**Severe Coronavirus Disease 2019 That Recovered from Respiratory Failure by Treatment That Included High-dose Intravenous Immunoglobulin**

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**Abstract:**
We herein report a case of severe coronavirus disease 2019 (COVID-19) in which high-dose intravenous immunoglobulin (IVIg) treatment achieved significant clinical improvement of deterioration of pulmonary inflammation after temporary clinical improvement. In the present case, clinical and radiological deterioration occurred despite a decrease in viral load, suggesting that deterioration was caused by reactivation of proinflammatory factors, such as tumor necrosis factor-α and interleukin-6, rather than direct viral effects. IVIg treatment may provide not only immunosuppressive effects but also inhibition of proinflammatory cytokines, indicating that treatment including IVIg may be effective by inhibiting cytokine storm in severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection.

**Key words:** coronavirus disease 2019, COVID-19, intravenous immunoglobulin, severe acute respiratory syndrome-coronavirus-2, acute respiratory distress syndrome, deterioration

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**Introduction**

Coronavirus disease 2019 (COVID-19) causes fatal clinical manifestations, which lead to acute respiratory distress syndrome (ARDS). Inflammatory cytokine storm is considered to be related to the development of ARDS in COVID-19 (1). Although some reports have described clinical and radiological recurrence during treatment for COVID-19 (2-5), the pathogenesis of the recurrence has not yet been elucidated.

Treatment for COVID-19 can mainly be divided into two types depending on the targets: severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), and systemic inflammation induced by the SARS-CoV-2 infection (6). Intravenous immunoglobulin (IVIg) has been used as an adjunctive therapy in patients with severe infection, and high-dose IVIg treatment was attempted in several COVID-19 patients (7-13).

We herein report the efficacy of treatment including high-dose IVIg for deterioration after temporary clinical improvement in the severe COVID-19 patient. While previous reports have shown the efficacy of high-dose IVIg in the early phase, to our knowledge, this is the first report showing the possible efficacy of this treatment even in the late phase, such as in cases of deterioration after clinical improvement.
in severe COVID-19 patients.

### Case Report

A 64-year-old man complaining of a fever, cough, fatigue and dyspnea for over a week visited a local hospital. Nasopharyngeal swabs were positive for SARS-CoV-2 by real-time polymerase chain reaction (rPCR), and the patient was transferred to our hospital for intensive care. He had a history of untreated diabetes and smoking for 35 pack-years. There were coarse crackles in the right lower zone on auscultation with 89% oxygen saturation on ambient air.

As shown in the Table, laboratory findings on admission revealed a slight increase in the white blood cell count (9,100/μL) with lymphopenia (11%), as well as elevated C-reactive protein (22.1 mg/dL) and d-dimer (1.2 μg/mL). In addition, the serum ferritin levels were dramatically increased (3,390 ng/mL). A blood gas analysis showed hypoxemia [arterial partial pressure of oxygen/fraction of inspired oxygen ratio (PaO2/FiO2): 264 mmHg]. Chest radiography showed bilateral lower lobe consolidation and multifocal ground glass opacities (Fig. 1A). CT: computed tomography showed bilateral infiltrates (Fig. 1A), and chest computed tomography (CT) demonstrated consolidation and multifocal ground glass opacities with bilateral lower lobe dominance (Fig. 1B).

