Original Article

Impact of Remdesivir on inflammatory and prognostic markers of COVID-19: Findings of an event-monitoring study

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Abstract

Introduction: Remdesivir is currently approved for treating hospitalised patients with COVID-19. However, it is a priority to monitor its safety and effectiveness in various clinical settings. This study was undertaken to assess the impact of remdesivir on inflammatory and prognostic markers of COVID-19. **Materials and Methods:** A hospital-based prospective longitudinal study was conducted over two months comprising event monitoring of COVID-19 patients administered remdesivir as per standard guidelines. The demographic details, risk factors and all baseline parameters were collected. The patients were followed up for the appearance of any adverse drug reactions (ADRs) after the start of remdesivir therapy from Day 1 to discharge or death every day. Repeat Lab tests were done on days 2, 4, 6 and 10 days to assess the impact of remdesivir on inflammatory and prognostic markers of COVID-19 over time. Significant predictors of survival in the cohort were also assessed. **Results:** A total of 60 COVID-19 patients were administered remdesivir. The mean age of the patients was 59.2 (+13.7) years. There was a significant improvement in the serum creatinine (decreased from 0.9 to 0.7 mg/dL), lymphocyte count {decreased from 9.2 to 7.3 (10^9 cells/L)} and serum sodium (increased from 134.6 to 137.4) of the patients over six days after the administration of remdesivir. The significant survival predictors were multiple organ failure (P 0.046) and WBC count on Day 10 (P 0.001). **Conclusion:** Remdesivir administration improved the prognostic biomarker profile in COVID-19 patients.

Keywords: Adverse drug reaction profile, Inflammatory biomarkers, Prognostic markers, Remdesivir, Survival analysis

Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has been an unprecedented tragedy, claiming more than 6.7 million lives till now.[1] It continues to take a toll on the world economy and healthcare systems. The catastrophic disease took the world completely by surprise and necessitated a mad rush for the development of several vaccines hitherto unavailable. A host of repurposed drugs from antivirals (i.e. Favipiravir, Lopinavir/Ritonavir, Oseltamivir, remdesivir) to immunomodulators (i.e. chloroquine, hydroxychloroquine), convalescent plasma, anticoagulants, dexamethasone and Azithromycin were all explored for their utility against the virus.[2] Around 16 monoclonal antibodies and

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Received: 21-02-2023 **Revised:** 04-07-2023
Accepted: 06-07-2023 **Published:** 21-12-2023

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_334_23

How to cite this article: Singh S, Sinha N, Lohani P, Agarwal N, Singh P, Singh CM. Impact of Remdesivir on inflammatory and prognostic markers of COVID-19: Findings of an event- monitoring study. J Family Med Prim Care 2023;12:3135-41.

multiple other compounds received emergency authorisation to augment the armamentarium against the disease.[3] Apilimod, a PIKfyve inhibitor, is currently undergoing Phase II trials; however, human efficacy or animal 2019 coronavirus disease (COVID-19) model data for Apilimod was unavailable at the time of this study.[4]

Remdesivir is currently approved for treating hospitalised patients with COVID-19, along with the protease inhibitor Paxlovid.[5] All through the COVID-19 pandemic, it has consistently travelled in and out of focus, beginning with its compassionate use in severe COVID-19 pneumonia in an intensive care unit (ICU) and non-ICU patients.[6,7]

However, evidence about the toxicities associated with remdesivir is patchy and fragmented. It is a well-known fact that hyperinflammation in COVID-19 patients is the most critical determinant of disease severity and mortality. D-dimers, ferritin, C-reactive protein, procalcitonin, and neutrophil–lymphocyte ratio are all elevated in COVID-19 patients.[8] Their continuous monitoring serves to monitor disease severity, progression, and outcome. However, it is frankly paradoxical that even though levels of inflammatory and prognostic markers of COVID-19 govern treatment strategies and predict outcomes, hardly any studies have researched the effects of remdesivir administration on inflammatory and prognostic features of COVID-19. It is clear that despite inconclusive observations and marked heterogeneities in its reported safety and efficacy, remdesivir is here to stay and will continue to be used for COVID-19. Consequently, continuous monitoring of its safety and effectiveness in various clinical settings is a priority. An intensive and complete evaluation of the efficacy of any drug against COVID-19 can only be possible if its impact on inflammatory and prognostic markers is also assessed.[9] With this study, the family physicians would be able to better understand the impact of the drug on inflammatory markers and would be able to recommend it safely to the COVID-19 patients.

