The effect of remdesivir on selective biomarkers and its value in predicting the clinical outcome in patients with COVID-19

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ABSTRACT

Background: To the best of our knowledge, there have been no studies to evaluate the effect of remdesivir on inflammatory markers. **Aims and Objectives:** To study the effect of Remdesivir on Selective biomarkers namely C-Reactive Protein (CRP), Lactate Dehydrogenase (LDH), Serum Ferritin and D-dimer and their value in predicting the clinical outcome in patients with COVID -19 infection. **Materials and Methods:** This is a retrospective observational study including 102 laboratory-confirmed COVID-19 patients of moderate and severe category who were subjected to complete blood count, liver function test, BUN, creatinine, C-reactive protein, lactate dehydrogenase, D-dimer, serum ferritin, ECG, and chest X-ray. The association was analyzed using independent sample t-test or Mann–Whitney U-test. Patients were divided into two groups. Both received corticosteroids and anticoagulants. Group A also received remdesivir. **Results:** Of the 102 patients, 90.2% of the patients in the non-remdesivir group and 94.1% in the remdesivir group were discharged. The mortality rate was 9.8% in the non-remdesivir group versus 5.9% in the remdesivir group (P = 0.71). There was no statistically significant difference in the decrease of the inflammatory markers overtime in both the groups, irrespective of whether they received remdesivir or not. **Conclusion:** High values of the inflammatory markers were seen at the time of admission. A 5 days course of remdesivir failed to demonstrate a statistically significant difference in the decrease in the levels of the inflammatory markers. However, we have observed a possible clinical benefit of remdesivir among patients with moderate and severe COVID-19 disease, as there was a trend toward better clinical outcomes. Further studies are needed to evaluate this therapeutic strategy.

Key words: COVID-19 infection; C-reactive protein; D-Dimer; Ferritin; Inflammatory markers; Lactate dehydrogenase; Remdesivir

INTRODUCTION

The outbreak of COVID-19 has imposed a huge threat to global public health.[1] The spectrum of the disease severity ranges from mild asymptomatic disease to pneumonia leading to acute respiratory distress syndrome, multiple organ dysfunction, and even death.[1]

The rapid viral replication of SARS-CoV-2 and destruction of cells stimulate the inflammatory response and recruit macrophages which release cytokines, chemokines that attract immune cells leading to cytokine storm, subsequent multiorgan dysfunction, and death.[1]

Remdesivir a nucleotide analog targets the viral RNA-dependent RNA polymerase needed for the replication of SARS-CoV-2.[2] Thus, inhibiting the viral replication it inhibits the inflammatory response, and improves the clinical outcome.

Hence, early administration of remdesivir might be crucial for ensuring an efficient treatment, decrease in mortality, and an early discharge.

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Furthermore, there is accumulating evidence that the inflammatory responses play a critical role in the progression of COVID-19.[1,3-5] Hence, severe COVID-19 is associated with higher levels of inflammatory markers as compared to mild disease.

There have been no studies to evaluate the effect of remdesivir on inflammatory markers to the best of our knowledge.

Hence, this study has been undertaken to study the effect of remdesivir on selective biomarkers, namely, C-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, and D-dimer and their value in predicting the clinical outcome in patients with COVID-19 infection.

Aims and objectives

To study the effect of remdesivir on selective biomarkers, namely, C-reactive protein (CRP), lactate dehydrogenase (LDH), serum ferritin, and D-dimer and their value in predicting the clinical outcome in patients with COVID-19 infection.

MATERIALS AND METHODS

This is a retrospective observational study, which was pre-approved by the Institutional Ethics Committee. It included 102 laboratory confirmed COVID-19 patients of moderate and severe category between the age group of 18 and 60 years by RT-PCR on nasopharyngeal swab between August 1, 2020, and October 30, 2020, admitted in the Department of General Medicine of Vydehi Institute of Medical Sciences and Research Centre.

