

Severe Coronavirus Disease 2019 (COVID-19) Pneumonia Patients Treated Successfully with a Combination of Lopinavir/Ritonavir plus Favipiravir: Case Series

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July 24, 2020

Abstract

Three COVID-19 patients who were received lopinavir/ritonavir plus favipiravir got to improved without any severe adverse events. Two patients harboring high fever, severe pneumonia and respiratory failure obtained dramatic improvement. The combination therapy might be a treatment option; earlier therapy onset may have needed to avoid lung sequela.

Introduction

While coronavirus disease 2019 (COVID-19) has spread rapidly worldwide, evidence on effective treatments for it is scant. To the best of our knowledge, we describe here the first report on patients undergoing a successful treatment consisting of a combination of antiviral agents that included favipiravir.

Informed consents from the patients were obtained, and a written consent for publication in this journal was also obtained from each patient. The ethics committee of the Komatsu Municipal Hospital approved the off-label use of both lopinavir/ritonavir and favipiravir before the administration of each drug.

Case Report

Case 1

A 61-year-old Japanese man was admitted to our hospital on February 23, 2020, with fever, general malaise, and diarrhea. He had a history of recent travel from Japan to Europe on February 9, and returned to Japan on February 15. On February 16, (day 1 of illness) he reported general malaise and a fever of less than 38°C. Because of continued fever and malaise and the onset of diarrhea, he visited our hospital on February 23 (day 8 of illness). Upon admission, his body temperature was 39.7°C, dyspnea was not observed, and his oxygen saturation was 99% on ambient air. Laboratory test results showed lymphocytopenia (592/ μ L) and elevated C-reactive protein (CRP 3.98 mg/dL) and ferritin (937 ng/mL) levels (Fig. 1). Chest radiography and chest computed tomography (CT) revealed multiple bilateral ground-glass opacities(GGO) in his lungs (Fig. 2). The day after admission (day 9 of illness), his nasal swab sample was positive for COVID-19 by a real-time reverse transcriptase (RT) polymerase chain reaction (PCR) assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Figure 1 shows the patient's clinical course. He was immediately admitted to the isolation ward. Regardless of immediate administration of empiric antibiotic therapy (ceftriaxone [2 g daily]) and antipyretic medication, his hyperpyrexia did not improve and his hypoxemia gradually worsened. On February 26 (day 11 of illness), oxygen administration was initiated because of the respiratory failure, and antiviral therapy with

lopinavir/ritonavir (400 mg/100 mg twice daily) was started. However, his respiratory failure got worsened. On February 29 (day 14 of illness), favipiravir (1800 mg twice daily on day 1; 800 mg twice daily, days 2-14) was added to the lopinavir/ritonavir therapy. Two days after the addition of favipiravir (day 16 of illness), his hyperpnea, pyrexia, appetite, and general malaise were clearly improved. On March 6 (day 20 of illness), the patient no longer required oxygen. The patient's course as reflected by the laboratory data showed that while the CRP and ferritin levels gradually increased after admission, those levels gradually decreased and the patient's lymphocytopenia gradually improved after the initiation of lopinavir/ritonavir and the addition of favipiravir. Representative cytokine levels were examined on March 4 (day 18 of illness); Interleukin (IL)-5 (4 pg/ml), IL-6 (10 pg/ml), Tumor Necrosing Factor α (TNF- α) (4.6 pg/ml) and Interferon γ (IFN- γ) (7.8 pg/ml) (Table 1). After twice confirmation of negative for RT-PCR for SARS-CoV-2, he was discharged on March 18 (day 32 of illness). The post-treatment chest CT revealed that GGO in bilateral lungs were increased, however intra- and interlobular septal thickening regeion, bronchioectasis within GGO were emarged on 17 Mar (Fig. 2). Obvious toxicity related to the combination therapy was never observed.

Case 2

A 50-year-old Japanese man was admitted to our hospital on February 26, 2020, with fever, nausea, and cough. His travel history was similar to that of Case 1. He reported that he first developed a fever of 38.5°C on February 16 (day 1 of illness). His initial laboratory test results showed an elevated CRP (4.44 mg/dL) level. Chest radiography revealed very small ground-glass opacities in the lower right lung and a linear shadow in the lower left lung. Chest CT revealed that the small amount of ground-glass opacities with linear shadows were located dorsally and bilaterally in the lower lobes of the lungs (Fig. 1). COVID-19 was confirmed from a nasal swab specimen assayed for SARS-CoV-2 by real-time RT-PCR.

