Journal of Microbiology, Immunology and Infection (2017) 50, 586–594

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Effects of corticosteroid and neuraminidase inhibitors on survival in patients with respiratory distress induced by influenza virus

Shiang-Fen Huang [a,b,c], Chang-Phone Fung [a], Diahn-Warng Perng [d], Fu-Der Wang [a,b,*]

[a] *Division of Infectious Disease, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[b] *School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[c] *Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan*
[d] *Department of Chest Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*

Received 14 May 2015; received in revised form 20 August 2015; accepted 25 August 2015
Available online 9 September 2015

KEYWORDS
corticosteroid;
H1N1;
influenza;
oseltamivir;
peramivir

Abstract *Background/Purpose:* Neuraminidase inhibitors (NAIs) including oseltamivir and peramivir are used for influenza treatment. A systemic corticosteroid is usually administrated for acute respiratory distress syndrome. The aim of this study was to investigate the effect of a systemic corticosteroid and its interaction with NAIs in patients with influenza infection and respiratory distress.
Methods: A retrospective survey of hospitalized patients infected with influenza from January 2012 to May 2014 was conducted in a medical center in Taiwan.
Results: Eighty-six patients were hospitalized during the study period. Forty-eight patients had respiratory distress and 39 of them (81.3%, 39/48) were supported by a mechanical ventilator. All patients with respiratory distress received oseltamivir; 60.4% (29/48) and 31.3% (15/48) of them received a corticosteroid and salvage intravenous peramivir, respectively. All-cause mortality was 29.1% (14/48), 20% (3/15), and 31% (9/29) in patients with respiratory distress, patients who received salvage peramivir, and patients who received a systemic corticosteroid, respectively. Salvage peramivir seemed to improve prognosis in patients with H1pdm09 or type B virus infection and respiratory distress ($p = 0.05$). Early initiating corticosteroid had a worse prognosis than initiation after 72 hours of NAI treatment ($p = 0.024$). In particular, a systemic

* Corresponding author. Division of Infectious Disease, Department of Medicine, Taipei Veterans General Hospital, Number 201, Section 2, Shih-Pai Road, Taipei, Taiwan.
E-mail address: fdwang@vghtpe.gov.tw (F.-D. Wang).

http://dx.doi.org/10.1016/j.jmii.2015.08.016

corticosteroid seemed to lead to a shorter survival time in patients with chronic lung disease ($p = 0.05$).
Conclusion: Salvage peramivir provided a better prognosis than monotherapy with oseltamivir in patients who were infected with H1pdm09 or type B virus and who developed respiratory distress. A systemic corticosteroid should be administered after initiating NAI therapy, especially in patients with chronic lung disease.

Introduction

The pandemic H1pdm09 virus spread in 2009 and has been prevalent since 2011. Clinical trials investigating the early use of multidose intravenous peramivir against seasonal influenza including H1N1, H3N2, and type B viruses showed similar outcomes to daily oseltamivir.[1,2] Intravenous peramivir was shown to be effective for the influenza virus infection with the H275Y mutant strain.[3] Emergency use of peramivir has been authorized in the USA since 2009[4] according to the high morbidities and morbidities related to H1N1 (2009) infection. After 2009, only a few reports on the treatment outcomes of peramivir against H1N1pdm09-related infection have been published,[1,5–7] and recent data regarding the clinical outcomes of salvage peramivir for influenza infection with respiratory distress is lacking.

Meanwhile, the benefits of medium-to-high doses of corticosteroid in patients with influenza virus infection and acute respiratory distress syndrome remain controversial.[8] Despite the facts that a corticosteroid is not recommended by some guidelines,[9] it remains standard treatment for physicians working in critical care units to treat acute respiratory distress syndrome[10] after influenza infection.

The newly emerged mutant H275Y strain has been detected in Taiwan,[11] and the use of peramivir was authorized by the Center of Disease and Infection of Taiwan in late 2013 for patients with severe illness who do not respond to oseltamivir. In this study, we aimed to investigate retrospectively clinical outcomes among patients hospitalized with influenza virus infection from 2012 to 2014 in northern Taiwan, and to assess the interaction between two types of neuraminidase inhibitors (NAIs) and administration of a systemic corticosteroid.

Methods

Patients

Patients with laboratory confirmed influenza virus infection from January 1, 2012 to May 31, 2014 in Taipei Veterans General Hospital, Taipei, Taiwan were assessed retrospectively by chart review. Only patients who were older than 18 years and hospitalized were included. Patients with hospital acquired influenza virus infection and contact history were excluded. Clinical characteristics, comorbidities, chest radiography results, laboratory results, and clinical outcome were recorded.

Laboratory confirmation of influenza virus

Confirmation of influenza infection was performed by using a rapid influenza antigen test (Directigen EZ Flu A+B test; BD, Franklin Lakes, NJ, USA) or real-time reverse-transcription polymerase chain reaction (RT-PCR). The primers and Taqman probes used for RT-PCR were those reported in the standard protocol of the Center of Disease Control of Taiwan, which was modified from that of the World Health Organization.[11–13] This protocol includes primers for the matrix gene of influenza A and B viruses, as well as the hemagglutinin gene of influenza A viruses (seasonal H1, H1pdm09, and H3 primers). If the presence of influenza A virus was detected, a further genotype was identified according to the RT-PCR results, i.e., seasonal H1, H1pdm09, or H3; otherwise, unidentified influenza A was recorded.

