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Original article

Efficacy of the combination of baricitinib, remdesivir, and dexamethasone in hypoxic adults with COVID-19: A retrospective study



Yuto Yasuda^{a,*}, Yutaka Hirayama^b, Kiyoshi Uemasu^a, Soichi Arasawa^c, Daisuke Iwashima^a, Ken-ichi Takahashi^a

^a Department of Respiratory Medicine, Kishiwada City Hospital, 1001 Gakuhara-cho, Kishiwada-shi, Osaka, 586-8501, Japan

^b Department of Respiratory Medicine, Kyoto University Graduate School of Medicine, 54 Kawahara-cho Shogoin Sakyoku, Kyoto, 606-8507, Japan

^c Department of Gastroenterology, Kishiwada City Hospital, 1001 Gakuhara-cho, Kishiwada-shi, Osaka, 586-8501, Japan

ARTICLE INFO

Article History:

Received 11 November 2021

Revised 2 March 2022

Accepted 8 March 2022

Available online 19 March 2022

Keywords:

Baricitinib
 Remdesivir
 Dexamethasone
 COVID-19

ABSTRACT

Background: Remdesivir with dexamethasone and remdesivir with baricitinib are effective in coronavirus disease 2019 (COVID-19) patients. However, there has been few evidence regarding the efficacy of the combination of baricitinib, remdesivir, and dexamethasone in hypoxic COVID-19 patients.

Methods: Consecutive patients who required oxygen therapy at the time of admission and received remdesivir and dexamethasone at Kishiwada City Hospital between March 1, 2021 and May 31, 2021 were retrospectively analyzed.

Results: A total of 90 patients were investigated, including 30 receiving a combination of remdesivir, dexamethasone, and baricitinib (baricitinib group) and 60 receiving remdesivir and dexamethasone (control group). The use of direct oral anticoagulants, the level of C-reactive protein, and chest X-ray abnormalities were significantly higher in the baricitinib group than in the control group. Patients in the baricitinib group recovered a median of four days faster than those in the control group (median, 7 days vs. 11 days; Gray's test, $p < 0.001$). The recovery rate was 90.0% in the baricitinib group and 63.3% in the control group ($p = 0.011$). Fine and Gray regression analysis showed that adjusted rate ratio for recovery with the baricitinib combination therapy was 5.26 (95% confidential interval, 1.99–13.9; $p < 0.001$). The incidence of new onset of bacterial infection was 6.7% in the baricitinib group and 16.7% in the control group ($p = 0.324$).

Conclusions: Our study suggests that the combination of baricitinib, dexamethasone, and remdesivir is effective and tolerable in hypoxic patients with COVID-19.

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1. Introduction

Remdesivir plus dexamethasone is effective for hospitalized adult patients with coronavirus disease 2019 (COVID-19) pneumonia [1]. Baricitinib plus remdesivir is more effective than remdesivir alone in patients with COVID-19. A major trial called the Adaptive COVID-19 Treatment Trial 4 (NCT04640168) is now ongoing to compare these two therapies. However, to date, there have been no randomized studies on the simultaneous administration of baricitinib, remdesivir, and dexamethasone.

Baricitinib is a Janus kinase inhibitor that reduces the serum levels of interleukin (IL)-1 β , IL-6, and Tumor Necrosis Factor- α [2]. The levels of IL-6 correlate with COVID-19 severity [3], and tocilizumab, a humanized monoclonal antibody that binds to the IL-6 receptor, is also effective against COVID-19 [4]. Since approval of baricitinib by the Japanese Ministry of Health, Labor and Welfare on April 23, 2021,

baricitinib has been widely used in Japan because tocilizumab has not yet been approved at the time of the study. Although the triple therapy may lead to uncontrollable infection, guidelines from the National Institutes of Health recommend adding baricitinib for patients on dexamethasone who have rapidly increasing oxygen needs and systemic inflammation [5]. Therefore, we retrospectively evaluated the efficacy of this triple therapy.

2. Methods

2.1. Patients and study design

This is a single-center, retrospective study. All patients who were hospitalized with COVID-19 at Kishiwada City Hospital (Osaka, Japan) between March 1, 2021 and May 31, 2021 were enrolled in this study. Of the 168 enrolled patients, 60 were excluded for the following reasons: 43 did not need oxygen at the time of admission, 11 received initial treatment at another hospital, 3 were in the terminal stage due to

* Corresponding author at.

