Received: 4 November 2019 | Revised: 16 July 2020 | Accepted: 17 July 2020

DOI: 10.1111/irv.12794

ORIGINAL ARTICLE

WILEY

Intravenous peramivir vs oral oseltamivir in high-risk emergency department patients with influenza: Results from a pilot randomized controlled study

Yu-Hsiang Hsieh[1] | Andrea F. Dugas[1] | Frank LoVecchio[2] | Breana McBryde[1] | Erin P. Ricketts[1] | Kathryn Saliba-Shaw[1] | Richard E. Rothman[1,3]

[1]Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

[2]Department of Emergency Medicine, University of Arizona College of Medicine, Phoenix, Arizona

[3]Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland

Correspondence
Richard E. Rothman and Yu-Hsiang Hsieh, Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.
Emails: rrothman@jhmi.edu; yhsieh1@jhmi.edu

Funding information
This project has been funded in whole or in part with Federal funds from the Department of Health and Human Services (HHS); Office of the Assistant Secretary for Preparedness and Response (ASPR); Biomedical Advanced Research and Development Authority (BARDA), under Grant No. IDSEP130014-01-00.

Abstract

Background: Peramivir offers a single-dose intravenous (IV) treatment option for influenza (vs 5-day oral dosing for oseltamivir). We sought to compare outcomes of emergency department (ED) patients at high risk for influenza complications treated with IV peramivir vs oral oseltamivir.

Methods: During the 2015-16 and 2016-17 influenza seasons, adult patients in two US EDs were randomized to either oral oseltamivir or IV peramivir treatment group. Eligibility included positive molecular influenza test; met CDC criteria for antiviral treatment; able to provide informed consent and agree to follow-up assessment. Outcomes were measured by clinical end-point indicators, including FLU-PRO Score, Ordinal Scale, Patient Global Impression on Severity Score, and Karnofsky Performance Scale for 14 days. Non-inferior *t* test was performed to assess comparative outcomes between the two groups.

Results: Five hundred and seventy-five (68%) of 847 influenza-positive patients were approached. Two hundred and eighty-four met enrollment criteria and 179 were enrolled; of these 95 (53%) were randomized to peramivir, and 84 to oseltamivir. Average FLU-PRO score at baseline was similar (peramivir: 2.67 vs oseltamivir: 2.52); the score decreased over time for both groups (day 5: peramivir: 1.71 vs oseltamivir: 1.62; day 10: peramivir: 1.48 vs oseltamivir: 1.37; day 14: peramivir: 1.40 vs oseltamivir: 1.33; all $P < .05$ for significantly non-inferior). Influenza-related complications were similar between two groups (All: peramivir: 31% vs oseltamivir: 21%, $P > .05$; pneumonia: peramivir: 11% vs oseltamivir: 14%, $P > .05$).

Conclusions: Clinical outcomes of influenza-infected patients treated with single-dose IV peramivir were comparable to those treated with oral oseltamivir, suggesting potential utility of peramivir for influenza-infected patients in the ED.

Hsieh and Dugas contributed equally to this manuscript and should be considered co-first authors. The peer review history for this article is available at https://publons.com/publon/10.1111/irv.12794

KEYWORDS
emergency department, influenza, oseltamivir, peramivir

1 | INTRODUCTION

Seasonal influenza causes up to 959 000 hospitalizations and 79 400 deaths in the United States annually since 2010.[1-3] As the frontline of the health care system, emergency departments (EDs) see up to three quarter of a million patients during each influenza season.[4,5] The Centers for Disease Control and Prevention (CDC) recommends that people infected with influenza should receive antiviral treatment, to decrease the occurrence of severe complications and shorten the course of illness, especially for those at high risk of influenza complications. This includes young children, adults 65 years of age and older, pregnant women, and people with certain co-morbid medical conditions.[6,7] Currently, there are four Food and Drug Administration (FDA)-approved antiviral drugs for treatment of influenza, including three influenza virus neuraminidase inhibitor (oseltamivir, zanamivir, and peramivir) and one polymerase acidic protein inhibitor (baloxavir).[8]

Since the 2003-2004 influenza season, oseltamivir has been the predominant antiviral drug used for ambulatory care patients, including those who come to the US EDs, with a diagnosis of influenza.[9] However, requirement for a 5 day, twice a day oral dosing regimen, make alternate antiviral drugs more appealing for both clinicians and patients, particularly those seen in acute care setting such as EDs, where filling and adhering with medications is well known to be challenging. Several alternative, single-dose medication options remain under investigation for ED use, but each has limitations. Zanamivir, which exists as a powder in an inhaled form in the United States, has similar efficacy to oseltamivir, but it is not generally recommended for people with asthma or chronic obstructive pulmonary disease according to CDC[8]; baloxavir which was recently approved in the United States by FDA in October 24, 2018,[10] 15 months after the end of our study, is restricted to use in those >12 years old and has not been studied in those >65 years old, pregnant, or lactating women.[8] In addition, there are concerns of rapid emergence of resistance to the use of baloxavir.[11,12] These leaves peramivir, which can be used in patients ≥2 years old, as a potential favorable alternative candidate antiviral drug for treating ED patients with influenza.

