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Original Article

Clinical outcomes and prognostic factors of patients with severe influenza receiving intravenous peramivir salvage therapy in intensive care units

Ching-Yuan Yeh [a], Fu-Der Wang [b,c], Yu-Chung Chuang [a], Chia-Jui Yang [d], Shiang-Fen Huang [b,c,e], Wen-Sung Weng [f], Chun-Hsin Liaw [d], Wang-Huei Sheng [a,*]

[a] *Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan*
[b] *Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[c] *School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[d] *Department of Internal Medicine, Far Eastern Memorial Hospital, Taipei, Taiwan*
[e] *Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan*
[f] *Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

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Abstract *Background:* Few studies have investigated patients with severe influenza who receive intravenous peramivir for salvage therapy.
Methods: We retrospectively analyzed data from 71 patients with severe influenza who received intravenous peramivir therapy in the intensive care units of three medical centers between 2012 and 2016. All patients received oseltamivir or zanamivir before the administration of peramivir.
Results: A total of 44 men and 27 women with a median age of 55 years were enrolled. Fifty-five (78%) had underlying comorbidities and 57 (80%) patients were infected with influenza type A. Forty-four (62%) patients survived and 27 (38%) died. Five patients (7%) had attributable adverse events, including elevated hepatic aminotransferase levels (n = 2), hyperbilirubinemia (n = 2), leukopenia (n = 1), and skin rash (n = 1). Multivariable logistic regression analysis revealed that initial bacteremia (odds ratio [OR], 27.59; 95% confidence interval [95% CI], 2.36–322.07; P = 0.008) and septic shock (OR, 8.00; 95% CI, 1.69–37.90; P = 0.009) were the independent predictors of mortality. However, there was also a trend towards a positive correlation between mortality and steroid use (OR, 11.29; 95% CI, 0.67–188.86; P = 0.092).

* Corresponding author. Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, 100, Taiwan. Fax: +886 2 23936192.
E-mail address: whsheng@ntu.edu.tw (W.-H. Sheng).

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Conclusion: As a salvage therapy, intravenous peramivir provided a survival rate of 62% and was well tolerated in patients with severe influenza. The initiation of effective antiviral treatment as early as possible within 48 h is recommended for hospitalized patients.

Introduction

Influenza is a major illness with social and economic impacts worldwide. It affects approximately 10% of the global population annually.[1] The illness is usually self-limiting. However, severe complications included pneumonia, myocarditis, encephalitis, septic shock, and death may occur. According to the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC), the influenza virus results in an estimated three to five million cases of severe illness and 250,000—500,000 deaths annually.[1,2] In 2009, the novel H1N1 virus (swine flu) caused a pandemic that spread to 214 countries and led to more than 18,000 deaths.[1,3]

Neuraminidase inhibitors (NAIs) and M2 inhibitors have been preferred for the treatment of influenza infection. However, the continuing high prevalence of M2 inhibitor resistance in influenza A virus has been reported.[4] Three NAIs are available for the treatment of patients with influenza infection, including oseltamivir, zanamivir, and peramivir. The WHO recommended oseltamivir and zanamivir for treatment during the 2009 H1N1 pandemic.[2] However, the development of oseltamivir-resistant influenza virus, including strains that carried H274Y neuraminidase mutation has been increasingly recognized.[5,6] Moreover, oseltamivir and zanamivir are oral and inhaled medications, respectively. They are not feasible for severely ill patients on ventilators or with consciousness disturbance or gut failure because of the inconvenience of administration and potential poor bioavailability. Because of its convenience of administration, peramivir, an intravenous NAI, was recommended for patients who could not tolerate enteral or inhaled medications. It also has advantages in in-vitro activity compared to zanamivir and oseltamivir.[7,8] During the 2009 H1N1 pandemic, Sugaya et al. demonstrated the efficacy and safety profile of peramivir for the treatment of critically ill pediatric patients.[8] Previous research also suggested that intravenous peramivir has a more rapid effect on fever resolution and less-affected sensitivity in resistant influenza strains compared to oseltamivir.[9] However, few studies have elucidated the efficacy of peramivir in critically ill patients with seasonal influenza infections. In the recent decade, there have been several outbreaks of emergent influenza strains in Asia, including H5N1 in Hong Kong and H7N9 in China. The rapid disease progression and potential antiviral resistance of these novel strains often result in severe complications and increased mortality. To understand the clinical effectiveness and safety of the newly released NAI, peramivir, in severe influenza patients in clinical practice, we report a 71-person case series of critically ill patients administered intravenous peramivir in Taiwan.