E-mail address: yyasuda0628@gmail.com (Y. Yasuda).

cancer or aging, 1 refused treatment, and 2 had no clinical information. COVID-19 diagnosis was confirmed by antigen or polymerase chain reaction tests. The relevant clinical data were collected by a retrospective review of the patients' medical charts. All laboratory data and chest anterior-posterior X-ray image were obtained on the day of hospitalization. Chest X-ray abnormalities were evaluated by whether or not the extent of lung lesion was more than 50% or not. Oxygen was started when the peripheral oxygen saturation dropped below 93% in room air.

2.2. Treatment

Remdesivir was administered intravenously as a 200 mg dose on day 1, followed by a 100 mg dose on days 2 through 5 or death. Oral or intravenous dexamethasone was administered as a daily dose of 6 mg for up to 10 days (or until no need for oxygen therapy, if sooner). Administration of dexamethasone for 10 days or more was allowed. Baricitinib was administered as a daily dose of 4 mg for up to 14 days (or until no need for oxygen therapy, if sooner). If the estimated glomerular filtration rate (eGFR) was less than 60 mL per minute, the dose of baricitinib was reduced to 2 mg once daily. Patients with high serum levels of D-dimer or those who received baricitinib were treated with direct oral anticoagulants (DOAC) to prevent venous thromboembolism. Prophylactic anticoagulation with DOAC was initiated only at the start of mechanical ventilation. Standard preventive anticoagulation for other patients with COVID-19 was not available at the time of the study due to limited resources. No prophylactic antibiotics were used. High-flow nasal cannula and noninvasive positive-pressure ventilation were not used.

2.3. Outcomes

The primary outcome measure was the time from the initiation of treatment to recovery. The recovery day was defined as 10 days or more following the onset of disease, without the need for oxygen therapy and with no fever for three days or more. If the patient was once under mechanical ventilation, the recovery day was defined as at least 15 days after the onset, without the need for oxygen therapy and with no fever for three days or more.

The secondary outcome measure was the incidence of mechanical ventilation and bacterial infection during hospitalization. Infection was confirmed by the clinical course; blood, urine, or sputum culture; chest X-ray; or computed tomography.

2.4. Statistics

Continuous variable data were expressed as mean \pm standard deviation. P-values of patient characteristics were calculated using Student's *t*-test or Fisher's exact test. Recovery and in-hospital mortality were evaluated by competing risks analysis using cumulative incidence function. The rate ratio of recovery was estimated using Fine and Gray regression model. All statistical analyses were

performed using R version 4.1.0. P-values of < 0.05 were considered statistically significant.

3. Results

3.1. Subjects

Of the 108 patients analyzed in this study, 16 were treated with only dexamethasone, and 2 were treated with only standard care (Fig. 1A). There were 90 patients who belonged to moderate disease with a score of 5 according to WHO clinical progression scale, including 30 who received a combination of remdesivir, dexamethasone, and baricitinib (baricitinib group) and 60 who received remdesivir plus dexamethasone (control group). None of them were vaccinated before hospitalization. Baricitinib was first administered in our hospital on April 28, 2021; 7 patients in the control group did not receive baricitinib because of low eGFR ($n = 2$) and difficulty in taking oral medications due to mental disorders or aging ($n = 5$).

3.2. Characteristics

Patients' characteristics are summarized in Table 1. There was no difference concerning sex, smoking history, previous history of diabetes or ischemic heart disease, fever, and requirement of oxygen at admission. The age of the patients in the baricitinib group was significantly younger than that of the control group (61.1 ± 2.7 vs. 70.5 ± 1.9 mg/dl; $p = 0.006$). Lymphocytes, white blood cell counts, and D-dimer were also not significantly different between the two groups. C-reactive protein (CRP) was significantly higher in the baricitinib group than in the control group (11.0 ± 7.4 mg/dl vs. 8.1 ± 5.3 mg/dl; $p = 0.0417$). Chest X-ray abnormalities were significantly more severe in the baricitinib group than in the control group (76.7% vs. 23.3%; $p = 0.0248$). DOACs were used in all patients in the baricitinib group and 15.0% of patients in the control group. The duration of dexamethasone was 7.7 ± 2.7 days in the baricitinib group and 7.7 ± 2.9 days in the control group.