The patient was treated with favipiravir (3,600 mg/day on Day 1 followed by 1,600 mg/day for 13 additional days),...
ally improved with the treatment, with methylprednisolone (total 1,200 mg) for the treatment of cytokine storm induced respiratory condition had deteriorated, he was intubated on methylprednisolone was initiated on the day of admission. Furthermore, 80 mg/day of piperacillin (13.5 mg/day) and azithromycin (500 mg/day) were also started due to the possibility of complication with bacterial pneumonia. Additionally, 400 mg/day of hydroxychloroquine, 100 mg/day of nafamostat and 1,200 μg/day of ciclesonide. Although no bacteria were detected in a sputum culture obtained on admission, ta- zobactam/piperacillin (13.5 mg/day) and azithromycin (500 mg/day) were also started due to the possibility of complica- tion with bacterial pneumonia. Furthermore, 80 mg/day of methylprednisolone was initiated on the day of admission because of his aggravated respiratory condition. Since his respiratory condition had deteriorated, he was intubated on Day 3 and maintained on mechanical ventilation. Tocilizu- mab was administrated at a dose of 400 mg every 12 hours (total 1,200 mg) for the treatment of cytokine storm induced by the SARS-CoV-2 infection. His respiratory status gradually improved with the treatment, with methylprednisolone being tapered over several days by 20 mg/day. The patient was extubated on Day 8.

On Day 15, CT showed improvement in the radiological findings in the lung fields (Fig. 2). However, unfractionated heparin was started because thrombus of the right pulmo- nary artery was found. On Day 23, his respiratory status suddenly worsened, and CT revealed deterioration of the consolidation in the bilateral lower lobes (Fig. 2). As no new thrombus of the pulmonary artery was found and clinical findings, such as negative sputum cultures, did not suggest bacterial pneumonia, we judged the condition to reflect deterioration of COVID-19. Mechanical ventilation was re- started along with favipiravir, methylprednisolone, tocilizu- mab and 200 μg/kg/day of ivermectin. Furthermore, high-

\begin{figure}
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\caption{Clinical course after admission. Chest CT demonstrated consolidation and multifocal ground glass opacities with bilateral lower lobe dominance (Day 1). Although these shadows improved temporarily after the initial treatment (Day 15), the bilateral consolidation in the bilateral lower lobes became exacerbated (Day 23). Second treatment including IVIg significantly improved the bilateral consolidation and multifocal ground glass opacities (Day 61). The viral loads in the naso- pharyngeal swabs and sputum samples decreased after the initial treatment and were not remarkably increased even after recurrence. Anti-SARS-CoV-2 IgG was measured using the Access SARS-CoV-2 IgG assay (Beckman Coulter, Brea, USA) according to the manufacturer’s protocol. Results were reported as signal sample/cut-off (S/CO) with S/CO values ≥ 1.0 interpreted as positive. AZM: azithromycin, CT: computed tomography, DRPM: doripenem, IgG: immunoglobulin G, IVIg: intravenous immunoglobulin, mPSL: methylprednisolone, N/A: not applicable, N/D: not detectable, PaO2/FIO2: the arterial partial pressure of oxygen/fraction of inspired oxygen ratio, SARS-CoV-2: severe acute respiratory syndrome-coronavirus-2, TAZ/PIP: tazobactam/piperacillin, TCZ: tocilizumab.}
\end{figure}
dose IVIg treatment was started at 25 g/day for 5 days.

His general status subsequently improved, and he was extubated on Day 28. On Day 46, rPCR showed negative results for SARS-CoV-2 in both nasopharyngeal swabs and sputum. On Day 61, CT revealed the significant improvement of the consolidation in both lung fields (Fig. 2) and the disappearance of the pulmonary artery thrombus. The direct oral anticoagulant, edoxaban (60 mg/day) was started, and he was discharged from our hospital on Day 64.

**Discussion**

To date, there have only been a few reports describing high-dose IVIg treatment for COVID-19. Xie et al. reported that the administration of high-dose IVIg (20 g/day for 5 days) as adjuvant treatment within 48 hours after admission significantly improved the survival rate of COVID-19 patients (7), and other studies have also demonstrated the efficacy of such treatment for severe COVID-19 patients (8-13). However, in those previous reports, high-dose IVIg was administered in the early phase after the onset of COVID-19. To our knowledge, this is the first report describing the efficacy of high-dose IVIg in the late phase of severe COVID-19, such as following deterioration after temporary improvement. Our case showed additional evidence supporting the efficacy of high-dose IVIg treatment for COVID-19.

