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Rapid Communication

Transient leukocytopenia following combination therapy for COVID-19

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ABSTRACT

Background: Combination therapy with dexamethasone, remdesivir, and baricitinib has become a promising treatment for moderate or severe COVID-19; however, we have observed transient leukocytopenia in COVID-19 patients who received combination therapy.
Methods: Twelve consecutive COVID-19 patients treated with combination therapy were included in this retrospective analysis. Blood cell counts collected at the following three time points were analyzed: before the start of therapy (period 1), within 24 h of starting therapy (period 2), and within 48 h of period 2 (period 3).
Results: The leukocyte count significantly decreased in period 2 compared to period 1 and then significantly increased in period 3 without withdrawal of baricitinib. The neutrophil count transiently decreased in period 2 and recovered in period 3.
Conclusions: Clinicians should be aware of transient leukocytopenia in patients with COVID-19 during the early phase of combination therapy.

1. Introduction

In Japan, the fourth wave of COVID-19 occurred from April to June 2021. In randomized clinical trials, treatment with baricitinib plus remdesivir has been shown to reduce recovery time and improve clinical symptoms in patients with COVID-19 [1]. Baricitinib was approved by Japan's Ministry of Health, Labour, and Welfare as a therapeutic drug for COVID-19 on April 23, 2021; therefore, three drugs, namely dexamethasone, remdesivir, and baricitinib, have now been approved for treating moderate or severe cases of COVID-19 in Japan. A

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randomized, double-blind study has demonstrated that the additional administration of baricitinib to standard therapy (corticosteroids or corticosteroids plus remdesivir) reduces the mortality rate for COVID-19 patients who required oxygenation [2]. Besides, a recent retrospective observational study has shown that combination therapy with baricitinib, remdesivir, and dexamethasone is safe and effective in moderate-to-severe COVID-19 patients in real-world clinical practice [3]. Based on these backgrounds, the three-drug regimen is expected to become a promising treatment for moderate-to-severe COVID-19 patients. While treating COVID-19 patients with combination therapy comprising these three agents, we have observed unusual transient leukocytopenia in the early phase of the combination therapy.

2. Patients and methods

Participants included 12 consecutive patients diagnosed with COVID-19 based on polymerase chain reaction testing of a nasopharyngeal swab, who received combination therapy with corticosteroid, remdesivir, and baricitinib at Hamamatsu University Hospital between May 5 and June 18, 2021. Blood cell counts including total and differential leukocyte count, hemoglobin concentration, and platelet count were retrospectively analyzed from samples collected at the following three time points: before the start of combination therapy (period 1), within 24 h of starting combination therapy (period 2), and within 48 h of period 2 (period 3). The data are expressed as the median with interquartile range (IQR). Statistical analyses were performed using GraphPad Prism Version 8 (GraphPad Software, San Diego, CA, USA). The Mann–Whitney *U* test was used for the analysis of continuous variables. Results with a *p*-value < 0.05 were considered to be statistically significant.

3. Results

The clinical characteristics of the enrolled patients are shown in Table 1. The median patient age was 56 years, and five patients (41.7%) were female. The median duration from onset to admission was 9 days. Eight cases required standard oxygen therapy from a nasal cannula, two required oxygen therapy from a high-flow nasal cannula, and one required mechanical ventilation support. Nine of the 12 patients had underlying diseases including respiratory disorders. All patients received systemic corticosteroids, remdesivir, and baricitinib soon after admission. The blood cell counts of each individual case are summarized in Table 2. The leukocyte count on admission (period 1) of all patients was within the normal range. As shown in Fig. 1A, the leukocyte count significantly decreased at period 2 with combination therapy compared to period 1 (median, 4915/μL; IQR, 4302.5–5910 vs. median, 2580/μL; IQR, 2355–3107.5, $p = 0.0006$), and subsequently increased at period 3 (median, 7205/μL; IQR, 5972.5–8605, $p = 0.0001$; Fig. 1A). There was no significant change in hemoglobin concentration or platelet count from period 1 to period 3 (Fig. 1B and C). We also analyzed changes in neutrophil and lymphocyte counts in the nine patients whose leukocyte fractions could be evaluated. As shown in

Table 1 – Clinical information of COVID-19 patients.