Figure 2 shows the patient's clinical course. Empiric antibiotic therapy (ceftriaxone [2 g daily]) was first administered. On February 28 (day 13 of illness), lopinavir/ritonavir (400 mg/100 mg twice daily) was started. On February 29 (day 14 of illness), favipiravir (1800 mg twice daily on day 1; 800 mg twice daily, days 2-7) was added. Throughout the patient's hospitalization, he remained afebrile and asymptomatic. Twice RT-PCR assay for SARS-CoV-2 was negative and he was discharged from the hospital on March 7 (day 22 of illness). The patient's course as reflected by the laboratory data showed that his CRP levels gradually decreased after admission. However, his ferritin level worsened once, and gradually improved after starting lopinavir/ritonavir and adding favipiravir. Post-treatment chest CT revealed while a part of GGO regions were improved improvement, the linear shadow in GGO were thickened March 17 (Fig. 2). Obvious toxicity related to the combination antiviral therapy was never observed.

Case 3

A 54-year-old Japanese man was admitted to our hospital on April 10, 2020, with fever, dyspnea and diarrhea. He had been Tokyo from March 30 to 31 to help his son with house-moving. He reported that he first developed a fever of 39°C on April 4 (day 1 of illness). His initial laboratory test results showed an elevated CRP (3.85 mg/dL) level. Chest CT revealed diffuse ground-glass opacities in bilateral lungs (Fig. 1). COVID-19 was confirmed from a nasal swab specimen assayed for SARS-CoV-2 by real-time RT-PCR.

Figure 2 shows the patient's clinical course. Although lopinavir/ritonavir (400 mg/100 mg twice daily) and meropenem (1 g thrice daily) was started on April 11 (day 8 of illness), he got to worse as a respiratory failure on the next day. On April 13 (day 10 of illness), favipiravir (1800 mg twice daily on day 1; 800 mg twice daily, days 2-14) was added. Four days after the addition of favipiravir (day 16 of illness), his hyperpnea, pyrexia, appetite, and general malaise were improved. On April 22 (day 19 of illness), the patient no longer required oxygen. The patient's course as reflected by the laboratory data showed that while the CRP, ferritin and β 2 microglobulin levels gradually increased after admission, those levels gradually decreased and the patient's lymphocytopenia gradually improved after the addition of favipiravir. Representative cytokine levels were examined on April 10, 13 and May 7 (day 7, 10 and 30 of illness, respectively). IL-6, TNF- α and Tumor Growth Factor β 1(TGF β 1) level were abnormally elevated (Table 1). After twice confirmation of negative for RT-PCR for SARS-CoV-2, he was discharged on May 11 (day 34 of illness). The post-treatment chest

CT revealed that bilateral intra- and interlobular septal thickening region were emerged on 11 May (Fig. 2). Obvious toxicity related to the combination therapy was never observed.

Discussions

To the best of our knowledge, this is the first report indicating that combination antiviral therapy consisting of lopinavir/ritonavir and favipiravir might prove beneficial for patients with COVID-19. These agents relieved life-threatening lung injury in Case 1, 3 and in the other case provided early negative RT-PCR for SARS-CoV-2 results from a nasal swab specimen on day 7 after the initiation of antiviral therapy.

Although approximately 80% of COVID-19 patients have been reported to have mild disease^{1,2}, the mortality rate of COVID-19 has so far been reported to range from 1.4% to 15%¹⁻³; and the case-fatality rate of patients classified as critical, such as Case 1, has been reported to be 49.0%¹. While the causes of death from these reports^{2,3} were unclear, the acute respiratory distress syndrome might have been related to disease severity. The histopathological features of COVID-19-induced lung injury resemble those of the Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome⁴. A higher incidence of physician-diagnosed pneumonia was observed in patients with severe disease than in those with less severe disease, and 3.4% of all COVID-19 patients progressed to acute respiratory distress syndrome afterward². Thus, the establishment of predictive markers for the degree of disease severity, followed by the appropriate treatment for severely ill patients, are urgent priorities. We think that this report might be valuable with regard to these issues (predictive markers and life-saving treatment).

The protease inhibitor lopinavir/ritonavir, which is approved for the treatment of human immunodeficiency virus-1 infection, was reported to be effective for 5 patients with COVID-19 in Singapore. They all were cured⁵. However, a randomized controlled trial to verify whether severe COVID-19 patients get clinical improvement to receive lopinavir/ritonavir in China reported no benefit⁶. Favipiravir, which is being stockpiled for use as a countermeasure for novel influenza, functions as a chain terminator at the site of the incorporation of viral RNA and reduces the viral load. The agent resembles a nucleoside analogue, functioning as a purine homologue, and therefore inhibits viral RNA synthesis⁷. It has broad spectrum activity against RNA viruses such as the Ebola virus, Lassa virus, rabies, and the virus that causes severe fever with thrombocytopenia syndrome^{7,8}. An open-label nonrandomized control study reported COVID-19 patients treated by favipiravir showed significantly higher improvement in chest imaging and faster viral clearance than those treated by lopinavir/ritonavir⁹.