Methods

Patients and hospitals

This study was a retrospective chart review of hospitalized patients administered peramivir between April 2012 and March 2016 at National Taiwan University Hospital, Taipei Veterans General Hospital, and Far-East Memorial Hospital. Located in northern Taiwan, the three hospitals are referral medical centers providing both primary and tertiary medical care. Patients hospitalized in these centers with laboratory (e.g., reverse-transcription PCR or influenza rapid antigen test) confirmed influenza A or B virus infections from April 2012 to March 2016 were included in the analysis. The intravenous peramivir was supplied by the Taiwan Centers for Disease Control (CDC). According to the Taiwan CDC regulations, peramivir was offered only for the treatment of patients with severe complicated influenza who failed or could not tolerate oral or inhaled anti-influenza medications. These patients were defined as those patients with flu-like symptoms followed by severe complications within two weeks, including pulmonary, neurological, and cardiac complications or invasive bacterial infection. Thus, these patients were admitted to the intensive care unit (ICU) and had previously received oseltamivir or zanamivir before the administration of peramivir. The medical records of the influenza cases were retrospectively reviewed. Chest radiography, laboratory data, and bacterial cultures were recorded. Oral oseltamivir and inhaled zanamivir were available for treatment at all sites and prescribed by the attending physicians based on clinical judgment. Seven major complications, including respiratory failure, acute respiratory distress syndrome (ARDS), bacteremia or fungemia, septic shock, acute kidney injury, hepatic injury, and consciousness change were recorded. Data on patient characteristics (age, sex, vaccination status, body weight, and body temperature), prior anti-influenza medication (oseltamivir and zanamivir), complications, treatments, and outcomes were collected retrospectively by a well-trained study nurse and a medical doctor (Ching-Yuan Yeh). A standard case record form was used for data collection. Ethical approval for data collection was obtained from the institutional review boards of the participating sites.

Definitions

The adult patients were defined as patients who were above 18 years old upon receiving peramivir. Comorbidity was defined as the presence of one or more pre-existing, major medical conditions that are known risk factors for influenza-related complications, such as malignancy,

chronic lung disease, steroid or immunosuppressant use, pregnancy, seizure, asthma, chronic heart disease, or diabetes mellitus.[10] Pneumonia was defined as the presentations of both clinical symptoms and radiographically identified pulmonary infiltrations. Bacterial superinfection was defined as the positive culture of a bacterial pathogen at the first medical visit from a lower respiratory tract specimen (sputum suction from endotracheal tube, bronchial washing/tracheal aspirates or bronchoalveolar lavage by bronchoscopy) and/or blood cultures collected during the acute illness, excluding results from other sites (e.g. urine, stool or skin wound). The onset of symptoms to admission, duration of hospitalization, days from onset of symptoms to oseltamivir administration, days from onset of symptoms to peramivir administration, durations of oseltamivir and peramivir administration, and duration of fever between the mortality and survival groups were recorded. Defervescence was defined as the lack of a fever for more than 24 h and the date of defervescence was defined as the first day of defervescence. Blood biochemistry tests, including hemogram, serum hepatic alanine/aspartate aminotransferase, bilirubin, serum creatinine, creatinine kinase, and electrolyte levels, were recorded.

Influenza-like illness (ILI) was defined as the sudden onset of fever (38 °C) and respiratory symptoms, as well as headache, arthralgia, or myalgia. Clinicians used influenza rapid diagnostic test kits licensed in Taiwan (Quick Ex flu [Denka Seiken, Tokyo, Japan], ESPLINE Influenza A&B-N [Fujirebio, Tokyo, Japan], and Check FluAB [Alfresa Pharma, Osaka, Japan]) in patients with ILI symptoms to screen for influenza A or B. Specimens from throat swabs, nasal swabs, or nasal aspirates taken at the time of the clinic visits were submitted for virus isolation. The typing and subtyping of influenza virus isolates into A(H1N1) pdm09, A(H3N2), and type B was performed by real-time polymerase chain reaction (RT-PCR).[11]

Peramivir was administered as an intravenous infusion of 600 mg daily in hospitalized adult patients at a high risk of developing complications and 10 mg/kg in children. All dosages followed the advisories issued by the Department of Health, Taiwan.

Statistical analysis

The patients were stratified into survival and mortality groups and each variable was compared between the two groups. The means and standard deviation (SD) were calculated for continuous variables, including age, weight, duration of fever and anti-influenza medication use. Percentages were calculated for categorical variables, including gender, influenza type, comorbidities, existence of symptoms, development of organ failure, and treatment modalities. Two-sample *t* and Fisher's exact tests were used to compare continuous and categorical variables, respectively, between two groups. Multivariate logistic regression was used for outcome analysis. Multivariable models were developed by backward stepwise minimizing Akaike's information criterion (AIC).[12] After stepwise AIC selection, variables with $P < 0.05$ were considered significant; variables with $P < 0.1$ were considered borderline significant and both were retained in the final multivariate prediction model. The dose-response relationship was estimated by the generalized additive model (GAM).[13,14] The possible interactions between the variables were examined by stratification and margin analysis. The analyses were performed using Stata (version 14, StataCorp, College Station, TX). Two-sided $P < 0.05$ was considered significant.

