and 1 multiple organ failure. Neonatal morbidity was more marked in this series probably due to greater prematurity, one baby died after being born at 34 weeks. Requiring admission at 30 minutes of life with respiratory difficulties, the baby deteriorated, developed shock, DIC, and multi-organ failure and dies at 8 days of life. 9/10 infants were tested for COVID-19, all testing was negative. Wang et al reported a baby born at 30 weeks in good condition with an uneventful neonatal course [38, 1].

Nearly 15% of pregnant patients developed severe Covid-19, which occurred primarily in overweight or obese women with underlying conditions. Obesity and Covid-19 may synergistically increase the risk for a medically-indicated preterm birth to improve maternal pulmonary status in late pregnancy [40]. Collectively, these findings support categorizing pregnant patients as a higher risk group, particularly for those with chronic co-morbidities [41].

There are limited data on the impact of the current COVID-19 outbreak on women affected in pregnancy and their babies. Studies were all case-reports or series and of low quality. Outcomes reported varied, one series on COVID-19 did not report on maternal outcomes. The need for provision for fetal monitoring including serial ultrasound for women with COVID-19 will be challenging for maternity services. Women will need to be cared for in units with appropriate neonatal intensive care facilities as COVID-19 is associated with pre-term delivery in 50% of reported cases [38, 42].

Therapeutics announced as being under consideration and trial in the outbreak include Remdesivir. Remdesivir has been used for the treatment of Ebola in pregnant women [43], however, it should be acknowledged that Ebola is a condition with a CFR of 50% for which there would be a higher tolerance for adverse effects of a potentially beneficial treatment than would be the case for COVID-19 where the CFR is around 1%. It would seem reasonable not to exclude seriously ill pregnant women from trials of these therapies for COVID-19 [44, 45].

Limited data obtained from cases of pregnant women with COVID-19 suggest that the transplacental transmission is unlikely in late pregnancy close to term, as the virus was not identified in the amniotic fluid, placenta, breast milk of these mothers or the nasal secretions of their neonates. However, infection can occur in neonates via close contact. Two such cases of neonatal COVID-19 infection have been confirmed so far at 36 hours and 17 days after birth, and both appear to have been infected postnatally. Therefore, early cord clamping and temporary separation of the newborn for at least 2 weeks is recommended to minimize the risk of viral transmission by avoiding longer, close contact with the infected mother [38, 46, 47]. The neonate should be cared for in an isolation ward and carefully monitored for any signs of infection. During this period, direct breastfeeding is not recommended. A possible option is for the mother to pump her breast milk, which can be fed to the baby by a healthy caregiver [11, 48].

However, timing of delivery should be individualized based on disease severity, existing comorbidities such as preeclampsia, diabetes, cardiac disease, obstetric history, and gestational age and fetal condition [49]. In mild and stable cases responding to treatment and in the absence of fetal compromise, pregnancy may be continued to term under close surveillance. In critical cases, continuing pregnancy may endanger the safety of the mother and her fetus. In such situations, the delivery may be indicated even if the baby is premature, and termination of pregnancy should be considered as an option before fetal viability is reached to save the pregnant woman's life after careful consultation with the patient, her family, and an ethical board [11].

In two published reports from China involving a total of 18 pregnant women with COVID-19, all but two were delivered vaginally, and none of these neonates were infected by SARS-COV-2. As the evidence for vaginal shedding of virus and vertical transmission is lacking, vaginal delivery may be considered in stable patients [11, 50].

Clinical recommendations for managing COVID-19 infection in pregnancy should be based on data from the current epidemic rather than drawing on limited experience from previous outbreaks of different types of coronaviruses, as their epidemiology, clinical course, and response to treatment may differ. Therefore, complete data on all pregnancies affected by COVID-19 should be collected and made publicly available. Sharing data, knowledge and expertise, and helping countries with poor resources and weaker healthcare systems are important in this respect [50]. The National Institutes of Health published updated treatment guidelines for COVID-19, including special considerations for pregnant women. Important considerations include early detection of severe illness and individualized decisions surrounding the use of adjunctive medications, as pregnant women are not included in many current clinical trials exploring treatment options for COVID- 19 [51].

CONCLUSION

The current COVID-19 pandemic is an international public health problem. There have been rapid advances in what we know about the pathogen, how it infects cells and causes disease, and clinical characteristics of the disease [7]. The complete lack of specific treatment forced clinicians to use old drugs, chosen for their efficacy against similar viruses or their in vitro activity. Trials on patients are ongoing but the majority of information about therapy for COVID-19 comes from small case series and single-center reports. In this complicated scenario, pregnant women represent a frail category of patients, systematically excluded from trials and thus candidate to compassionate treatments. COVID-19 pandemic is ongoing and new evidences regarding its therapy are emerging daily. Nevertheless, in the current situation of uncertainty and poor knowledge about the management of COVID-19 during pregnancy, this present overview may provide useful information for clinicians with practical implications.

To summarize, even though remdesivir was proposed as a viable option for treating COVID-19 based on laboratory experiments and reports from compassionate use, its safety and effect in humans requires high-quality evidence from well-designed and adequately-powered clinical trials for further clarification, particularly in pregnancies.

At present, limited data are available on critically ill pregnant women with COVID-19. Clinical recommendations will surely continue to evolve as we learn more about this disease in pregnant and non-pregnant adults. As the pandemic unfolds and more microbiologic, pharmacologic, and clinical information about COVID-19 comes to light, it is important to consider the unique needs of critically ill pregnant patients in formulating specific guidelines and treatment plans. Besides, clinical trials are not often conducted among pregnant patients for safety reasons and this means that drugs that may be effective in the general population cannot be used for pregnant women due to the lack of knowledge of side effects in this category of people. Additional trials may be planned in special populations such as patients with pregnancy use of remdesivir and other drugs to treat COVID-19.

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