Case Report
COVID-19 pneumonia with rapid symptom improvement and conversion to negative result on PCR after administration of favipiravir (Avigan®)

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Introduction

The new coronavirus disease (COVID19), which occurred in Wuhan City, Hubei Province, China in December 2019, is spreading rapidly around the world. At present there are no proven treatments, and we must rely on quarantine, isolation, and control of infections and supportive care of patients to prevent the spread of the disease. In this report, we report a case in which administration of favipiravir (Avigan®) was considered to have resulted in rapid improvement of symptoms and a negative conversion of PCR, which was considered to help establish a future treatment method.

Case Report

[Case] 39-year-old male Japanese
[Chief complaint] fever, malaise
[Past medical history] None
[History of close contact with covid-19 patients] None
[Travel history] None
[Social history]
smoking history: none, history of alcohol intake: daily, occupational history: consulting
[Findings on admission]
Clear consciousness, body temperature 38.2℃, blood pressure 111/92mmHg, pulse 99/min, SpO_2 90% (ambient air)
[Present illness]
Fever and malaise appeared on March 11, 2020. He received a symptomatic treatment at a primary care clinic, but didn't improve. He consulted a health center and was recommended to go to our hospital. At initial consultation, the body temperature was 37.7℃, there was no respiratory distress, and SpO_2 was 96% in ambient air. Laboratory findings showed a slight increase in CRP (3.30mg/dL), a slight increase in LDH (249IU/L), and an increase in fibrinogen (635mg/dL). The leukocyte count and leukocyte fraction were normal. Influenza rapid test was negative. We performed a PCR test because COVID-19 pneumonia was suspected from imaging findings and administrated oseltamivir (75mg x 2 times / day) due to the possibility of influenza pneumonia, clarithromycin (200mg x 2 times /day) considering the possibility of atypical pneumonia and the immunomodulatory action and Symbicort®(budesonide formoterol fumarate hydrate) because we expected the symptomatic relief and the effect of inhaled steroids on COVID-19. On March 21, the result of PCR was positive and the patient was diagnosed with COVID-19 pneumonia, and was admitted to our department for treatment.

[Image findings]
Chest CT at the first outpatient visit (Fig. 1):
Bilateral and diffuse ground glass opacities with dominant lower lobes were showed and subpleural curvilinear shadow was showed in part.

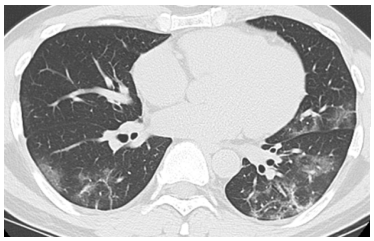

Fig. 1. Bilateral and diffuse ground glass opacities with dominant lower lobes were showed and subpleural curvilinear shadow was showed in part.

Chest X-ray on admission (Fig. 2):
Chest X-ray showed diffuse ground-glass opacities in both lung fields.

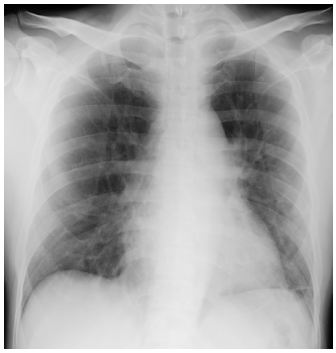

Fig. 2. Chest X-ray on admission
Chest X-ray showed diffuse ground-glass opacities in both lung fields.

[Laboratory findings on admission] (Table 1):

Biochemistry			**Hematology**		
TP	6.9	g/dL	WBC	6,300	μL
ALB	3.8	g/dL	neutrophils	76.7	%
T-Bil	0.63	mg/dL	lymphocytes	14.0	%
AST	33	IU/L	monocytes	9.0	%
ALT	23	IU/L	eosinophils	0.0	%
ALP	97	IU/L	RBC	479	$\times 10^4/\mu L$
LDH	323	IU/L	Hb	14.2	g/dL
γ-GTP	80	IU/L	Hct	40.6	%
CK	88	IU/L	Plt	26.6	$\times 10^4/\mu L$
AMY	53	mg/dL	Blood gas analysis(ambient air)		
BUN	11.9	mg/dL	pH	7.464	
Cr	0.72	mg/dL	$PaCO_2$	41.0	Torr
Na	134	mEq/L	PaO_2	74.1	Torr
K	3.8	mEq/L	HCO_3-	29.1	mmol/L
Cl	97	mEq/L	Rapid influenza diagnostic test		
GLU	103	mEq/L	A	-	
CRP	8.16	mEq/L	B	-	

Table 1. Laboratory findings on admission

LDH (323IU/L) and CRP (8.16mg/dL) were elevated, and blood gas analysis showed PaO_2 of 74.1 torr. There was no increase in white blood cell count, but the neutrophil fraction (76.7%) was elevated.