Aims and Objective

To assess the impact of remdesivir on inflammatory and prognostic markers in COVID-19 patients admitted in a tertiary care centre of Eastern India.

Materials and Methods

A hospital-based prospective longitudinal study was conducted, which comprised event monitoring. The event monitoring was done for all the COVID-19 patients admitted to the tertiary care centre and administered remdesivir as per standard guidelines over two months. A non-probability convenient sampling was conducted, and all the consenting patients were included in the study. Remdesivir was administered as a loading dose (200 mg) on Day 1, followed by daily IV maintenance doses (100 mg) for five days.

The demographic details (age, sex, height, weight, outcome), risk factors (H/O alcohol, smoking, hepatitis, drug/any other allergy) and all baseline parameters (oxygen support, temperature, BP, respiratory rate, CXR findings, CBC, LFT, KFT, ECG) of the patients who meet inclusion criteria were collected using Google Form. The patients were followed up for the appearance of any adverse drug reactions (ADRs) after the start of remdesivir therapy from Day 1 to discharge or death every day. Repeat Lab tests were done on days 2, 4, 6 and 10 (if patients were still admitted). Changes in the lab values (KFT, LFT, CXR, CBC) reflecting potential ADRs were also recorded. The lab values were categorised into normal and deranged for ease of analysis. The following values were taken as reference for BUN (mmol/l) is 6–13.8, albumin (g/L) 27.4–33.6, creatinine (mg/dl) 0.5 to 1.5, AST (U/L) 18–70, ALT (U/L) 29–33, Hb (g/dl), WBC (x10 _9/L) 4.5–11, lymphocytes (x10 _9/L) 0.4–1.4, neutrophils (x10 _9/L) 2.6–11, platelets (×10_9/l) 150–450, and D-dimers (ug/ml) 0.4–5.3.

Data analysis

The data entered on Google Forms were conceived on Google spreadsheet. The quantitative and categorical variables were summarised as means (standard deviation), percentages, and proportions. Interpretation and analysis of the association of ADRs with various risk factors were carried out by applying the Chi-square test to ascertain the significance level. Mortality in the cohort has been described using Kaplan–Meier analysis. As the laboratory tests were conducted at multiple time points, repeated measure ANOVA was conducted to assess the impact of remdesivir on deranged lab values. Cox-regression hazard model was constructed to identify the independent predictors of mortality among COVID-19 patients who were administered remdesivir. The predictors were identified through a log-rank test having a significance value of $P < 0.2$. The significance level was set at $P < 0.005$. All the analysis was done on STATA 12.0 and Jamovi 2.2.5.

Results

A total of 60 COVID-19 patients were administered remdesivir. Their age ranged from 27 to 89 years, with a mean age of 59.2 (+13.7). Of the 60 patients, 14 were female, and 46 were male. The mean duration of stay in the hospital was 19.8 (+11.5) days, while the median was 15 days (range 10–60 days). Almost half of the patients (31, 51.7%) were on non-invasive high-flow oxygen, followed by 40% (24) on low-flow supplemental oxygen. The mean length of stay was 20 days, with a maximum of 60 days. Approximately, one-fourth of the patients (25) survived and were discharged from the hospital on recovery, while three–fifth (35) succumbed. The most common co-morbidity was hypertension (25, 41.7%) and diabetes (22, 36.7%). Thirty per cent of patients were obese, asthmatic and had a history of hyperlipidaemia and smoking [Table 1].