Results

Data from a total of 71 critically ill patients from three medical centers in northern Taiwan were analyzed retrospectively. Their demographic and clinical characteristics are shown in Table 1. There were 44 (62%) male patients and 27 (38%) female patients with a mean age of 49 years (median age 55 years, ranging from 3 months to 106 years). All patients received broad-spectrum empirical antibiotics along with peramivir upon the initial suspicion of severe complicated influenza. Univariate analysis revealed that chronic lung disease ($P = 0.075$), complications with the occurrence of bacteremia ($P = 0.005$) and septic shock ($P = 0.005$), acute renal injury ($P = 0.009$), use of inotropic agents ($P = 0.010$), higher CURB-65 scores ($P = 0.010$), and bacterial superinfection ($P = 0.030$) were potential prognostic factors for mortality. After multivariate logistic regression, only influenza complicated with bacteremia (odds ratio [OR], 27.59; 95% confidence interval [95% CI], 2.36—322.07; $P = 0.008$) and septic shock (OR, 8.00; 95% CI, 1.69—37.90; $P = 0.009$) were the independent predictors of mortality. Patients with underlying chronic lung disease (OR, 6.40; 95% CI, 0.82—50.11; $P = 0.077$) and initial steroid use for influenza (OR, 11.29; 95% CI, 0.67—188.86; $P = 0.092$) were borderline significant factors for mortality.

We further analyzed the results of 57 adult patients. Univariate analysis showed that lower body weight ($P = 0.009$), complications with the occurrence of bacteremia ($P = 0.006$) and septic shock ($P = 0.019$), acute renal injury ($P = 0.021$), use of inotropic agents ($P = 0.034$), higher CURB-65 score ($P = 0.066$), bacterial superinfection ($P = 0.012$), and higher steroid dosage ($P = 0.015$) were potential prognostic factors for mortality. After multivariate logistic regression, lower body weight (OR, 0.91; 95% CI, 0.84—0.99; $P = 0.028$), complications with bacteremia (OR, 51.73; 95% CI, 1.53—1750.34; $P = 0.028$), acute renal injury (OR, 10.00; 95% CI, 1.38—72.36; $P = 0.023$), and higher steroid use (OR, 6.59; 95% CI, 1.24—35.05; $P = 0.027$) were the independent predictors of mortality. Septic shock (OR, 10.95; 95% CI, 0.95—126.97; $P = 0.056$) was a borderline significant factor for mortality (see Table 2). Overall, influenza complicated with septic shock and bacteremia were the risk factors for death among both adult and the overall study population. The use of higher steroid doses might be a potential prognostic factor for mortality.

In the GAM, mortality was associated with steroid dose (Fig. 1a). The logit of mortality increased approximately linearly with steroid dose increasing from 0 to 2 mg/kg/day equivalent of methylprednisolone. When the patient received a 1 mg/kg/day equivalent of methylprednisolone, the odds ratio for mortality was 1. With more than 2 mg/kg/

Table 1 Comparison of the demographics and clinical characteristics of all influenza patients with peramivir use according to mortality or survival.