[Clinical course] (Fig. 3)

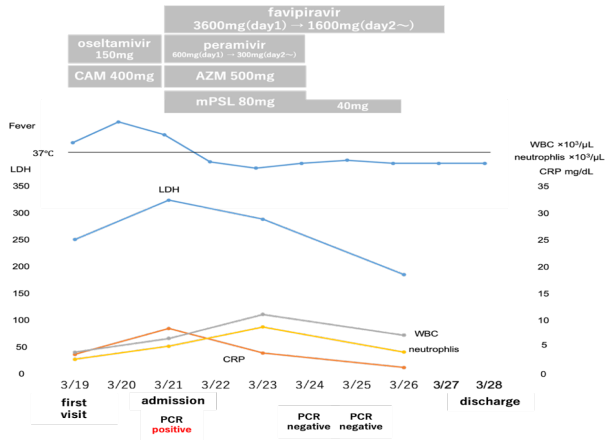

Fig. 3. Clinical course

SpO_2 (ambient air) at the first visit was 96%, but SpO_2 (ambient air) on admission showed a rapid decrease of 90%, and his respiratory symptom was markedly worse. With supportive care alone, the condition had become severe. With the consent of the patient, Favipiravir (Abigan®) was started for compassionate use (1,800mg orally on the evening of March 21st and on the morning of March 22nd, 800mg x 2 times/day from the evening of March 22nd). Intravenous (IV) methylprednisolone (80mg daily) was administrated according to steroid supplementary therapy for severe pneumonia and the guideline of the treatment for acute respiratory distress syndrome (ARDS) in 2016. Azithromycin (500mg IV daily) was started for the immunomodulatory action. Peramivir was started as an antiviral drug (600mg IV daily on the first day, 300mg IV daily from the second day). On the first day after the administration of favipiravir (Avigan®), fever was alleviated and malaise disappeared. The results of PCR were negative on the 3rd and 4th day after the administration of favipiravir (Avigan®). We administered favipiravir until the 7th day after admission (for total of six days) and discharged on the 8th day after admission. A CT scan immediately before discharge showed that ground-glass shadow was getting better but the subpleural curvilinear shadow was appeared (Figure 4). He is currently being followed up in an outpatient setting.

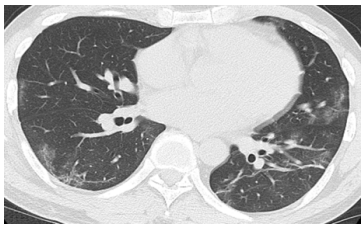

Fig. 4. A CT scan immediately before discharge

Discussion

Fabipiravir obtained manufacturing and marketing approval in March 2014 for "new or re-emerging influenza virus infections (provided that other anti-influenza virus drugs are ineffective)". The mechanism of action of this drug is that favipiravir taken up into cells is metabolized and converted by intracellular enzymes to become favipiravir ribofuranosyl triphosphate, which selectively inhibits viral RNA-dependent RNA polymerase. Therefore, it is suggested that it may also be effective against RNA viruses other than influenza virus, and it is reported in nonclinical studies that it is effective against RNA viruses from Ebola virus [1)], Arenaviridae and Bunyaviridae [2)]. In this case, favipiravir was administered to patients who were concerned about progression to ARDS. The day after administration, rapid antipyresis and improvement in hypoxemia were observed. On the third and the fourth day after the administration of favipiravir, the results of PCR were negative. In two COVID-19 patients with respiratory failure who had been treated at our hospital, the same treatments as these in this case

were performed except that favipiravir was administered and the period from the onset of respiratory failure to PCR negative were 27 and 37 days. However, in this case, the result of PCR become negative very quickly. The preliminary results of clinical studies have shown favipiravir to have promising potency in treatment of Chinese patients with SARS-CoV-2 infection and it is highly likely that favipiravir contributed to the early time until becoming negative in this case. Favipiravir might have make PCR negative early and potential to avoid ARDS. However it is necessary to accumulate further cases.

In conclusion, we administered favipiravir to a patient with rapidly progressing hypoxemia, and the symptoms were alleviated rapidly and PCR became negative early. We might considered that favipiravir was effective for COVID-19 infection.

Reference

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3) Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, *et al*. Experimental Treatment with Favipiravir for COVID- 19: An Open-Label Control Study. Engineering. 2020. In press.