Case report

Successful treatment with methyl-prednisolone pulses for the late phase of COVID-19 with respiratory failure: A single-center case series

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ABSTRACT

Although some prospective studies provided the evidence of corticosteroids for critically ill patients with COVID-19, the optimal dosage or timing of corticosteroids is still unknown. This is a case series of four patients on methyl-prednisolone pulses for the late phase of Coronavirus disease 2019 (COVID-19) with respiratory failure in our hospital. All patients needed invasive mechanical ventilation and had bimodal worsening of their respiratory status with consolidation and volume loss after intubation. All cases could successfully discontinue oxygen therapy without any severe adverse events after this pulse therapy in the late phase of COVID-19. This therapy is believed to be effective on some optimal patients. Hence, further studies to explore this efficacy and safety were needed.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 has been spreading worldwide since the first outbreak in Wuhan, China, in December 2019.

Some reports suggested that the steroid therapy might suppress a cytokine storm by COVID-19 [1]. The RECOVERY trial firstly provided the evidence of the efficacy of dexamethasone for patients with COVID-19 who received oxygen therapy [2]. The prospective meta-analysis of clinical trials including the RECOVERY trial also showed that systemic corticosteroids were effective on critically ill patients with COVID-19 [3]. However the optimal dosage or timing of corticosteroids is still unknown. One prospective study proved that methyl-prednisolone pulses (MP) administered within the second week after the onset of symptoms improved outcome of patients with COVID-19 who have inflammatory activity [4]. We would like to share our experience in using MP in the late phase of severe COVID-19 with respiratory failure. This study was approved by the ethics committee of this hospital (approval number: R2-07).

2. Case series

2.1. Day 1 was defined as the first onset of the symptoms

2.1.1. Case 1

This is the case of a 61-year-old man with hypertension and who is an ex-smoker, who presented with fever, upper respiratory tract symptoms, and myalgia. He was diagnosed with COVID-19 on day 11. Lopinavir/ritonavir, ciclesonide, azithromycin and ampicillin/sulbactam were initiated after diagnosis. He needed invasive mechanical ventilation (IMV) due to a rapid progressive respiratory failure on day 13. The ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F) was 136, which was classified as moderate acute respiratory distress syndrome (ARDS) at that time. Low-dose steroid (hydrocortisone 250mg/day), intravenous immunoglobulin, and sivelestat were started after intubation. The respiratory status improved temporarily, but P/F and consolidation with traction bronchiectasis and volume loss worsened. MP (methyl-prednisolone 1000mg for three days) was started from day 19. After this therapy, P/F, LDH, and computed tomography (CT) findings were improved (Fig. 1, Fig. 2).

Prednisolone (PSL) 40mg (0.5mg/kg/day) was started after the pulse
therapy, and the dose was gradually tapered. He was successful extu-
bated on day 23, negative conversion of the reverse transcription po-
lymerase chain reaction test (RT-PCR) was confirmed on day 43, and
finally he was discharged without oxygen demand on day 48. PSL was
finished on day 49.

2.1.2. Case 2
This is the case of a 43-year-old woman with bronchial asthma who
presented with fever, cough, malaise, arthralgia, and dysgeusia. She was
diagnosed with COVID-19 on day 6. Lopinavir/ritonavir was initiated
when she had pneumonia with oxygen demand on day 8. Hydroxy-
chloroquine, azithromycin, and ampicillin/sulbactam were added on
day 9 since her respiratory status worsened. She needed IMV due to a
rapid progressive respiratory failure on day 10. P/F was 149, which was
classified as moderate ARDS at that time. Ciclesonide, low-dose steroid
(hydrocortisone 250mg/day), intravenous immunoglobulin, and sive-
lestat were started after intubation. The respiratory status improved
temporarily, but P/F and consolidation with traction bronchiectasis and
volume loss worsened. Initially, prone position therapy was started from
day 14, and MP (methyl-prednisolone 1000mg for three days) was
initiated from day 15. After this therapy, P/F, LDH, and CT findings were
improved (Fig. 1). After the pulse therapy, PSL 30mg (0.5mg/kg/day)
was started, and the dose was gradually tapered. She was successfully
extubated on day 21, negative conversion of RT-PCR was confirmed on
day 27, and finally she was discharged without oxygen demand on day
31. PSL was finished on day 38.