Medical treatment

The antiviral treatments were according to the manufacturer's guidance: 5 mg of zanamivir powder was inhaled twice daily for 5 days, or 75 mg of oral oseltamivir was given daily for 5 days. Intravenous peramivir was prescribed as 300–600 mg (adjusted by creatinine clearance rate) per 12 hours for at least 3 days, and extended to 5–10 days if clinical symptoms were not completely resolved. Medium-to-high dose corticosteroid was defined as systemic administration of a dose $\geq$ 0.5–2 mg/kg/d.

Clinical manifestations and outcomes

Respiratory distress was defined as desaturation with a ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2) of $<$ 200 mmHg or an oxygen saturation (SaO_2) $<$ 90% with a $FiO_2 >$ 50%. The incidence of organ dysfunction including shock, hematological abnormality (white blood cell count of $>$10,000 cells/mm^3 or $<$ 4000 cells/mm^3, or thrombocytopenia of $<$ 8000 cells/mm^3), respiratory distress, acute disturbance of consciousness levels, acute renal distress with renal replacement therapy, and hepatic failure with decomposition was recorded. The metabolic syndrome was defined according to the World Health Organization[14] and included type 2 diabetes, hyperlipidemia or hypercholesterolemia, cardiovascular disease (including hypertension), and obesity (body mass index $>$ 30 kg/cm^2). Late onset superinfection and colonization were defined as laboratory evidence of

positive conversion of pathogenic bacteria from endotracheal aspiration or sputum with adequate sampling, or by the presence of laboratory evidence from a sterile site (e.g., blood culture) after 72 hours of hospitalization.

Statistical analysis

Continuous data were compared with the Student *t* test or a nonparametric test if they were not normally distributed. Categorical results were compared with the Pearson Chi-square test or Fisher's exact test if the excepted number was < 5. Odds ratios with 95% confidence intervals (95% CIs) were obtained. Survival analysis was performed using the Kaplan–Meier method and nonparametric tests were used to analyze differences. A p value < 0.05 was defined as significant.

Ethics statement

The informed consent was waved in this retrospective study by approval from the Ethics Committee of Taipei Veterans General Hospital (VGHIRB No:2014-05-001BC).

Results

Genotypes

Eighty-six hospitalized patients older than 18 years were enrolled. The influenza viral genotypes are demonstrated in Table 1. Type A viruses were predominant (91.8%, 79/86) during the study period. Furthermore, 30.2% of patients had the type A H1pdm09 strain, and 29.1% of patients had both seasonal H1 and H1pdm09 from 2012 to 2014.

Patient characteristics

The clinical characteristics of the study participants are demonstrated in Table 2. In the 86 hospitalized patients, the mean age was 65.9 years (standard deviation: 19.2 years), and more patients were male (65%, 56/86). With regards to comorbidities, 25.6% of patients had chronic lung disease, 30.2% had congestive heart failure, 23.3% had cardiovascular disease, and 43.0% had diabetes.

Clinical manifestations

Virology results showed that 64.6% of the patients with respiratory distress were infected with H1pdm09. Clinically, more than half of the patients (55.8%, 48/86) suffered from respiratory distress; 81.3% (39/48) of these patients were supported by mechanical ventilation. The second most frequent clinical manifestation was acute kidney injury (52.3%, 45/86), followed by shock (34.9%, 30/86), gastrointestinal bleeding (30.2%, 26/86), and acute myocardial infarction (9%, 8/86).

Acute kidney injury (64.6%), shock (58.3%), and the requirement for hemodialysis (20.8%) developed more frequently in patients with respiratory distress than in patients without respiratory distress ($p < 0.05$). A total of 20% of the patients were supported with extracorporeal membrane oxygenation.

Table 1 Genotypes of influenza virus detected by real-time reverse-transcription polymerase chain reaction (RT-PCR) from study participants during 2012–2014.

Genotype	*N*	Year		
		2012	2013	2014
Influenza A				
H3	10	4 (50)	1 (20)	5 (6.8)
Seasonal H1	5		2 (40)	3 (4.1)
H1pdm09	26			26 (35.6)
Seasonal H1+H1pdm09[a]	25		1 (20)	24 (32.9)
Unidentified[b]	13		1 (20)	12 (16.4)
Influenza B	7	4 (50)		3 (4.1)
Total	86	8	5	73

[a] The results of RT-PCR showed double positive for seasonal H1 and H1pdm09 genetic sequence.
[b] Influenza A with genotypes other than H1 or H3.
Data are presented as *n* (%).

Clinical outcomes

The all-cause mortality rate was 29.1% among patients with respiratory distress; this rate was higher in patients older than 65 years (43.5%, $p < 0.05$) and those with chronic lung disease (46.2%, $p < 0.05$; Table 3). The influenza genotype, types of NAI, and time to administration of systemic corticosteroid were not associated with all-cause mortality in patients with respiratory distress ($p > 0.05$; Table 3).

