Combination Therapy With Remdesivir, Dexamethasone, and Tocilizumab in Patients With Severe Corona Virus Disease 2019 in Clinical Practice

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Abstract

Background

The use of several promising drugs for coronavirus disease 2019 (COVID-19) has emerged. However, considering the pathophysiology of COVID-19, the effect of a single agent is limited. Hence, the current study aimed to compare the clinical outcomes between patients who received combination treatment with remdesivir, dexamethasone, and tocilizumab (RDT) and those who did not.

Methods

Patients who received combination therapy with RDT at Japanese Red Cross Medical Center were included in the RDT group, and those who did not in the control group. The mortality rate and presence of severe adverse events were compared between the two groups.

Results

In total, 46 patients (n = 29, control group and n = 17, RDT group) with severe COVID-19 were enrolled in this study. The 28-day mortality rate was significantly lower in the RDT group than in the control group, with 1 (6%) and 9 (31%) deaths recorded, respectively (P = 0.04). Further, both groups did not present with severe adverse events.

Conclusions

Information on the outcomes of combination therapy with RDT was considered useful for the treatment of severe COVID-19.

Background

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is spreading worldwide [1]. Approximately 80% of patients present with mild COVID-19; however, some become severely ill. The pathogenesis of this disease mainly involves severe respiratory failure caused by pneumonia. Moreover, coagulopathy and multiple organ failure are observed. Nevertheless, its actual mechanism has not been fully elucidated [2]. To control this infectious disease, strong policies including lockdowns have been implemented worldwide. Further, medical strategies for saving the lives of patients with COVID-19 are developed day and night in the medical field [3]. In particular, the establishment of drug therapies for patients with severe COVID-19 is extremely important.

There are various reports on [4-7], and remdesivir and dexamethasone are considered effective for the treatment of patients with severe COVID-19.

Remdesivir was developed for the management of Ebola hemorrhagic fever and Marburg virus disease. Moreover, it was found to have antiviral activity against single-stranded RNA viruses such as Middle East
respiratory syndrome coronavirus, SARS-CoV, and SARS-CoV-2. This drug therapeutically targets RNA-dependent RNA polymerase, which is essential for the self-renewal of RNA viruses [4, 8] [9]. These preliminary findings support the use of remdesivir in patients hospitalized due to COVID-19 who require supplemental oxygen therapy. However, considering the high mortality rate despite the use of remdesivir, whether treatment with an antiviral drug alone is sufficient remains unclear.

Dexamethasone is used for the management of various diseases worldwide [10]. Organ damage caused by an excessive host immune response may be a mechanism associated with COVID-19, and such a drug can inhibit this immune response. In a large, multicenter, randomized, open-label study conducted in the United Kingdom, patients who received dexamethasone had a lower mortality rate than those who received standard treatment [5].

Tocilizumab is a humanized anti-interleukin (IL)-6 receptor monoclonal antibody used for different conditions, including rheumatoid arthritis and acute lymphoid leukemia [11]. In a retrospective observational study of patients with severe COVID-19 in Italy, the tocilizumab group was at low risk of invasive mechanical ventilation and death [12]. Further, a retrospective observational study was conducted on patients with severe COVID-19 who required mechanical ventilation in the United States. Results showed that patients who received tocilizumab had a lower fatality rate than those who did not [13]. By contrast, an observational study in Italy revealed that patients with severe COVID-19 did not significantly differ in terms of clinical improvement and prognosis 28 days after receiving tocilizumab [14]. Therefore, the efficacy of tocilizumab remains controversial.

In severe COVID-19, excessive inflammation and immune response are caused by viral infection [15]. Therefore, combinations of a plurality of drugs are required to control infection.

Hence, this study comprehensively evaluated the clinical efficacy of remdesivir, dexamethasone, and tocilizumab (RDT) in patients with severe COVID-19 who were admitted at Japanese Red Cross Medical Center. We compared the clinical outcomes between patients who received combination treatment with RDT and those who did not.