	Age, yr	Sex	Days from onset to admission	Status of oxygen demand	Underlying disease	Treatment
Case 1	62	Female	8	Nasal cannula	Bronchial asthma	Dexamethasone, remdesivir, and baricitinib
Case 2	71	Male	8	Nasal cannula	Atrial fibrillation	Dexamethasone, remdesivir, and baricitinib
Case 3	76	Male	5	Mechanical ventilation	Interstitial pneumonia, HT	Methylprednisolone, remdesivir, and baricitinib
Case 4	55	Female	6	Nasal cannula	DM, HT	Dexamethasone, remdesivir, and baricitinib
Case 5	56	Male	9	Nasal cannula	HT	Dexamethasone, remdesivir, and baricitinib
Case 6	49	Female	9	High-flow nasal cannula	Bronchiectasis	Methylprednisolone, remdesivir, and baricitinib
Case 7	43	Female	12	Nasal cannula	(–)	Dexamethasone, remdesivir, and baricitinib
Case 8	48	Male	12	Not used (due to transient desaturation)	(–)	Dexamethasone, remdesivir, and baricitinib
Case 9	43	Female	8	Nasal cannula	(–)	Dexamethasone, remdesivir, and baricitinib
Case 10	65	Male	10	Nasal cannula	DM, HT, hyperlipidemia	Dexamethasone, remdesivir, and baricitinib
Case 11	65	Male	9	High-flow nasal cannula	DM, HT	Methylprednisolone, remdesivir, and baricitinib
Case 12	58	Male	4	Nasal cannula	Rheumatoid arthritis, HT	Dexamethasone, remdesivir, and baricitinib

HT: hypertension, DM: Diabetes mellitus.

Table 2 – The results of the hematological examination in COVID-19 patients.

	Leukocyte count (/μL)			Hemoglobin (g/dL)			Platelet count (× 10^4/μL)		
	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3	Period 1	Period 2	Period 3
Case 1	5910	1790	5740	12.1	11.1	10.5	24.1	26.3	29.5
Case 2	4340	2530	4750	14.9	15.5	14.6	8.2	8.6	10.4
Case 3	5910	2160	6940	12.0	9.9	9.9	17.3	15.3	16.6
Case 4	4190	2870	3460	12.5	13.7	12.6	17.1	19.6	21.3
Case 5	3640	1990	8040	16.4	17.0	15.1	11.1	11.9	16.2
Case 6	4560	2420	10,720	11.6	11.8	11.6	22.3	26.6	38.6
Case 7	4130	2440	7470	11.4	11.5	10.3	41.7	46	50.2
Case 8	8930	9720	10,360	14.1	13.5	14.1	33.4	39.7	47.7
Case 9	5610	3020	6240	13.3	13.7	13.4	22	25.6	36.4
Case 10	4980	3370	10,300	13.1	13.5	12.5	20.2	23.5	27.4
Case 11	7440	4430	7830	14.0	13.2	12.6	19.2	19.0	24.1
Case 12	4850	2630	6050	15.2	14.1	13.9	17.9	19.0	24.6

Period 1 was defined as the start of therapy. Period 2 was defined as within 24 ho of therapy. Period 3 was defined as within 48 h of period 2.

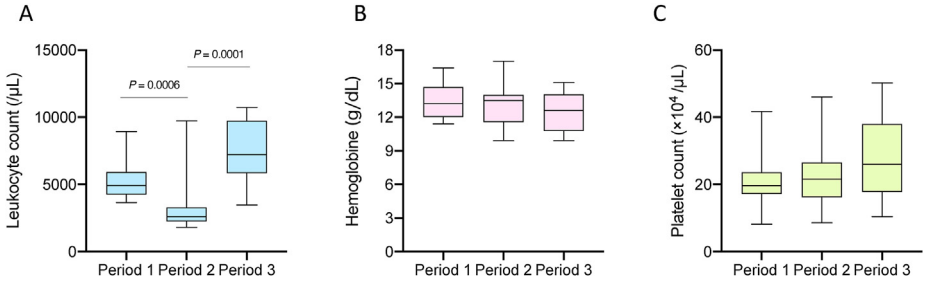

Fig. 1 – Changes in blood cell counts in patients (n = 12) with COVID-19 receiving combination therapy with corticosteroid, remdesivir, and baricitinib. Box-and-whiskers plots reveal the changes in leukocyte count (A), hemoglobin concentration (B), and platelet count (C) from period 1 to period 3. Period 1 was defined as the start of combination therapy. Period 2 was defined as within 24 h of starting combination therapy. Period 3 was defined as within 48 h of period 2. Plots show the median and interquartile range (IQR) with the whiskers ranging between the minimum and maximum values.