Impact of Remdesivir on inflammatory and prognostic markers (repeated measure ANOVA)

One-way repeated measure ANOVA was run to assess the impact of remdesivir on inflammatory markers of COVID-19

Table 1: Background characteristics of COVID-19 patients administered remdesivir (*n*=60)

Background characteristics	*n* (%)
Age categories	
<60 years	23 (38.3%)
≥60 years	37 (61.7%)
Gender	
Male	46 (76.7%)
Female	14 (23.3%)
Fever present	26 (43.3%)
Six category scale	
Low flow supplemental oxygen	24 (40.0%)
Non-invasive ventilation or high-flow oxygen	31 (51.7%)
Invasive mechanical ventilation	05 (8.3%)
Mean length of stay in hospital (days)	19.9 (±11.5)
Outcome	
Cured	25 (41.7%)
Died	35 (58.3%)
Co-morbidities	
Smoking history	15 (25%)
Hypertension	25 (41.7%)
Diabetes	22 (36.7%)
Coronary heart disease	05 (8.3%)
Asthma	18 (30%)
Hyperlipidaemia	18 (30%)
Obesity	15 (25%)

over different time points (Day 1, Day 2 and Day 6). Since the assumption of sphericity still needed to be met, Greenhouse Geisser was used to calculate significance. It can be deduced from Table 2 that significant improvement was observed in serum creatinine, lymphocyte count and serum sodium. The serum creatinine levels reduced from 0.9 to 0.7 mg/dL in the patients over six days after the administration of remdesivir. No change in serum bilirubin level was seen. Aspartate aminotransferase also decreased, but alanine aminotransferase increased from 88 to 92 IU/L. The haemoglobin levels, WBC count and platelet count did not improve over time. The lymphocyte count decreased to 7.3 from 9.2 (10^9 cells/L). The sodium levels increased from 134.6 to 137.4 (*P* value 0.007), while the potassium level did not change over time. A decrease in serum ferritin levels by 113 units was noted over two days.

Table 2: Change in inflammatory markers after administration of remdesivir over time using repeated measure ANOVA

Inflammatory markers	Mean (+SD)	*F* (df1, df2)	*P*
Creatinine			
Day 1	0.9 (0.36)	17.39 (2.0, 115.8)	<0.000
Day 2	0.8 (0.32)		
Day 6	0.7 (0.31)		
T. Bilirubin			
Day 1	1.0 (0.39)	0.58 (2, 118)	0.541
Day 2	1.1 (0.53)		
Day 6	1.1 (0.57)		
AST			
Day 1	73.9 (60.70)	0.88 (2, 118)	0.401
Day 2	64.5 (48.69)		
Day 6	64.1 (63.75)		
ALT			
Day 1	88.5 (84.4)	0.17 (2, 118)	0.7688
Day 2	86.6 (82.2)		
Day 6	92 (117.49)		
Haemoglobin			
Day 1	11.9 (2.09)	3.03 (2, 118)	0.0648
Day 2	11.5 (1.87)		
Day 6	11.5 (2.04)		
WBC count			
Day 1	14.3 (7.74)	0.402 (2, 116)	0.667
Day 2	14.8 (6.55)		
Day 6	14.1 (5.96)		
Lymphocyte count			
Day 1	9.2 (6.21)	4.38 (2, 115)	0.015
Day 2	7.5 (4.89)		
Day 6	7.3 (5.49)		
Platelet			
Day 1	210.4 (105.32)	1.117 (2, 87)	0.318
Day 2	226.7 (108.44)		
Day 6	223.7 (108.76)		
Sodium			
Day 1	134.6 (6.15)	6.18 (2, 88)	0.007
Day 2	136.3 (5.16)		
Day 6	137.4 (5.41)		
Potassium			
Day 1	4.4 (0.82)	0.603 (2, 117)	0.547
Day 2	4.3 (0.75)		
Day 6	4.3 (0.62)		
Serum ferritin			
Day 1	799.6 (575.34)	2.96 (1, 30)	0.096
Day 2	686.9 (506.32)		

Predictors of mortality among COVID-19 patients administered Remdesivir

Next, the Kaplan–Meier curve was plotted to compare the median survival probability based on gender, multiple organ failure and WBC count at Day 10. The survival among females was two days more than males (*P* 0.066). Similarly, patients with multiple organ failure had 05 days less survival than those without multiple organ failure (*P* 0.07). Statistically, more survival was observed among patients with normal WBC count compared to those with deranged counts (*P* 0.035) [Figures 1a-c].