3.3. Outcomes

Patients who received combination treatment with remdesivir, dexamethasone, and baricitinib recovered a median of three days faster than those who received remdesivir plus dexamethasone (median, 7 days vs. 11 days; Gray's test, $p < 0.001$) (Fig. 2A). The recovery rate was 90.0% in the baricitinib group and 63.3% in the control group ($p = 0.011$). All-cause mortality was significantly different between the two groups (6.7% vs. 28.3%; $p = 0.0263$). Fine and Gray regression analysis showed that adjusted rate ratio for recovery with the baricitinib combination therapy was 5.26 (95% confidential interval, 1.99–13.9; $p < 0.001$). Age, and DOACs were also significantly associated with recovery time (Table 2). Among the 39 patients who received DOACs, the recovery rate was 90.0% vs. 44.4% (baricitinib group vs. control group; $p = 0.0089$), and 77.8% of patients receiving DOACs without baricitinib were intubated in the control group.

Next, we investigated age-stratified recovery time since age was associated with recovery time. Stratification was performed in patients aged 65 years because those aged 65 years or older were defined as the elderly in Japan and the median age of all study subjects was approximately 65 years. The median recovery time among patients aged 65 years or older was 7 days in the baricitinib group ($n = 10$) and 13 days in the control group ($n = 41$) (Gray's test, $p = 0.039$), whereas it was 7 days in the baricitinib group ($n = 20$) and 6 days in the control group ($n = 19$) (Gray's test $p = 0.307$) among patients younger than 65 years (Fig. 2B, C). The characteristics of patients aged 65 years or older were not significantly different between the two groups, except for the use of DOACs. However, CRP, chest X-ray abnormalities, and the use of DOACs of patients younger

List of abbreviations

COVID-19	Coronavirus disease 2019
IL	Interleukin
eGFR	Estimated glomerular filtration rate
DOAC	Direct oral anticoagulants
CRP	C-reactive protein
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
DEX	dexamethasone
BAR	baricitinib
RDV	remdesivir

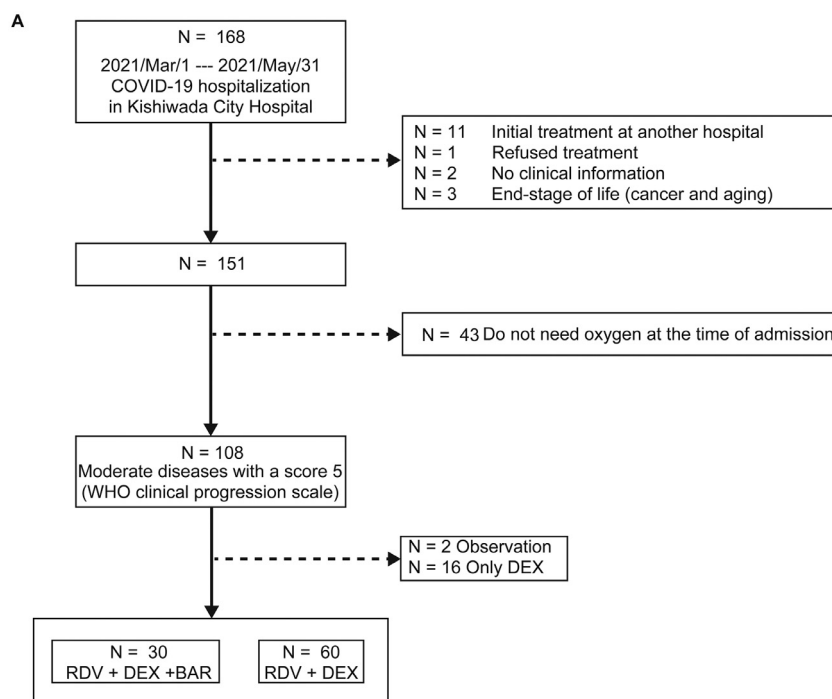


Fig. 1. CONSORT Flow diagram of a study in patients with COVID-19. DEX, dexamethasone, BAR, baricitinib; RDV, remdesivir.

than 65 years were significantly higher in the baricitinib group than in the control group (Table 3).