	Total (n = 71)	Survival (n = 44)	Mortality (n = 27)	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Age	49.0 (25.7)	45.9 (25.1)	54.2 (26.3)	1.01 (0.99–1.03)	0.192		
Male	44 (62.0)	27 (61.4)	17 (63.0)	1.07 (0.40–2.88)	0.893		
Body weight (Kg)	58.4 (24.2)	60.5 (26.6)	55.1 (19.7)	0.99 (0.97–1.01)	0.364		
Influenza type A	57 (80.3)	37 (84.1)	20 (74.1)	0.54 (0.17–1.76)	0.307		
ACIP comorbidity[a]	55 (77.5)	32 (72.7)	23 (85.2)	2.16 (0.62–7.54)	0.229		
Chronic lung disease	7 (9.9)	2 (4.5)	5 (18.5)	4.77 (0.86–26.63)	0.075	6.40 (0.82–50.11)	0.077
Cancer	11 (15.5)	7 (15.9)	4 (14.8)	0.92 (0.24–3.49)	0.902		
Steroid or immunosuppressant	9 (12.7)	4 (9.1)	5 (18.5)	2.27 (0.55–9.35)	0.255		
Pregnancy	2 (2.8)	2 (4.5)	0 (0)	N.A.			
Seizure	4 (5.6)	3 (6.8)	1 (3.7)	0.53 (0.05–5.33)	0.586		
Asthma	6 (8.5)	4 (9.1)	2 (7.4)	0.80 (0.13–4.69)	0.805		
Chronic heart disease	17 (23.9)	10 (22.7)	7 (25.9)	1.19 (0.39–3.62)	0.759		
Diabetes mellitus	27 (38.0)	17 (38.6)	10 (37.0)	0.93 (0.35–2.51)	0.893		
URI symptoms signs	43 (60.6)	27 (61.4)	16 (59.3)	0.92 (0.34–2.44)	0.860		
Productive cough	52 (73.2)	33 (75.0)	19 (70.4)	0.79 (0.27–2.31)	0.669		
Fever	64 (90.1)	41 (93.2)	23 (85.2)	0.42 (0.09–2.05)	0.283		
Dyspnea	61 (85.9)	38 (86.4)	23 (85.2)	0.91 (0.23–3.56)	0.890		
Respiratory failure	67 (94.4)	41 (93.2)	26 (96.3)	1.90 (0.19–19.28)	0.586		
ARDS	45 (63.4)	26 (59.1)	19 (70.4)	1.64 (0.59–4.57)	0.340		
ECMO	31 (43.7)	17 (38.6)	14 (51.9)	1.71 (0.65–4.51)	0.277		
Bacteremia	10 (14.1)	1 (2.3)	9 (33.3)	21.50 (2.53–182.37)	0.005	27.59 (2.36–322.07)	0.008
Shock	48 (67.6)	24 (54.5)	24 (88.9)	6.67 (1.75–25.43)	0.005	8.00 (1.69–37.90)	0.009
Inotropes use	52 (73.2)	27 (61.4)	25 (92.6)	7.87 (1.65–37.56)	0.010		
Acute kidney injury	28 (39.4)	12 (27.3)	16 (59.3)	3.88 (1.41–10.70)	0.009		
CVVH	17 (23.9)	8 (18.2)	9 (33.3)	2.25 (0.74–6.81)	0.151		
Hepatic injury	14 (19.7)	8 (18.2)	6 (22.2)	1.29 (0.39–4.21)	0.678		
Consciousness change	44 (62.0)	28 (63.6)	16 (59.3)	0.83 (0.31–2.22)	0.712		
CURB-65 score	2.7 (1.0)	2.5 (1.0)	3.1 (1.0)	2.01 (1.18–3.43)	0.010		
TPN	12 (16.9)	7 (15.9)	5 (18.5)	1.20 (0.34–4.25)	0.776		
Bacterial superinfection	14 (19.7)	5 (11.4)	9 (33.3)	3.90 (1.14–13.31)	0.030		
Steroid use	63 (88.7)	37 (84.1)	26 (96.3)	4.92 (0.57–42.42)	0.147	11.29 (0.67–188.86)	0.092
Time to steroid[b]	9.8 (6.6)	10.2 (6.1)	9.3 (7.3)	0.98 (0.90–1.06)	0.574		
Steroid dose (mg/kg)[c]	2.5 (5.1)	2.3 (4.8)	2.9 (5.6)	1.03 (0.94–1.12)	0.590		
Antibiotic use	71 (100)	44 (100)	27 (100)	N.A.			
IVIG	3 (4.2)	2 (4.5)	1 (3.7)	0.81 (0.07–9.36)	0.864		
CXR no infiltrate	2 (2.8)	1 (2.3)	1 (3.7)				
Unilateral infiltrate[d]	7 (9.9)	4 (9.1)	3 (11.1)	0.75 (0.03–17.51)	0.858		
Bilateral infiltrate[e]	62 (87.3)	39 (88.6)	23 (85.2)	0.59 (0.04–9.89)	0.714		
Time to oseltamivir[f]	4.6 (3.0)	4.5 (2.9)	4.7 (3.3)	1.03 (0.88–1.21)	0.721		
Time to peramivir[g]	8.6 (5.5)	8.0 (4.3)	9.5 (7.0)	1.05 (0.96–1.15)	0.281		

URI = upper respiratory infection; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; CVVH = continuous venous venous hemofiltration; CURB-65 = TPN = total parenteral nutrition; IVIG = intravenous immunoglobulin; CXR = chest X-ray; N.A. = not applicable.
Area under ROC: 0.8169, R2: 0.465.

[a] ACIP comorbidity is the comorbid condition of patients with high risk for influenza complication from recommendation of the Advisory Committee on Immunization Practices.

[b] Time to steroid is the time from first symptom onset to first dose of steroid.

[c] Steroid dose(mg/kg) indicates the maximal methylprednisolone-equivalent dose of steroid administered during hospitalization.

[d] Unilateral infiltration on chest radiograph.

[e] Bilateral infiltration from chest radiograph.

[f] Time to steroid is the time from first symptom onset to first dose of oseltamivir.

[g] Time to steroid is the time from first symptom onset to first dose of peramivir.

Table 2 Comparison of the demographics and clinical characteristics of adult influenza patients with peramivir use according to mortality or survival.

