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Effectiveness of Corticosteroid Therapy for Non-Severe COVID-19 in Patients Not Requiring Supplemental Oxygen Who Have Risk Factors for Severe Disease

Toru Tanaka, Yoshinobu Saito, Takeru Kashiwada, Shinji Nakamichi, Masaru Matsumoto, Akihiko Miyanaga, Yosuke Tanaka, Kazue Fujita, Masahiro Seike and Akihiko Gemma

Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

Background: Because they suppress cytokine production, corticosteroids are a candidate therapy for coronavirus disease 2019 (COVID-19). However, the effectiveness of corticosteroids is unclear for non-severe COVID-19 that does not require supplemental oxygen. This study investigated the effectiveness of corticosteroid therapy for patients with non-severe COVID-19.

Methods: This retrospective observational study analyzed data from 10 patients with non-severe COVID-19 who received corticosteroid therapy at our center between July 1, 2020 and January 31, 2021.

Results: The median age of the 10 patients was 60 years, and nine were male. Nine of the 10 patients had multiple comorbid conditions (e.g., hypertension, diabetes, and obesity). Although blood oxygen saturation was maintained above 95%, all patients had persistent fever and deterioration in chest imaging findings, which led to initiation of corticosteroid treatment. The median duration symptom onset to initiation of corticosteroid therapy was 8 days. All patients received dexamethasone 6 mg/day as corticosteroid therapy, and the median period was 7.5 days. After the start of corticosteroid therapy, clinical improvement was rapid in all patients, and no patient developed severe disease.

Conclusion: The latest World Health Organization guidance recommends against corticosteroid treatment for patients with non-severe COVID-19. In this report, early administration of corticosteroids during the non-critical phase, when oxygen supplementation was not required, was associated with early improvement and prevention of severe disease in patients with risk factors for severe COVID-19 and worsening clinical symptoms. (J Nippon Med Sch 2022; 89: 422–427)

Key words: coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, corticosteroid therapy, non-severe

Introduction

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which emerged in Wuhan, China in late 2019. Although the disease course is mild in most patients, some patients develop severe pneumonia, which can progress to life-threatening acute respiratory distress syndrome (ARDS) and multiple organ failure[1,2]. ARDS is the main cause of death in COVID-19; thus, there is an urgent need to establish an early treatment strategy to prevent progression to fatal ARDS at the non-severe stage.

Although the precise mechanisms are unknown, inflammatory cytokine overproduction is thought to play a key role in the pathophysiological effects of ARDS[2,3]. Corticosteroids are a promising therapeutic agent for COVID-19 because they suppress cytokine production[4]. In a meta-analysis of prospective clinical trials of patients with severe to critical disease, corticosteroid therapy reduced 28-day all-cause mortality[5]. On the basis of these results, the World Health Organization (WHO) guidance

Correspondence to Yoshinobu Saito, Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: yo-saito@nms.ac.jp
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recommends corticosteroids for severe to critically ill patients with COVID-19[6]. Most clinical trials of the efficacy of corticosteroids were limited to patients with severe to critical disease requiring respiratory support[7–9]. The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial—a multicenter, randomized, open-label trial that included patients hospitalized with COVID—19-recruited patients with non-severe disease, as well as those with severe to critical disease[10]. In that trial, the survival benefit of dexamethasone was observed only in patients who were mechanically ventilated or required supplemental oxygen; no survival benefit was seen for patients with non-severe disease who did not require supplemental oxygen. The latest WHO guidance recommending against the use of corticosteroids for non-severe disease is based only on this result; however, the efficacy of corticosteroids for non-severe disease, as well as the appropriate administration time, dose, and period, is unclear and should be reevaluated.

We investigated the effectiveness of corticosteroid therapy for non-severe COVID-19 in patients who did not require supplemental oxygen.

