



Effect of Corticosteroid Therapy on the Duration of SARS-CoV-2 Clearance in Patients with Mild COVID-19: A Retrospective Cohort Study

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ABSTRACT

Introduction: In December, 2019, an outbreak of the coronavirus disease 2019 (COVID-19), which was caused by a novel coronavirus, started in Wuhan, China. So far, there is limited clinical evidence on the effect of corticosteroid therapy

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for this disease. This study aims to investigate the association between corticosteroid therapy and the duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) clearance among patients with mild COVID-19.

Methods: Patients with mild COVID-19 were enrolled from two medical centers in China between January 13, 2020 and February 29, 2020. Baseline characteristics and durations of RNA clearance were compared between the corticosteroid and non-corticosteroid therapy groups. The independent effects of corticosteroid therapy on the duration of RNA clearance were estimated by generalized linear models.

Results: Of 82 patients with a mild infection, 40 patients were male (48.8%), with a median age of 49 years (interquartile range, IQR 36–61). Among those patients, 36 patients (43.9%) received corticosteroid therapy. The adjusted multivariate models showed that the effects of corticosteroids were non-significant on the durations of onset to first RNA clearance [β 2.48, 95% CI (95% confidence interval) – 0.42 to 5.38, $P = 0.0926$] and to persistent RNA clearance (β 1.54, 95% CI – 1.41 to 4.48, $P = 0.3016$), and durations of therapy to first RNA clearance (β 2.16, 95% CI – 0.56 to 4.89, $P = 0.1184$) and to persistent RNA clearance (β 1.22, 95% CI – 1.52 to 3.95, $P = 0.3787$).

Conclusions: Corticosteroid therapy in patients with mild COVID-19 was not associated with the duration of SARS-CoV-2 clearance, suggesting that the use of corticosteroids may not be

beneficial for patients with mild COVID-19 and should be prudently recommended in clinical practice. However, further studies are needed to verify the findings.

Keywords: Corticosteroid; COVID-19; RNA clearance; SARS-CoV-2

Key Summary Points

Why carry out this study?

COVID-19 has caused a global pandemic and represents a continuous threat worldwide, and clinical evidence towards effective treatment is required and essential in practice.

Does corticosteroid therapy have a positive effect on the clearance of SARS-CoV-2 among patients with mild COVID-19?

What was learned from the study?

Patients with mild COVID-19 may not benefit from corticosteroid therapy in terms of SARS-CoV-2 clearance.

Corticosteroids should be prudently recommended among patients with mild infection in clinical practice.

and the novel coronavirus pneumonia was named coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) [3].

The epidemic of COVID-19 represents a continuous threat [4]. WHO increased the assessment of the risk of spread and impact to very high at the global level [5] and characterized it as a pandemic since March 11, 2020 [6]. As of July 29, 2020, a total of 14,348,858 confirmed cases (603,691 deaths) have been reported from 215 countries or territories globally [7]. This figure is strongly expected to increase in the near future with the confirmed person-to-person transmission of SARS-CoV-2 [8] and the lack of effective vaccines or specific medications [9, 10]. Infections with the human coronavirus (CoVs) strains usually resulted in mild, self-limiting upper respiratory tract infections in humans [11]. Disease spectrum analysis by the Chinese Center for Disease Control and Prevention showed that patients with mild infection (including mild with non-pneumonia) account for the vast majority (81.4%) among 44,415 confirmed cases [12].

