A study to assess the outcome in COVID-19 confirmed cases receiving Remdesivir as compared to conventional therapy: Medical records-based audit
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ABSTRACT

Introduction: COVID-19 infection caused by SARS-CoV-2 (SARS-CoV-2) has caused large number of infections and mortality globally. There are no proven medications to prevent and treat COVID-19, nevertheless several potential pharmacotherapeutic agents have been tried. Remdesivir was found to be effective in few studies. Aims: To assess the outcome in COVID-19 confirmed cases receiving Remdesivir as compared to conventional therapy. Methodology: This study was conducted in a tertiary hospital in South India after the approval of the Institutional ethical committee. It was a medical records-based retrospective, longitudinal study. Medical records of the inpatients with confirmed COVID-19 infection were reviewed from the period of June 15, 2020 to September 15, 2020. This study was conducted to assess the clinical and laboratory profile and outcome in the patients admitted with moderate and severe COVID-19 disease who received Remdesivir. Statistical Analysis: The analysis was done using SPSS Inc. released 2009, PASW statistics for Windows version 18.0, Chicago. Results: One hundred eleven (N = 111) patients were included in the study, 56 patients received the conventional treatment (Hydroxychloroquine HCQ) and 55 patients received Remdesivir. It was seen that among patients treated with HCQ, 24 (42.9%) required non-invasive ventilation and seven (12.7%) patients treated with Remdesivir required it (P = 0.001). It was noticed that the mean duration of hospitalization was 16.6 days in HCQ group and was 11.4 days in Remdesivir group (P = 0.021). Conclusion: The study demonstrates that Remdesivir does have benefit in reducing the mortality and duration of hospital stay. There was reduced requirement of non-invasive and invasive ventilation among patients treated with Remdesivir.

Keywords: Hydroxychloroquine, moderate and severe COVID-19, remdesivir

Introduction

COVID-19 infection is caused by SARS-CoV-2, which is transmitted through infected fluid droplets from the respiratory tract of infected patients.[1] Efforts have been ongoing to develop an effective and affordable drug against SARS-CoV-2 virus. Remdesivir is an antiviral agent approved under emergency use authorization by Government of India as an investigational drug for management of moderate to severe COVID-19. There are studies that demonstrate the efficacy of Remdesivir in vitro. However, in vivo data on the use of Remdesivir is less. Also, studies from Indian subcontinent are sparse. There are no proven drugs to protect against the infection or to treat the viral infection, and several potential pharmacotherapeutic agents have been tried.[2] Remdesivir is an adenosine analog, which competes with the natural ATP.

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substrate to selectively inhibit viral RNA-dependent RNA polymerase (RdRp).[^9]

### Objectives

To assess the outcome in COVID-19 confirmed cases receiving Remdesivir as compared to conventional therapy.

### Materials and Methods

This study was conducted in a tertiary hospital in south India from June to September 2020. It was a medical records-based retrospective, longitudinal study. The institutional ethical committee approval was taken (MSRMC/EC/AP-04/09-2020). The patients admitted having age more than 18 years and moderate and severe COVID-19 confirmed by RTPCR method or Rapid Antigen Test were included. Pregnant and lactating women as well as patients with chronic kidney and liver diseases were excluded.

Appropriate care was taken not to extract the personal details of the patients from the medical records. Data such as demographic details, duration of illness before hospitalization, clinical features at the time of presentation, co-morbidities, laboratory parameters, radiological findings, need for ICU care, oxygen requirement, ventilator requirement, other therapy details and outcome in the form of number of days of oxygen requirement, oxygen delivery device, discharge of patient, and even mortality details were extracted in a predesigned proforma. Patients enrolled into the study were divided into two groups. Group 1 included patients in whom Remdesivir was not used (due to non-availability, patients who refused to take Remdesivir). This group of patients received the conventional treatment, namely Tab Hydroxychloroquine 400 mg BD for first day, followed by 200 mg BD for 5 days. They also received systemic corticosteroids (Dexamethasone or Methyl prednisolone) and low molecular weight heparin. Group 2 included patients who received Injection Remdesivir 200 mg on first day followed by 100 mg once a day for 4 days. These patients also received systemic corticosteroids and low molecular weight heparin. The two groups were matched for age, gender, co-morbidities, and severity of the disease. The data was statistically analyzed. Outcome measures studied were the need for mechanical ventilation, survival/death, oxygen requirement, duration and delivery device, duration of hospital stay, and discharge.

