Helmet mask and tocilizumab for a patient with hemophagocytic lymphohistiocytosis syndrome and COVID-19: a case report

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Abstract The management of acute hypoxemic respiratory failure and the effect of antiviral drugs in patients with severe COVID-19 have been debated. This case presents the management of a 64-year-old man COVID-19 patient admitted to the Intensive Care Unit with fever, fatigue, shortness of breath and hemophagocytic lymphohistiocytosis syndrome. Helmet mask was successfully used to treat his hypoxemic respiratory failure without any aerosol problems. Tocilizumab, an antagonist interleukin-6, was intravenously infused as an alternative drug. After administration, the high level of IL-6, CRP, ferritin, D-dimer, triglyceride, and H-scores decreased, and the patient observed good clinical and laboratory improvements. In this case report, we describe the effect of noninvasive ventilation delivered by helmet mask and antiviral drugs, and the intravenous administration of tocilizumab in a patient with hemophagocytic lymphohistiocytosis syndrome and COVID-19.

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Introduction

The management of acute hypoxemic respiratory failure and the effect of antiviral drugs in patients with severe COVID-19 have been debated. The clinical spectrum of COVID-19 varies from asymptomatic to requiring mechanical ventilation and advanced support in the Inten-
sive Care Unit. Conventional oxygen therapy, oxygen mask with reservoir bag, HFNC, NIPPV, and invasive mechanical ventilation have been recommended to treat hypoxic respiratory failure in patients with severe COVID-19. The helmet mask, a transparent hood that covers the entire head of the patient with a soft collar neck seal, is used to treat acute hypoxic respiratory failure in Acute Respiratory Distress Syndrome (ARDS) cardiogenic pulmonary edema, and hematological malignancy patients. A randomized clinical trial reported that noninvasive ventilation delivered by helmet mask reduced the rate of endotracheal intubation and improved other patient outcomes in ARDS patients.

Antimalarial drugs like hydroxychloroquine, because of the potential antiviral effect, and some antiviral drugs such as favipiravir, remdesivir, and lopinavir/ritonavir have been tested in the treatment of patients with coronavirus disease. Tocilizumab, a known interleukin-6 blocker, can be used in the management of cytokine storms.

In this case report we describe the effect of noninvasive ventilation delivered by helmet mask and antiviral drugs, and the intravenously administration of tocilizumab in a patient with hemophagocytic lymphohistiocytosis syndrome and COVID-19.

Case report

A 64-year-old man was admitted with fever, cough, fatigue, and shortness of breath on March 30, 2020. His medical history had hypertension, but no drug use. The diagnosis of COVID-19 was made after obtaining a chest tomography that showed bilateral multilobar ground-glass opacities, bilateral pulmonary infiltrates, and positive real-time PCR test for COVID-19.

In the Intensive Care Unit, the patient’s temperature was 38.7 °C, respiratory rate was 36 per minute, and oxygen saturation was 82. His heart rate and blood pressure were 88 per min and 130/80 mmHg, respectively. Oxygen mask with reservoir bag was applied as 4 L min⁻¹, and azithromycin for community-acquired pneumonia (500 mg orally on day 1, followed by 250 mg 1×/day on days 2–5), paracetamol for high fever (1000 mg intravenously 3×/day) were administered. Oseltamivir (75 mg 2×/day) was started because influenza could not be ruled out, and hydroxychloroquine as a potential antiviral effect (400 mg orally 2×/day on day 1, then 200 mg 2×/day on days 2–5) was added to the treatment for 5 days. The close ECG including QT prolongation and hemodynamic monitoring of the patients was performed. The nasopharyngeal swab of the patient was cultured. Enoxaparin 40 mg subcutaneously 2×/day as an anticoagulant, acetylcysteine 100 mg 3×/day to loo mucus in the airways, vitamin C, and vitamin D were administered, and the patient’s nutrition was supplemented orally or parenterally on the ICU days. On day 4, because of tachypnea and decrease of oxygen saturation oseltamivir and azithromycin were stopped and favipiravir (1600 mg 2×/day on day 1, then 600 mg 2×/day on days 2–5), as an inhibitor of the RNA-dependent RNA polymerase and with potential antiviral effect, was added to the treatment for 5 days. Helmet mask was applied due to insufficiency of oxygen mask with reservoir bag. Patient tolerability to the helmet mask was good. When needed, we administered 2 mg of midazolam intravenously for patient sedation. On day 4 of the favipiravir, tocilizumab 400 mg was infused intravenously 2×/day for 2 days because of increased IL-6 levels and secondary hemophagocytic lymphohistiocytosis syndrome (H-Score > 169). After tocilizumab administration the high levels of IL-6, CRP, ferritin, D-dimer, triglyceride, and H-scores decreased (Table 1). On day 11 the patient showed good clinical and laboratory improvements, such as lower fever and higher oxygen saturation. On day 14 the patient was transferred to a negative COVID-19 service with better clinical condition and negative PCR test.