The cox-proportional model was significant (LR Chi = 16.64, df = 04, *P* 0.0022). The significant predictors were multiple organ failure (*P* 0.046) and WBC count on Day 10 (*P* 0.001). Each unit increase in WBC led to a 9% higher risk of death, and those with multiple organ failure had 2.87 times higher risks of death compared to those patients who did not have multiple organ failure. Surprisingly, patients with diabetes had better survival than non-diabetic patients (HR 0.59, *P*- 0.216). Although insignificant, male (OR 1.32, *P*- 0.632) gender and each increasing unit of creatinine had a 59% (*P*- 0.229) higher risk of death than females and normal creatinine, respectively [Figure 2].

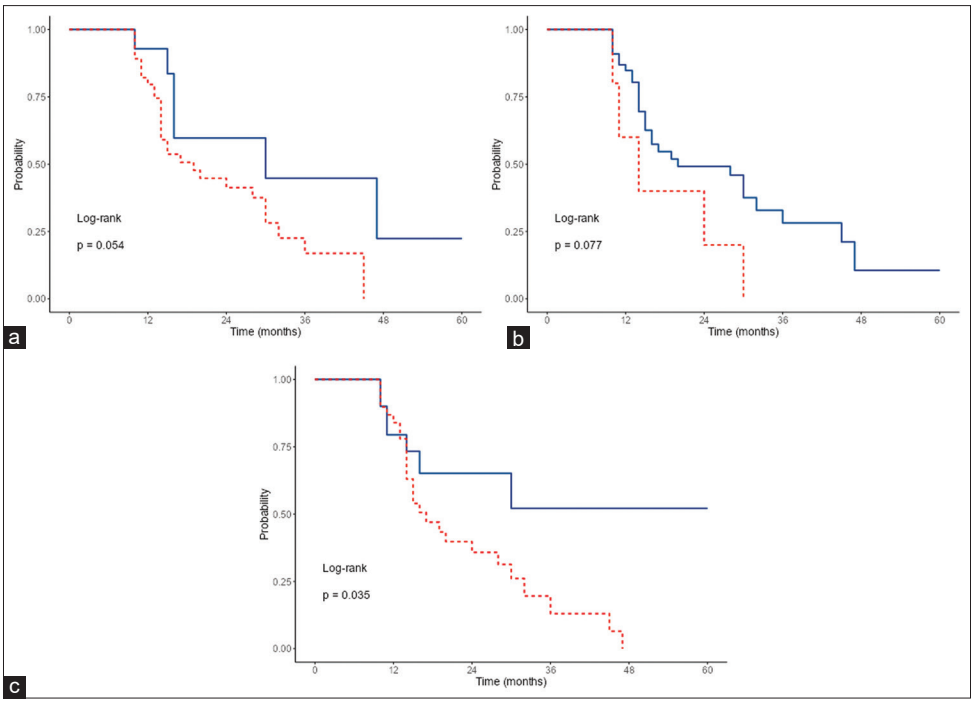

Figure 1: Survival probability of COVID-19 patients administered remdesivir based on gender, WBC count Day 10 and multi-organ failure. (a) Median survival probability based on gender (blue line: female, red broken lines: male). (b) Median survival probability based on multiple organ failure (blue line: Multiple-organ failure absent, red broken lines: Multiple-organ failure present). (c) Median survival probability based on WBC count Day 10 (blue line: Normal WBC count on day 10, red broken lines: Deranged WBC count on day 10)

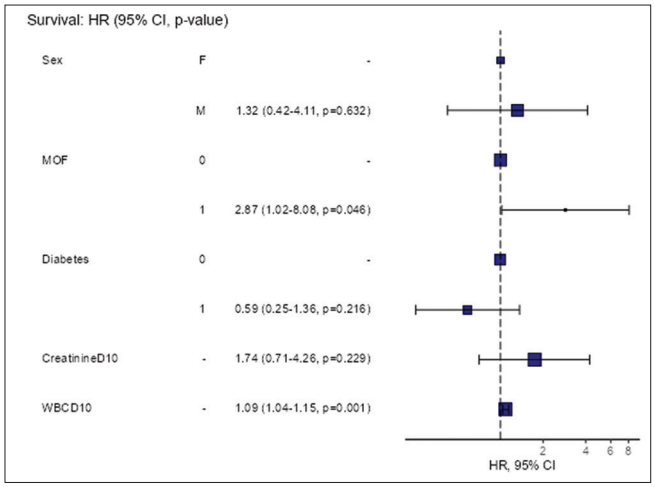

Figure 2: Hazard ratio plot of cox-proportional hazard model with independent predictors of death in patients administered remdesivir. MOF = multiple organ failure, creatinine D10 = creatinine levels on Day 10, WBC D10 = WBC levels on Day 10

