Case Report

The First Case Report on Peramivir and Favipiravir for Avian Influenza A (H7N9) in Taiwan

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Novel H7N9 influenza is belong to critical illness with high mortality, which might cause severe sepsis or multiple organ failure. Extracorporeal membrane oxygenation and renal replacement therapy play important roles as life supporting systems for critical cases. Correct drug and sufficient dosage are of great importance for the emergency. We described the first case under multiple anti-viral agents (peramivir and favipiravir) for H7N9 infection in Taiwan. Severe pneumonia, respiratory failure, and acute kidney injury had been observed on this patient. Under the limited reference on dosing recommendation, clinical pharmacist proposed dosing regimen for continuous venovenous hemodiafiltration based on the pharmacokinetic parameters of separated anti-viral agents. Diminished lung infiltration and improved lung function were noted after optimal dosage application.

Key words: avian influenza A virus, H7N9, peramivir, favipiravir, continuous venovenous hemodiafiltration

Introduction

The avian influenza A (H7N9) virus was first identified in February 2013 in China, followed by outbreak and severe infection among human. Mortality rate has been more than 30%. Patients were mainly characterized by symptoms related to severe lower respiratory tract infection, including rapidly progressive pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), leading to more than 60% of institution in the intensive care unit.[1] Acute kidney injury derived from renal hypo-perfusion is associated with higher rate of critically ill influenza, and renal replacement therapy might be necessitated for patient with severe infectious condition.[2] Dosing adjustment of anti-viral drugs for influenza on severely ill population possess an important issue.

Due to the rapidly mutated characteris-

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tic of this virus, routine vaccination failed to prevent the influenza epidemic. Early treatment with anti-viral agents could lead to clinical benefits. Binding affinity between neuraminidase inhibitors (oseltamivir, zanamivir and peramivir) and H7N9 virus is associated with R292K protein. R292K mutation can destroy the combination of neuraminidase inhibitors and virus, leading to emerging drug resistance.[3] Favipiravir inhibits influenza viral RNA polymerase, and is effective against all subtypes and strains of influenza viruses which are sensitive or resistant to marketed neuraminidase and M2 inhibitors.[4] Due to lack of specific dosing recommendation on dialysis or renal replacement therapy, pharmacist provide clinical recommendation through consideration on pharmacokinetics properties of selected drug.

Case Report

The patient was a 69-year-old man with history of hypertension. He returned from the Guangdong province of mainland China without exposure to swine recently. Symptoms of fever, chills, and sore throat were observed from the patient two days before returning from China. He sought for medical service for those symptoms, novel influenza was suspected, and oseltamivir was prescribed. The patient went home under voluntary health management. He went to clinics again due to intermittent fever, severe dyspnea, and cough with massive sputum. The patient was diagnosed pneumonia, and admitted to intensive care unit (ICU) with empirical antibiotics use. Later, the patient had been shifted to negative pressure isolation room under the suspicion of novel influenza A or pneumonia with unknown source. The sputum specimen showed the first laboratory-confirmed human infection with avian influenza A (H7N9) virus from Centers for Disease Control, Taiwan (CDC). Furthermore, the full-length genomic sequences were analyzed, and found that R292K substitution in the neuraminidase proteins is resistant to oseltamivir and zanamivir.

Extracorporeal Membrane Oxygenation (ECMO) and continuous renal replacement therapy (CRRT) as continuous venovenous hemodiafiltration (CVVH) were applied on the patient due to cardiopulmonary failure and acute kidney failure (blood urea nitrogen 126 mg/dL, serum creatinine 8.2 mg/dL and urine output less than 50 mL/day) during ICU period. Peramivir has been prescribed for the patient under 16 days course (Fig. 1). Due to