2.1.3. Case 3
This is the case of a 68-year-old man with hypertension who pre-
sented with fever, diarrhea, and dry cough. He was diagnosed with
COVID-19 on day 11. Although lopinavir/ritonavir was initiated after
diagnosis, he manifested respiratory failure from day 12. Hydroxy-
chloroquine has been added for his treatment on day 16, ampicillin/
sulbactam on day 18, ciclesonide on day 19, and azithromycin and low-

Fig. 1. Clinical course of P/F (the ratio of arterial oxygen partial pressure to fractional inspired oxygen) and LDH (IU/l). Black triangle: the day of intubation. Black square: the day of extubation. Day 1 was set as the initiation of steroid pulse therapy.

Fig. 2. Computed tomography of the chest during the clinical course in case 1. It showed bilateral peripheral ground glass opacities on day 11 (on admission). These opacities progressed consolidation with traction bronchiectasis and volume loss on day 19 (the day steroid pulse therapy was started). Patient almost recovered from these findings on day 61.
dose steroid (hydrocortisone 250mg/day) on day 22. He needed IMV due to a progressive respiratory failure on day 23. P/F was 170, which was classified as moderate ARDS at that time. Invasive immunoglobulin, sivelestat, and prone position therapy were administered after intubation. The respiratory status improved temporarily, but P/F and consolidation with traction bronchiectasis and volume loss worsened. MP (methyl-prednisolone 1000mg for three days) was initiated from day 29. After this therapy, P/F, LDH, and CT findings were improved (Fig. 1). PSL was not administered after the pulse therapy. He was successfully extubated on day 30, negative conversion of RT-PCR was confirmed on day 51, and finally he was transferred to a rehabilitation hospital due to disuse syndrome without oxygen demand on day 59.

2.1.4. Case 4

This is the case of a 77-year-old man with hypertension, emphysema, and old tuberculosis, who is an ex-smoker and who presented with fever and sore throat. Levofloxacain and ciclesonide were administered on day 8 for bilateral pneumonia with respiratory failure. He was diagnosed with COVID-19 on day 10. He needed IMV due to a rapid progressive respiratory failure on day 11. P/F was 170, which was classified as moderate ARDS at that time. Although favipiravir has been initiated, low-dose steroid (hydrocortisone 250mg/day), intravenous immunoglobulin, sivelestat, and prone position therapy were administered after intubation. The respiratory status improved temporarily, but P/F and consolidation with traction bronchiectasis and volume loss worsened. MP (methyl-prednisolone 1000mg for three days) was initiated from day 14. After this therapy, P/F, LDH, and CT findings were improved (Fig. 1). PSL 30mg (0.5mg/kg/day) was started after the pulse therapy, and the dose was gradually tapered. He was successfully extubated on day 30, negative conversion of RT-PCR was confirmed on day 24, and finally he was discharged without oxygen demand on day 30. PSL was finished on day 33.