The mean hospital stay in patients with respiratory distress was 27.6 days (95% CI: 22.2–33.1 days), and none of the patients without respiratory distress died in hospital. Survival analysis showed that among the patients with respiratory distress, the H1pdm09 and type B viruses seemed to be more virulent, with a worse prognosis compared to the other type A viruses (Figure S1).

The median length of ventilator support was 11.0 days (mean: 19.2 days, 95% CI: 11.8–26.6 days) and patients with chronic lung disease had a longer period of ventilator support (mean: 36.8 days, 95% CI: 16.1–57.6 days, $p = 0.12$). Administration of a corticosteroid, types of NAI, and other factors including age and gender were not related to the length of ventilator support.

NAIs and corticosteroid

All patients with respiratory distress received oral oseltamivir. Of the patients studied, 39.3% received intravenous peramivir, either sequentially (14.3%) or overlapping (25%) with oseltamivir (Table 2). Among the patients with respiratory distress who were infected with influenza H1pdm09 or type B viruses, salvage peramivir (mortality rate: 10%, 1/10) had a better prognosis than monotherapy with oseltamivir (mortality rate: 44%, 11/25; Figure 1). In these patients, one of the nine patients treated with salvage peramivir who also received a systemic corticosteroid died in hospital, and the systemic corticosteroid only improved

Table 2 Characteristics of adult patients with influenza virus infection during 2012—2014.

	Subtotal	Respiratory distress		*p**
		No	Yes	
Gender				
Male	56	27 (71.1)	30 (62.5)	
Female	30	11 (28.9)	18 (37.5)	
Age (y)				
≤ 65	39	14 (36.8)	25 (52.1)	0.074
> 65	47	24 (63.2)	23 (47.9)	
Comorbidities				
Cardiovascular disease	20	10 (26.3)	10 (20.8)	
Congestive heart failure	26	9 (23.7)	17 (35.4)	
Chronic pulmonary disease	22	9 (23.7)	13 (27.1)	
Chronic kidney disease stage III—IV	20	8 (21.1)	12 (25.0)	
Chronic hepatic disease	10	2 (5.3)	8 (16.7)	0.09
Neurological/neuromuscular disease	19	11 (28.9)	8 (16.7)	
Diabetes	37	15 (39.5)	22 (45.8)	0.011
Hyperlipidemia/hypercholesterolemia	12	9 (23.7)	3 (6.3)	
Obesity (BMI > 30)[a]	6	5 (13.1)	1 (2.1)	0.07
Metabolic syndrome	47	22 (64.7)	25 (53.2)	
Immunosuppression	30	14 (36.8)	16 (33.3)	
Hematologic disorders	8	3 (7.9)	5 (10.4)	
Solid organ malignancy	9	4 (10.5)	5 (10.4)	
Clinical manifestation				
Acute kidney injury	45	14 (36.8)	31 (64.6)	0.027
Acute myocardial infarction	8	2 (5.3)	6 (12.5)	
Gastrointestinal bleeding	26	9 (23.7)	17 (35.4)	
Hepatic failure	4	0	4 (8.3)	
Shock	30	2 (5.3)	28 (58.3)	< 0.01
Mechanical ventilation	39	0	39 (81.3)	< 0.01
Extracorporeal membrane oxygenation (ECMO)	10	0	10 (20.8)	< 0.01
Hemodialysis	12	2 (5.3)	10 (20.8)	0.039
No. of organ failures ≤ 1	49	38 (100)	11 (22.9)	
No. of organ failures ≥ 2	37	0	37 (77.1)	
Influenza rapid test				
Positive	42	25 (65.8)	17 (35.4)	0.002
Negative	37	8 (21.1)	29 (60.4)	
NA	7	5 (13.2)	2 (4.2)	
Influenza genotype				
Type A	79	35 (92.1)	44 (91.7)	
With H1pdm09	51	20 (52.6)	31 (64.6)	
Without H1pdm09	28	15 (39.4)	13 (27.1)	
Type B	7	3 (7.9)	4 (8.3)	
Treatment[b]				0.016
Zanamivir	6	6 (15.8)		
Oseltamivir	79	31 (81.6)	48 (100)	
Oseltamivir, peramivir—sequential	7	0	7 (14.5)	
Oseltamivir, peramivir—combined or overlap	8	0	8 (16.7)	
Administration of systemic corticosteroid	33	6 (15.8)	27 (56.3)	< 0.01
Total	86	38 (100)	48 (100)	

[a] The data regarding to height was unavailable in six patients.
[b] One patient did not receive neuraminidase inhibitor treatment.
Data are presented as *n* (%).
*The *p* values were shown when the probability was significantly different ($p < 0.05$) between patients with or without respiratory failure.
BMI = body mass index; NA = Not available.

Table 3 All-cause mortality in patients with influenza infection and respiratory distress.