### Sample size

A study titled “Remdesivir for the Treatment of COVID-19—Preliminary Report” has revealed that the median recovery time and the interquartile range for patients treated with Remdesivir was 11 days and 9–12 days as compared to placebo, which was 15 days and 13–19 days. Assuming that a true difference in mean recovery time between the two groups is 4 days and a standard deviation of 3 days, it is estimated that a minimum of 28 patients need to be recruited for the study to achieve a power of 80% and a level of significance of 5% for declaring that Remdesivir treatment is superior to conventional therapy.

### Statistical methods

All the quantitative variables were analyzed using descriptive statistics such as mean and standard deviation or median and interquartile range. All the categorical variables were expressed in terms of percentages. Differences in average duration of stay between patients in the two arms were tested for statistical significance either by Student’s t-test or Mann–Whitney U test. Similarly, the association of various categorical variables was tested for statistical significance by Chi-square test. No personal details like name, address were extracted from the records. The analysis was done using SPSS Inc. released 2009, PASW statistics for Windows version 18.0, Chicago.

### Results

One hundred eleven (N = 111) subjects were included in the study. 56 patients were in the Hydroxychloroquine (HCQ) group and 55 were in the Remdesivir group. Mean age of patients in Hydroxychloroquine (HCQ) group was 55.7 years and in Remdesivir group was 57.5 years (p = 0.481) [Table 1]. There were 37 male patients and 19 female patients in the HCQ group. There were 37 male patients and 18 female patients in the Remdesivir group (p = 0.893) [Table 2]. There were 50% of patients with Diabetes mellitus in HCQ group and 49.2% patients with Diabetes in Remdesivir group. About 48.2% of patients in HCQ group were hypertensive and 42.8% were hypertensive in Remdesivir group [Table 3]. Other co-morbidities like obesity, malignancy, and thyroid disorders were matched in both the groups. At the time of admission, HCQ group had 33 (58.9%) patients of moderate severity, 23 (41.1%) had severe disease. In the Remdesivir group, 32 (58.2%) had moderate disease and 23 (41.8%) had severe disease (P = 0.936) [Table 4]. Hence, the severity of the disease at the time of admission was matched. The two groups were also matched for the duration of symptoms onset prior to admission [Table 5]. The oxygen requirement at the time of admission of the patients in both the groups was similar [Table 6 and 7]. It was seen that during the course of illness, among patients treated with HCQ, 24 (42.9%) required

### Table 1: Age distribution between the two groups (Student’s t-test)

|          | n  | Mean | SD  | Min. | Max. | P      |
|----------|----|------|-----|------|------|--------|
| HCQ group| 56 | 55.7 | 14.957 | 19 | 87 | 0.481 |
| REMDESIVIR group | 55 | 57.5 | 12.162 | 28 | 89 |       |

### Table 2: Gender distribution in the two groups (Chi-square test)

|          | HCQ Group (n=56) | REMDESIVIR Group (n=55) | P  |
|----------|------------------|-------------------------|----|
| Male     | 37 (66.1%)       | 37 (67.3%)              | 0.893 |
| Female   | 19 (33.9%)       | 18 (32.7%)              |     |
non-invasive ventilation and seven (12.7%) of patients treated with Remdesivir required non-invasive ventilation. This difference was statistically significant with \( P \text{ value} < 0.001 \) [Table 8]. It was seen that during the course of illness, in patients treated with HCQ, 23 (41.07%) required invasive ventilation and four (7.27%) of patients treated with Remdesivir required invasive ventilation. This difference was found to be statistically significant \( (p = 0.032) \) [Table 9]. It was observed that 22 (39.2%) of patients in HCQ group died as compared to four (7.3%) of the patients in Remdesivir group. This difference was seen to be statistically significant \( (p < 0.001) \) [Table 10]. It was noticed that the mean duration of hospitalization was 16.6 days in HCQ group and was 11.4 days in Remdesivir group. This difference was statistically significant \( (p = 0.021) \) [Table 11].