Materials and Methods

Study Design and Participants

This single-center, retrospective, observational study screened data from 87 consecutive patients who received a diagnosis of COVID-19 at Nippon Medical School Hospital between July 1, 2020 and January 31, 2021, and 10 patients with non-severe COVID-19 who received corticosteroid therapy during the non-critical phase, when oxygen supplementation was not required, were included in the final analysis. COVID-19 was diagnosed when SARS-CoV-2 RNA was detected by a polymerase chain reaction test of a nasopharyngeal swab sample. This study was approved by the ethics committee at our center (No. B-2021-391).

Procedures

Data extracted from electronic medical records included patient characteristics (e.g., age, sex, body mass index, smoking history, and comorbidities), fever status, oxygen saturation (SpO_2), laboratory data, chest imaging, and treatment received. Corticosteroid therapy was reviewed, including administration time, dose, period, and clinical outcome after corticosteroid treatment. A patient was classified as having severe disease when they required invasive or noninvasive mechanical ventilation or supplemental oxygen, when SpO_2 was ≤94% in room air, or when tachypnea (respiratory rate >24 breaths per minute) was present[11].

Statistical Analyses

Patient characteristics and laboratory values were reported by using simple descriptive statistics (frequencies, percentages, medians). There was no hypothesis testing.

Results

Patient Characteristics

The clinical characteristics of the 10 patients are shown in **Table 1**. The median age was 60 years, and nine patients were male. The median body mass index was 25.05. Seven patients were former or current smokers, and all but one patient (Case 3) had comorbid conditions (e.g., hypertension, diabetes, and obesity). At the time of initial diagnosis, all patients showed infiltration on chest imaging, and all were considered to have non-severe disease because they did not meet any of the criteria for severe disease. Initially, five patients received inhaled ciclesonide alone, one patient received both inhaled ciclesonide and favipiravir, and four patients received no treatment for COVID-19. Ciclesonide inhalation and favipiravir were used as part of another multicenter observational study.

After initial treatment, all patients had persistent fever and deterioration in chest imaging findings. Although SpO_2 was maintained at >95% in all patients, corticosteroid therapy was started because of concerns regarding disease progression.

Corticosteroid Therapy and Clinical Outcomes

The median interval from symptom onset to administration of corticosteroids was 8 days (range 7-13 days). All patients used dexamethasone (6 mg/day) as corticosteroid therapy; the median duration was 7.5 days (range 5-28 days). After administration of corticosteroids, all patients showed rapid improvement of fever, chest imaging findings, and laboratory data, and no patient developed severe disease. In Case 7, lung infiltration on chest imaging and malaise remained on the 10th day of corticosteroid therapy. Corticosteroid therapy was thus extended and gradually tapered over 1 month. No patient experienced a relapse of disease after completion of corticosteroid therapy. Corticosteroid therapy was not associated with any serious adverse effects.

Case Report: Case 5

A 72-year-old man who initially presented with fever was diagnosed as having COVID-19 and was admitted to our hospital 3 days after onset of symptoms, because of persistent fever and worsening fatigue. He had smoked 30 cigarettes per day for the past 40 years and had multi-