Variable	*N*	All-cause mortality	Hospital LOS (d)	*p***
Gender				
Male	30	10 (33.3)	26.9 (19.9–33.9)	
Female	18	4 (22.2)	28.1 (16.8–39.3)	
Age (y)				
≤ 65	25	4 (16)	22.9 (16.6–29.3)	
> 65	23	10 (43.5)*	32.8 (22.4–43.2)	
Immune status				
Immunocompetent	32	8 (25.0)	26.7 (19.9–33.5)	
Immunocompromised	16	6 (37.5)	29.8 (16.2–41.5)	
Malignancy	9	3 (33.3)	32.3 (10.8–53.6)	
Chronic lung disease	13	6 (46.2)*	30.0 (19.3–40.7)	
Diabetes	22	9 (40.9)	27.7 (18.1–37.4)	
Obesity (BMI > 30)	6	0	21.0 (3.2–38.7)	
Metabolic syndrome				
No	22	4 (18)	27.0 (18.7–35.4)	
Yes	25	10 (40)	27.6 (19.0–36.1)	0.09
No. of organ failures ≤ 1	11	0	17.9 (10.8–24.9)	
No. of organ failures ≥ 2	37	14 (37.8)	30.0 (23.0–37.1)	
Corticosteroid				
No	19	5 (26.3)	25.7 (14.1–37.0)	
Yes	29	9 (31.0)	29.0 (23.3–34.7)	
Before & within 72 h of NAIs	17	7 (41.2)	20.9 (11.1–30.7)[a]	0.02
After72 h of NAIs	12	2 (16.7)	34.5 (20.3–48.6)	
Short-term use (≤ 3 d)	4	0 (0)	36.3 (11.1–30.7)	
Continuous use for 4–13 d	14	9 (64.2)	26.1 (8.2–33.9)	
Continuous use for ≥ 14 d	10	4 (40%)	32.3 (20.5–44.0)	
Influenza virus genotype				
Type A	44	12 (27.2)	27.9 (22.1–33.8)	
With H1pdm09	31	10 (32.2)	25.0 (19.6–30.6)	
Without H1pdm09	13	2 (15.3)	34.7 (8.7–50.8)	
Type B	4	2 (50)	24.5 (4.7–44.2)	
Neuraminidase inhibitors				
Oseltamivir monotherapy	33	11 (33.3)	26.1 (18.9–33.2)	
Oseltamivir & peramivir				
Sequential	7	1 (14.3)	33.2 (16.4–50.1)	
Combine/overlap	8	2 (25.0)	29.3 (17.3–41.2)	
Total	48	14 (29.1)	27.6 (22.2–33.1)	

[a] Compared with corticosteroid use after 72 hours of antiviral treatment.
Data are presented as *n* (%) or mean (95% CI).
*$p < 0.05$ by the Chi-square test.
**$p < 0.05$ was shown by the log-rank test in Kaplan–Meier analysis.
BMI = body mass index; CI = confidence intervals; LOS = length of stay; NAIs = neuraminidase inhibitors.

short term survival ($p = 0.04$; Figure S2), rather than overall prognosis. By contrast, patients who received oseltamivir had the worst prognosis and this was unrelated to the systemic corticosteroid.

Regarding the time to initiation of corticosteroid, patients who received early systemic corticosteroid prior to or within 72 hours of effective NAIs had a poorer prognosis when compared to those who received a corticosteroid 72 hours after the initiation of NAIs ($p = 0.02$; Figure 2).

Chronic lung disease

Thirteen patients with chronic lung disease and respiratory distress were selected for subgroup analysis. The all-cause mortality was not related to administration of salvage peramivir or not (3/6 vs. 3/7, $p > 0.05$). In addition, the types of NAI used did not affect the length of hospital stay (Figure S3). Among them, 10 received a corticosteroid with all-cause mortality of 60% (6/10). Systemic corticosteroid was a poor prognosis factor for overall survival ($p = 0.05$; Figure 3). Of the six patients who died, five had received a corticosteroid prior to or within 72 hours of effective NAI, and the other patient died in hospital when he received a corticosteroid after 72 hours of an effective NAI.

Metabolic syndrome

There were 37 patients without chronic lung disease but with metabolic syndrome. Among them, 18 patients developed respiratory distress, and the all-cause mortality

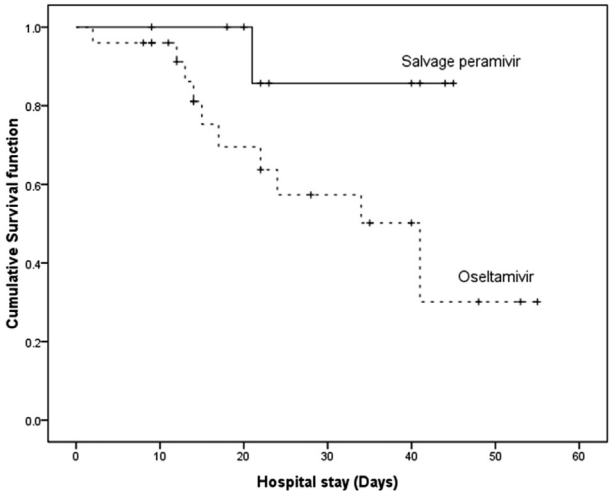

Figure 1. Survival analysis for patients infected with H1pdm09 or type B virus and with respiratory distress, stratified by types of neuraminidase inhibitors ($p = 0.05$, Log-rank test).