	Total (n = 57)	Survival (n = 34)	Mortality (n = 23)	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
Age	59.8 (14.9)	57.9 (12.8)	62.7 (17.4)	1.02 (0.99—1.06)	0.241		
Male	37 (64.9)	22 (64.7)	15 (65.2)	1.02 (0.34—3.10)	0.968		
Body weight (Kg)	68.2 (14.5)	72.6 (14.8)	61.7 (11.6)	0.94 (0.89—0.98)	0.009	0.91 (0.84—0.99)	0.028
Influenza type A	48 (0.84)	30 (88.2)	18 (78.3)	0.48 (0.11—2.02)	0.317		
ACIP comorbidity[a]	46 (80.7)	26 (76.5)	20 (87.0)	2.05 (0.48—8.74)	0.331		
Chronic lung disease	6 (10.5)	2 (5.9)	4 (17.4)	3.37 (0.56—20.17)	0.184		
Cancer	11 (19.3)	7 (20.6)	4 (17.4)	0.81 (0.21—3.17)	0.764		
Steroid or immunosuppressant	8 (14.0)	3 (8.8)	5 (21.7)	2.87 (0.61—13.45)	0.181		
Pregnancy	2(3.5)	2 (5.9)	0 (0)	N.A.			
Seizure	1 (1.8)	1 (2.9)	0 (0)	N.A.			
Asthma	4 (7.0)	3 (8.8)	1 (4.4)	0.47 (0.05—4.82)	0.525		
Chronic heart disease	15 (26.3)	9 (26.5)	6 (26.1)	0.98 (0.29—3.26)	0.974		
Diabetes mellitus	27 (47.4)	17 (50)	10 (43.5)	0.77 (0.27—2.23)	0.629		
URI symptoms signs	37 (64.9)	23 (67.6)	14 (60.9)	0.74 (0.25—2.24)	0.599		
Productive cough	43 (75.4)	28 (82.4)	15 (65.2)	0.40 (0.12—1.38)	0.146		
Fever	50 (87.7)	31 (91.2)	19 (82.6)	0.46 (0.09—2.28)	0.342		
Dyspnea	51 (89.5)	31 (91.2)	20 (87.0)	0.65 (0.12—3.52)	0.613		
Respiratory failure	56 (98.2)	33 (97.1)	23 (100)	N.A.			
ARDS	39 (68.4)	22 (64.7)	17 (73.9)	1.55 (0.48—4.96)	0.465		
ECMO	25 (43.9)	13 (38.2)	12 (52.2)	1.76 (0.25—1.09)	0.300		
Bacteremia	10 (17.5)	1 (2.9)	9 (39.1)	21.21 (2.45—183.67)	0.006	51.73 (1.53—1750.34)	0.028
Shock	39 (68.4)	19 (55.9)	20 (87.0)	5.26 (1.31—21.12)	0.019	10.95 (0.95—126.97)	0.056
Inotropes use	43 (75.4)	22 (64.7)	21 (91.3)	5.72 (1.14—28.71)	0.034		
Acute kidney injury	24 (42.1)	10 (29.4)	14 (60.9)	3.73 (1.22—11.40)	0.021	10.00 (1.38—72.36)	0.023
CVVH	16 (28.1)	7 (20.6)	9 (39.1)	2.48 (0.76—8.07)	0.131		
Hepatic injury	14 (24.6)	8 (23.5)	6 (26.1)	1.14 (0.34—3.89)	0.826		
Consciousness change	37 (64.9)	24 (70.6)	13 (56.5)	0.54 (0.18—1.64)	0.277		
CURB-65 score	2.9 (1.0)	2.7 (0.9)	3.2 (1.0)	1.74 (0.96—3.13)	0.066		
TPN	6 (10.5)	3 (8.8)	3 (13.0)	1.55 (0.28—8.45)	0.613		
Bacterial superinfection	10 (17.5)	2 (5.9)	8 (34.8)	8.53 (1.61—45.17)	0.012		
Steroid use	52 (91.2)	29 (85.3)	23 (100)	N.A.			
Time to steroid[b]	10.1 (6.7)	10.0 (6.3)	10.1 (7.4)	1.00 (0.92—1.09)	0.959		
Steroid dose (mg/kg)[c]	1.2 (1.0)	0.9 (0.6)	1.6 (1.2)	3.18 (1.25—8.10)	0.015	6.59 (1.24—35.05)	0.027
Antibiotics use	57 (100)	34 (100)	23 (100)	N.A.			
IVIG	0(0)	0 (0)	0 (0)	N.A.			
CXR no infiltrate	1 (1.8)	0 (0)	1 (4.3)				
Unilateral infiltrate[d]	3 (5.3)	2 (5.9)	1 (4.3)	0.76 (0.06—8.94)	0.829		
Bilateral infiltrate[e]	53 (93.0)	32 (94.1)	21 (91.3)	N.A.			
Time to oseltamivir[f]	5.1 (2.9)	5.1 (2.8)	5.2 (3.2)	1.01 (0.84—1.21)	0.913		
Time to peramivir[g]	9.3 (5.8)	8.6 (4.4)	10.4 (7.2)	1.06 (0.96—1.17)	0.258		

URI = upper respiratory infection; ARDS = acute respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; CVVH = continuous venous venous hemofiltration; TPN = total parenteral nutrition; IVIG = intravenous immunoglobulin; CXR = chest X-ray; N.A. = not applicable.

Area under ROC: 0.9169, R2: 0.660.

[a] ACIP comorbidity is the comorbid condition of patients with high risk for influenza complication from recommendation of the Advisory Committee on Immunization Practices.

[b] Time to steroid is the time from first symptom onset to first dose of steroid.

[c] Steroid dose(mg/kg) indicates the maximal methylprednisolone-equivalent dose of steroid administered during hospitalization.

[d] Unilateral infiltration on chest radiograph.

[e] Bilateral infiltration from chest radiograph.

[f] Time to steroid is the time from first symptom onset to first dose of oseltamivir.