**Methods**

**Eligibility criteria**

We retrospectively assessed 129 consecutive patients diagnosed with COVID-19 at Japanese Red Cross Medical Center, Tokyo, Japan, from February 2020 to August 2020. The diagnosis of COVID-19 was confirmed via polymerase chain reaction (PCR) for SARS-CoV-2 using sputum or nasopharyngeal swab samples. Patients with positive test results were enrolled in the current study. SARS-CoV-2 RNA was detected using the TaqMan one-step real-time PCR kits (QIAGEN, Co., Ltd, Hilden, Germany). According to the National Institutes of Health classification criteria, COVID-19 patients were classified into four categories. The groups were as follows: 1) mild illness group, patients who had different signs and symptoms of COVID-19 except for shortness of breath, dyspnea, or abnormal chest imaging finding; 2)
moderate illness group, patients who had lower respiratory disease based on clinical assessment or imaging and a blood oxygen saturation level (SpO2) of ≥ 94% in room air at sea level; 3) severe illness group, patients who had a respiratory rate of > 30 breaths per minute, SpO2 of < 94% in room air at sea level, arterial partial pressure of oxygen to fraction of inspired oxygen ratio of < 300 Torr, or lung infiltrates of > 50%; and 4) critical illness group, patients who had respiratory failure, septic shock, and/or multiple organ dysfunction (National Institutes of Health. Management of persons with COVID-19. 2020. https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/).

From February 2020 to May 2020, patients with severe COVID-19 were consecutively screened, and eligible patients were included in the control group. Severe or critical COVID-19 patients treated with RDT from June 2020 to August 2020 were screened, and eligible patients were included in the RDT group.

Procedures

All patients in the RDT group received combination treatment with RDT. Remdesivir was administered intravenously as a 200-mg loading dose on day 1, followed by 100 mg from days 2 to 5 (without invasive mechanical ventilation) or 10 (with invasive mechanical ventilation) [8]. Oral or intravenous dexamethasone was administered at a dose of 6 mg daily for up to 10 days [5]. Moreover, the patients received intravenous tocilizumab twice with a dose of 8 mg/kg (up to a maximum of 800 mg) at a 24-h interval [13].

In the control group, based on the physician’s discretion, the standard treatment included oxygen therapy (including invasive mechanical ventilation), hydroxychloroquine, lopinavir–ritonavir, favipiravir, and tocilizumab.

Statistical analysis

Patients who presented with control group and patients deteriorated to RDT group, respectively. The Fisher’s exact test was used to assess differences in categorical variables between the two groups. Then, univariate and multivariate logistic regression analyses were performed to determine factors associated with the yield. Variables with a P value < 0.10 in the univariate analysis were utilized in the multivariate logistic regression analysis. A one-tailed P value < 0.05 was considered statistically significant. A correlation analysis was performed with EZR (Saitama Medical Center, Jichi Medical University; www.jichi.ac.jp/saitama-sct/SaitamaHPfiles/statmed.html), a graphical user interface for R (version 2.13.0, The R Project for Statistical Computing; http://www.r-project.org) and a modified version of R commander [16].

Ethics approval and consent to participate

This study was approved by the Ethical Committee for Clinical Studies of Japanese Red Cross Medical Center (no. 1111). Due to the retrospective design of this study and based on the Japanese ethical guidelines for clinical research, the need for informed consent was waived.
Results

In total, 46 patients with severe COVID-19 were enrolled in this study. The patient’s median age was 65 (range: 26–91) years, and there were 31 (67%) male patients. Moreover, the median body mass index (BMI) was 23.1 (range: 15.5–37.1) kg/m$^2$. There were no significant differences between the two groups in terms of age, sex, BMI, smoking history, comorbidities, and type of oxygen support (Table 1).

The 28-day mortality rate was significantly lower in the RDT group than in the control group, with 1 (6%) and 9 (31%) deaths recorded, respectively ($P = 0.04$) (Fig. 1).

In the univariate and multivariate analyses according to the factors of mortality in patients with severe COVID-19, combination therapy with RDT was the only significant factor (Table 2). Both groups did not present with significant adverse events.