To date, there is no specific treatment or antiviral drug available for the Middle East respiratory syndrome (MERS) or severe acute respiratory syndrome (SARS), and management is largely supportive [13, 14]. Clinical improvement was observed in 36 of 53 patients with severe COVID-19 receiving compassionate-use remdesivir [15]. Another trial showed that remdesivir was superior to placebo in shortening the recovery time, while it has no statistical significance in reducing mortality [16]. A retrospective study reported that the 28-day all-cause mortality was 5.2% in the statin used group, which was lower than that of 9.4% in the matched non-statin used group [17]. Likewise, no pharmacological therapies (of proven efficacy) or no Food and Drug Administration-approved medications yet exist to treat the emerging COVID-19 [1, 9, 18], and vaccine or new interventions are likely to require months to years for testing and development [10]. Corticosteroids have been widely used during the previous outbreaks of SARS [19], MERS [14], and are currently used along with other therapeutics in patients with COVID-19 [1]. The clinical use of corticosteroids was controversial, and there

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INTRODUCTION

A cluster of pneumonia cases associated with the novel betacoronavirus was reported in Wuhan, China, in late December, 2019 [1]. The coronavirus was classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]

was insufficient evidence on the benefits in patients with coronavirus infections. A systematic review on SARS showed that 25 studies were inconclusive and the remaining four studies provided conclusive data of harm—not benefiting the patients [19]. Another study reported that corticosteroid therapy in patients with MERS was not associated with mortality but was associated with delayed coronavirus RNA clearance [14]. Since there is limited data on the overall benefit of applying corticosteroids in the treatment of respiratory infections caused by respiratory syncytial virus (RSV), influenza, SARS-CoV, and MERS-CoV, corticosteroids are not recommended for the treatment of lung injury or shock caused by COVID-19 [18, 20]. Clinical evidence for the effect of corticosteroids on COVID-19 remains limited (currently, one trial has shown that low-dose dexamethasone reduces mortality in patients with COVID-19 who need ventilation [21]). The aim of our study was to provide a clinical evaluation of corticosteroid therapy on the duration of RNA clearance among patients with mild COVID-19, to support clinical practices and management.

METHODS

Participants

For this retrospective cohort study, we recruited patients (mild or mild with non-pneumonia) with COVID-19 at hospital admission in the First Affiliated Hospital, School of Medicine, Zhejiang University from January 19, 2020 and the Third People's Hospital of Shenzhen from January 13, 2020, in China. The last patient was followed till February 29, 2020 and all patients were under inpatient management.

Throat swabs from each patient were collected during the hospitalization. The real-time reverse-transcriptase polymerase chain reaction (RT-PCR) assay was used to detect viral RNA, with the SARS-CoV-2 nucleic acid detection kit (Shanghai bio-germ Medical Technology Co. Ltd.). A cycle threshold value (C_t value) less than 37 was defined as positive, and a C_t value of 40 or more was defined as negative. A C_t

value of 37 to less than 40 required confirmation by retesting. RT-PCR assay was conducted throughout the study according to the manufacturer's protocol.

The severity of illness at admission was assessed according to the guideline released by the National Health Commission of China [22]. The severity of symptoms was categorized as mild with non-pneumonia, mild, severe, or critical. Mild infection included non-pneumonia and mild pneumonia (fever, respiratory symptoms, and manifestation of pneumonia on imaging). Severe infection was characterized by one of the following: dyspnea, respiratory rate $\geq 30/\text{min}$, arterial oxygen saturation (SaO_2) $\leq 93\%$, the ratio of partial pressure of oxygen/absorption concentration of oxygen ($\text{PaO}_2/\text{FiO}_2$) $< 300 \text{ mmHg}$ (1 mmHg = 0.133 kPa), and/or lung infiltrates $> 50\%$ within 24–48 h. Critical infection was characterized by one of the following: respiratory failure, septic shock, and/or multiple organ dysfunction/failure.

Patients were divided into two groups based on whether they received corticosteroid therapy: a corticosteroid therapy group and a non-corticosteroid therapy group. We converted all preparations to methylprednisolone equivalent doses (mg/day) (hydrocortisone 5:1, dexamethasone 1:5, prednisolone 1:0.8) when patients received different types of corticosteroids.