[g] Time to steroid is the time from first symptom onset to first dose of peramivir.

day equivalent dose of methylprednisolone, the logit of mortality remained consistently around 2. The GAM also revealed a negative association between mortality and body weight (Fig. 1b).

Investigation of the interaction between risk factors revealed an interaction between steroid use and shock or bacteremia. Among patients with bacteremia, all those administered steroids (9 patients) died, while the non-steroid user (1 patient) survived, which indicates the possible harmful effect of steroid use in bacteremia patients. In patients without septic shock, steroid dose was not significantly correlated with mortality. However, in shock patients, there was a dose-dependent relationship between mortality and steroid use, which reached a risk plateau (>80%) at doses above 2 mg/kg/day equivalent of methylprednisolone (Fig. 2).

Five patients (7.0%) experienced attributable adverse events, including elevated liver aminotransferase level (n = 2), hyperbilirubinemia (n = 2), leukopenia (n = 1), and skin rash (n = 1). All the adverse events were mild and improved after discontinuation of intravenous peramivir. There were no differences in the incidence of adverse events between the mortality and survival groups.

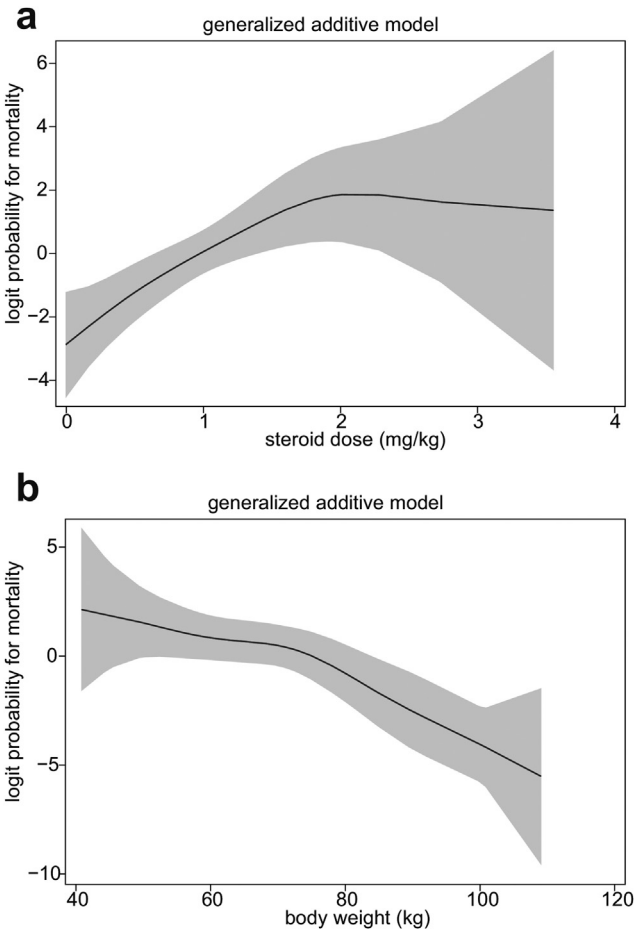

Figure 1. (a) Generalized additive model analysis of the relationship between steroid dose and the probability for mortality. Data are presented as the fitted regression (line) and 95% confidence interval (gray area). (b) Generalized additive model analysis of the relationship between body weight and the probability for mortality. Data are presented as the fitted regression (line) and 95% confidence interval (gray area).

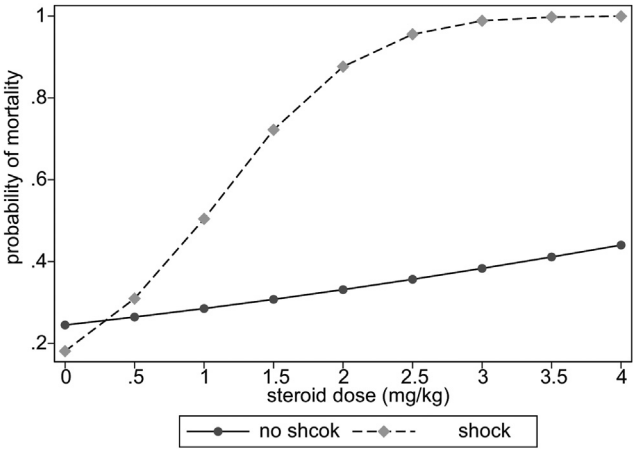

Figure 2. Interaction analysis between shock status and steroid dose.

Discussion

Our study presented a relatively large case series of 71 critically ill patients receiving intravenous peramivir as a salvage therapy for severe influenza, with a 38% mortality rate and 7% adverse events. Our results revealed the efficacy and tolerance of peramivir use in patients with severe influenza.

The most significant predictors of mortality in this study were the initial presentation of bacteremia and shock as influenza-associated complications. Furthermore, patients with bacteremia had a 90% mortality rate. Use of vasopressors and comorbidity with chronic lung disease were also important indicators, although they were not significant in multiple regression analysis. These results are similar to those of previous studies.[15–18] Leung et al. reported that 50% of adult patients with the complication of bacteremia died eventually, indicating that bacteremia is a poor prognostic factor for influenza patients.[18] In the 2012 case series reported by Louie et al. presented, patients with acute renal failure that required hemodialysis were more likely to die.[17] In the 2015 retrospective study by Yoo et al., multivariate logistic regression revealed that only age was a significant predictor of 28-day mortality, while male gender, use of peramivir, and use of corticosteroids were also possible risk factors in NAI-treated patients.[16] However, the population sizes of these studies were small.