The incidence of first use of mechanical ventilation was 13.3% in the baricitinib group and 18.3% in the control group ($p = 0.765$) (Table 4). The intubated patients who were not transferred to another hospital did not receive extracorporeal membrane oxygenation. The incidence of new onset of bacterial infection was 6.7% in the baricitinib group and 16.7% in the control group ($p = 0.324$). The incidence of mortality among the infected patients was 0% in the baricitinib group and 27.3% in the control group ($p = 0.517$). Other complications in the control group were intestinal perforation in two cases and cerebral infarction in two cases. One case with severe interstitial pneumonia was observed in the baricitinib group.

4. Discussion

This is the report investigating the efficacy and safety of the combination of remdesivir, dexamethasone, and baricitinib (triple

therapy) in hypoxic patients with COVID-19. Previously, Izumo et al. reported that triple therapy was effective with 2.3% mortality rate [6]. Thus, the add-on efficacy of baricitinib was expected in hypoxic patients with COVID-19. The triple therapy reduced mortality and the recovery time by approximately four days without increasing the incidence of infection.

During the study period in Osaka, the alpha (B.1.1.7, VOC 202,012/01) variant was prevalent as the fourth wave of the epidemic in Japan. Since most patients were diagnosed as COVID-19 at other clinics or surveillance centers, the precise variant was not confirmed by scientific methods. Baricitinib was approved during the period, and triple therapy was first started on April 28, 2021.

The treatment strategy was modified from the original studies [1, 7]. First, remdesivir was administered for five days. Furthermore, the hazard ratios of 28-day mortality of patients who received remdesivir for 5 and 10 days were 0.51 and 0.69, respectively [8]. Second, dexamethasone and baricitinib were discontinued when oxygen therapy was no longer needed. The combination of dexamethasone and

Table 1
Patient characteristics.

	RDV + DEX + BAR $n = 30$	RDV + DEX $n = 60$	P value
Age, year-old	61.1 ± 2.7	70.5 ± 1.9	0.006
Sex (Female/Male)	8 (26.7%) / 22 (73.3%)	20 (33.3%) / 40 (66.7%)	0.632
Smoking History (Yes/No/Unknown)	15 (50.0%) / 15 (50.0%) / 0 (0%)	24 (40.0%) / 32 (53.3%) / 4 (6.7%)	0.376
Previous history of diabetes (Yes/No)	5 (16.7%) / 25 (83.3%)	12 (20.0%) / 48 (80.0%)	0.782
Previous history of ischemic heart diseases (Yes/No)	1 (3.3%) / 29 (96.7%)	6 (10.0%) / 54 (90.0%)	0.417
Lymphocyte count, / μ l	767 ± 400	744 ± 319	0.770
WBC, / μ l	5506 ± 2152	5465 ± 3247	0.950
CRP, mg/dl	11.0 ± 7.4	8.1 ± 5.3	0.0417
D-dimer, mg/dl	1.8 ± 0.9	2.8 ± 5.9	0.362
Oxygen therapy at hospitalization, l/min	3.1 ± 1.9	2.8 ± 1.6	0.491
Chest X-ray abnormalities (>50%) (Yes/No)	23 (76.7%) / 7 (23.3%)	31 (51.7%) / 29 (48.3%)	0.0248
Fever at hospitalization (Yes/No)	18 (60.0%) / 12 (40.0%)	39 (65.0%) / 21 (35.0%)	0.650
Duration from onset to treatment	7.0 ± 3.0	6.5 ± 3.9	0.498
Anticoagulants (Yes/No)	30 (100%) / 0 (0%)	9 (15.0%) / 51 (85.0%)	<0.001
Duration of DEX, days	7.7 ± 2.7	7.7 ± 2.9	1.000
Duration of BAR, days	6.9 ± 3.2	NA	NA

WBC, white blood cell; CRP, c-reacting protein; DEX, dexamethasone, BAR, baricitinib; RDV, remdesivir; NA, not available.