Data Collection

Epidemiological, clinical, laboratory and radiological characteristic data of patients were obtained with standardized data collection forms by using EpiData software (version 3.1). The data included age, gender, smoking status, comorbidity (diabetes, hypertension, cardiovascular disease, etc.), disease onset time (self-reported the start of either fever or cough during epidemiological investigation), therapy time (start time of an antiviral drug, supportive care, etc., except for corticosteroids use), antiviral regimens (duration of a drug used for more than 3 days), corticosteroids (start time, corticosteroid type, daily dose, and maximum dose), progress to severe or critical, non-invasive assisted ventilation (non-invasive ventilation or high-flow nasal cannula), invasive mechanical

ventilation, time of body temperature recovery (lower than 37.5 °C and being stable), and time of radiological recovery (improvement or absorption of initial pulmonary lesions and no new radiological lesions occurred at other parts); the main outcomes were first RNA clearance time (the first time of RNA negative) and persistent RNA clearance time (initial time of three consecutive RNA negatives with at least 24 h apart per time; the first two results were from local sites and the last one was checked by the local Center for Disease Control and Prevention). Ethics approval was obtained from the Institutional Review Board of the First Affiliated Hospital, School of Medicine, Zhejiang University (2020IIT83).

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR) and were compared between the groups by the Kruskal–Wallis test. Categorical variables were expressed as number (%) and compared by chi-square (χ^2) test or Fisher's exact test as appropriate. The durations of SARS-CoV-2 RNA clearance (first and persistent) from onset or therapy were compared by univariate analysis. Multiple regressions by generalized linear models with identity-link function were used to evaluate the independent effect of corticosteroid therapy on the duration of RNA clearance. The age, sex, and covariates such as oxygen inhalation, invasive mechanical ventilation, and progress to severe or critical were included in adjusted models. All statistical analyses were performed using the SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). The significance level of the hypothesis tests was set at 0.05 (two-sided).

RESULTS

During the study period, a total of 82 patients with mild infection were enrolled (Fig. S1 in the supplementary material). The median age of the patients was 49 years (IQR 36–61), and there were 40 male patients (48.8%) and 42 female patients (51.2%). There were 17 (20.7%) patients with normal body temperature and 3

(3.7%) patients with normal CT imaging at hospital admission.

There were 36 patients (43.9%) who received corticosteroid therapy. Patients in both groups were similar in most baseline characteristics (sex, smoking status, comorbidities, therapy, duration of onset to hospital admission or therapy, and death) (Table 1). The median age in the corticosteroid group was 59 years (IQR 45–65.5), which was older than that in the non-corticosteroid group (45 years, IQR 34–55). For the use of antiviral drugs or therapy (arbidol, darunavir/cobicistat, favipiravir, lopinavir/ritonavir, or interferon- α), there was no significant difference between the groups—except for the ribavirin (8.7% vs. 25%, $P = 0.0448$), non-invasive assisted ventilation (41.67% vs. 8.7%, $P = 0.0004$), and invasive mechanical ventilation (22.22% vs. 2.17%, $P = 0.0088$). In the corticosteroid group, 19 patients (52.78%) progressed from mild to severe or critical compared to 5 patients (10.87%) in the non-corticosteroid group ($P < 0.0001$). There was no statistically significant difference in the cure rates between the two groups (97.22% vs. 100%, $P = 0.4390$).

From the univariate analysis, the median duration of onset to persistent RNA clearance in the corticosteroid group was delayed (18.5 days vs. 15 days, $P = 0.0161$). A similar delay was observed for onset to first RNA clearance (17 days vs. 13 days, $P = 0.0042$), to body temperature recovery (11.5 days vs. 9 days, $P = 0.0088$), and to radiological recovery (16 days vs. 13 days, $P = 0.0082$). Also, the median durations of therapy to (1) persistent RNA clearance (11.5 days vs. 9 days, $P = 0.0275$), (2) first RNA clearance (11 days vs. 7.5 days, $P = 0.0081$), (3) body temperature recovery (6.5 days vs. 3 days, $P = 0.0040$), and (4) radiological recovery (13 days vs. 8 days, $P = 0.0264$) were delayed (Table 1).