Commonly reported adverse reactions to lopinavir/ritonavir have included diarrhea, nausea, vomiting, hypertriglyceridemia, and hypercholesterolemia¹⁰. The adverse reactions to favipiravir include teratogenicity, increased blood levels of uric acid, diarrhea, and neutropenia. Hypertriglyceridemia and hypercholesterolemia were observed in Case 1. Although there are no safety data on the simultaneous use of lopinavir/ritonavir plus favipiravir, based on the kinetic mechanisms of the agents, the drug-drug interactions appear to be minimal¹⁰. Immediately after termination of favipiravir medication in Case 3, transient febrile reaction was observed. Although it is not easy to distinguish infectious-fever from iatrogenic drug fever, it makes us suggest the importance to remember the chemical fever even in antiviral therapy.

The progression of COVID-19 seems to be associated with a 'cytokine storm', which is also true of SARS and Middle Eastern Respiratory Syndrome. Elevated ferritin levels and lymphocytopenia seemed to be an accurate reflection of the severity of COVID-19 in our 3 patients, based on their clinical courses (Fig. 1). COVID-19 patients who needed admission to intensive care unit had less lymphocyte counts than counterpart³. Our findings suggest that IL-6 and TNF- α which were reflected by the serum CRP and ferritin level, has a central role in the progression of COVID-19, as opposed to IFN- γ (Table 1). Chaolin H *et al* . reported that a patient with severe COVID-19 had high concentrations of GCSF, IP10, MCP1, MIP1A and TNF- α , which led to activation of T-helper 1 cells³. On the other hand, they also reported increased secretion of T-helper 2 cytokines³. The ferritin, CRP and β 2-microglobulin levels decreased in Case 1 and 3 after the administration of favipiravir. These findings suggest that favipiravir not only reduces the levels of inflammatory cytokines in vitro, but might also reduce the levels in vivo⁷. Furthermore, earlier therapy onset

may have needed to avoid lung sequela now that chest CT findings at post-treatment suggests remaining pulmonary fibrosis(Fig. 2). According to the radiological study^{11,12}, COVID-19 must leave pulmonary scars like SARS^{13,14}.

This case series has limitations. First, we described only 3 patients. Second, they may have improved without any antiviral therapy. Third, the unavoidable delay to the diagnosis of COVID-19 impedes the ability to determine when we should initiate antiviral therapy.

In conclusion, the combination therapy of lopinavir/ritonavir plus favipiravir might be a treatment option for patients with COVID-19. Serum ferritin levels and lymphocytopenia are promising markers for disease severity and disease progression that are commonly available in general clinical practice.

Statements

Author Contributions:

H Koba: Conceptualization, Investigation, Writing-Original Draft, Visualization,

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T Ueda: Investigation,

H Kimura: Writing-Review & Editing, Visualization,

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Acknowledgments:

We sincerely thank all persons who related with the diagnosis, treatment and nursing for the patients.

Statement of Ethics:

Informed consent from the patient was obtained, and a written consent for publication in this journal was also obtained from each patient. The ethics committee of the Komatsu Municipal Hospital approved the off-label use of both lopinavir/ritonavir and favipiravir before the administration of each drug, and the presentation or publication about these cases. Notation of prior abstract/presentation: This paper of any similar paper has not been submitted nor published in any other journal.

Disclosure: The authors have reported to Respiration that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in the article.

Funding information:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Acquisition of favipiravir was supported by retrospective registry study that was planned by National Center for Global Health and Medicine, Japan.

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Figure legends

Figure 1. Timeline of the patients' clinical courses from the time of admission.

Abbreviation: COVID-19, coronavirus disease 2019; CT, computed tomography; iv, intravenous; po, orally; BT, body temperature; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, real-time reverse transcriptase polymerase chain reaction; CRP, c-reactive protein; β 2-MG, β 2-microglobulin; Cr, creatinine; Lym; lymphocyte.

Figure 2. Comparison of CT findings between pre- and post-treatment for COVID-19 pneumonia. In Case 1, the post-treatment chest CT revealed that GGO in bilateral lungs were increased, furthermore intra- and interlobular septal thickening region, bronchioectasis within GGO were emerged. In case 2, the chest CT images reveal bilateral small ground-glass opacities with linear shadows located dorsally in the lower lung lobes. Post-treatment chest CT revealed while a part of GGO regions were improved improvement, the linear shadow in GGO were thickened. In case 3, bilateral GGO and septal thickening region were progressed. The regions were predominantly in dorsal.

Abbreviation: CT, computed tomography; COVID-19, coronavirus disease 2019; GGO, ground-glass opacities.