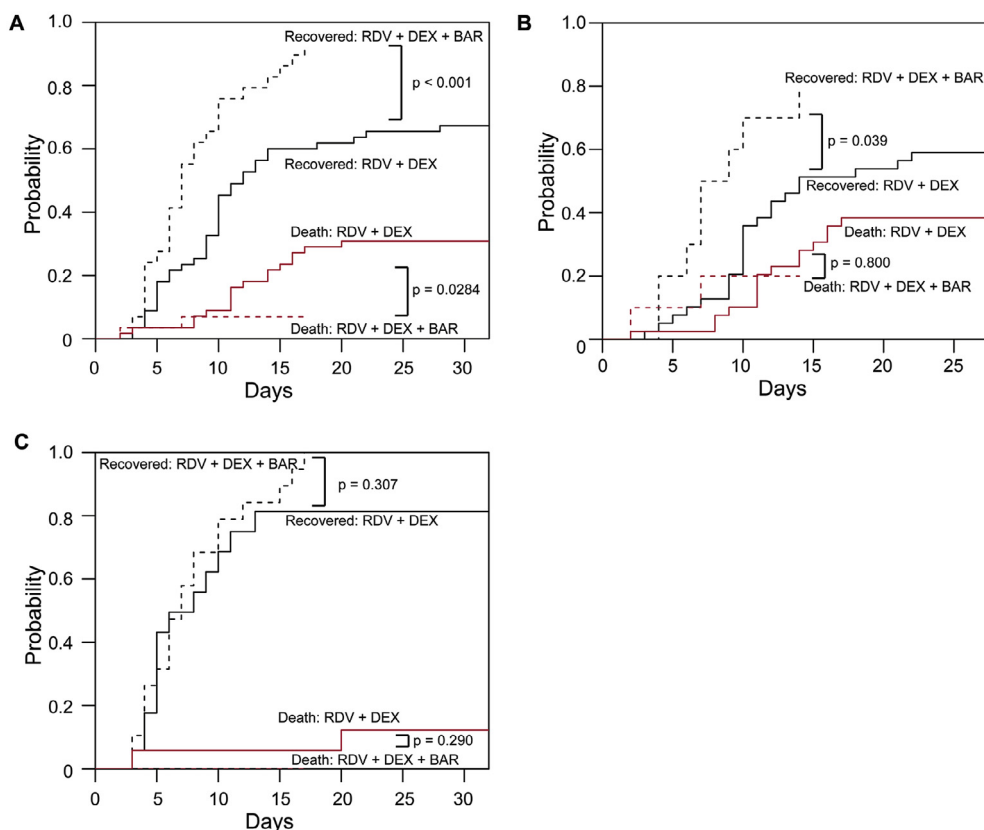


Fig. 2. Kaplan-Meier Estimates of cumulative recoveries.

Cumulative recovery estimates are shown in the overall population (A), in patients aged 65 years or older (B), and in those younger than 65 years (C). Recovery and in-hospital mortality were evaluated by competing risks analysis using cumulative incidence function.

Table 2

Fine and Gray regression analysis for recovery time in hypoxic COVID-19 patients (n = 90).

Variables	RR	95%CI	P value
Baricitinib	5.26	1.99–13.9	<0.001
Anticoagulants	0.32	0.11–0.92	0.034
Age (years)	0.96	0.94–0.98	<0.001
CRP	0.98	0.94–1.01	0.184
Chest X-ray abnormalities (>50%)	0.70	0.40–1.22	0.213

RR, rate ratio; CI, Confidence intervals; CRP, c-reacting protein.

baricitinib increased the incidence of infection [7]. Since the short-term use of corticosteroids was associated with increased rates of sepsis, venous thromboembolism, and fracture [9], dexamethasone and baricitinib were discontinued as soon as possible.

Triple therapy significantly reduced the time from the initiation of treatment to recovery. Since the days of onset, inspection, and hospitalization were influenced by social situation or patient's memory, the first day of treatment was chosen as the starting point to ensure a certain degree of severity. Since patients with mild-to-moderate COVID-19 are highly unlikely to be infectious beyond 10 days of symptoms [10] and the median duration of shedding infectious virus by patients with severe COVID-19 disease drops below 5% after 15.2 days post onset of symptoms [11], the recovery day was defined as 10 days in patients without mechanical ventilation and 15 days in those with mechanical ventilation.

The recovery rate and time was better with triple therapy. Age was associated with recovery time, and the recovery time was evaluated and stratified in patients aged 65 years. A previous report indicated that the age distribution of mortality in patients less than

65 years of age is strongly consistent across different settings [12]. However, there was no difference of recovery time between triple therapy and remdesivir plus dexamethasone therapy in patients aged 65 or younger. Significantly higher CRP and more extensive radiographic lung involvement lesions in the baricitinib group may affect outcomes, or triple therapy may be not necessary in younger population.