Discussion

There is no specific treatment or therapy recommended for coronavirus disease 2019. The following therapeutic approaches can be suggested according to the severity of the disease, respectively: isolation, rest, fluid and food intake; oxygen support; respiratory treatment; anticoagulant treatment; hydroxychloroquine and combination therapy; antiviral drugs (remdesivir, favipiravir, lopinavir/ritonavir) and other immunomodulator drugs like tocilizumab; convalescent plasma therapy; mesenchymal stem cells therapy; and vaccination.

To our best knowledge, there is no trial comparing helmet mask and face mask or intubation for the management of acute hypoxic respiratory failure in patients with severe COVID-19. We observed the helmet mask delivered higher airway pressures without substantial air leak. We did not observe any aerosol problems during the helmet mask applications. Healthcare workers wore the FFP3 (filtering face piece) mask under a standard surgical mask, and personal protective equipment during the applications. The helmet mask application has difficulties like patient tolerability, CO₂ rebreathing, mask deflation, skin ulceration, gastric distention, eye irritation, and pain but the patient tolerated it well. When needed, we administered 2 mg of midazolam intravenously for sedation. As a result, a significant reduction in the respiratory rate and higher oxygen saturation levels were recorded. At the same time, the administration of the drugs against coronavirus, especially tocilizumab with no contraindication contributed to reduce the cytokine storm syndrome, or secondary Hemophagocytic Lymphohistiocytosis (sHLH).

