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Original article

Clinical impact of combination therapy with baricitinib, remdesivir, and dexamethasone in patients with severe COVID-19

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ARTICLE INFO

Article history:
Received 28 April 2021
Received in revised form
15 June 2021
Accepted 19 July 2021
Available online 10 August 2021

Keywords:
Coronavirus disease 2019
Severe acute respiratory syndrome coronavirus 2
Acute respiratory distress syndrome
Adverse event
Efficacy

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has spread worldwide and is also an important disease in Japan. Thus, the optimal treatment strategy for severe COVID-19 should be established urgently. The effects of combination treatment with baricitinib—a Janus kinase inhibitor, remdesivir, and dexamethasone (BRD) are unknown.

Methods: Patients who received combination therapy with BRD at the Japanese Red Cross Medical Center were enrolled in the study. All patients received baricitinib (≤14 d), remdesivir (≤10 d), and dexamethasone (≤10 d). The efficacy and adverse events were evaluated.

Results: In total, 44 patients with severe COVID-19 were enrolled in this study. The 28-d mortality rate was low at 2.3% (1/44 patients). The need for invasive mechanical ventilation was avoided in most patients (90%, 17/19 patients). Patients who received BRD therapy had a median hospitalization duration of 11 d, time to recovery of 9 d, duration of intensive care unit stay of 6 d, duration of invasive mechanical ventilation of 5 d, and duration of supplemental oxygen therapy of 5 d. Adverse events occurred in 15 patients (34%). Liver dysfunction, thrombosis, iliopsoas hematoma, renal dysfunction, ventilator-associated pneumonia, infective endocarditis, and herpes zoster occurred in 11%, 11%, 2%, 2%, 2%, 2%, and 2% of patients, respectively.

Conclusions: Combination therapy with BRD was effective in treating severe COVID-19, and the incidence rate of adverse events was low. The results of the present study are encouraging; however, further randomized clinical studies are needed.

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; BRD, baricitinib: remdesivir: and dexamethasone; PCR, polymerase chain reaction; IQR, interquartile range; ACTT-2, Adaptive COVID-19 Treatment Trial 2; SpO2, blood oxygen saturation; eGFR, estimated glomerular filtration rate; CTCAE, Common Terminology Criteria for Adverse Events.

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https://doi.org/10.1016/j.resinv.2021.07.004

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread worldwide [1]. The development of treatment strategies for patients with severe COVID-19 is extremely important. Recently, the usefulness of remdesivir as an antiviral drug and dexamethasone as an anti-inflammatory drug for COVID-19 treatment has been reported [2,3]. However, the therapeutic effect of each drug alone is not satisfactory. Recently, the results of a combination therapy with remdesivir and baricitinib were reported in the Adaptive COVID-19 Treatment Trial 2 (ACTT-2) study [4]. Baricitinib, an orally administered selective inhibitor of Janus kinase (JAK) 1 and 2, is considered a potential therapeutic agent against SARS-CoV-2 [5,6]. Baricitinib inhibits the intracellular signaling pathway of cytokines that are known to have elevated levels in severe COVID-19, including interleukin-2, interleukin-6, interleukin-10, interferon-γ, and granulocyte-macrophage colony-stimulating factor; suppresses SARS-CoV-2 through the impairment of AP2-associated protein kinase 1 and the prevention of SARS-CoV-2 cellular entry and infectivity; and improves lymphocyte counts in COVID-19 patients [7,8]. According to the ACTT-2 report, the median time to recovery for patients receiving baricitinib was 7 d as compared to 8 d in the control group, with the odds of 30% improvement in clinical status on day 15. Further, patients receiving high-flow oxygen therapy or non-invasive ventilation at enrollment had an average time to recovery of 10 d with the combination therapy and 18 d with the control [4]. The 28-d mortality rate was 5.1% in the combination group and 7.8% in the control group. Serious adverse events were less frequent in the combination group than in the control group. Thus, the combination therapy with remdesivir and baricitinib was clinically more effective than monotherapy with remdesivir [4]. However, in clinical practice, dexamethasone and remdesivir are used worldwide as standard therapies [2,3]. Dexamethasone has been reported to reduce mortality in patients with severe COVID-19 on oxygen support [3]. Further, a study on the effectiveness of baricitinib (LY3009104) in combination with steroids or remdesivir in COVID-19 patients (COV-BARRIER study) has been conducted. However, the efficacy and safety of baricitinib-containing combination therapy for COVID-19 in Japan are unknown. Therefore, we investigated the efficacy and safety of a combination therapy of baricitinib, remdesivir, and dexamethasone (BRD), which are used in clinical practice, for treating patients with severe COVID-19.