was 41.6% (5/12) in those who received oseltamivir alone, compared to zero mortality (0/6) in those who received salvage peramivir (0/6, $p = 0.1$) therapy. The all-cause mortality in patients who developed respiratory distress and received a corticosteroid was 16.6% (1/6), compared to the patients without systemic corticosteroid (41.6%, 5/12, $p = 0.3$). Three patients received a corticosteroid prior to or within 72 hours of effective NAIs and one died in hospital. The median lengths of hospital stay were 25 (Interquartile Range: 33.7) and 12.5 (IQR: 11) days in patients with or without systemic corticosteroid, respectively, ($p > 0.05$; Figure S4).

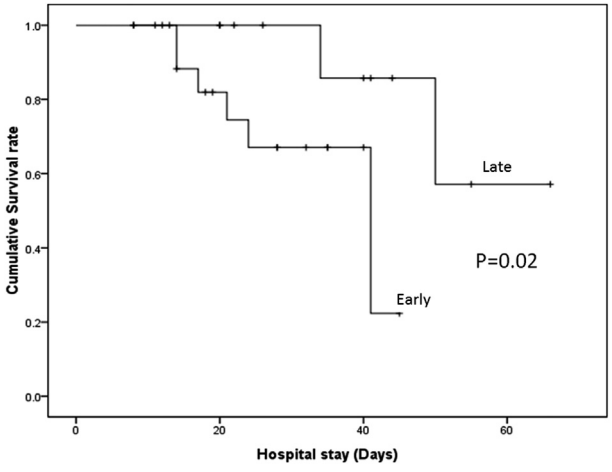

Figure 2. Survival analysis in patients with influenza infection and respiratory distress. The survival functions were stratified by prescribing a systemic corticosteroid before or within 72 hours (early) and after 72 hours (late) of initiation of antiviral therapy ($p = 0.02$; Log-rank test).

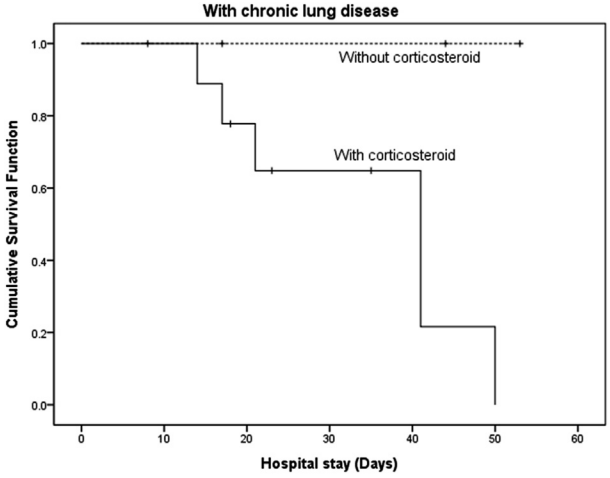

Figure 3. Survival analysis for patients with chronic lung disease who developed respiratory distress. The analysis was stratified by administration of a systemic corticosteroid ($p = 0.05$; Log-rank test).

Superinfection and colonization

Late onset superinfection and colonization were more frequently observed in patients with a hospital stay of > 7 days (53.1% vs. 12.5%, $p < 0.05$). The colonization or superinfection of Gram-negative bacteria was 19.7% overall and 33% in patients with respiratory distress. The most common bacteria isolated were pandrug-resistant or imipenem-resistant *Acinetobacter baumannii* (PDRAB or

Table 4 Superinfection and colonization in sputa of patients with respiratory distress and mechanical ventilation.

	N	Hospital LOS			
		< 7 d	≥ 7 d		
		n	*n*	With steroid	Without steroid
Gram-negative bacteria					
IRAB or PDRAB	6		6	4	2
Acinetobacter baumannii	3		3	3	
Pseudomonas aeruginosa	4	1	3	2	1
Corynebacterium species	1		1	1	
Enterobacter spp.	1		1	1	
Stenotrophomonas spp.	1	1			
Not identified	3	1	2	2	
Gram-positive bacteria					
MRSA	1		1	1	
Yeast	3		3	2	1
Subtotal	19	2 *	17	13	4
No bacteria or normal flora	29	14	15	9	6
Total	48	16	32	22	10

*$p < 0.05$ when compared with hospital LOS ≥ 7 days.
IRAB = imipenem-resistant *Acinetobacter baumannii*; LOS = length of stay; MRSA = methicillin-resistant *Staphylococcus aureus*; PDRAB = pandrug-resistant *Acinetobacter baumannii*.

IRAB, 28.2%; Table 4). It was not associated with all-cause mortality ($p = 0.1$) but was marginally associated with systemic corticosteroid in patients with respiratory distress [44.8% (13/29) vs. 15.7% (3/19), $p = 0.06$].