Fig. 2A, the neutrophil count was significantly decreased at period 2 compared to period 1 (median, 4669/μL; IQR, 4039–5024, vs. median, 1631/μL; IQR, 1264–2161, $p = 0.019$), and significantly increased at period 3 (median, 5453/μL; IQR, 4383.5–6642.5, $p = 0.018$; Fig. 2A); however, no significant change was observed in lymphocyte count from period 1 to period 3 (Fig. 2B).

4. Discussion

This study provides the first evidence that combination therapy for COVID-19 with dexamethasone, remdesivir, and baricitinib induces transient leukocytopenia, which is mainly due to transient reduction of neutrophils.

The mechanism of transient leukocytopenia soon after combination therapy is unknown; however, considering that leukocytopenia occurred in a very short period, the temporally abnormal distribution of leukocytes may be a potential cause. Indeed, inhibition of signal transducer and activator of transcription 3 (STAT3) phosphorylation reduces intracellular adhesion molecule 1 (ICAM1) expression [4], which may inhibit the adhesion of neutrophils to blood vessel walls and facilitate extravascular migration. Given that baricitinib is a reversible inhibitor of Janus kinase (JAK) 1/JAK2, which suppresses cytokine-induced phosphorylation of STAT3, baricitinib potentially induces short-term leukocyte depletion in blood, and thus, transient leukocytopenia.

Clinicians should be aware that transient leukocytopenia occurs in the early phase of combination therapy with dexamethasone, remdesivir, and baricitinib for COVID-19. According to the drug information for baricitinib [5,6], persistent leukocytopenia is a criterion for the withdrawal of baricitinib; however, leukocytopenia is transient during combination therapy, and the leukocyte count recovered to the normal range without withdrawal of baricitinib. The underlying mechanisms of transient leukocytopenia during combination therapy are not fully understood and should be elucidated in future studies.

This study is subject to several limitations. First, the number of enrolled cases was small. Nevertheless, we believe that transient leukocytopenia in 11 of 12 cases (Table 2) was unlikely to be a coincidence. Second, the cause of transient leukocytopenia could not be precisely determined in this study. Since changes in leukocyte count occurred during the combination therapy, drug-induced effects may have resulted in the leukocytopenia. Considering the mechanism of action of baricitinib [7], it is a potential candidate for inducing transient leukocytopenia. Interactions between baricitinib and remdesivir may have affected transient leukocytopenia. Further studies with larger numbers of patients are required to address these issues.

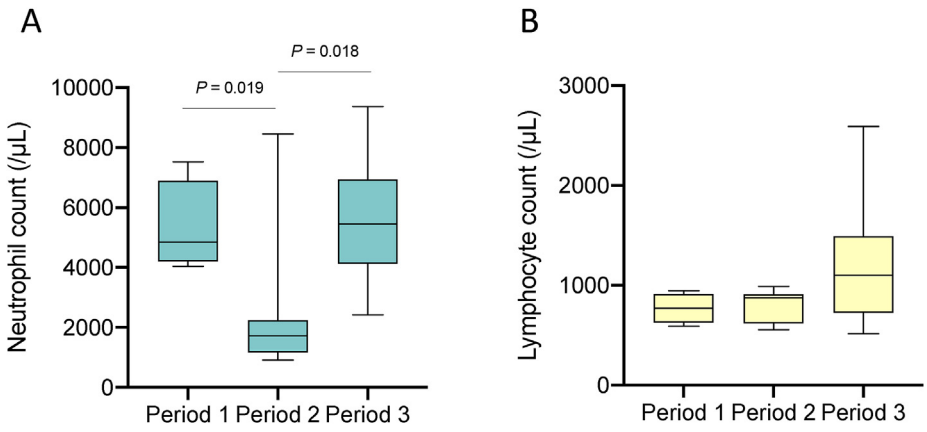

Fig. 2 – Neutrophil and lymphocyte count in patients with COVID-19 who received combination therapy. Box-and-whiskers plots reveal the neutrophil count (A) and lymphocyte count (B) at each period. Period 1 was defined as the start of combination therapy. Period 2 was defined as within 24 h of starting combination therapy. Period 3 was defined as within 48 h of period 2. The number of cases at each time point is as follows: Period 1 (n = 5), Period 2 (n = 9), and Period 3 (n = 7). Plots show the median and interquartile range (IQR) with the whiskers ranging between the minimum and maximum values.

5. Conclusions

Clinicians should be aware of transient leukocytopenia occurring in the early phase of combination therapy with dexamethasone, remdesivir, and baricitinib in COVID-19 patients.

Conflict of Interest

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

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