2. Materials and methods

2.1. *Eligibility criteria*

The diagnosis of COVID-19 was confirmed via polymerase chain reaction (PCR) for SARS-CoV-2 using sputum or nasopharyngeal swab samples. SARS-CoV-2 RNA was detected using TaqMan one-step real-time PCR kits (QIAGEN, Co., Ltd., Hilden, Germany). In accordance with the National Institutes of Health classification criteria, COVID-19 patients were classified into four categories as follows: 1) mild illness group, patients with different signs and symptoms of COVID-19 except for shortness of breath, dyspnea, or abnormal chest imaging finding; 2) moderate illness group, patients with lower respiratory diseases diagnosed based on clinical assessment or imaging examination and a blood oxygen saturation level (SpO_2) $\geq$ 94% in room air at sea level; 3) severe illness group, patients with respiratory rate > 30 breaths per minute, SpO_2 < 94% in room air at sea level, arterial partial pressure of oxygen to fraction of inspired oxygen ratio < 300 Torr, or lung infiltrates > 50%; and 4) critical illness group, patients with respiratory failure, septic shock, and/or multiorgan dysfunction [9].

From December 2020 to January 2021, patients who were severely or critically ill with COVID-19 without severe renal dysfunction (with an estimated glomerular filtration rate [eGFR] < 30 mL/min) on admission were consecutively enrolled in this study.

2.2. *Procedures*

Remdesivir was administered intravenously at a 200-mg loading dose on day 1, followed by 100 mg from days 2–5 (without invasive mechanical ventilation) or days 2–10 (with invasive mechanical ventilation) [10]. Oral or intravenous dexamethasone was administered at a dose of 6 mg daily for up to 10 d [3]. Baricitinib was administered at a 4-mg daily dose (either orally or through a nasogastric tube) for 14 d or until hospital discharge. Patients with an eGFR ranging from 30 to 60 mL/min received baricitinib at a dose of 2 mg once daily [4].

2.3. *Statistical analyses*

All data are presented as medians with interquartile ranges (IQRs) or absolute numbers with percentages. Data were analyzed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan; http://www.jichi.ac.jp/saitama-

Table 1 – Clinical characteristics of the patients at baseline.

Characteristic	Measurement
Age, years (IQR)	61 (55–75)
Sex, n (%)	
Male	35 (80)
Female	9 (20)
BMI, kg/m^2 (IQR)	25.2 (22.3–28.5)
Body temperature, °C (IQR)	37.3 (36.7–38.0)
Symptom duration before admission (IQR)	8 (6–11)
Respiratory support received, n (%)	
Oxygen only	19 (43)
Invasive mechanical ventilation	25 (57)
Previous coexisting disease, n (%)	
Hypertension	23 (52)
Diabetes	12 (27)
Heart disease	5 (11)
Chronic obstructive pulmonary disease	2 (5)
Bronchial asthma	3 (7)
Cancer	4 (9)
Liver disease	1 (2)

IQR, interquartile range.

Table 2 – Clinical laboratory data of the patients at baseline.

Characteristic	Measurement
WBC count, per mm^3, median (IQR)	6100 (5500–7500)
Lymphocyte count, per mm^3, median (IQR)	840 (530–1085)
Eosinophil count, per mm^3, median (IQR)	0 (0–10)
AST level, U/L, median (IQR)	45 (34–61)
ALT level, U/L, median (IQR)	35 (24–49)
LDH level, U/L, median (IQR)	327 (283–390)
CK level, U/L, median (IQR)	95 (53–179)
BUN level, mg/dL, median (IQR)	16 (13–24)
Cre level, mg/dL, median (IQR)	0.85 (0.63–1.05)
eGFR, ml/min/1.7 m^2, median (IQR)	71.3 (54.8–83.1)
Zn level, μg/dL, median (IQR)	55 (46–69)
Alb level, μg/dL, median (IQR)	3.0 (2.8–3.5)
CRP level, mg/dL, median (IQR)	7.4 (4.0–11.9)
Ferritin level, ng/mL, median (IQR)	635 (412–1235)
PCT level, ng/mL, median (IQR)	0.08 (0.05–0.16)
D-dimer level, μg/dL, median (IQR)	0.6 (0.5–1.8)
sIL-2R level, U/mL, median (IQR)	837 (740–1155)
KL-6 level, U/mL, median (IQR)	327 (269–458)