Discussion

This study is the first manuscript to describe salvage peramivir treatment in oseltamivir nonresponders during the flu season from 2012 to 2014 in Taiwan, and the first investigation regarding the interaction between two NAIs and a systemic corticosteroid in patients with influenza infection.

The all-cause mortality was similar to previous findings[6] in patients who received peramivir and had severe illness (20% vs.16%), as well as the proportion of patients who had previous oseltamivir treatment (31.3% vs. 23%). Further, virulent influenza viruses, including H1N1pdm09 and type B viruses, with a poor prognosis were observed in our cohort. However, the information regarding the H275Y mutation or NAI susceptibility was lacking because the necessary laboratory facilities were unavailable in the study hospital. Rapid and effective clinical diagnosis methods allowing the prediction of NAI susceptibility is warranted.

Aside from oseltamivir provided negligible competitively inhibition affinity against NA enzyme when combined with peramivir,[15] single peramivir use was found to be partially effective in oseltamivir-resistant type A influenza infected mice.[16] Combination of peramivir and oseltamivir was better than the single use of one NAI against influenza infection.[17] Further, in pediatric patients it was shown that there was no significant difference between early combination of peramivir with oseltamivir or zanamivir.[18] Although a small sample size was enrolled in the current study, a higher all-cause mortality rate was observed in patients with respiratory distress who were treated with overlapping peramivir and oseltamivir (25%, 2/8) when compared to patients treated with peramivir sequentially after oseltamivir (14%, 1/7). Further research to increase the number of cases is suggested.

Clinical trials on the early use of multidose intravenous peramivir against seasonal influenza including H1N1, H3N2, and type B viruses have shown similar outcomes to those with daily oseltamivir.[1,2]. Recent investigation showed the benefit of intravenous peramivir within 48 hours of the onset of symptoms,[19] and for treating severe illness,[6,20] and its effectiveness against viruses resistant to oseltamivir has been proven.[21,22] Our results showed that salvage peramivir was superior to oseltamivir alone for patients infected with H1pdm09 and type B viruses with respiratory distress. Since the effectiveness of peramivir was found to be optimal initiated within the first 48 hours of onset of symptoms, the early use of intravenous peramivir in order to prevent further respiratory distress is warranted in Taiwan.

Our results showed that monotherapy with oseltamivir had the worst prognosis, and it was unrelated to administration of a systemic corticosteroid. The co-existence of peramivir and corticosteroid-sparing treatment might indicate the benefit of peramivir itself. Few patients who received a corticosteroid and peramivir showed poor prognosis, but this may be due to selection bias, and further investigation should be continued. Most of the observations indicated that corticosteroid was a poor prognosis factor in influenza virus infection,[8,19] because corticosteroid was significantly related to increased viral replication[23] and viral shedding, despite the use of antiviral therapy.[24] However, we found that the influence of corticosteroid administration was different in two alternate populations: those with chronic lung disease and those with metabolic syndrome. In patients with chronic lung disease, a corticosteroid was harmful (Figure 3) to them and early administration of a corticosteroid was observed. Patients with influenza infection are more likely to have acute exacerbation of chronic obstructive pulmonary disease,[25,26] early administration of a corticosteroid thus occurs in this scenario. Second, immune dysfunction among patients with chronic obstructive pulmonary disease results in a deficiency in effective T cell responses against viral infection[23] that resulted in poor prognosis.

Among patients without chronic lung disease, administration of a systemic corticosteroid seemed to be a good prognosis factor in patients with metabolic syndrome (Figure S4), and the benefits remained if the patients were infected with H1pdm09 and type B viruses. Although the small sample size may result in statistical insignificance, it hinted at the role of corticosteroid in different populations. In patients with diabetes, obesity, hypertension, and hyperlipidemia, there were higher probabilities of respiratory failure and mortality during H1pdm09 viral infection.[20,27] Proinflammatory cytokines such as C-peptide, procalcitonin, interleukin (IL)-6, interferon-gamma, and C-reactive protein are also increased after H1pdm09 viral infection.[28,29] Pre-existing serum leptin levels were found to be related to acute respiratory distress syndrome, and this could be improved by antileptin or anti-IL-6 antibodies.[29] Impaired T-cell function against viral infection and reduced interferon-gamma production after influenza virus infection[30,31] were also observed in obesity hosts. Since glucocorticoids have an anti-inflammatory effect[32] on IL-6 and IL-8[33] in bronchial epithelial cells, this could explain the observation and further study was considered.

Regarding the superinfection or colonization after 72 hours of hospitalization, the community acquired pathogens (i.e., *Streptococcus* spp, methicillin-sensitive *Staphylococcus aureus*) were seldom observed. By contrast, most patients were recorded with no bacteria or normal mixed flora in sputum (60.4%, 29/48). The ventilator associated methicillin-resistant *S. aureus* (MRSA) was only isolated in one patient without mortality; by contrast, fatal community-acquired MRSA pneumonia was usually observed in other countries.[34–37] The GNBs, usually to be considered as nosocomial pathogens, were more frequently found in the current study. Compatible with a previous study[19,38], this was associated with prolonged hospitalization and possibly with a systemic corticosteroid (Table 4). However, the all-cause mortality was unrelated to the GNBs, opposite to the results of a retrospective survey.[19] The insignificances may be explained by heterogeneous comorbidities, limited sample size, administration of antibiotics, and colonization rather than true infection. A further large scaled survey is warranted.