Table 1 Clinical characteristics of the 10 patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age (years)	71	46	57	42	72	53	69	57	63	67
Sex	male	male	male	male	male	male	male	female	male	male
BMI	NE	25.1	20.5	25	22.7	26.4	NE	25.6	24	25.1
Smoking status	former	former	former	current	former	current	never	never	never	former
Comorbidities										
HT	+	–	–	–	+	–	–	+	+	+
DL	–	–	–	–	+	–	+	+	+	+
DM	–	–	–	–	–	–	–	+	–	+
CKD	–	–	–	–	+	–	–	–	–	–
Obesity (BMI >25 kg/m^2)	NE	+	–	+	–	+	NE	+	–	+
Solid tumor	–	–	–	–	–	–	–	–	–	+
Other	–	–	–	–	–	–	–	–	BrS	hypothroidism
Infiltration on initial CT	+	+	+	+	+	+	+	+	+	+
Treatment before corticosteroid therapy	Ciclesonide	none	Ciclesonide Favipiravir	Ciclesonide	Ciclesonide	Ciclesonide	Ciclesonide	none	none	none
Clinical course from onset to corticosteroid use										
Persistence of fever	+	+	+	+	+	+	+	+	+	+
Worsening of chest imaging findings	+	+	+	+	+	+	+	+	+	+
Elevation of CRP	+	–	–	+	+	+	+	+	+	+
Decrease of lymphocyte count	–	–	–	–	–	–	–	–	–	–
SpO_2 in room air at corticosteroid use (%)	96	96	95	97	95	97	95	95	97	96
Laboratory findings at corticosteroid use										
LDH (U/L)	245	233	171	296	288	198	318	303	528	222
CRP (mg/dL)	8.18	1.44	0.29	6.71	16.31	3.78	7.27	4.3	21.55	9.04
WBC count (×10^9/L)	6,800	3,700	5,300	5,400	6,900	5,400	6,600	4,300	6,600	6,400
Lymphocyte count (×10^9/L)	1,496	1,313	1,314	1,112	897	1,301	838	1,272	996	1,580
Duration from onset to corticosteroid use	13	10	8	7	8	10	13	8	8	7
Corticosteroid therapy	DEXA 6 mg	DEXA 6 mg	DEXA 6 mg	DEXA 6 mg	DEXA 6 mg	DEXA 6 mg	DEXA 6 mg	DEXA 6 mg	DEXA 6 mg	DEXA 6 mg
Corticosteroid period (days)	8	7	5	10	5	5	28	10	6	8
Clinical outcomes	improved	improved	improved	improved	improved	improved	improved	improved	improved	improved
Duration of hospitalization (days)	16	13	13	14	16	12	15	19	11	14

BMI, body mass index; NE, not evaluated; HT, hypertension; DL, dyslipidemia; DM, diabetes mellitus; CKD, chronic kidney disease; BrS, Brugada syndrome; CT, computed tomography; CRP, C-reactive protein; LDH, lactate dehydrogenase; WBC, white blood cell; SpO_2, oxygen saturation; DEXA, dexamethasone

ple comorbidities (hypertension, dyslipidemia, and chronic kidney disease). On admission, his body temperature was 36.9°C and his SpO_2 was 98% in room air. The results of laboratory testing were WBC count, 6,200/

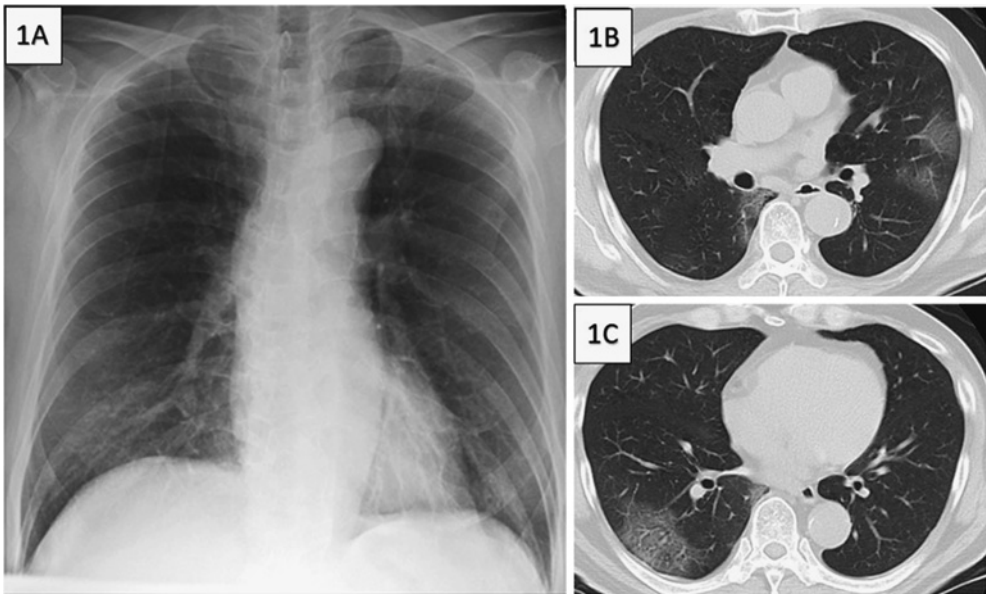

Fig. 1 Chest X-ray and CT findings
(A) Chest X-ray showing faint infiltrative shadows in both lower lung fields. (B and C) Chest CT at diagnosis showing bilateral multifocal ground-glass opacities.