The crude models also showed that corticosteroid therapy delayed the durations of the onset to first RNA clearance (β 3.99, $P = 0.0044$) and to persistent RNA clearance (β 3.43, $P = 0.0148$). The durations were also delayed from therapy to first RNA clearance (β 3.85, $P = 0.0031$) and to persistent RNA clearance (β 3.29, $P = 0.0126$). The crude models showed that corticosteroid therapy would delay the

Table 1 Baseline and outcome characteristics between the corticosteroid and non-corticosteroid therapy groups in patients with mild COVID-19

Variable(s)	Non-corticosteroid therapy Median (IQR)/ <i>n</i> (%)	Corticosteroid therapy Median (IQR)/ <i>n</i> (%)	χ^2 value ^a	<i>P</i> value
Age, years	45 (34, 55)	59 (45, 65.5)	9.9017	0.0017
Sex (male)	21 (45.65)	19 (52.78)	0.4104	0.5218
Smoking status	2 (4.35)	2 (5.56)	–	1
Comorbidities				
Hypertension	7 (15.22)	6 (16.67)	0.0318	0.8585
Cardiovascular disease	2 (4.35)	2 (5.56)	–	1
Diabetes	3 (6.52)	3 (8.33)	–	1
Normal body temperature at admission	13 (28.26)	4 (11.11)	3.6143	0.0573
Normal imaging at admission	3 (6.52)	0 (0)	–	0.2520
Therapy ^b				
Arbidol	18 (39.13)	15 (41.67)	0.0540	0.8162
Darunavir/cobicistat	2 (4.35)	3 (8.33)	–	0.6495
Favipiravir	2 (4.35)	1 (2.78)	–	1
Lopinavir/ritonavir	41 (89.13)	35 (97.22)	–	0.2228
Ribavirin	4 (8.7)	9 (25)	4.0243	0.0448
Interferon- α	46 (100)	34 (94.44)	–	0.1897
Non-invasive assisted ventilation	4 (8.7)	15 (41.67)	12.3323	0.0004
Invasive mechanical ventilation	1 (2.17)	8 (22.22)	–	0.0088
Progress to severe or critical	5 (10.87)	19 (52.78)	17.133	< 0.0001
Duration of onset to, days				
Hospital admission	4 (3, 6)	5 (2.5, 7)	0.5791	0.4466
Therapy	5 (3, 7)	5 (3, 7)	0.0213	0.8839
Body temperature recovery ^c	9 (7, 11)	11.5 (9, 14.5)	6.8641	0.0088
Radiological recovery ^c	13 (10, 16)	16 (12, 23)	6.9917	0.0082
First RNA clearance	13 (9, 16)	17 (13, 21)	8.1876	0.0042
Persistent RNA clearance	15 (10, 19)	18.5 (14, 21)	5.7939	0.0161
Duration of therapy to, days				
Body temperature recovery ^c	3 (2, 6)	6.5 (4, 10.5)	8.2995	0.0040
Radiological recovery ^c	8 (6, 11)	13 (5, 19)	4.9314	0.0264
First RNA clearance	7.5 (5, 13)	11 (7, 17)	7.0011	0.0081
Persistent RNA clearance	9 (5, 15)	11.5 (9, 17.7)	4.8602	0.0275

Table 1 continued

Variable(s)	Non-corticosteroid therapy Median (IQR)/n (%)	Corticosteroid therapy Median (IQR)/n (%)	χ^2 value ^a	P value
Clinical outcomes			–	0.4390
Cured	46 (100)	35 (97.22)		
Death	0 (0)	1 (2.78)		
Research sites	16 (34.78)		2.6731	0.1021
Hangzhou	30 (65.22)	19 (52.78)		
Shenzhen	45 (55, 81)	17 (47.22)		

IQR interquartile range

^a Kruskal–Wallis or chi-square or Fisher’s exact test

^b Without corticosteroids use

^c Except for normal cases at admission

Table 2 Estimations for the effect of corticosteroid therapy on RNA clearance by multivariate analysis