Interestingly, deterioration occurred after temporary improvement during the course of COVID-19 in the present case. Although there are few reports describing the clinical course of COVID-19 in detail, some have mentioned recurrence of COVID-19 (2-5). In those reports, negative results of rPCR before recurrence turned positive when recurrence was observed, suggesting that the reactivation of SARS-CoV-2 induced recurrence. However, in the present case, the results of sputum samples were still positive according to rPCR at the time of deterioration, although the viral loads had decreased.

The mechanisms underlying the deterioration in the present case are unclear. However, Liu et al. reported the possible involvement of anti-SARS-CoV-2 antibody in the pathogenesis of deterioration (14). They demonstrated using SARS-CoV-macaque models that viral surface antigen S and host antibody complex (anti-spike-IgG) facilitate the activation of proinflammatory signals in macrophages through interaction with membrane receptors for the Fc portion of the immunoglobulin (FcR), leading to severe lung injury. In addition, the injection of purified anti-spike-IgG-neutralizing antibody to infected macaques led to acute diffuse alveolar damage despite a reduction in SARS-CoV loads (14). Furthermore, the peak levels of serum anti-spike-IgG-neutralizing antibody in non-survivors had been reached at 14.7 days from the onset of their symptoms, a shorter duration than in survivors (20 days) (15). These studies indicate that even if the viral loads decrease, anti-spike-IgG antibodies, which persist until the late stages of SARS-CoV infection, may induce severe lung injury. These results suggest that SARS-CoV-2 infection causes lung damage via similar mechanisms.

Furthermore, it is well-known that sub-optimal antibodies that cannot completely clear the virus induce inflammation [antibody-dependent enhancement (ADE)]. ADE is a phenomenon induced by the interaction of infectious viral antibody complexes with FcR and is reported in infectious cases of some viruses, such as dengue and influenza (16). Although the role of ADE in SARS-CoV-2 infection has not yet been clarified, it may be involved in deterioration. In fact, in the present case, seroconversion had occurred and IgG for SARS-CoV-2 was already positive before deterioration.

Because these results showed the importance of inflammatory responses via FcR, the anti-inflammatory effects of IVIg treatment may be induced by blocking the activation of Fcγ receptors (FcγR) on innate immune effector cells (17). In addition, IVIg treatment shows not only these immunosuppressive effects but also the inhibition of proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-6 (13, 18). These results suggest that IVIg treatment may be useful by inhibiting cytokine storm in SARS-CoV-2 infection. Furthermore, IVIg treatment has been available for decades with limited side effects (19), and in fact, we did not note any significant side effects in our case. Taken together, these findings suggest that IVIg is an ideal treatment for COVID-19 patients.

In the present case, ivermectin was also administered when deterioration was observed. Therefore, ivermectin, a potent inhibitor against SARS-CoV-2 replication (20), might have played some role in the improvement of the patient. However, because viral loads were low and remained almost the same during the deteriorating phase (Fig. 2), the improvement by the treatment after deterioration was thought to be largely due to the suppression of pro-inflammatory signals through the treatment, which included high-dose IVIg.

Several limitations associated with the present study warrant mention. First, it may be difficult to assess the efficacy of IVIg treatment because IVIg, methylprednisolone and tocilizumab were all started simultaneously at the time of deterioration. However, after the onset of deterioration, the effects of methylprednisolone and tocilizumab were inadequate to suppress the inflammation, and additional IVIg treatment significantly improved the clinical condition, suggesting the anti-inflammatory effect of IVIg treatment. Second, our report concerns only one patient.

In conclusion, we described a case of severe COVID-19 administered treatment including high-dose IVIg, resulting in significant clinical improvement. Our present case suggests that high-dose IVIg is effective against severe COVID-19 not only in the early phase but also in the late phase, such as after deterioration. Although accumulating more cases is necessary to confirm the precise role of IVIg treatment in severe COVID-19 patients, it will be worthwhile to conduct this treatment until effective treatments are estab-
lished.

The authors state that they have no Conflict of Interest (COI).

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