Drug Corner

Remdesivir in the Horizon

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The pandemic of corona virus disease 2019 presents an unprecedented challenge to identify drugs for prevention and treatment. Remdesivir, a broad spectrum antiviral drug has been authorized by the U.S Food and Drug Administration (FDA) under Emergency Use Authorization (EUA) for treatment of hospitalized patients with severe disease on 1st May 2020.

[*J Indian Med Assoc* 2020; **118(5):** 42-4]

Key words **: COVID-19, SARS-CoV-2, Remdesivir.**

The Corona Virus Disease 2019 (COVID 19) pandemic declared by WHO on 11th March 2020, is posing a veritable threat to the existence of mankind[1]. No specific drug has been proven fully effective for treatment of patients with COVID 19 infection. Remdesivir, a prodrug (GS-5734), is an adenosine triphosphate analogue first described in the literature in 2016 as a potential treatment for Ebola virus infection. This antiviral drug has shown inhibitory effects on pathogenic human and animal coronavirus infection,that includes Middle East Respiratory Syndrome, Severe acute respiratory syndrome corona virus 2 in vitro and SARSCoV-1 and SARS CoV2 in animal models[2].

Remdesivir has been authorized by the U.S Food and Drug Administration (FDA) under Emergency Use Authorization(EUA) for treatment of hospitalized patientswith severe disease on 1st May 2020[3]. It was originally invented to manage Ebola virus and Marburg virus infections[4]. This drug is given via intravenous route[5].

Indications :

Treatment of COVID 19 underEUA for treatment of hospitalized adult and paediatric patient with severe disease.

Severe disease is defined as patients with an oxygen saturation (SpO2≤94%) in room air or requiring supplemental oxygen or mechanical ventilation or extracorporeal membrane oxygenation(ECMO)

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Received on : 18/04/2020
Accepted on : 12/05/2020

Editor's Comment :

- Remdesivir, a prodrug (GS-5734), converted to its active metabolite which acts by inhibiting the action of RNA dependent RNA polymerase.
- Remdesivir can be used in both adult and pediatric age group. It can also be used in pregnancy. Nausea, vomiting, diaphoresis and shivering and increase in liver enzymes are common adverse drug reactions of this preparation.
- Remdesivir is contraindicated only in patients with known hypersensitivity to the drug.

Dose Recommendations for Treatment[7] :

Adult Patients : The FDA Emergency Use Authorization suggests a loading dose of 200mg I.V(infused over 30 to 120 mins) in patients ≥40 kg followed by a maintenance dose of 100mg I.V(infused over 30 to 120 mins)once daily. Patients not needing invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) should be treated for 5 days (including the loading dose on day 1). It can be extended up to 10 days if they do not show improvement. Patients requiring invasive mechanical ventilation or ECMO should be treated for 10 days[7].

Paediatric patients : If bodyweight of child is more than 40 Kg, we will follow same protocol as mentioned above for adult patients.

If bodyweight is between 3.5 kg to 40 kg remdesivir is to be used as lyophilized powder preparation for injection,5mg/kg of bodyweight(infused over 30 to 120 mins) in day 1 followed by 2.5 mg/kg of bodyweight(infused over 30 to 120 mins). Patients not needing invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) should be treated for 5 days (including the loading dose on day 1). It can be extended

up to 10 days if they do not show improvement. Patients requiring invasive mechanical ventilation or ECMO should be treated for 10 days.

Storage : Diluted Remdesivir solution for infusion may be kept up to 4 hours at room temperature(20ºC to 25ºC) or 24 hours at refrigerated temperature (2ºC to 8ºC).

After infusion is complete, to flush with at-least 30 ml of 0.9% saline.Discard any remaining reconstituted Remdesivir lyophilized powder and dilute solution.