IQR, interquartile range; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CK, creatinine kinase; BUN, blood urea nitrogen; Cre, creatinine; eGFR, estimated glomerular filtration rate; Alb, albumin; CRP, C-reactive protein; PCT, procalcitonin; sIL-2R, soluble interleukin-2 receptor; KL-6, Krebs von den Lungen-6.

sct/SaitamaHP.files/statmed.html), a graphical user interface for R software (version 2.13.0; The R Project for Statistical Computing; http://www.r-project.org) and a modified version of R Commander [11]. Adverse effects were reported in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

2.4. *Ethics approval and consent to participate*

This study was approved by the Ethics Committee for Clinical Studies of the Japanese Red Cross Medical Center (no. 1155; October 2, 2020). Written informed consent for off-label use was obtained from all patients. Additional informed consent for this study was waived owing to the nature of the study design, which involved retrospective chart review for obtaining clinical information. In accordance with the Japanese ethical guidelines for clinical research, the need for informed consent was waived.

Table 4 – Adverse events.

Event	no./total no. of patients (%)
All adverse events	15/44 (34)
Liver dysfunction	5/44 (11)
Thrombosis	5/44 (11)
Iliopsoas hematoma	1/44 (2)
Renal dysfunction	1/44 (2)
Ventilator-associated pneumonia	1/44 (2)
Infective endocarditis	1/44 (2)
Herpes zoster	1/44 (2)

3. Results

In total, 44 patients with severe COVID-19 were enrolled in this study.

The clinical characteristics of the patients at baseline are presented in Table 1. Briefly, the median patient age was 61 y (IQR: 55–75 y), and 35 patients (80%) were men. Respiratory support with oxygen was administered to only 19 patients (43%) and 25 patients (57%) required invasive mechanical ventilation.

The clinical laboratory data of the patients at baseline are presented in Table 2. Briefly, the median white blood cell (WBC) count was 6100/mm^3 (IQR: 5500–7500/mm^3), lymphocyte count was 840/mm^3 (IQR: 530–1085/mm^3), and eosinophil count was 0/mm^3 (IQR: 0–10/mm^3). There were no significant increases in WBC count or decreases in lymphocyte and eosinophil counts, despite the marked decrease in median eosinophil count to 0. The median C-reactive protein and ferritin levels increased to 7.4 mg/mL and 635 ng/mL, respectively.

The patient outcomes are presented in Table 3 and were as follows: 28-d mortality rate, 2.3% (1/44 patients); avoidance of invasive mechanical ventilation, 90% (17/19 patients); extubation from invasive mechanical ventilation, 96% (24/25 patients); median hospitalization duration, 11 d (IQR: 7–17 d); median time to recovery, 9 d (IQR: 6–16 d); median duration of intensive care unit (ICU) stay, 6 d (IQR: 4–9 d); median duration of invasive mechanical ventilation, 5 d (IQR: 4–8 d); and median duration of supplemental oxygen therapy, 5 d (IQR: 2–8 d).

The adverse events are presented in Table 4 and were reported in accordance with CTCAE version 5.0. Adverse events occurred in total 15 patients (34%), wherein liver dysfunction

Table 3 – Patient outcomes.

Outcome	
Mortality at 28 d, no./total no. of patients (%)	1/44 (2.3)
Avoidance of invasive mechanical ventilation, no./total no. of patients (%)	17/19 (90)
Extubation from invasive mechanical ventilation, no./total no. of patients (%)	24/25 (96)
Hospitalization duration, days, median (IQR)	11 (7–17)
Time to recovery, days, median (IQR)	9 (6–15)
Duration of intensive care unit stay, days, median (IQR)	6 (4–9)
Duration of invasive mechanical ventilation, days, median (IQR)	5 (4–8)
Duration of supplemental oxygen therapy, days, median (IQR)	5 (2–8)

IQR, interquartile range.

occurred in 11% of patients, thrombosis in 11%, iliopsoas hematoma in 2%, renal dysfunction in 2%, ventilator-associated pneumonia in 2%, infective endocarditis in 2%, and herpes zoster in 2%.

4. Discussion

To the best of our knowledge, this is the first study on the efficacy and safety of BRD combination therapy in patients with severe COVID-19 in clinical practice. In this study, BRD therapy was found to be highly effective, with acceptable adverse events, against severe COVID-19.