All-cause mortality was significantly different between the baricitinib group and the control group. The significant difference in DOAC use between the two groups may have affected the result. DOACs were used in all patients receiving triple therapy and in 15.0% of patients receiving remdesivir plus dexamethasone therapy in our study. Anticoagulants were only recommended in patients with high serum levels of D-dimer and patients who concomitantly used baricitinib at the time of the study. Recent study showed that therapeutic-dose anticoagulation with heparin improved survival until hospital discharge [13]. DOAC may improve the recovery time since heparin reduces mortality [13, 14]. Although no study regarding the efficacy of DOAC was reported at the time of the study, in our hospital, DOAC was used instead of heparin due to limited human resources in the epidemic. However, the ACTION trial reported that 11% of patients who received rivaroxaban for 30 days and 8% of patients who received heparin died, but the difference was not significant [15]. DOAC may have counteracted the mortality-suppressing effect of baricitinib. On the other hand, our data showed that the recovery rate and time was also better in the baricitinib group regardless of high percentage of DOAC use. This may reinforce the hypothesis that triple therapy is superior to remdesivir plus dexamethasone.

Mechanical ventilation was required in 13.3% of patients in the baricitinib group and 18.3% of patients in the control group. A previous report showed that 10% of patients receiving baricitinib plus

Table 3
Patient characteristics stratified by age.

	RDV + DEX + BARAge >= 65n = 10	RDV + DEXAge >= 65n = 41	P value	RDV + DEX + BARAge < 65n = 20	RDV + DEXAge < 65n = 19	P value
Age, year-old	78.5 ± 8.7	79.1 ± 7.3	0.811	52.4 ± 9.0	51.8 ± 7.6	0.851
Sex (Female/Male)	4 (40%) /6 (60%)	16 (39.0%) /25 (61.0%)	1.000	4 (20%) /16 (80%)	4 (21.1%) /15 (79.0%)	1.000
Smoking History (Yes/No/Unknown)	5 (50%) /5 (50%) /0 (0%)	17 (41.5%) /20 (48.8%) /4 (9.8%)	0.878	10 (50%) /10 (50%) /0 (0%)	7 (36.8%) /12 (63.2%) /0 (0%)	0.523
Previous history of diabetes (Yes/No)	2 (20%) /8 (80%)	9 (22.0%) /32 (78.1%)	1.000	3 (15%) /17 (85%)	3 (15.8%) /16 (84.2%)	1.000
Previous history of ischemic heart diseases (Yes/No)	0 (0%) /10 (100%)	5 (12.2%) /36 (87.8%)	0.569	1 (5%) /19 (95%)	1 (5.3%) /18 (94.7%)	1.000
Lymphocyte count, /μl	693±309	731±292	0.715	804±441	771±380	0.809
WBC count, /μl	5523±1988	5628±2728	0.910	5498±2280	5115±4224	0.725
CRP, mg/dl	9.5 ± 6.4	8.6 ± 5.4	0.634	11.7 ± 8.0	7.2 ± 5.0	0.0446
D-dimer, mg/dl	2.1 ± 1.3	3.4 ± 7.0	0.577	1.7 ± 0.7	1.6 ± 1.3	0.808
Oxygen therapy at hospitalization, L/min	3.4 ± 2.8	2.8 ± 1.7	0.408	2.9 ± 1.3	2.7 ± 1.6	0.723
Chest X-ray abnormalities (>50%) (Yes/No)	5 (50%) /5 (50%)	20 (48.8%) /21 (51.2%)	1.000	18 (90%) /2 (10%)	11 (57.9%) /8 (42.1%)	0.031
Fever at hospitalization (Yes/No)	4 (40%) /6 (60%)	24 (58.5%) /17 (41.5%)	0.316	14 (70%) /6 (30%)	15 (79.0%) /4 (21.1%)	0.738
Anticoagulants (Yes/No)	10 (100%) /0 (0%)	4 (9.8%) /37 (90.2%)	<0.001	20 (100%) /0 (0%)	5 (26.3%) /14 (73.7%)	<0.001
Duration of DEX, days	7.3 ± 2.6	8.2 ± 2.8	0.358	7.9 ± 2.8	6.5 ± 2.9	0.155
Duration of BAR, days	6.9 ± 2.9	NA	NA	6.9 ± 3.4	NA	NA

WBC, white blood cell; CRP, c-reacting protein; DEX, dexamethasone, BAR, baricitinib; RDV, remdesivir; NA, not available.