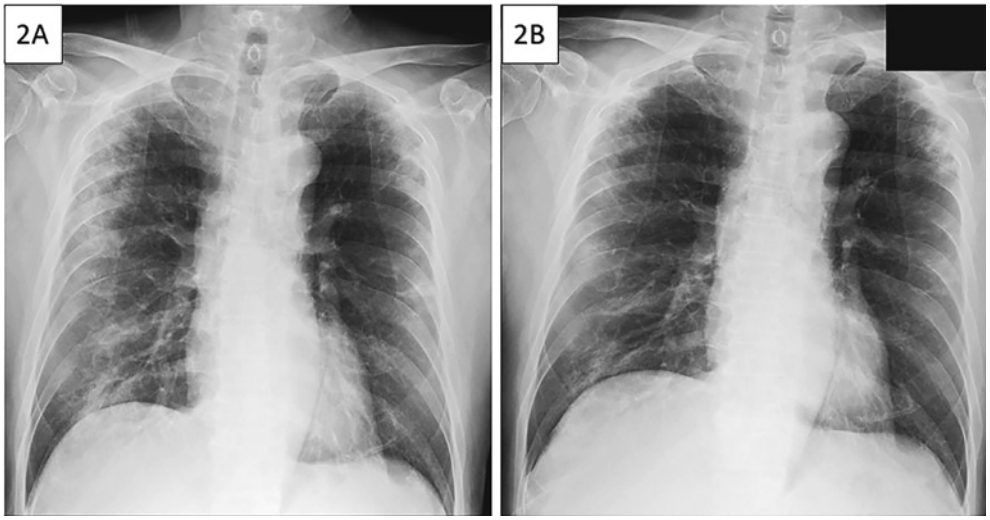

Fig. 2
(A) Chest X-ray at 8 days after onset showing worsening of infiltrative shadows, mainly in the periphery of both lung fields.
(B) Chest X-ray on fifth day of corticosteroid therapy showing improvement of infiltrative shadows in both lung fields.

μL with 75.0% neutrophils and 19.4% lymphocytes; creatinine, 1.66 mg/dL; and C-reactive protein (CRP), 6.29 mg/dL. A chest X-ray showed faint infiltrative shadows in both lower lung fields, and CT showed bilateral multifocal ground-glass opacities (**Fig. 1A-C**). The patient received inhaled ciclesonide (1,200 μg/day for 2 weeks) as initial treatment for non-severe COVID-19; however, a fever of 38-39°C persisted. Eight days after onset, his CRP level increased to 16.3 mg/dL, and his chest imaging findings worsened (**Fig. 2A**). At this time, there was no respiratory failure (SpO_2 was 95%); however, dexamethasone (6 mg/day) was started as corticosteroid therapy. Immediately after the start of corticosteroid therapy, his fever rapidly improved. On the fifth day of corticosteroid therapy, his chest imaging findings improved (**Fig. 2B**) and his CRP level decreased to 0.37 mg/dL. Corticosteroid therapy was stopped after 5 days and resulted in early improvement and discharge without disease re-

lapse.

Discussion

We reported 10 cases of non-severe COVID-19 treated with corticosteroid in patients not requiring supplemental oxygen. Before corticosteroid therapy, all patients had persistent fever and showed worsening findings on chest imaging, which raised concerns about disease progression. However, corticosteroid therapy was associated with rapid clinical improvement, and no patient developed severe disease.