COVID-19 is an infection caused by SARS-CoV-2. Further, in patients with severe disease who require oxygen therapy and invasive mechanical ventilation, excessive inflammation and cytokine storm-like conditions are considered serious [12]. Therefore, steroid therapy and antiviral drug therapy with remdesivir are currently being used for COVID-19 patients who require oxygen support [2,3]. According to the ACTT-1 study, the secondary endpoint of mortality by day 15 was 6.7% in patients receiving remdesivir compared to 11.9% in patients receiving placebo, whereas that by day 29 was 11.4% and 15.2% in the two groups, respectively, although the differences were not statistically significant [2]. In the RECOVERY trial, mortality was significantly lower in the dexamethasone group than in the usual care group in patients receiving invasive ventilation (29.3% vs. 41.4%) and in those receiving oxygen support without invasive ventilation (23.3% vs. 26.2%) at the time of randomization. However, there was no statistically significant difference in the mortality rates of patients who were not receiving oxygen support at the time of randomization (17.8% vs. 14.0%) [3]. However, in clinical practice, the effects of remdesivir and dexamethasone monotherapies are often limited. Recently, SARS-CoV-2 variants have appeared worldwide, and the number of cases of each variant has been increasing in Japan as well. COVID-19 caused by SARS-CoV-2 variants has been reported to worsen the condition of patients faster than the strain before the current variant [13]. Therefore, a treatment strategy that suppresses the worsening of this medical condition must be developed.

In the present study, BRD therapy was found to be highly effective, with 2.3% mortality rate and 90% of patients not requiring invasive mechanical ventilation. In addition, 96% of patients could be extubated from invasive mechanical ventilation. The length of ICU stay is a critical problem in patients with severe COVID-19; however, in this study, the median duration of ICU stay was as short as 6 d among patients receiving BRD therapy—this might be advantageous in clinical practice.

The incidence of adverse events was 34%. Combined administration of the two types of immunomodulators, dexamethasone and baricitinib, did not cause major problems, which indicates that combination therapy should be seriously considered for COVID-19 treatment in clinical practice. According to the ACTT-2 trial, despite concerns regarding immunosuppression, secondary infections, and thrombosis with the use of JAK inhibitors, the addition of baricitinib was not associated with a significantly higher incidence of adverse or thromboembolic events [4]. In fact, patients who received baricitinib plus remdesivir had significantly lower incidence rates of adverse events, adverse events leading to discontinuation of the trial drug, serious adverse events, serious adverse events with a fatal outcome, and infection-related adverse events than patients who received remdesivir alone. The consistently lower incidence rate of adverse events with baricitinib monotherapy may be related to its ability to reduce inflammatory lung injury and improve lymphocyte counts, its antiviral properties, or its associated shorter recovery time and faster clinical improvement, all of which could reduce the risk of nosocomial infections [4]. To summarize, the incidence of adverse events was low with BRD therapy in our study, wherein dexamethasone and remdesivir were included with baricitinib for treating severe COVID-19.

The present study had several limitations. First, the study was conducted at a single center, and only few patients were included. Second, a control group of patients with severe COVID-19 receiving the standard of care was not included in this study. In clinical practice, setting a control group was difficult because of patient care. Moreover, the standard of care differed depending on the season, variants, and medical supply system. Therefore, even if we tried propensity matching, it was difficult to perform a comparative study. Third, the study was conducted without preparing a special environment as much as possible for examination in clinical practice. Further investigations are needed to clarify this aspect.

5. Conclusions

Combination therapy with BRD was effective for treating severe COVID-19, and the incidence of adverse events was low. The results of the present study are promising, given the significant impact of the global spread of COVID-19, although further randomized clinical trials must be conducted to confirm these findings.

Ethics approval and consent to participate

This study was approved by the Ethics Committee for Clinical Studies of Japanese Red Cross Medical Center (no. 1155; October 2, 2020).

Funding source

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

Study concept and design: TI; acquisition of data: all authors; analysis and interpretation of data: TI and MI; writing of the

manuscript: TI; statistical analysis: TI. All authors approved the final version of the manuscript for publication.

Conflict of Interest

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

Acknowledgments

We would like to thank all the participants and staff members involved in this study. We express our gratitude to Akihiro Ueda, Momoko Mawatari, Yu Akagi, Munehiro Hayashi, Yuta Moroe, Yuji Kondo, Tomoyuki Yamashita, Shogo Sagisaka, Akira Noumi, Kayo Okubo, and Miyuki Nishikawa for their outstanding support. Furthermore, the authors also thank Enago for English-language editing. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit the findings for publication.

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