Table 4
Secondary outcomes.

	RDV + DEX + BARn = 30	RDV + DEXn = 60	P value
Mechanical ventilation	4 (13.3%)	11 (18.3%)	0.765
- Recovered	3	3	
- Died	0	3	
- Transferred	1	5	
Bacterial infection	2 (6.7%)	10 (16.7%)	0.324
- Pneumonia	1	5	
- UTI	0	3	
- Pulmonary abscess	0	1	
- Sinusitis	1	0	
- Bacteremia	0	1	

DEX, dexamethasone, BAR, baricitinib; RDV, remdesivir; UTI, urinary tract infection.

remdesivir were intubated [7]. Although there was no significant difference between the two groups, none of the intubated patients died in the baricitinib group.

The incidence of infection was lower in the baricitinib group (6.7%) than in the control group (16.7%). Previous reports indicated that 7.2% of patients with COVID-19 had other microbiologically confirmed infections, and the incidence of infection was lower in the baricitinib plus remdesivir group (5.9%) than in the control group (11.2%) [7, 16]. The reason for the low infection rate in baricitinib-treated patients is unknown, but our study showed a similar trend. Although short-term use of dexamethasone may not increase the incidence of infection, the high mortality rate of infection (0–27.3%) suggested empiric and prophylactic use of antibiotics.

This study has several limitations which need to be considered. First, the use of DOAC, the level of CRP, and chest X-ray abnormalities were significantly higher in the baricitinib group than in the control group. Since there is insufficient evidence to determine whether DOAC affects COVID-19 outcomes, further study is needed to determine whether DOAC or heparin are more appropriate for COVID-19. In addition, the initial severity seemed to be worse in the baricitinib group than in the control group. These may affect the efficacy of baricitinib. Second, it was a retrospective chart review study, and observational prognostic factor was not investigated. Height, body weight, HbA1c, ferritin, IL-6, and PaO₂/FiO₂ ratio should be included in the analysis, but many missing values could not be analyzed. Mutations of SARS-CoV-2 were not confirmed. However, the basic data were

not different between the two groups, and the patients seemed to be infected to the alpha variant of SARS-CoV-2 because they were enrolled in a short-term period during the fourth wave of alpha variants. Third, post-acute COVID-19 syndrome was not evaluated. Recently, there have been increasing reports of prolonged and persistent effects after recovery from COVID-19 [17]. Since we did not usually follow up patients after discharge, our treatment protocol may influence post-acute COVID-19 syndrome. Forth, the population of the study was small and treatment strategy was not randomized. Further randomized larger studies are required to confirm and elucidate the efficacy of triple therapy. Finally, genetic evolution of SARS-CoV-2 is progressing with mutations over time. The activity of triple therapy in the Omicron era awaits further investigation.

5. Conclusions

In conclusion, our study suggested that the combination of baricitinib, dexamethasone, and remdesivir was effective and tolerable in hypoxic patients with COVID-19. This study supports the conduct of a prospective clinical trial to confirm the clinical benefit of triple therapy.

Declarations

Ethics approval and consent to participate.

The study protocol had been prepared in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Kishiwada City Hospital for using retrospective data (Kishi-Byou-Rin 23: September 25, 2020). Oral informed consent was obtained and recorded on an electronic chart.

Consent for publication

Not required.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Author contributions

YY: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, visualization, writing original draft, writing. YH, KU, SA, DI: Resources, validation. KT: Supervision, review & editing. All authors have read and approved the manuscript.

Competing interests

The authors have no conflicts of interest directly relevant to the content of this article.

Acknowledgements

The authors thank all doctors, nurses, pharmacist, technicians, radiological technologist, and clerks fighting against COVID-19 in Kishiwada City hospital. The authors are grateful to Dr. Takahiro Tsuji who gave us instructive advice. We would like to thank Editage (www.editage.com) for English language editing.

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