In this study, nine of the ten patients received corticosteroid therapy according to criteria of the RECOVERY trial (dexamethasone [6 mg/day] for up to 10 days). Although corticosteroid therapy was not associated with a survival benefit in patients who did not require supplemental oxygen at randomization in that trial, the present patients differ from the patient population of the RECOVERY trial. First, patients who did not require supplemental oxygen in the RECOVERY trial had a median interval from symptom onset to randomization of 6 days (range 3-10 days), which was shorter than in this study (median 8 days [range 7-13 days] from onset to administration of corticosteroids)[10]. In a retrospective cohort study that showed the usefulness of corticosteroid therapy for prevention of disease progression in non-severe COVID-19 cases, corticosteroids were administered at a median of 9 days (interquartile range 7-10 days) after symptom onset in clinically worsening cases[12]. In another case report that showed the usefulness of corticosteroid therapy for non-severe COVID-19, corticosteroids were also administered at 8 days after onset of symptoms[13]. Consideration of COVID-19 phase seems important when determining when to start corticosteroid therapy[3]. In the early phase, within 1 week after onset, corticosteroids may be more harmful than helpful because viral replication is dominant and inflammation is minimal at this phase[3,10]. Indeed, the RECOVERY trial showed an adverse effect in patients who received corticosteroid therapy during the first week after onset. Corticosteroid therapy may be beneficial after the first week since viral replication is attenuated and cytokine-associated immunopathological elements become the main factor in patients with progressive disease. Second, in this study, dexamethasone was administered only to patients at high risk of disease progression. In a study of the registry of hospitalized COVID-19 patients in Japan, severe cases were more likely to be male, to have a past smoking history, to be ≥60 years of age, and had more comorbid conditions (e.g., cardiovascular disease, diabetes, chronic lung disease, and obesity) than non-severe cases[14]. Furthermore, fever was more likely to be present in severe cases. In this study, there was concern about disease progression in all patients, since nine of the 10 patients had multiple risk factors for severe COVID-19 and all had persistent fever and deterioration in chest imaging findings. However, as many as 41% of patients have no comorbidities, and the clinical course from onset of symptoms to corticosteroid treatment in the RECOVERY trial was unknown. In summary, physicians should not administer corticosteroids shortly after onset of symptoms to patients with non-severe disease. Rather, clinical course should be carefully followed. Then, for patients at high risk of disease progression because of their clinical characteristics and course, corticosteroid treatment should be initiated at least 1 week after symptom onset. In this setting, corticosteroid therapy may be beneficial, even for non-severe cases.

As of October 2021, remdesivir and casirivimab/imdevimab are available in Japan for non-severe cases, which increases treatment options. Remdesivir was not administered to the present patients because its supply was limited during the study period. Administration required an application to the Ministry of Health, Labor and Welfare and was restricted to severe cases. In several clinical trials of remdesivir among patients with COVID-19, its efficacy has been controversial[11,15–18]. One trial showed that patients with non-severe disease treated with a 5-day course of remdesivir had a significantly better clinical status than those who received standard care; however, the clinical importance of the difference was uncertain[16]. Casirivimab/imdevimab, a cocktail of two human monoclonal antibodies that neutralize SARS-CoV-2, and another human monoclonal antibody, sotrovimab, were not approved during this study period and were not used for the present patients. Casirivimab/imdevimab and sotrovimab were shown to reduce the risk of Covid-19-related hospitalization and death from any cause in outpatients with risk factors for severe disease; however, evidence was limited to early-onset patients within 7 days and 5 days of onset of symptoms, respectively[19,20]. Although treatment options are increasing for non-severe disease in patients who do not require supplemental oxygen, the effectiveness of corticosteroid therapy should be investigated for patients with non-severe disease who experience disease progression while receiving non-corticosteroid therapy.

The present study has some limitations. It was retro-

spective, limited to a small number of patients, and had no comparison group. Large-scale, prospective, multicenter studies are therefore required in order to confirm our findings.

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