Outcomes	Crude model ^a		Adjusted model ^b	
	β (95% CI)	P value	β (95% CI)	P value
Duration of onset to, days				
First RNA clearance	3.99 (1.28, 6.70)	0.0044	2.48 (– 0.42, 5.38)	0.0926
Persistent RNA clearance	3.43 (0.69, 6.16)	0.0148	1.54 (– 1.41, 4.48)	0.3016
Duration of therapy ^c to, days				
First RNA clearance	3.85 (1.34, 6.36)	0.0031	2.16 (– 0.56, 4.89)	0.1184
Persistent RNA clearance	3.29 (0.72, 5.85)	0.0126	1.22 (– 1.52, 3.95)	0.3787

95% CI 95% confidence interval

^a Only the variable “corticosteroid therapy” was included

^b Adjusted by age, sex, invasive mechanical ventilation, and progression to severe or critical; the variable “non-invasive assisted ventilation” was excluded because of collinearity

^c Without corticosteroids use

RNA clearance time by 3.29–3.99 days (all $P < 0.05$) (Table 2), while results from adjusted models with covariates of age, sex, invasive mechanical ventilation, and progression of disease to severe or critical showed that the effects of corticosteroids on the durations of RNA clearance [onset to first clearance, β 2.48, 95% CI (95% confidence interval) – 0.42 to 5.38, $P = 0.0926$; onset to persistent clearance, β 1.54, 95% CI – 1.41 to 4.48, $P = 0.3016$; therapy to

first clearance, β 2.16, 95% CI – 0.56 to 4.89, $P = 0.1184$; therapy to persistent clearance, β 1.22, 95% CI – 1.52 to 3.95, $P = 0.3787$] were not statistically significant. The adjusted models indicated that the phenomenon of delayed RNA clearance in the corticosteroid therapy group was likely due to other factors (such as progression of disease).

All patients in the corticosteroid group received methylprednisolone, the median

duration of onset to corticosteroids use was 8 days (IQR 6–9), and the duration of therapy of corticosteroids use was 3 days (IQR 1–5). The maximum methylprednisolone equivalent dose of corticosteroid was low to medium, except for the only mortality case which had a maximum dose of 500 mg. The median duration of steroid use was 7.5 days (IQR 5–13). The median daily dose of corticosteroid was 40 mg/day (IQR 28–50), while the median maximum dose was 55 mg (IQR 40–80).

DISCUSSION

The urgency of the COVID-19 outbreak did not allow sufficient time for testing the efficacy of antiviral regimens and treatments—although they were the most needed. Clinicians were left with no option other than to repurpose existing antiviral agents (e.g., for viral infections such as HIV-1), to test drugs in development, or to rely on therapeutic experience with SARS or MERS [10]. The SARS-CoV-2 infection could result in severe diseases such as acute respiratory distress syndrome and septic shock [23]. Corticosteroids could downregulate proinflammatory cytokine transcription and have been shown to improve innate immunity in patients with septic shock [24].

Corticosteroids possess potent anti-inflammatory, immunomodulatory and antineoplastic properties, and they are integral in the treatment of numerous conditions including autoimmune diseases, allergic reactions, asthma exacerbations, chronic obstructive pulmonary disease, and malignancies [25]. During the outbreak of SARS, standard treatment protocols involved the combination treatment with ribavirin and methylprednisolone [26]. However, there is no standard protocol for clinical use of corticosteroids among patients with COVID-19, and it is empirically applied in our study by clinicians under the following conditions [27]: (1) high body temperature ($> 39\text{ }^{\circ}\text{C}$) persists, (2) widely affected areas of the lung lobe ($> 30\%$ are involved), (3) ground-glass exudation lesions, and (4) the affected areas in the lung increased rapidly (the areas progress $> 50\%$ in 48 h).