Discussion

The drug development process is usually an extremely long drawn, exhaustive and time taking process, and it takes approximately 11–15 years for a new molecule to reach the market. All through, the safety of the molecule is of utmost priority. Even after the molecule is granted approval (with stringent labelling for dose, duration, indication, etc.) and marketing authorisation, extensive post-marketing surveillance and pharmacovigilance practice further serve as a constant monitoring process for those adverse drug reactions (ADRs) that were missed (due to a small number of patients, small duration of clinical trials, small and specific population, etc.) during the clinical trials. Even for repurposed drugs or drugs used for newer indications, Phase II studies are a must. For generics, too, we stress bioequivalence studies. These kinds of studies too can take anywhere between 6 months and 2 years. It is clear then that the emergency approval of a drug, in our context remdesivir, although necessary, has its inherent disadvantages; unclear safety profile in a new indication, new disease, new and population being the most critical disadvantage.

There are considerable discussions among researchers about the benefit–risk ratio of remdesivir therapy in COVID-19.

Since its approval, several studies have reported some benefits in reducing time to recovery and mortality in hospitalised patients with moderate disease with ten days of therapy with remdesivir.[8,10] In a randomised phase 3 trial involving hospitalised COVID-19 patients, no significant difference was seen between a 5-day course and a 10-day course of remdesivir.[11] Another randomised trial on 1062 patients reported a lesser median time to recovery and greater adjusted odds in the remdesivir group, especially when given in the early phase of the disease than in the placebo group. Recommendation of an early institution of remdesivir revolves around its anti-viral efficacy, as evidenced through primate models.[12,13] The solidarity trial conclusively reported non-significant differences between mortality in remdesivir and control groups.[14] Several systematic reviews and meta-analyses have evaluated the results of these RCTs and cohort studies. One of them concluded that remdesivir was

associated with better clinical outcomes in time to recovery/clinical improvement and lesser serious adverse events. However, the meta-analysis did not find any difference in all-cause mortality and adverse events between placebo and remdesivir groups.[15] A network meta-analysis systematically evaluating the safety and efficacy of all pharmacological interventions employed against COVID-19 reported that remdesivir and corticosteroids significantly impacted the reduction of mortality in moderate to severe patients and the progression to severe disease.[16] A recently completed meta-analysis based on five randomised controlled trials, and one cohort study reported that remdesivir was associated with improved clinical outcomes and a reduction in serious adverse events but had no impact on mortality at 14 days. KP Singh *et al.* recently reported that adding remdesivir to the standard of care did not reduce in-hospital mortality in adults hospitalised with COVID-19.[17] In contrast, a case series of 11 patients on anti-CD20 monoclonal antibodies, treated with remdesivir for COVID-19 2019, observed clinical improvement, reduction in viral load, and no clinical relapse at one year of follow-up.[18]

Sekkarie PA *et al.* reported that pregnant females with COVID-19 were less likely to receive recommended remdesivir compared to hospitalised non-pregnant women, whereas SMA Alavi *et al.* published a case report suggesting that remdesivir and dexamethasone combination therapy is a suitable option in pregnant COVID-19 positive females.[19,20]

Our study mainly focussed on assessing changes in lab parameters in the remdesivir cohort. Toxicity data from research concluded that -remdesivir non-significantly increased the risk of anaemia, headaches, hypokalaemia, hypalbuminaemia, thrombocytopenia, nausea and other adverse events compared to placebo.[21] A recently concluded single-centre retrospective study analysed bradycardia in 600 patients who were given remdesivir for COVID-19 by univariate and multivariate statistical tests. Bradycardia was significantly associated with higher inpatient mortality, elevated D-dimer levels and endotracheal intubation.[22] Fan Q *et al.* updated the safety profile of remdesivir in 2020. Various studies reported hepatic, gastrointestinal, respiratory, cardiovascular, renal, and reproductive toxicities.[23]