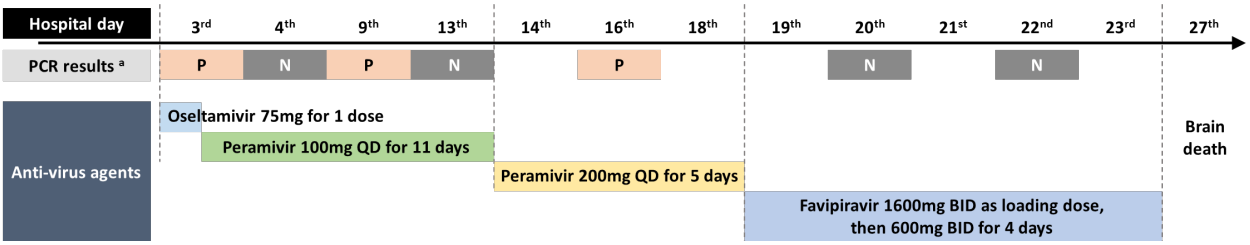

Fig. 1 Temporal relation from result of real-time PCR and anti-influenza agent application course after admission. The patient received oseltamivir 75 mg BID for 5 days course before admission. The patient was admitted for severe symptoms related to pneumonia after oseltamivir course. CDC report was available 3 days later after admission, and manifested as positive avian influenza A (H7N9) virus. Considering the critically clinical condition on the patient, CDC recommended that peramivir might be a rational alternative to oseltamivir. Persistent sputum sampling for culture was applied for efficacy evaluation on peramivir use. Treatment course should be completed after two consecutive samples showed negative. We shifted to favipiravir use tailored to the genomic sequences of the specific pathogen. Diminished viral load was observed after effective treatment had been completed. [a.] Sputum sample was applied on real-time PCR test. P indicated that the specimen collection showed avian influenza A (H7N9) positive, while N indicated negative.

the viral load from sputum specimen cannot achieve sufficient infection control under intravenous peramivir 100 mg once daily infusion, dose titration to 200 mg once daily for peramivir has been scheduled to avoid the excessive clearance from CVVH. However, left lung infiltration under high dosage of peramivir treatment was still observed on chest X-ray. Positive polymerase chain reaction (PCR) test for influenza A (H7N9) virus was also noted in sputum spcecimen. Peramivir had been shifted to oral favipiravir with different mechanism for 5 days course tailored to the results of genome report that indicated resistant virus strain. PCR