A detailed history comprising demographic characteristics, presenting complaints, and comorbidities was recorded, the patients then were categorized as mild, moderate, and severe disease based on the clinical criteria according to the Karnataka Government guidelines of August 2020. Category B (moderate) patients were those who had the features of respiratory rate 24–30/min, SpO_2 90–94% at room air. Category C (severe) patients were those who had the features of respiratory rate >30/min, SpO_2 <90% at room air or <94% with oxygen, acute respiratory distress syndrome, or septic shock. In addition to examination, all the patients were subjected to complete blood count using DXH-900 automated hematology analyzer with six part differentials, liver function test using Beckman Coulter Unicel DXC 800 Synchron Clinical system, blood urea nitrogen by urease UV method, creatinine by Jaffe's kinetic method, CRP by Nephelometry method, LDH by lactate to pyruvate method, D-dimer by latex immunoassay and serum ferritin levels by Clinical Laboratory Improvement

Amendments method, ECG, and chest X-ray. Both the groups received corticosteroids and anticoagulants. In addition, Group A received intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–5 in single daily infusions) as per Karnataka Government Treatment protocol and Group B did not receive intravenous remdesivir. The patients excluded from the study were category A (mild) patients with respiratory rate <24 cycles/min, SpO_2 >94% in room air; patients with pre-existing comorbidities, namely, chronic liver disease, chronic kidney disease, malignancy, thromboembolism, diabetes mellitus, hypertension, ischemic heart disease, chronic lung disease, sepsis, anemia, pregnant women, and children.

Statistical analysis

Statistical analysis was carried out for the laboratory confirmed moderate to severe COVID-19 patients.

The association was analyzed using independent sample t-test or Mann–Whitney U-test.

Microsoft Excel 2013 and Statistical Package for the Social Sciences Version 19.0 software were used for data entry and analysis.

$P < 0.05$ will be considered as statistically significant.

Informed consent has been waived off as it is a retrospective study.

RESULTS

In this study, we had a cohort of patients that did not receive remdesivir and those that did. The first 51 patients in each group were selected the non-remdesivir group (Group A) and remdesivir group (Group B) for the study.

The median age of patients was 42 years in Group A and 41 years in Group B with a majority of the patients being males, 80.4% in Group A and 76.5% in Group B (Table 1).

Table 1: Patient Characteristics and outcome		
Variables	**Remdesivir N (%)**	
	Not received	**Received**
Age (Median Q_1, Q_3)	42 (35.55)	41 (33.50)
Gender		
Male	41 (80.4)	39 (76.5)
Female	10 (19.6)	12 (23.5)
Severity		
Moderate	44 (86.3)	30 (58.8)
Severe	7 (13.7)	21 (4.2)
Outcome		
Discharged with government protocols	46 (90.2)	48 (94.1)
Mortality	5 (9.8)	3 (5.9)

In the non-remdesivir group, 86.3% had moderate illness and 13.7% had severe illness. Whereas, in the remdesivir group, the patients with moderate and severe disease were 58.8% and 41.2%, respectively (P=0.002) (Table 1).

Correlation of inflammatory markers between the groups (Table 2)

The inflammatory markers, namely, D-dimer, ferritin, LDH, and CRP were serially monitored in all patients on day 1, day 3, and day 5 of hospital admission. These markers were seen to be higher at presentation (day 1) in the non-remdesivir group as compared to the remdesivir group (Table 2).

There was a significant decrease in the mean ferritin (P<0.001) and LDH (P=0.001) values over these time points in both the groups, irrespective of whether they received remdesivir or not (Table 2).

There was no statistically significant difference in the decrease in the mean values of any of the inflammatory markers between the two groups (Table 2).

Clinical outcome

In our study, 90.2% of the patients in the non-remdesivir group and 94.1% in the remdesivir group were discharged. The mortality rate was 9.8% in the non-remdesivir group versus 5.9% in the remdesivir group. Fisher's exact test was performed to see the association between outcome and group. This difference was not found to be significant (P=0.71) (Table 1). There was a significant decrease in the mean ferritin (P<0.001) and LDH (P=0.001) values overtime in both the groups, irrespective of whether they received remdesivir or not. A 5 days course of remdesivir failed to demonstrate a statistically significant difference in the decrease in the levels of the inflammatory markers.