A representative case of a patient with severe COVID-19 who received combination therapy with RDT is shown in Figure 2. A male patient who was in his 70s was diagnosed with severe COVID-19 at another hospital. The patient’s oxygen level was low, with an SpO2 of <90%. Hence, he was transferred to our hospital. The patient was intubated, and invasive mechanical ventilation was started. Combination therapy with RDT was started on day 1. Chest radiography was performed on day 2, which is after the start of treatment, and results showed improvement in bilateral shadows. The patient was weaned from invasive mechanical ventilation on day 6. Chest radiography and computed tomography scan on day 8 showed marked improvement in bilateral lung field shadows. On day 13, the patient did not require oxygen therapy, and his chest radiography results were almost normal. The patient was then discharged to home on day 14.

Discussion

This is the first report on the use of combination therapy with remdesivir, dexamethasone, and tocilizumab in patients with severe COVID-19 in clinical practice. The 28-day mortality rate was significantly lower in the RDT group than in the control group, and severe adverse events were not observed.

COVID-19 is an infection caused by SARS-CoV-2. However, in patients with severe disease requiring oxygen therapy and invasive mechanical ventilation, excessive inflammation and cytokine storm-like conditions are considered serious [17]. Remdesivir is currently used against severe COVID-19. Patients hospitalized due to COVID-19 who were treated with remdesivir had a shorter time to recovery and rate of lower respiratory tract infection. Hence, it is considered superior to placebo. However, the mortality rate of patients treated with remdesivir alone did not significantly reduce [4]. Dexamethasone, an anti-inflammatory drug, reduces mortality in patients with severe COVID-19 [5]. However, viral activity is challenging to suppress with anti-inflammatory drugs alone. Hence, even in patients with severe COVID-19 who received dexamethasone, the mortality rate is still > 20%. Tocilizumab is used for the treatment of
rheumatoid arthritis worldwide. Previous studies have shown a decrease in mortality. Nevertheless, severe COVID-19 is challenging to treat with a single drug [13].

COVID-19 is an extremely serious threat to global health [17]. Unfortunately, there are extremely few medications found to be effective against SARC-CoV-2 and its associated inflammatory complications [15]. Drugs with different indications are used in various combinations as supportive treatments [18]. In severe COVID-19, SRAS-CoV-2 infection causes not only viral pneumonia but also cytokine storm-like conditions [19]. Antiviral drugs alone are not sufficient to control this condition, and combination therapy with anti-inflammatory and anti-cytokine drugs might be necessary.

A study conducted in Japan showed that combination therapy with favipiravir and nafomostat was effective [20]. However, the effect of neither favipiravir nor nafomostat has been comprehensively assessed, and its use in clinical practice is extremely limited. In contrast, remdesivir, dexamethasone, and tocilizumab have been extensively evaluated and are considered safe. Moreover, their adverse events are understood to some extent. In addition, this is a single group report and case series, and the efficacy of the drugs without comparison with a target group is challenging to assess.

The current study had several limitations. First, this retrospective study was conducted at a single center, and only a small number of patients were included. Second, this was a clinical practice study, and various therapeutic agents were used for the management of patients with severe COVID-19 in the control group. Finally, as this is not a randomized, double-blind trial, further well-designed and large-scale confirmatory trials should be conducted. However, considering the significant influence caused by the spread of COVID-19 worldwide, combination therapy with RDT may be effective for the treatment of this emerging disease.

**Conclusions**

Combination therapy with RDT reduced the mortality rate of severe COVID-19, and severe adverse events were not observed. The result of the current study is encouraging. However, in the future, randomized clinical studies should be performed to confirm such a finding.

**Abbreviations**

COVID-19, Coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; IL, interleukin; RDT, remdesivir, dexamethasone, and tocilizumab; PCR, polymerase chain reaction

**Declarations**

**Ethics approval and consent to participate**

This study was approved by the Ethical Committee for Clinical Studies of Japanese Red Cross Medical Center (no. 1111).
Conflict of interest

The authors have no conflicts of interest to declare in relation to this work.

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Author’s contribution

Study concept and design: TI. Acquisition of data: all authors. Analysis and interpretation of data: TI, MI. Writing of the manuscript: TI. Statistical analysis: TI. All authors approved the final version of the manuscript for publication.