Our observational results revealed that corticosteroid therapy had no positive effect on the

durations of SARS-CoV-2 RNA clearance among patients with mild COVID-19. Preliminary results from the RECOVERY trial showed that low-dose dexamethasone reduced deaths by one-third; however, the results were restricted to patients who needed ventilation [21, 28]. Clinical outcomes are the most important endpoints; however, the duration of RNA clearance was used as an observational indicator in previous studies [14, 29, 30]. Studies on MERS showed that corticosteroid therapy was associated with delayed RNA clearance [14]. In addition, the median viral shedding time in patients with influenza A (H7N9) viral pneumonia was longer in the high-dose corticosteroids group [31]. Observational studies on SARS reported that a high dose of corticosteroid was associated not only with delayed viral clearance but also with adverse effects and increased risk of mortality [32, 33]. Thus, it remains difficult to make a clear recommendation about whether corticosteroids should be used to treat SARS-associated lung injury [33]. The delayed durations of RNA clearance were found to be highly associated with the age and progress of the disease (potential confounding factors) instead of corticosteroid therapy in our study. Since no benefit was observed from corticosteroid therapy and there was a high cure rate (81 of 82, 98.8%) among patients with mild COVID-19 evident through our study, corticosteroid therapy is unnecessary unless there is a specific condition (such as clinical, chest radiographic, or laboratory findings suggestive of worsening; or oxygen saturation $< 95\%$ [26]).

On the other hand, well-known adverse effects (osteoporosis, cardiovascular disease, etc.) are associated with the systemic use of corticosteroids [25, 34, 35]. It is clear that such complications may decrease a patient's quality of life and are costly to be managed after therapy.

Clinical studies, preferably randomized controlled trials (RCTs), are needed to evaluate the role of corticosteroid therapy. It is also valuable to monitor long-term and specific adverse effects [35]. The collaborations among clinicians, scientists, and public health administrators have made confronting the SARS-CoV-2 outbreak effectively, and greatly promoted the

prevention and control of disease on different levels including virus traceability, diagnostics, drugs and vaccines development, and management of patients.

Limitations

Our study is limited by the following. First, the sensitivity and specificity of the used RT-PCR assay were not specified and this might influence our evaluations of the viral RNA clearance. Second, the number of participants was limited, which would result in a lack of power, and evidence from clinical studies (especially RCTs) with a larger sample size are needed. Third, patients with severe or critical COVID-19 were not included—the use of corticosteroid therapy at this group would be more controversial. Fourth, our retrospective observational study design might have recall bias, especially during the pre-hospital phase, and time-dependent variables were not involved, which may potentially cause confounding bias.

CONCLUSIONS

Results from this study suggested that patients with mild COVID-19 may not benefit from corticosteroid therapy in terms of the duration of SARS-CoV-2 clearance. There were no differences in the duration of onset or therapy to RNA clearance between patients in the corticosteroid and non-corticosteroid therapy groups. Given the evidence of high cure rate among patients with mild COVID-19, and considering the possible long-term side effects, corticosteroids should be prudently recommended in clinical practice. However, further studies with large sample size are needed to verify our findings.

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Authorship Contributions. KX, LL, and CD conceived and designed the study; XF, YC, JY, PY, YL, QN, RZ, and XL collected data; CD, XF, and JS cleaned, analyzed the data and interpreted the results; YC, RZ, and XF contributed to figures; CD wrote the first draft; All authors critically revised the paper and gave final approval for publication.

Disclosures. Cheng Ding, Xuewen Feng, Yanfei Chen, Jing Yuan, Ping Yi, Yongtao Li, Qin Ni, Rongrong Zou, Xiaohe Li, Jifang Sheng, Lanjuan Li, and Kaijin Xu have no conflicts of interest to declare.

Compliance with Ethics Guidelines. Ethics approval was obtained from the Institutional Review Board of the First Affiliated Hospital, School of Medicine, Zhejiang University (2020IIT83).

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy of participants.

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