DISCUSSION

In our study of 102 patients, it was observed that men had a significantly higher rate of hospitalization as compared to women which is in agreement with other studies done by Gomez et al., and Bischof et al.[6,7]

Our study also showed, 90.2% of the patients in the non-remdesivir group and 94.1% in the remdesivir group were discharged. The mortality rate was 9.8% in the non-remdesivir group versus 5.9% in the remdesivir group.

Our findings corresponded with the ACTT-1 trial, which is an multinational study of 1062 patients where the patients were randomized in a 1:1 ratio to receive remdesivir or placebo showed that the recovery time among the remdesivir group was shortened by 5 days (P <0.001) and a lower mortality rate among the remdesivir group which was not statistically significant.[8]

Furthermore, a study by Mehta et al., showed mortality benefit with initiation of remdesivir ≤9 days from symptom onset which reinforced the need for appropriately timed remdesivir in moderate-to-severe COVID-19.[9]

Our study showed high levels of inflammatory markers, namely, D-dimer, ferritin, LDH, and CRP among the patients who were categorized among the moderate and severe illness category on admission.

This was similar to results of a meta-analysis comprising 3962 patients done by Zeng et al., which showed higher levels of CRP, LDH, procalcitonin, and serum ferritin among the severe illness patients as compared to the mild illness patients.[1]

A meta-analysis by Ghahramani et al., also showed higher levels of inflammatory markers among the severe group versus non-severe group.[10]

Table 2: Correlation of inflammatory markers between the groups						
Variables	Group	Day 1	Day 3	Day 5	P value (between groups)	P value (between time)
D-dimer	Remdesivir	1236.33±2089.19	1362.51±2358.57	1300.08±2165.98	0.39	0.33
	Not received	802.65±882.35	1189.80±1839.76	1211.63±1925.07		
Ferritin	Received remdesivir	742.76±459.95	726.63±407.52	679.28±311.11	0.24	0.001
	Not received Received	695.07±435.44	655.06±354.87	553.41±304.33		Day 1 vs. Day 3: 0.78 Day 1 vs. Day 5: 0.002* Day 3 vs. Day 5: 0.005*
LDH	Remdesivir	335.41±149.84	333.77±132.92	307.35±127.87	0.24	0.001*
	Not received Received	316.90±87.87	314.33±82.36	280.12±73.10		Day 1 vs. Day 3: 1 Day 1 vs. Day 5: 0.001* Day 3 vs. Day 5: 0.008*
CRP	Remdesivir	6.79±6.26	5.95±6.06	5.97±6.21	0.11	0.05
	Not received Received	5.98±4.54	4.81±4.63	3.98±5.32		

CRP, a hepatic protein which is regulated at the transcriptional level by the cytokine IL-6 and IL-1, is a reliable marker of inflammation.[11] There is accumulating evidence that higher levels of CRP are associated with severe COVID-19 infection.[12-14]

Our study showed that patients with moderate and severe COVID-19 infection had high values of CRP in moderate and severe COVID-19 infection at the time of admission. However, there was no statistical difference in the reduction of the CRP values among the patients who received inj. remdesivir.

Our findings were similar to a study by Smilowitz which showed that higher levels of CRP were associated with critical illness and mortality in COVID-19 patients.[15]

Similarly, a study of 131 patients showed persistently rising values of CRP was associated with higher levels of mortality among COVID-19 patients.[16]

D-dimer, formed by the activation of the plasmin enzyme, indicates the presence of broken-down fibrin in the bloodstream and represents the activation of coagulation and fibrinolysis systems.[17] Studies have indicated that higher levels of D-dimer were associated with more severe disease due to various reasons like increased levels of pro-inflammatory cytokines, thrombosis leading to venous thromboembolism and severe sepsis which leads to increased levels of plasminogen activator inhibitor 1, and excessive fibrinolysis.[18]

Our study showed that patients with moderate and severe COVID-19 infection had high values of D-dimer at admission. However, there was no statistical difference in the reduction of the D-dimer values among the patients who received inj. remdesivir.