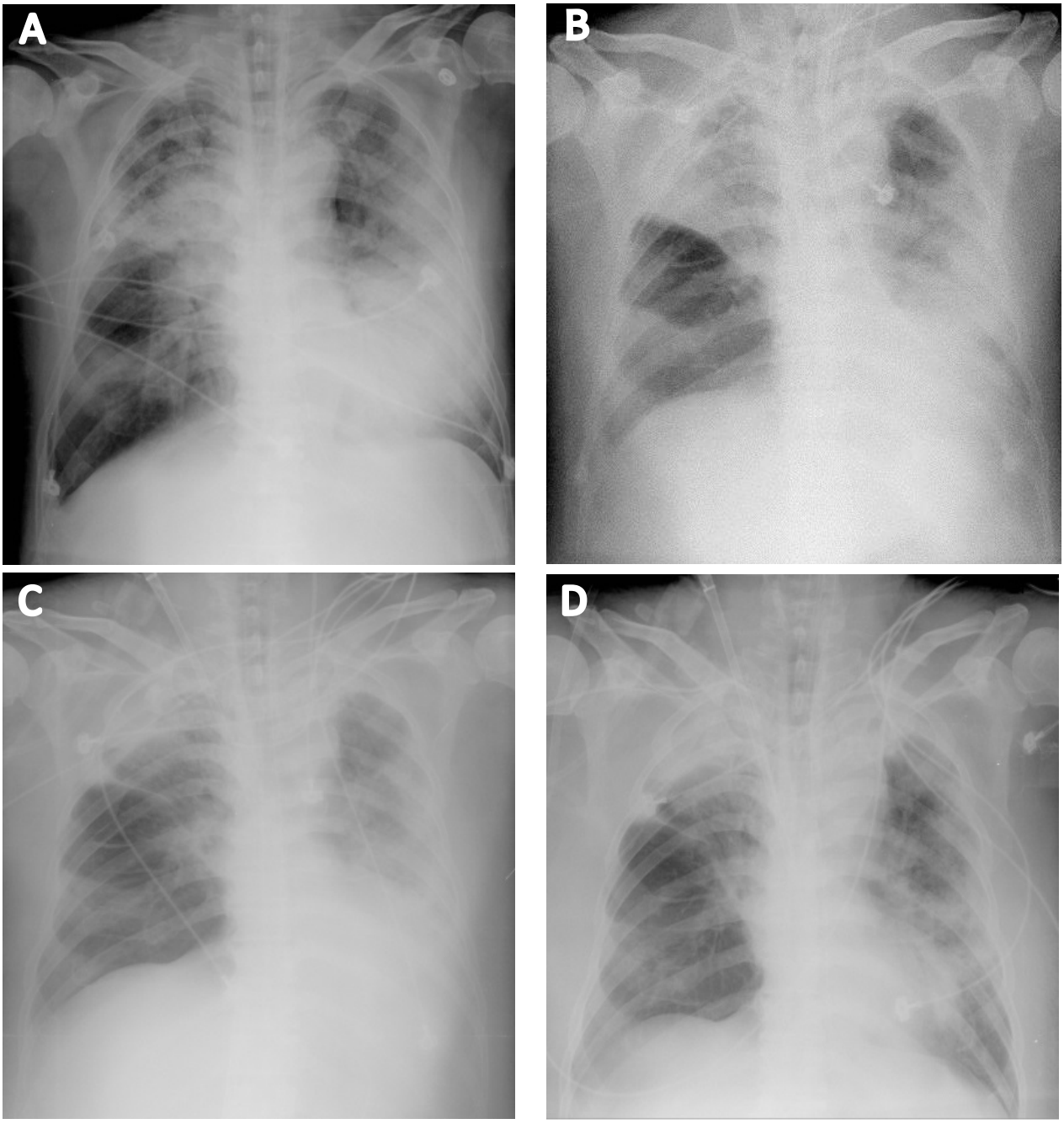

Fig. 2 Chest X-ray over the days of illness. (A) chest X-ray showed infiltration when admitted (day 3). (B) peramivir 100 mg QD (day 13). (C) peramivir 200 mg QD (day 18). Mixed infiltration and pulmonary consolidations were noted after peramivir treatment. Considering CVVH application might lead to excessive clearance of peramivir, dose titration was applied on the patient. Less infiltration was noted. (D) favipiravir (day 24). Favipiravir was prescribed for the patient under the suggestion from CDC due to resistant strain of H7N9 was isolated. Lung function has been improved after 5 days course.

Table 1. Peramivir dosing recommendations in adults with renal impairment from different references

Renal impairment	Rapiacta™ package insert	Rapivab™ package insert	UpToDate	Sanford guide	2009 H1N1 Outbreak [a, 8]
CrCl ≥ 50 mL/min	300 mg once	600 mg once	600 mg once	600 mg q24h	600 mg/day
CrCl 30 – 49 mL/min	100 mg once	200 mg once	200 mg once	200 mg q24h	150 mg/day
CrCl 10 – 29 mL/min	50 mg once	100 mg once	100 mg once	100 mg q24h	100 mg/day
CrCl < 10 mL/min, not on HD	--	--	--	100 mg x 1, then 15 mg q24h	100 mg on day 1 followed by 15 mg/day
ESRD on HD	--	Based on CrCl AD	100 mg once, AD	100 mg on day 1, then 100 mg given 2 hours after each HD session on dialysis days only	100 mg on day 1, then 100 mg given 2 hours after each HD session on dialysis days only
ESRD on CRRT		--	--	--	Based on CrCl

Abbreviations: AD = After dialysis; CrCl = Creatinine clearance; CRRT = Continuous renal replacement therapy; ESRD = End-stage renal disease; HD = Hemodialysis. [a]Duration of therapy 5 – 10 days.

test of the isolated virus shows negative during 5 days course of favipiravir confirmed by CDC. Results on chest X-ray (Fig. 2) have been showed less infiltration. Negative virus culture result and improved symptoms on pneumonia were recognized by doctor, and isolation was discontinued later. However, the patient was diagnosed brain death without any nerve reflex sign.

Discussion

Multiple organ dysfunction syndrome (MODS) can be related to underlying diseases and complication. Pharmacokinetic (PK) parameters of selected drugs exist extensive variation on critically ill patient. Furthermore, ECMO or CRRT can alter the PK as well under the process of supporting organ function. Complicated characteristics were observed between ECMO and drug, including molecular weight, proportion of protein binding, and its hydrophilicity or lipophilicity.[5]