In our study, steroid use was tentatively associated with increased mortality in patients with severe influenza. This result is compatible those of previous studies.[19,20] In a retrospective analysis of 86 patients, Huang et al. observed that the initiation of corticosteroid therapy within 72 h of antiviral therapy was associated with poor prognosis.[20] In a meta-analysis, Rodrigo et al. concluded that initial corticosteroid use for severe influenza patients was related to increased mortality.[19] Moreover, our analysis demonstrated that the steroid dose was positively associated with

mortality. There are two possible explanations for this phenomenon. First, steroid suppresses human immunity and may cause influenza virus flare-up. However, the second explanation suggests that patients with poorer condition might require higher doses of steroids. Further research is needed to clarify this phenomenon.

Differences in clinical characteristics between adults and children were also observed. In our study, the mortality rates in adults and children were 40.4% and 28.5%, respectively. In general, adults had increased risk for complications than children, especially bacteremia (17.5% vs. 0%) and hepatic injury (24.5% vs. 0%). The only exception was simultaneous bacterial superinfection (17.5% vs. 28%), most of which could be attributed to superimposed bacterial pneumonia. The results are in agreement with research on hospitalized influenza patients in Taiwan by Leung et al.[18] In addition, our study failed to identify any risk factor for mortality in children patients, while a previous report by Ma et al. reported digestive tract disease, seizure, and consciousness change to be risk factors for severe influenza.[21] The most likely explanation for this difference is the small size of the pediatric population in our study.

The recommendations of the CDC in the USA suggest NAI administration within 48 h after symptom onset in patients not at high risk for complications.[4] Some studies suggest that antiviral treatment might still be beneficial in hospitalized patients when started up to 4 or 5 days after illness onset.[22,23] Critically ill patients with respiratory failure can have prolonged influenza viral replication in the lower respiratory tract. Antiviral treatment of pregnant women (during any trimester) with influenza A (2009 H1N1) virus infection was shown to be most beneficial in preventing respiratory failure and death when started within less than three days of illness onset, but still provided benefit when started 3—4 days after onset compared to five or more days.[24] For patients who are hospitalized, severely ill, or at high risk for complications, administration of NAIs could be considered as long as five days after symptom onset. Louie et al. also reported that treatment initiated within five days from symptom onset was associated with improved survival compared to those who did not receive treatment.[17] In our study, 10 (40%) patients initiated oseltamivir after five days from their symptom onset. The duration from their symptom onset to oseltamivir exposure was not significantly different between patients those who died and those who survived. Without the delay of treatment, the mortality rate might be lower. The reason for delayed treatment was not understood but might be associated with delayed medical visits by patients, lack of physician suspicion because of initial atypical presentations, and lack of initial laboratory confirmation for influenza.

Two of the 71 patients report possible adverse events associated with peramivir use. Five patients had attributable adverse events, including leukopenia, hyperbilirubinemia, skin rash, and acute hepatitis. All patients were concurrently administered antimicrobial agents and had an unstable hemodynamic status. Although the clinical conditions are complex in critically-ill patients, we could not exclude the possibility of adverse events associated with peramivir use. The incidence of these events associated with peramivir use in our study (7%) was lower than in other reports.[15—17]

Our study had several limitations. First, due to regulations regarding peramivir supply, peramivir was only provided to patients who failed or could not tolerate oral or inhaled anti-influenza medications. Patients were unlikely to receive peramivir as an initial therapy as the guidelines recommend. This fact alone makes the evaluation of efficacy of peramivir difficult, and previous exposures to oseltamivir and zanamivir could also contribute to treatment outcomes. Second, the government regulation of peramivir use also hindered us from selecting a comparable control group, since those patients who did not require peramivir as a salvage therapy were likely to be less ill. The retrospective, uncontrolled nature of the study design makes evaluation of efficacy difficult. Third, although our data were collected from three large hospitals, the limited usage of peramivir due to government regulations in Taiwan confined the population size of our study.

In conclusion, our study showed a 62% survival rate in critically ill patients who received peramivir as a salvage therapy after oseltamivir administration. The major risk factors for death included simultaneous bacteremia complications, septic shock, and initial use of steroids. Initiation of effective antiviral treatment as early as possible within 48 h is recommended for hospitalized patients. Further large prospective studies are necessary to evaluate the safety and efficacy of peramivir.