2.2. Summary of the results for four cases

MP with respiratory failure due to COVID-19 was administered to four patients (three males, one female). The median day of MP administration was day 17 (14–29), the late phase of COVID-19. The median age was 64.5 years (43–77). The comorbidities were hypertension in three cases, history of smoking in two cases, and bronchial asthma, emphysema, and old pulmonary tuberculosis in one case. The median time to diagnosis, respiratory failure, or intubation was 10.5 days (6–11), 9.5 days (8–12), or 12 days (10–23), respectively. The median findings of body temperature, lymphocyte, LDH, and C-reactive protein on intubation were 38.5°C (36.8–38.6), 393.5/μl (219–1227), 442.5IU/l (364–599), and 15.7mg/dl (12.8–35.8), respectively. Lopinavir/ritonavir, hydroxychloroquine, favipiravir, and ciclesonide which were expected to have an antiviral effect were administered on day 10.5 (8–19) (median, range). Intravenous immunoglobulin and antibiotics were administered in all cases. Prone position therapy was performed in three cases. Low-dose corticosteroids were administered in all cases around the timing of intubation. MP improved P/F, LDH, and CT findings in all cases in spite of bimodal worsening after intubation (Figs. 1 and 2). The median duration of systemic corticosteroid, intubation, ICU stay, and negative conversion of RT-PCR was 26 days (13–37), 9.5 days (8–12), 11 days (9–17), and 35 days (24–51), respectively. All cases succeeded in withdrawing from oxygen therapy, but one patient was transferred to a rehabilitation hospital due to disuse symptom. No other adverse events were observed.

3. Discussion

All cases showed that P/F and consolidation with traction bronchiectasis and volume loss worsened after the temporary improvement on intubation. MP in the late phase of COVID-19 improved pneumonia and P/F without oxygen demand. They were discharged to go home except one patient.

The Radiological Society of North America suggested that typical CT findings for COVID-19 revealed peripheral and bilateral or multifocal ground grass opacities of rounded morphology with or without consolidation or crazy-paving appearance [5]. This society also reported that consolidation, reserve halo sign, and other findings of organizing pneumonia (OP) were found in the late phase of COVID-19 [5]. A retrospective study in China showed that CT findings including consolidation, linear opacities, crazy-paving pattern, and bronchial wall thickening were associated with disease severity [6]. In general, the treatment for secondary OP is similar to that for cryptogenic OP. The British Thoracic Society guidelines proposed that corticosteroids were the current standard treatment for cryptogenic OP, although the initial dose of corticosteroids was unknown [7]. This society also suggested a steroid pulse therapy for some cases with fulminant cryptogenic OP. Although no histopathological examination was presented to diagnose OP in our cases, CT findings in the late phase of COVID-19 were characteristic of OP. The prospective meta-analysis of clinical trials including the RECOVERY trial and some retrospective studies showed that systemic corticosteroids were effective on critically ill patients with COVID-19 although these studies didn’t refer to OP [2,3,8,9]. One prospective study proved that MP administered within the second week after the onset of symptoms improved outcome of patients with COVID-19 [4]. As a result, MP might be effective in patients with the late phase of COVID-19.

A routine use of systemic corticosteroids for COVID-19 wasn’t firstly recommended because a previous report showed that systemic corticosteroids delayed viral shedding and that they were harmful due to adverse events for severe acute respiratory syndrome. Middle East respiratory syndrome, and especially increased mortality for influenza [10]. It was reported that the time to negative conversion of RT-PCR was 20 days in mild to severe cases [11,12]. This study had it longer than that of the previous study. It was suggested that systemic corticosteroids might delay viral shedding. Since RT-PCR tests were not performed on continuous days, the time to negative conversion of RT-PCR might be shorter in some cases. One patient was transferred to a rehabilitation hospital due to disuse syndrome. Disuse syndrome might be associated with systemic corticosteroids and bed rest for a long time. However, it was significant that all patients could survive without oxygen therapy. Therefore, a MP therapy might be beneficial because viral load might be low in the late phase of COVID-19. However, corticosteroids should be used in a short-term to diminish this toxicity.

This study has several limitations. Firstly, this was a single-center case series with small sample. We couldn’t set a control group because of small sample. Further investigations are needed in the future. Secondly, no histopathological examination was presented to diagnose OP. Identifying the etiology was based primarily on images and laboratory findings since invasive procedures such as bronchoscopy to reduce viral exposure were not performed.

In conclusion, MP is effective for patients with respiratory failure in the late phase of COVID-19. Although the use of systemic corticosteroids is of concern due to the delay of viral shedding or toxicity, they can be used safely by selecting optimal cases, timing, and dose. It is necessary to establish its evidence for further case accumulation and research.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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