**Discussion**

This was a retrospective, case record-based study conducted in a tertiary care center, which involved comparison of clinical course and outcome between the moderate and severe COVID-19 patients who received either Hydroxychloroquine or Remdesivir. The study period was from 15th June to 15th September 2020. During this time, Hydroxychloroquine was still recommended for COVID-19 management as per guidelines issued by Government of India. DCGI had just approved Remdesivir use in COVID-19 under as an experimental therapy. There was lot of apprehension regarding the drug and its adverse effects that could be the reason some patients preferred hydroxychloroquine instead of Remdesivir. The availability of the drug during the period was also limited. Hence, this set of patients was included as group and were compared with the patients who received Remdesivir.

The study consisted of patients suffering from moderate and severe COVID-19 illness. Most of these patients required supplemental oxygen therapy at the time of admission. The two groups were matched with regard to the disease severity, in addition to the demographic characteristics like age, gender, co-morbidities, and so on. All patients included in the study had received steroids and anticoagulants as per the guidelines. It was noteworthy that there was a difference in the requirement of non-invasive and mechanical ventilation between the two groups with those who received Remdesivir, having not progressed to requiring ventilatory support. As per a study conducted by Spinner et al.,\textsuperscript{[8]} which included 584 patients who were randomized to receive Remdesivir or standard of care, it was observed that those who received Remdesivir had higher odds of having clinical improvements than those who received standard of care.

As per the results of the study by Grein et al.,\textsuperscript{[9]} hospitalized lab confirmed severe COVID-19 patients were monitored for improvement in clinical parameters after the use of Remdesivir. They followed the patients for 28 days after the beginning of treatment with Remdesivir or until discharge or death. They noted that over a median follow-up of 18 days, 68% showed improvement in oxygen support class, whereas 15% showed worsening.

Wang et al.,\textsuperscript{[10]} conducted a double-blind, placebo-controlled, multicentric trial in China in 2020, which studied 237 severe COVID-19 patients randomly allocated to receive either Remdesivir or placebo. They observed that there was no statistical significance with respect to the clinical benefit with administration of Remdesivir in hospitalized patients with severe COVID-19 needing mechanical ventilation.

**Table 3: Co-morbidities in the two groups (Chi-square test)**

| Parameter | HCQ Group (n=56) | REMDESIVIR Group (n=55) | \( P \) |
|-----------|-----------------|------------------------|------|
| DM        | 28 (50%)        | 27 (49.2%)             | 0.924 |
| HTN       | 27 (48.2%)      | 24 (43.6%)             | 0.628 |
| Obesity   | 6 (10.7%)       | 1 (1.8%)               | 0.054 |
| IHD       | 2 (3.6%)        | 5 (9.1%)               | 0.232 |
| Asthma    | 3 (5.4%)        | 0                      | 0.082 |
| Malignancy| 2 (3.6%)        | 0                      | 0.157 |
| ESRD      | 2 (3.6%)        | 0                      | 0.157 |

**Table 4: Severity of the disease (Chi-square test)**

| Severity  | HCQ Group (n=56) | REMDESIVIR Group (n=55) | \( P \) |
|-----------|------------------|-------------------------|------|
| Moderate  | 33 (58.9%)       | 32 (62.3%)              | 0.936 |
| Severe    | 23 (41.1%)       | 23 (37.5%)              |       |