Our findings were in agreement with a meta-analysis of 1807 patients done by Paliogiannis which revealed that higher D-dimer levels were associated with more severe COVID-19 infection as compared to non-severe infection.[19]

Similarly, a study done by Huang et al., on 676 revealed that a persisting increase in D-dimer levels was associated with higher incidence of mortality in COVID-19 patients.[20]

LDH, an intracellular enzyme, is found in cells in almost all organ systems, and it catalyzes the interconversion of pyruvate and lactate, with concomitant interconversion of NADH and NAD^+.[21] Isoenzyme 3 of LDH is present in lung tissue. Hence, greater levels of LDH are seen in patients with severe COVID-19 infection who have severe interstitial pneumonia, often evolving into acute respiratory distress syndrome.[22]

Our study showed that patients with moderate and severe COVID-19 infection had high values of LDH on admission. However, there was statistical decrease in the reduction of the LDH values among the patients irrespective who received inj. remdesivir.

Similarly, a study by Henry et al., showed that higher levels of S. LDH were associated with 6 times higher risk of developing more serious infection and 16 times increase in the odds of mortality.[22]

Furthermore, a study done by Martha on 10,399 showed a higher probability of worse outcomes in patients with COVID-19 infection.[23]

Ferritin in COVID-19 is characterized as an acute-phase reactant, as well as a mediator of immune dysregulation. Several complex feedback mechanisms between ferritin and cytokines exist in the control of pro-inflammatory and anti-inflammatory mediators. Cytokines induce the expression of ferritin. Furthermore, ferritin can induce the expression of pro- and anti-inflammatory cytokines.[24]

Our study showed that patients with moderate and severe COVID-19 infection had high values of ferritin in COVID-19 infection. However, there was statistical decrease in the reduction of the serum ferritin values among the patients irrespective who received inj. remdesivir.

A study done by Bo Zhou on 20 patients of COVID-19 patients showed higher levels of serum ferritin among patients with severe disease.[25]

Similarly, a study by Onur et al., showed high values S. ferritin among the non-survivors.[26]

Hence, higher levels of serum ferritin can be associated with severe COVID-19 infection.

Limitations of the study

To begin with our study is a retrospective analysis. Furthermore, the duration of follow-up was relatively short (5 days). Following up on inflammatory markers for a week after completing the course of remdesivir could have shown a difference between the groups. Furthermore, there is inhomogeneity in the groups studied with higher number of severe cases in the remdesivir group. Finally, we were not able to get a statistical analysis in the remdesivir subgroup due to very few patients with severe disease in the non-remdesivir

group. Probably looking at moderate and severe illness separately would be more conclusive.

CONCLUSION

High values of the inflammatory markers were seen among the moderate and severe illness patients at the time of admission. A 5 days course of remdesivir failed to demonstrate a statistically significant difference in the decrease of the levels of the inflammatory markers. However, we have observed a possible clinical benefit of remdesivir among patients with moderate and severe COVID-19 disease, as there was a trend toward better clinical outcome among the patients receiving remdesivir. Further studies are needed to evaluate this therapeutic strategy.

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PROFORMA

Code number: Date of admission:
Age: Date of Discharge:
Sex: Hospital number:
COVID RT-PCR:
Co-morbidities:
Severity of the illness at presentation (Based on clinical parameters): Mild/Moderate/Severe
Biomarkers:

First test	Second test	Third test	Fourth test	Fifth test
Day 1	Day 3	Day 6	Day 9	Day 12

Serum ferritin
CRP
LDH
D-dimer
Remdesivir: Not Received/Received
Oxygen requirement: Yes/No   Number of days:
Ventilator requirement: Yes/No   Number of days:
Days of ICU stay:
Days of Hospital stay:
Condition at discharge:

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