Hemophagocytic Lymphohistiocytosis (HLH) syndrome is a severe hyperinflammatory condition caused most commonly by viral infection in adults. Its cardinal clinical and laboratory features include fever, hepatosplenomegaly, hemophagocytosis, pancytopenia, hyperferritinemia, hypertriglyceridemia and liver enzyme levels. For the diagnosis of HLH syndrome, the H-scores should be over 169.4,5 In our case, the levels of ALT, AST, ferritin, triglycerides, CRP, D-dimer and IL-6 were elevated before the tocilizumab administration so we calculated the H-score was 195. After the tocilizumab intravenous infusion of 8 mg kg⁻¹, the levels of the mentioned parameters, and the calculated H-score were incrementally decreased (Table 1). Tocilizumab, an IL-6 receptor block-
|                          | At admission | Day 1 | Day 3 | Day 4 | Day 8 | Day 11 | Day 14 |
|--------------------------|--------------|-------|-------|-------|-------|--------|-------|
| Fever (°C)               | 38.7         | 37.8  | 38.2  | 38.4  | 38.8  | 36.8   | 36.3  |
| Respiratory rate (per min)| 36           | 26    | 24    | 34    | 32    | 14     | 12    |
| Ventilation support      | Oxygen mask  | OMRB  | OMRB  | Helmet mask | Helmet mask | Oxygen mask | Air room |
| sPO2 (%)                 | 82           | 92    | 76    | 96    | 98    | 98     | 96    |
| PO2 (mmHg)               | 68           | 43    | 72    | 84    | 82    | 78     | 40    |
| PCO2 (mmHg)              | 42           | 49    | 38    | 36    | 38    | 38     | 38    |
| PO2/FIO2                 | 7.32         | 7.25  | 7.30  | 7.36  | 7.34  | 7.42   |       |
| Bicarbonate (mmol.L⁻¹)   | (22-26)      | 24    | 26    | 18    | 30    | 22     | 22    |
| Laktat (mmol.L⁻¹)        | (0.5-1)      | 1,1   | 2,1   | 2,3   | 2,2   | 1,6    | 0.9   |
| Hemoglobin (g.L⁻¹)       | (12-17)      | 12    | 11    | 9     | 8     | 10     | 11    |
| White-cell count (per mm³)| 2600         | 2500  | 2400  | 2200  | 3300  | 3800   | 4200  |
| Platelet count (per mm³) | (400–10,000) | 192,000 | 158,000 | 102,000 | 72,000 | 88,000 | 186,000 | 224,000 |
| BUN (mg.dL⁻¹)            | (8-20)       | 24    | 26    | 28    | 30    | 25     | 20    | 16    |
| Creatinine (mmol.L⁻¹)    | (0.51-0.95)  | 092   | 093   | 1,1   | 1,4   | 1,2    | 096   | 084   |
| ALT (U.L⁻¹)              | (0-35)       | 21    | 23    | 39    | 78    | 55     | 49    | 27    |
| AST (U.L⁻¹)              | (0-35)       | 24    | 52    | 62    | 83    | 64     | 53    | 28    |
|                          | At admission | Day 1 | Day 3 | Day 4 | Day 8 | Day 11 | Day 14 |
|--------------------------|--------------|-------|-------|-------|-------|--------|--------|
| **Fibrinogen (mg.dL⁻¹)** | 320          | 280   | 160   | 120   | 140   | 220    | 340    |
| (200–400)                |              |       |       |       |       |        |        |
| **Ferritin (ng.mL⁻¹)**   | 1400         | 2560  | 3400  | 4200  | 5800  | 1800   | 1200   |
| (11–306)                 |              |       |       |       |       |        |        |
| **Triglycerides (mg.dL⁻¹)** | 123         | 138   | 264   | 316   | 320   | 126    | 122    |
| (<130)                   |              |       |       |       |       |        |        |
| **INR**                  | 1.2          | 1.3   | 1.5   | 1.7   | 1.6   | 1.5    | 1.3    |
| (0.8–1.2)                |              |       |       |       |       |        |        |
| **IL-6 (pg.mL⁻¹)**       | 78           | 104   | 136   | 265   | 138   | 82     | 11     |
| (0–6.4)                  |              |       |       |       |       |        |        |
| **CRP (mg.dL⁻¹)**        | 4            | 7     | 8     | 10    | 9     | 8      | 4      |
| (0–5)                    |              |       |       |       |       |        |        |
| **Troponin (ng.L⁻¹)**    | 307          | 871   | 1839  | 1980  | 1873  | 1271   | 420    |
| (0–11.6)                 |              |       |       |       |       |        |        |
| **D-dimer (mg.L⁻¹)**     | 195          | 73    |       |       |       |        |        |
| (0–500)                  |              |       |       |       |       |        |        |
| **PCR**                  | Positive PAR 3 × 1 g | PAR 3 × 1 g | PAR 3 × 1 g | Positive FAVI 2 × 1600 mg, then 2 × 600 mg ENO 2 × 40 mg | TCZ 2 × 400 mg IV ENO 2 × 40 mg | Negative ENO 2 × 40 mg |
| **Drugs**                |              |       |       |       |       |        |        |
| AZI 500 mg               |              |       |       |       |       |        |        |
| OSE 2 × 75 mg            |              |       |       |       |       |        |        |
| HCLQ 2 × 400 mg          |              |       |       |       |       |        |        |
| AZI 4 × 250 mg           |              |       |       |       |       |        |        |
| OSE 2 × 75 mg            |              |       |       |       |       |        |        |
| HCLQ 2 × 200 mg          |              |       |       |       |       |        |        |
| AZI 4 × 250 mg           |              |       |       |       |       |        |        |
| OSE 2 × 75 mg            |              |       |       |       |       |        |        |
| HCLQ 2 × 200 mg          |              |       |       |       |       |        |        |
| AZI 4 × 250 mg           |              |       |       |       |       |        |        |
| OSE 2 × 75 mg            |              |       |       |       |       |        |        |
| HCLQ 2 × 200 mg          |              |       |       |       |       |        |        |
| AZI 4 × 250 mg           |              |       |       |       |       |        |        |
| OSE 2 × 75 mg            |              |       |       |       |       |        |        |
| HCLQ 2 × 200 mg          |              |       |       |       |       |        |        |

OMRB, Oxygen Mask with Reservoir Bag; PAR, Paracetamol; AZL, Azithromycin; OSE, Oseltamivir; HCLQ, Hydroxychloroquine; FAVI, Favipiravir; TCZ, Tocilizumab; ENO, Enoxaparin; iv, intravenous. ( - ) Normal range of a parameter.
ade, has been used in patients with severe COVID-19 presenting ARDS and elevated IL-6 levels. In our patient with severe COVID-19 and secondary HLH syndrome, we observed clinical improvements using the helmet mask without invasive mechanic ventilation and the tocilizumab administration.

**Conclusion**

Consequently, we suggest that all severe COVID-19 patients should be closely monitored for HLH syndrome, and the available anti-coronavirus drugs, especially tocilizumab, can be used early under noninvasive ventilation delivered by helmet mask.

**Conflicts of interest**

The authors declare no conflicts of interest.

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