**Table 5: Duration of symptoms prior to admission**

| Treatment | n | Mean | SD | Median | Min. | Max. | \( P \) |
|-----------|---|------|----|--------|------|------|------|
| HCQ       | 56 | 4.66 | 2.185 | 4.00   | 1    | 10   | 0.143 |
| Remdesivir| 55 | 3.20 | 1.311 | 3.00   | 1    | 7    |       |
| Total     | 111| 3.94 | 1.941 | 4.00   | 1    | 10   |       |

**Table 6: Oxygen requirement at admission (Chi-square test)**

| Parameter | HCQ Group (n=56) | REMDESIVIR Group (n=55) | \( P \) |
|-----------|------------------|-------------------------|------|
| No        | 1 (1.8%)         | 4 (7.4%)                | 0.157 |
| Yes       | 55 (98.2%)       | 50 (92.6%)              |       |

**Table 7: Inflammatory markers in the two groups (Chi-square test)**

| Inflammatory Marker | Normal Value | HCQ (n=56) | Remdesivir (n=55) | \( P \) |
|--------------------|--------------|------------|-------------------|------|
| D-Dimer            | 0-0.5        | 4 (7.1%)   | 0                 | 0.065 |
|                    | >0.05        | 52 (92.9%) | 55 (100%)         |      |
| CRP                | 0-0.5        | 2 (3.6%)   | 0                 | 0.157 |
|                    | >0.05        | 54 (96.4%) | 55 (100%)         |      |
| Ferritin           | <30          | 1 (1.8%)   | 4 (7.3%)          | 0.194 |
|                    | 30-400       | 24 (42.9%) | 28 (50.9%)        |      |
|                    | >400         | 31 (55.4%) | 23 (41.8%)        |      |
| LDH                | 135-225      | 8 (14.3%)  | 2 (3.6%)          | 0.050 |
|                    | >225         | 48 (85.7%) | 53 (96.4%)        |      |
who were admitted with COVID-19. A study conducted by Buckland et al.\textsuperscript{[10]} observed a temporally correlated clinical and virological response leading to clinical improvement and anti-viral properties and no evidence of drug resistance. The study provided a proof for the antiviral effect of Remdesivir and its potential utility in selected patients.

Research conducted by Antinori et al.\textsuperscript{[10]} demonstrated that Remdesivir can benefit patients with SARS-CoV-2 pneumonia hospitalized outside ICU where clinical outcome was better and adverse events were less frequently observed. As per a study conducted by Thalha et al.\textsuperscript{[11]} in Malaysia, patients treated with Remdesivir (68%) had shown improvement in the need for oxygen support, of which 17 of 30 (57%) ventilated patients were out of ventilatory support and 75% stopped ECMO. A total of 25 patients (47%) were discharged, whereas seven patients (13%) died. At 28 days’ follow-up, total incidence of clinical improvement was seen in 84% of patients. The results of study conducted by Lakshmi Mahajan et al.\textsuperscript{[12]} in India demonstrated that high-flow oxygen support and non-invasive ventilation was required at baseline by lesser patients who were treated with Remdesivir. The study demonstrated that both groups, one with Remdesivir and other group without it, had similar outcomes. There was no statistical difference in mortality between the two groups ($p = 0.749$).

As this was a medical record-based study, there is a need to conduct prospective randomized control trials to affirm the findings. With the Ministry of Health and Family welfare, Government of India reintroducing Hydroxychloroquine in its guidelines issued in 2021, there is renewed interest in the drug.\textsuperscript{[13],[14]} These observations pave the way to guide further studies especially those including newer drugs approved for management in COVID-19.

### Conclusions

This study shows that Remdesivir has a benefit in reducing the mortality and duration of hospital stay. There was reduced requirement of non-invasive and invasive ventilation in the patients who were administered Remdesivir. However, more prospective studies are required to confirm these findings and generalize it to the whole population.

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### Conflicts of interest

There are no conflicts of interest.

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