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## Tables

### Table 1. Characteristics of patients with severe COVID-19 in the control and RDT groups

|                      | All patients (n = 46) | Control group (n = 29) | RDT group (n = 17) | P value |
|----------------------|-----------------------|------------------------|--------------------|---------|
| **Age, n (%)**       |                       |                        |                    |         |
| ≥65 years            | 23 (50)               | 15 (52)                | 8 (47)             | 0.66    |
| <65 years            | 23 (50)               | 14 (48)                | 9 (53)             |         |
| **Male patients, n (%)** |                       |                        |                    |         |
| 31 (67)              | 19 (66)               | 12 (71)                | 1.0                |         |
| **Body mass index, n (%)** |                       |                        |                    |         |
| ≥23 kg/m²            | 24 (52)               | 12 (41)                | 12 (70)            | 0.07    |
| <23 kg/m²            | 22 (48)               | 17 (59)                | 5 (30)             |         |
| **Smoking history**  |                       |                        |                    |         |
| Yes, n (%)           | 24 (52)               | 16 (55)                | 8 (47)             | 0.76    |
| No, n (%)            | 22 (48)               | 13 (45)                | 9 (53)             |         |
| **Comorbidities**    |                       |                        |                    |         |
| Diabetes, n (%)      | 24 (52)               | 16 (55)                | 8 (47)             | 0.76    |
| Hypertension, n (%)  | 20 (43)               | 11 (38)                | 9 (53)             | 0.37    |
| Oxygen support       |                       |                        |                    |         |
| Oxygen only, n (%)   | 24 (52)               | 15 (52)                | 9 (53)             | 1.0     |
| Invasive mechanical ventilation, n (%) | 22 (48)               | 14 (48)                | 8 (47)             | 1.0     |

COVID-19: coronavirus disease 2019, RDT: remdesivir, dexamethasone, and tocilizumab.

Variables were presented as number (%).
The Fisher’s exact test was used to compare differences in categorical variables between the control and RDT groups.

**Table 2. Impact of different factors on mortality in patients with severe COVID-19**

| Variable                                      | Univariate analysis | P value |
|-----------------------------------------------|---------------------|---------|
| Age, n (%)                                    |                     | 1.0     |
| ≥ 65 years                                    | 23 (50)             |         |
| < 65 years                                    | 23 (50)             |         |
| Male patients, n (%)                          | 31 (67)             | 0.71    |
| Body mass index, n (%)                        |                     | 1.0     |
| ≥ 23 kg/m²                                    | 24 (52)             |         |
| < 23 kg/m²                                    | 22 (48)             |         |
| Smoking history                               |                     | 0.48    |
| Yes, n (%)                                    | 24 (52)             |         |
| No, n (%)                                     | 22 (48)             |         |
| Comorbidities                                 |                     | 0.73    |
| Diabetes, n (%)                               | 24 (52)             |         |
| Hypertension, n (%)                           | 20 (43)             |         |
| Invasive mechanical ventilation, n (%)        | 22 (48)             | 0.16    |
| Combination therapy with RDT, n (%)           | 17 (37)             | 0.04    |
| Multivariate analysis                         | OR (95% CI)         |         |
| Combination therapy with RDT                  | 0.025 (0.0009–0.68) | 0.03    |

COVID-19: coronavirus disease 2019, RDT: remdesivir, dexamethasone, and tocilizumab. CI: confidence interval, OR: odds ratio

Variables were presented as number (%).

Univariate and multivariate analyses were performed to assess for categorical variables.

**Figures**
Effect of combination therapy with RDT on mortality in patients with COVID-19. The 28-day mortality rate was significantly lower in the RDT group than in the control group, with 1 (6%) and 9 (31%) deaths recorded, respectively (P = 0.04). COVID-19: coronavirus disease 2019, RDT: remdesivir, dexamethasone, and tocilizumab.
Figure 2

Chest imaging results after combination therapy with RDT in a patient with severe COVID-19. A) Chest radiography revealed abnormal infiltrative shadows in both lung fields on day 1 of admission. B) Chest CT scan showed GGO in both lung fields on day 1 of admission. C) Abnormal infiltrative shadows slightly improved after combination therapy with RDT on day 2. D, E) Abnormal infiltrative shadows on chest radiography and CT scan significantly improved after combination therapy with RDT on day 8. F) Chest radiography findings a day before discharge revealed no infiltrative shadows on day 13. COVID-19: coronavirus disease 2019, RDT: remdesivir, dexamethasone, and tocilizumab, CT: computed tomography, GGO: ground-glass opacities