References

1. Centers for Disease Control and Prevention. People at high risk of developing flu-related complications. www.cdc.gov/flu/index.htm. [Accessed 7 January 2016].
2. World Health Organization. Fact sheet on influenza. www.who.int/mediacentre/factsheets/fs211/en/index.html. [Accessed 7 January 2016].
3. Shrestha SS, Swerdlow DL, Borse RH, Prabhu VS, Finelli L, Atkins CY. Estimating the burden of 2009 pandemic influenza A (H1N1) in the United States (April 2009—April 2010). *Clin Infect Dis* 2011;**52**:S75—82.
4. Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. [Accessed 7 January 2016].
5. Hurt AC, Ernest J, Deng YM, Iannello P, Besselaar TG, Birch C, et al. Emergence and spread of oseltamivir-resistant A(H1N1) influenza viruses in Oceania, South East Asia and South Africa. *Antivir Res* 2009;**83**:90—3.
6. Dharan NJ, Gubareva LV, Klimov AI, Fiore AE, Bresee JS, Fry AM. Antiviral treatment of patients with oseltamivir-resistant and oseltamivir-susceptible seasonal influenza A (H1N1) infection during the 2007—2008 influenza season in the United States. *Clin Infect Dis* 2010;**50**:621—2.
7. Yoshino Y, Seo K, Koga I, Kitazawa T, Ota Y. Clinical efficacy of peramivir in adult patients with seasonal influenza during the winter of 2012 in Japan. *Clin Respir J* 2015;**9**:229—32.
8. Sugaya N, Kohno S, Ishibashi T, Wajima T, Takahashi T. Efficacy, safety, and pharmacokinetics of intravenous peramivir in children with 2009 pandemic H1N1 influenza A virus infection. *Antimicrob Agents Chemother* 2012;**56**:369—77.
9. Kohno S, Yen MY, Cheong HJ, Hirotsu N, Ishida T, Kadota J, et al. Phase III randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection. *Antimicrob Agents Chemother* 2011;**55**:5267—76.

10. Lee N, Chan PK, Lui GC, Wong BC, Sin WW, Choi KW, et al. Complications and outcomes of pandemic 2009 influenza A (H1N1) virus infection in hospitalized adults: how do they differ from those in seasonal influenza? *J Infect Dis* 2011;**203**:1739—47.
11. Nakauchi M, Yasui Y, Miyoshi T, Minagawa H, Tanaka T, Tashiro M, et al. One-step real-time reverse transcription-PCR assays for detecting and subtyping pandemic influenza A/H1N1 2009, seasonal influenza A/H1N1, and seasonal influenza A/H3N2 viruses. *J Virol Methods* 2011;**171**:156—62.
12. Bozdogan H. Model selection and Akaike's Information Criterion (AIC): the general theory and its analytical extensions. *Psychometrika* 1987;**52**:345—70.
13. Hastie T, Tibshirani R. Generalized additive models for medical research. *Stat Methods Med Res* 1995;**4**:187—96.
14. Nygard O, Nordrehaug JE, Refsum H, Ueland PM, Farstad M, Vollset SE. Plasma homocysteine levels and mortality in patients with coronary artery disease. *N Engl J Med* 1997;**337**:230—6.
15. Sorbello A, Jones SC, Carter W, Struble K, Boucher R, Truffa M, et al. Emergency use authorization for intravenous peramivir: evaluation of safety in the treatment of hospitalized patients infected with 2009 H1N1 influenza A virus. *Clin Infect Dis* 2012;**55**:1—7.
16. Yoo JW, Choi SH, Huh JW, Lim CM, Koh Y, Hong SB. Peramivir is as effective as oral oseltamivir in the treatment of severe seasonal influenza. *J Med Virol* 2015;**87**:1649—55.
17. Louie JK, Yang S, Yen C, Acosta M, Schechter R, Uyeki TM. Use of intravenous peramivir for treatment of severe influenza A(H1N1)pdm09. *PLoS One* 2012;**7**:e40261.
18. Leung CH, Tseng HK, Wang WS, Chiang HT, Wu AYJ, Liu CP. Clinical characteristics of children and adults hospitalized for influenza virus infection. *J Microbiol Immunol Infect* 2014;**47**:518—25.
19. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam JS, Lim WS. Effect of corticosteroid therapy on influenza-related mortality: a systematic review and meta-analysis. *J Infect Dis* 2015;**212**:183—94.
20. Huang SF, Fung CP, Perng DW, Wang FD. Effect of corticosteroid and neuraminidase inhibitor on survival in patients with respiratory distress induced by influenza virus. *J Microbiol Immunol Infect* 2017;**50**:586—94.
21. Ma HY, Wu JL, Lu CY, Chen JM, Lee PI, Chang LY, et al. Risk factors associated with severe influenza virus infections in hospitalized children during the 2013 to 2014 season. *J Microbiol Immunol Infect* 2016;**49**:387—93.
22. Louie JK, Yang S, Acosta M, Yen C, Samuel MC, Schechter R, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. *Clin Infect Dis* 2012;**55**(9):1198—204.
23. Yu H, Feng Z, Uyeki TM, Liao Q, Zhou L, Feng L, et al. Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China. *Clin Infect Dis* 2011;**52**:457—65.
24. Siston AM, Rasmussen SA, Honein MA, Fry AM, Seib K, Callaghan WM, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA* 2010;**303**:1517—25.