A one-way repeated measure ANOVA to assess the impact of remdesivir on inflammatory markers over different time points (Day 1, Day 2 and Day 6) in our study found a significant decrease in serum creatinine and lymphocyte count and an increase in serum sodium. No significant changes were seen in other inflammatory markers in this study. Unlike our study, a retrospective cohort study evaluating the prognostic factors in remdesivir-treated patients in New York in 2020 reported that CRP levels decreased significantly after remdesivir administration in non-intubated patients.[24] Similar to our study, a statistically significant decrease in total leukocyte count, absolute lymphocyte counts and C-reactive protein was found post-remdesivir treatment in patients with end-stage renal disease.[25] In the NOR-solidarity trial, 185 patients were randomly assigned to the remdesivir or standard of care group. Secondary outcomes included changes in the degree of respiratory failure and inflammatory variables. A significant decrease in ferritin, lactate dehydrogenase and procalcitonin was observed in the first week of remdesivir therapy. Unlike the NOR-solidarity trial, our study did not find a substantial decrease in ferritin after remdesivir treatment. However, it is interesting that remdesivir did not exert a sustained effect on these inflammatory markers. In contrast to the popular claim that remdesivir could be important in the early stages of the disease, retarding the progression to hyperinflammation, the NOR-solidarity trial did not report any such finding.[26,27] A linear mixed models study assessing longitudinal changes in clinical indices of COVID-19 during remdesivir therapy found a significant decrease in ESR, CRP, and alkaline phosphatase.[28]

Finally, a cox-regression hazard model was devised to identify the independent predictors of mortality among COVID-19 patients on remdesivir. The significant independent predictors were only the presence of multiple organ failure and deranged WBC count. Various studies have reported that these predictors are associated with fatal outcomes in COVID-19 patients.[29,30] Surprisingly, diabetes which is an established independent predictor of mortality in various studies was observed to be an insignificant factor.[29,31] These findings imply that the adverse drug reactions due to remdesivir do not specifically increase the probability of death among COVID-19 patients. A case-control study conducted on 352 COVID-19 patients ascertains borderline reduction in odds of death (odds ratio: 0.39, 95% confidence interval: 0.14–1.04, $P = 0.06$) and significant reduction in mechanical ventilation among the same patients.[32]

Thus, although it remains unclear to which degree remdesivir therapy is warranted, the study would guide the family physicians and alter their perceptions about the aspects of remdesivir dosing and duration and the choice of the ideal candidate.

Further, concerns have been raised about the potential of generating anti-viral drug-resistant SARS-CoV-2 strains, another area where further research is warranted.[33]

Strengths and limitations

1. The main limitation of this study is the lack of a matched comparison group.
2. Due to the unavailability of data, the effect of remdesivir on CRP, ESR, procalcitonin, and other critical inflammatory markers could not be assessed.

Conclusion

This event-monitoring prospective study ascertains that a significant reduction in serum creatinine levels, lymphocyte and sodium was noticed among the COVID-19 patients. It was also seen that remdesivir did not independently increase the risk of mortality among the patients. Thus, this study is in favour of recommending the drug to hospitalised patients.

Recommendations

1. Studies evaluating the role of remdesivir in special populations, pregnancy, paediatric age groups, and populations with co-morbidities should be conducted.
2. The potential of developing drug-resistant strains with remdesivir should be kept in mind, and approaches to attenuate this possibility should be explored.
3. Long-term side effect profiles of remdesivir should be generated through well-planned studies.

Evaluation of drugs that alter inflammatory response associated with COVID-19, directly and indirectly, should be a priority.

Authors contribution

Conceptualisation (SS), methodology (SS, PL), software (SS, NS, PL), validation (SS, PL), formal analysis (SS, PL), investigation (SS, NS), resources (SS, NS, N), data curation (SS, PL, NS), writing original draft (SS, PL, PS), writing review and editing (SS, CMS, PL, PS), visualisation (SS, NS, N), supervision (SS, CMS), project administration (SS, NS). The final manuscript is read and approved by all authors.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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