The limitations of this study are as follows: (1) a lack of virological evidence regarding viral mutation and NAI

susceptibility; (2) a limited number of patients and a lack of multivariable analysis, therefore, selection bias may be present; (3) a retrospective study design with heterogeneous comorbidities and incomplete clinical data; and (4) a lack of laboratory evidence of pro- and anti-inflammatory cytokine profiles in different populations.

In conclusion, H1pdm09 and type B were the main genotypes of influenza infection in patients with respiratory distress from 2012 to 2014 in Taiwan, and salvage peramivir treatment had a better prognosis than monotherapy with oseltamivir. The early administration of medium-to-high dose corticosteroid prior to or within 72 hours of antiviral therapy was a significant risk factor for shorter survival time. In addition, a systemic corticosteroid was related to poor prognosis in patients with chronic lung disease.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. 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**:228—32.
2. Ison MG, Hui DS, Clezy K, O'Neil BJ, Flynt A, Collis PJ, et al. A clinical trial of intravenous peramivir compared with oral oseltamivir for the treatment of seasonal influenza in hospitalized adults. *Antivir Ther* 2013;**18**:651—61.
3. Abed Y, Boivin G, Yoshida R, Kodama M, Hernandez JE. Parenteral peramivir treatment for Oseltamivir-resistant 2009 pandemic influenza A H1N1 viruses. *J Infect Dis* 2011;**204**:1641—2.
4. Birnkrant D, Cox E. The Emergency Use Authorization of peramivir for treatment of 2009 H1N1 influenza. *N Engl J Med* 2009;**361**:2204—7.
5. Yu Y, Garg S, Yu PA, Kim HJ, Patel A, Merlin T. Peramivir use for treatment of hospitalized patients with influenza A(H1N1) pdm09 under emergency use authorization, October 2009-June 2010. *Clin Infect Dis* 2012;**55**:8—15.
6. 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.
7. Hernandez JE, Adiga R, Armstrong R, Bazan J, Bonilla H, Bradley J, et al. Clinical experience in adults and children treated with intravenous peramivir for 2009 influenza A (H1N1) under an Emergency IND program in the United States. *Clin Infect Dis* 2011;**52**:695—706.
8. 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.
9. Cortoos PJ, Gilissen C, Mol PG, Van den Bossche F, Simoens S, Willems L, et al. Empirical management of community-acquired pneumonia: impact of concurrent A/H1N1 influenza pandemic on guideline implementation. *J Antimicrob Chemother* 2011;**66**:2864—71.
10. Spieth PM, Zhang H. Pharmacological therapies for acute respiratory distress syndrome. *Curr Opin Crit Care* 2014;**20**:113—21.
11. Yang JR, Kuo CY, Huang HY, Wu FT, Huang YL, Cheng CY, et al. Newly emerging mutations in the matrix genes of the human influenza A(H1N1)pdm09 and A(H3N2) viruses reduce the detection sensitivity of real-time reverse transcription-PCR. *J Clin Microbiol* 2014;**52**:76—82.
12. Yang JR, Lo J, Liu JL, Lin CH, Ho YL, Chen CJ, et al. Rapid SYBR green I and modified probe real-time reverse transcription-PCR assays identify influenza H1N1 viruses and distinguish between pandemic and seasonal strains. *J Clin Microbiol* 2009;**47**:3714—6.
13. Ward CL, Dempsey MH, Ring CJ, Kempson RE, Zhang L, Gor D, et al. Design and performance testing of quantitative real time PCR assays for influenza A and B viral load measurement. *J Clin Virol* 2004;**29**:179—88.
14. Swho G, editor. *Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO Consultation. Part 1: diagnosis and classification of diabetes mellitus*. Geneva: World Health Organization; 1999.
15. Bantia S, Upshaw R, Babu YS. Characterization of the binding affinities of peramivir and oseltamivir carboxylate to the neuraminidase enzyme. *Antiviral Res* 2011;**91**:288—91.
16. Park S, Kim JI, Lee I, Lee S, Hwang MW, Bae JY, et al. Combination effects of peramivir and favipiravir against oseltamivir-resistant 2009 pandemic influenza A(H1N1) infection in mice. *PLoS One* 2014;**9**:e101325.
17. Smee DF, Hurst BL, Wong MH, Tarbet EB, Babu YS, Klumpp K, et al. Combinations of oseltamivir and peramivir for the treatment of influenza A (H1N1) virus infections in cell culture and in mice. *Antiviral Res* 2010;**88**:38—44.
18. Hikita T, Hikita H, Hikita F, Hikita N, Hikita S. Clinical effectiveness of peramivir in comparison with other neuraminidase inhibitors in pediatric influenza patients. *Int J Pediatr* 2012;**2012**:834181.
19. Lee N, Leo YS, Cao B, Chan PK, Kyaw WM, Uyeki TM, et al. Neuraminidase inhibitors, superinfection and corticosteroids affect survival of influenza patients. *Eur Respir J* 2015;**45**:1642—52.
20. de Jong MD, Ison MG, Monto AS, Metev H, Clark C, O'Neil B, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. *Clin Infect Dis* 2014;**59**:e172—85.
21. Sato M, Ito M, Suzuki S, Sakuma H, Takeyama A, Oda S, et al. Influenza viral load and peramivir kinetics after single administration and proposal of regimens for peramivir administration against resistant variants. *Antimicrob Agents Chemother* 2015;**59**:1643—9.
22. Hata A, Akashi-Ueda R, Takamatsu K, Matsumura T. Safety and efficacy of peramivir for influenza treatment. *Drug Des Devel Ther* 2014;**8**:2017—38.
23. Almansa R, Bermejo-Martin JF, de Lejarazu Leonardo RO. Immunopathogenesis of 2009 pandemic influenza. *Enferm Infecc Microbiol Clin* 2012;**30**(Suppl. 4):18—24.
24. Hu Y, Lu S, Song Z, Wang W, Hao P, Li J, et al. Association between adverse clinical outcome in human disease caused by novel influenza A H7N9 virus and sustained viral shedding and emergence of antiviral resistance. *Lancet* 2013;**381**:2273—9.
25. Koul PA, Khan UH, Asad R, Yousuf R, Broor S, Lal RB, et al. Contribution of influenza to acute exacerbations of chronic obstructive pulmonary disease in Kashmir, India, 2010-2012. *Influenza Other Respir Viruses* 2015;**9**:40—2.
26. Wang YC, Lin JM, Li CY, Lee LT, Guo YL, Sung FC. Prevalence and risks of chronic airway obstruction: a population cohort study in Taiwan. *Chest* 2007;**131**:705—10.
27. Zhou Y, Cowling BJ, Wu P, Chan WM, Lee SY, Lau EH, et al. Adiposity and influenza-associated respiratory mortality: a cohort study. *Clin Infect Dis* 2015;**60**:e49—57.
28. Cruz-Lagunas A, Jiménez-Alvarez L, Ramírez G, Mendoza-Milla C, García-Sancho MC, Avila-Moreno F, et al. Obesity and pro-inflammatory mediators are associated with acute kidney

