Drug Corner

Remdesivir — First USFDA Approved On-Label Anti COVID-19 Viral Agent

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On 1st May, 2020 USFDA had authorized to use remdesivir under an Emergency Use Authorization (EUA) for entire population of USA for COVID 19 management. But very recently on 22nd October, 2020 USFDA approved remdesivir for use in hospitalized adult and pediatric patients (≥12 years of age and weighing at least 40 Kg) for the treatment of COVID-19. Remdesivir is the first USFDA approved treatment for COVID-19 management.

Clinical studies showing benefits with remdesivir:

1. NIAID ACTT-1 Study in Subjects with Mild/ Moderate and Severe COVID-19[1]: Among 1062 randomized patients (541 receiving remdesivir and 521 on placebo), remdesivir arm had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), and placebo arm had median recovery time of 15 days (95% CI, 13 to 18). Rate ratio for recovery was 1.29 (95% CI, 1.12 to 1.49; P<0.001). Mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).This study had shown that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.

2. Study GS-US-540-5773 in Subjects with Severe COVID-19[2] : This study had showed that there were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups. All-cause mortality at Day 28 was 12% vs 14% in the 5-day and 10-day treatment groups, respectively.

3. Study GS-US-540-5774 in Subjects with Moderate COVID-19[3] : This study showed that the odds of improvement in the ordinal scale were higher in the 5-day remdesivir group at Day 11 when compared to those receiving only standard of care (odds ratio 1.65 [95% CI 1.09 to 2.48], p=0.017).

Editor's Comment :

- **On 22nd October, 2020 USFDA approved remdesivir for use in hospitalized adult and pediatric patients (≥12 years of age and weighing at least 40 Kg) for the treatment of COVID-19.**
- **Use of remdesivir in India is still under Emergency Use Authorization.**

SOLIDARITY Trials: No Benefit with remdesivir :

From the recently published interim results of the Solidarity Trial[4], we came to know that all 4 treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ ritonavir and interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients. Though there is no data on baseline status of the patients who were included in the study. Lag time between symptoms initiation and treatment initiation is a very critical issue regarding outcome assessment. Late initiation of antiviral may have reduced response compared to early start.

Relationship between day of illness and morbidity due to virus and immune triggering :

Initial seven to ten days are generally responsible for virus related morbidity whereas after five to seven days of symptoms onset, immune triggering is responsible for morbidity. Between 5th and 10th day of symptoms onset, generally there is some overlap between virus and immune triggering mediated morbidity. After 10th day when generally virus associated morbidity is reduced as viral replication ends; there is very less role of any antiviral therapeutics. It is important to initiate antiviral drugs timely to get optimum benefits.

Indication of remdesivir[5] :

As per USFDA SARS-CoV-2 nucleotide analog RNA polymerase inhibitor, remdesivir is indicated for adults and pediatric patients (12 years of age and older, and weighing at least 40 kg) for the treatment of hospitalized COVID-19 patients. Use of remdesivir in India is still under Emergency Use Authorization. Remdesivir may be considered in moderate COVID 19 patients on oxygen therapy. There should not be any contraindications like a) AST/ALT > 5 times Upper limit of normal (ULN) b) Severe renal impairment (ie, eGFR < 30ml/min/m2 or

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need for hemodialysis) c) Pregnancy or lactating females and d) Children (< 12 years of age) as per updated Clinical Management Protocol for COVID-19 by Government of India[6]. It needs immense discussion to understand the timing of initiation of remdesivir. Delayed initiation of remdesivir due to wait for need of oxygenation may be less beneficial for the patient because initial few days for viral replication may pass out. In adults and pediatric patients 12 years of age and older and weighing at least 40 kg, recommended dosage is as following – A single loading dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg from Day 2 infused over 30 to 120 minutes. The recommended duration of treatment for patients not requiring invasive mechanical ventilation and/or ECMO is 5 days as per USFDA. If a patient does not show improvement in clinical parameters, treatment may be extended for up to 10 days. For patients on invasive mechanical ventilation and/or ECMO, the USFDA has recommended for 10 days remdesivir therapy.

Warning and Precautions :

Hypersensitivity reactions have been seen during and following administration of remdesivir. Slowing down the rate of infusion with a maximum infusion time of up to 120 minutes, can be considered to prevent signs and symptoms of hypersensitivity. Need to be vigilant for signs and symptoms of a clinically significant hypersensitivity reaction and immediately discontinue remdesivir infusion and initiate appropriate management. If ALT increased by 10 times of baseline value after initiation of remdesivir therapy it is important to discontinue it. Stop remdesivir infusion if ALT elevation is associated with signs or symptoms of liver inflammation. There is a chance of decreased antiviral activity when co-administered with chloroquine phosphate or hydroxychloroquine sulfate. In-vitro drug-drug interaction between remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is seen. A cell culture data had demonstrated an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.

Remdesivir in Special Populations :

1. Pregnancy – Data from published case reports regarding compassionate use of remdesivir in pregnant females are available but are relatively insufficient to evaluate for adverse maternal or fetal outcomes. Remdesivir demonstrated no adverse effect on embryo-fetal development in nonclinical reproductive toxicity studies. Pregnant women hospitalized with COVID-19 are at risk for serious morbidity and mortality due to disease. It is important to weigh the risk of giving remdesivir and risk of not giving remdesivir to those patients. Informed prescribing, necessary consents and compassionate risk benefit explanation are extremely important in this regard.

2. Lactation – It is important to consider developmental and health benefits of breastfeeding along with the mother's clinical need for remdesivir. It is also necessary to stress upon the potential adverse effects on the breastfed child from remdesivir or from the underlying maternal COVID 19 infection related condition.

3. Pediatric Use – As per USFDA safety and effectiveness of remdesivir for the treatment of COVID-19 have been established in pediatric patients 12 years and older and weighing at least 40 kg.

4. Geriatric Use – No dose adjustment is required for geriatric population whose age is more than 65 years. Need to be cautious regarding renal, hepatic condition of the patient.

5. Renal Impairment – Though there is no clinical pharmacokinetics data available for renal compromised patients, it is important to consider that patients having eGFR greater than or equal to 30 mL per minute can continue remdesivir for treatment of COVID-19 with no dose adjustment.

Adverse Drug Reaction of Remdesivir :

Need to be vigilant about following adverse drug reactions which has a incidence greater than or equal to 5% like nausea, ALT increased, and AST increased. There is also a chance of development of rash, local site erythema, seizure, anaphylaxis and angioedema following remdesivir infusion. It is important to identify early and de-challenge remdesivir if any adverse drug reaction appears.

Conclusion :

Remdesivir is shown to be efficacious in three well conducted RCT and therefore approved by USFDA to use it in COVID 19 treatment SOLIDARITY trial conducted by WHO contradicts these RCT results. We need to conduct more RCTs and prospective observational studies considering the timely initiation of remdesivir. Time will say whether Indian drug regulators will be convinced enough to approve remdesivir as first anti-COVID 19 viral agent.

References

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5 PRESCRIBING INFORMATION: VEKLURY® (remdesivir) for injection, for intravenous use VEKLURY® (remdesivir) injection, for intravenous use Initial U.S. Approval: 2020

6 MOHFW – GOI, Updated Clinical Management Protocol for COVID-19à03.07.2020.