Mechanism of Action :

Remdesivir is a nucleoside analogue and a prodrug having broad spectrum antiviral activity.It is converted to its active metabolite adenosine nucleotide triphosphate analogue.(8)This metabolite(GS-441524) acts by inhibiting the action of RNA dependent RNA polymerase. It incorporates into RNA and terminates RNA transcription. But viruses with mutations in RNA polymerase may develop partial resistance to Remdesivir.

SARS-Cov2 is an RNA virus. It is dependent on an RNA polymerase enzyme to grow the RNA chain. Remdesivir substitutes this RNA polymerase enzyme.Hence this RNA cannot develop so the virus cannot replicate itself.

Adverse Drug Reactions :

- Nausea, vomiting, diaphoresis and shivering
- Increased liver enzyme levels in blood that may indicate possible liver damage.
- Hypoalbuminemia
- Hypokalaemia

Pregnancy : Remdesivir can be used in pregnancy if the potential benefit justifies the potential risk for the mother and the foetus. It is the risk-benefit ratio that justifies use of this drug in this special group[7].

Monitoring :

Complete hemogram,electrolytes, liver function test, renal function test.

Drug Interactions :

Co-administration of other drugs mayaffect Remdesivir concentration in blood.This drug is partially metabolized by Cytochrome P-450 system(CYP3A4,CYP2D6). Enzyme inducer(CYP 450) drugs like rifampicin,carbamazepine and phenobarbitone will reduce therapeutic concentration of Remdesivir.(6). Remdesivir itself is not believed to affect any other medication.

Contraindications: Remdesivir is contraindicated in patients with known hypersensitivity to the drug**.** It should be used cautiously in associated liver disease. No information is available related to use of this drug in paediatric patients less than 3.5 kg body weight.

Relative contraindications : Renal compromised patients eGFR<30ml/hr.

Critical Appraisal :

Remdesivir was used as a treatment option against Ebola Virus and adequate data is not available to use it as drug of choice in COVID-19. Much information in this article were taken from recently published small trials[2,8] where Remdesivir in patients with severe COVID-19 was used. Hence it is important to discuss the relevance and limitation of thesestudies from clinicians perspective.

These studies providing us initial information of safety and efficacy of Remdesivir in SARS-CoV2 had a limited number of study population.Theyaremostly under-powered e.g statistical power 58% instead of 80% in one trial[2] with more subjects with invasive mechanical ventilation placed in placebo group in comparison to study group. Relatively delayed initiation of investigational drug in study subjects compared to animal study was seen.Study was uncertain about the effect of other drugs (lopinavir/ritonavir, INF-α2b) on Remdesivir pharmacodynamics. In another study[8] though they have shown relative effectiveness with compassionate use of Remdesivir,inadequate sample size (out of 61 data analysed only in 53 patients) and funding by company marketing the drug minimised the credibility of the drug.

Ideally some study subjects should be sampled for plasma drug monitoring to confirm that this therapeutic regimen is sufficient to achieve desired plasma/bronchial lavage fluid drug concentration.Also with the genetic variability of the virus, we need to confirm drug response with strain subtypes in a particular region.

More randomized trials with larger sample size(8,9)and more stringent study designs are required to substantiateRemdesivir as a significantly effectiveweapon against SARS-CoV2.

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Learning Points :

- **Remdesivir, a prodrug (GS-5734), is an adenosine triphosphate analogue first described in the literature in 2016 as a potential treatment for Ebola virus infection**
- **Remdesivir has been authorized by the U.S Food and Drug Administration(FDA) under Emergency Use Authorization(EUA) for treatment of hospitalized patients with severe disease on 1st May 2020**
- **Remdesivir is a prodrug converted to its active metabolite which acts by inhibiting the action of RNA dependent RNA polymerase**
- **Remdesivir can be used in both adult and pediatric age group. It can be used in pregnancy considering risk-benefit ratio for the mother and the foetus.**
- **Nausea, vomiting, diaphoresis and shivering and increase in liver enzymes are common adverse drug reactions of this preparation.**