injury in patients with A/H1N1 influenza and acute respiratory distress syndrome. *Exp Mol Pathol* 2014;**97**:453—7.
29. Zhang AJ, To KK, Li C, Lau CC, Poon VK, Chan CC, et al. Leptin mediates the pathogenesis of severe 2009 pandemic influenza A(H1N1) infection associated with cytokine dysregulation in mice with diet-induced obesity. *J Infect Dis* 2013;**207**: 1270—80.
30. Costanzo AE, Taylor KR, Dutt S, Han PP, Fujioka K, Jameson JM. Obesity impairs $\gamma\delta$ T cell homeostasis and antiviral function in humans. *PLoS One* 2015;**10**:e0120918.
31. Karlsson EA, Sheridan PA, Beck MA. Diet-induced obesity impairs the T cell memory response to influenza virus infection. *J Immunol* 2010;**184**:3127—33.
32. Quante T, Ng YC, Ramsay EE, Henness S, Allen JC, Parmentier J, et al. Corticosteroids reduce IL-6 in ASM cells via up-regulation of MKP-1. *Am J Respir Cell Mol Biol* 2008;**39**:208—17.
33. Levine SJ, Larivée P, Logun C, Angus CW, Shelhamer JH. Corticosteroids differentially regulate secretion of IL-6, IL-8, and G-CSF by a human bronchial epithelial cell line. *Am J Physiol* 1993;**265**:L360—8.
34. Cheng VC, Lau YK, Lee KL, Yiu KH, Chan KH, et al. Fatal coinfection with swine origin influenza virus A/H1N1 and community-acquired methicillin-resistant *Staphylococcus aureus*. *J Infect* 2009;**59**:366—70.
35. Hayashi Y, Vaska VL, Baba H, Nimmo GR, Davis L, Paterson DL. Influenza-associated bacterial pathogens in patients with 2009 influenza A (H1N1) infection: impact of community-associated methicillin-resistant *Staphylococcus aureus* in Queensland, Australia. *Intern Med J* 2012;**42**:755—60.
36. Chung DR, Huh K. Novel pandemic influenza A (H1N1) and community-associated methicillin-resistant *Staphylococcus aureus* pneumonia. *Expert Rev Anti Infect Ther* 2015;**13**: 197—207.
37. Rynda-Apple A, Harmsen A, Erickson AS, Larson K, Morton RV, Richert LE, et al. Regulation of IFN-gamma by IL-13 dictates susceptibility to secondary postinfluenza MRSA pneumonia. *Eur J Immunol* 2014;**44**:3263—72.
38. Nin N, Soto L, Hurtado J, Lorente JA, Buroni M, Arancibia F, et al. Clinical characteristics and outcomes of patients with 2009 influenza A(H1N1) virus infection with respiratory failure requiring mechanical ventilation. *J Crit Care* 2011;**26**: 186—92.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2015.08.016.