Drugs can be removed via CVVH lies on low molecular weight ($\leq$ 2000 Da), low protein binding and limited volume of distribution ($V_d \leq 1$ L/kg). Initial loading dose should be given under the consumption that CVVH is an important source of drug clearance, followed by recommended maintenance doses should be approximately equal to a patient with a creatinine clearance (CrCl) of 30 – 50 mL⁄min.[6] Similarly, case report on peramivir use proved that this drug can be easily cleared through CVVH.[7] There is lack of recommended dosage of peramivir for CRRT patient until now, while adjust dosage by creatinine clearance was proposed.[8] Anuria was noted during CVVH, so CVVH is considered to be a major source of drug clearance.[6] Calculated creatinine clearance of CVVH is around 30 mL/min. Under the circumstance of limited information, pharmacist surmised that high-dose (600 mg/day) regimen can be the preferred choice for critically ill patient, and adjust the recommended dose for CrCl 30 – 50 mL⁄min under CVVH. 200 mg per day is the rational recommendation based on limited experience (Table 1).

To date, rare clinical experience on novel anti-viral agent favipiravir and limited researches on renal adjustment recommendation or safety outcome had been published. New drug application (NDA) review report of favipiravir submitted by manufacturer to Ministry of Health, Labour and Welfare in Japan contains information on renal dysfunction population. Considering the safety concerns of favipiravir, the report mentioned mildly elevated uric acid concentration has been observed on those with normal renal function and moderate renal dysfunction.[9] Besides, favipiravir is mainly metabolized via liver, which is associated with aldehyde oxidase and xanthine oxidase, involving the main mechanism on increased uric acid concentration.[10] Under the consideration of metabolic pathway and available safety data, we surmised there is no need of dosing adjustment. In our case, pharmacist speculated the dosage of favipiravir applied on CVVH, and discussed with infection disease specialty. Initial normal loading dosage 1600 mg BID on day 1 followed by 600 mg BID on day 2 – 5 is the final regimen used on the patient. Pharma-

Table 2. Pharmacokinetic parameters related to removing by CVVH

	Peramivir[7]	Favipiravir[9]
Molecular weight	328 Da	157 Da
Protein binding	< 30%	53.4 ~ 54.4%
V_d	12.56 L	16.73 L

Abbreviations: V_d = Volume of distribution

cokinetic parameters of peramivir and favipiravir which are related to removing by CVVH are shown in Table 2.

Lack of dosage recommendation related to safety outcome possesses great difficulty on clinical decision. Close monitoring on the disease progression is of importance, while adverse effect detection is definitely the essential part of pharmaceutical care. According to the information from package insert, common adverse effects of peramivir include diarrhea, neutropenia, proteinuria, altered liver function, and jaundice. Diarrhea, neutropenia, and altered liver dysfunction are also noted as side effects of favipiravir, while hyperuricemia is only noted on favipiravir use. Diarrhea and neutropenia were not observed in this case. However, elevated liver enzyme without jaundice was noted in the initial phase of peramivir use (Fig. 3, day 11). Liver enzyme value has been subsided under favipiravir. Although no

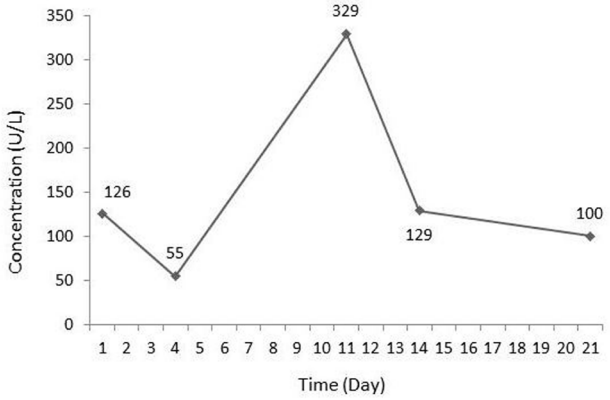

Fig. 3 Serum level of alanine aminotransferase (ALT) over the course of illness.

data on uric acid value, there is decreased risk on the uric acid accumulation due to CVVH has been applied.

This is the first experience on the patient with oseltamivir, peramivir, and favipiravir in Taiwan. Favipiravir shows significant efficacy on the viral pneumonia with resistant strains. Limited information on renal dysfunction adjustment on peramivir and favipiravir for critically ill patient with ECMO and CVVH remains big challenge on clinical care. We proposed rational dosage regimen under the consideration from pharmacokinetics parameter. However, close monitoring on adverse effects is warranted due to no safety data has been constructed.

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