Peramivir, a neuraminidase inhibitor agent with the same mechanism of action as oseltamivir, has been demonstrated to have activity against both influenza A and B viruses, and shorten duration of influenza symptoms for outpatient adults with uncomplicated influenza.[13,14] Several studies previously demonstrated both safety and non-inferiority of peramivir hospitalized patients and outpatients with influenza.[13,15,16] A multinational, multicenter, double-blind randomized trial in East Asia showed that the duration of influenza symptoms in adult influenza-infected patients treated with a single dose of 300 mg of IV peramivir, or 600 mg of peramivir was non-inferior to that treated with 5-day twice a day oseltamivir. The incidence of severe adverse events by peramivir was similar to oseltamivir.[13] de Jong and colleagues conducted a trial in hospitalized patients with suspected influenza randomized to 5-day treatment with intravenous peramivir (600 mg once daily) or placebo; all received the institution's standard of care treatment. That also showed that no difference in median time to clinical resolution between the two groups. However, there was a trend toward a shorter time to clinical resolution in ≥4 of 5 vital sign abnormalities (temperature, oxygen saturation, respiration rate, heart rate, and systolic blood pressure) for 24 hours, among those who required intensive care who received peramivir (vs oseltamivir).[16] In another small randomized trial of 92 adult inpatients and outpatients with high-risk factors, the results also showed that patients treated with single-dose 600 mg peramivir had similar outcomes with regard to time to reduce fever, total symptom scores, and virus titer as compared to those treated with orally administrated oseltamivir (75 mg, twice per day for 5 days).[15] Accordingly, CDC includes peramivir as a recommended agent, which can be administered intravenously which should be considered for patients who cannot tolerate or absorb orally or enterically administered oseltamivir.[7] Given that only one-dose via intravenous (IV) is required for use of peramivir for influenza treatment, the agent might be a welcome alternate antiviral in acute episodic setting such as EDs; further during future influenza seasons (or during a pandemic) it is possible that selectively increased resistance to oseltamivir (vs peramivir) could occur.[17] To date, there are no studies comparing the outcome of ED patients treated with peramivir vs oseltamivir patients considered at high risk for influenza complications.

We sought to determine the outcomes and safety of peramivir vs oseltamivir in patients diagnosed in the ED with influenza, who are at high risk for influenza complications according to CDC risk criteria. Data for this analysis were collected from a pilot randomized controlled trial intended to evaluate the practical feasibility of enrolling subjects for influenza therapeutic trials in the ED setting. The outcomes of antiviral treatment were measured using several clinical end-point indicators, including FLU-PRO Score, Ordinal Scale, Patient Global Impression on Severity (PGIS) Score, and Karnofsky Performance Scale, collected via patient's daily diaries and phone follow-ups.

2 | METHODS

An open-label randomized controlled clinical trial was conducted at two academic EDs: The Johns Hopkins Hospital (JHH), Baltimore, Maryland, and Maricopa Medical Center (MMC), Phoenix, Arizona. ED patients who tested positive for influenza (see below) during their ED encounter were randomized to receive either oral oseltamivir or IV peramivir antiviral treatment.

Eligible patients were those (a) 18 years or older; (b) with an ED positive influenza test by rapid molecular influenza assay (GeneXpert

Flu/RSV; Cepheid); (c) meeting the 2011 CDC criteria for antiviral treatment; (d) with symptoms onset of less than 96 hours; (e) able to provide informed consent; and (f) expressed willingness to comply with all study procedures including follow-up requirements (completing daily diary logs and available for phone calls with a study coordinator). A patient was considered ineligible if (a) they did not speak or understanding English (JHH); or English or Spanish (MMC site); (b) unable or unwilling to provide informed consent; (c) previously enrolled in the study during the current influenza season; (d) unable to take oral medication; (e) using any neuraminidase inhibitors within the past 7 days; (f) known allergic reaction to neuraminidase inhibitors; (g) pregnant or breastfeeding; and (h) having end-stage renal disease, end-stage liver disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or immunodeficiency. Dedicated trained study coordinators recruited eligible patients 24 hours a day, 7 days a week from 11/2015-04/2016 (JHH only) to 11/2016-04/2017 (JHH & MMC). Study coordinators first screened all ED patient charts to identify patients who had a positive laboratory-confirmed rapid PCR influenza test, then approached potentially eligible patient to gauge their interest in participating in the study and to determine if the patient met eligibility criteria before conducting written informed consent. Potentially eligible patients were approached for the study when the positive result of rapid molecular influenza test came back. All Emergency Medicine physicians were trained by the site PI, on study protocol and procedures, completing and signing a Statement of Investigator, Form FDA 1572. A study trained physician provided written informed consent to patients who were eligible and expressed interested in participating, explaining the risks and benefits of the study to the patient and ensuring that the patient understood all aspects of the study (study coordinators were present with the physician, to assist where needed). Consented patients were randomized to oral oseltamivir or IV peramivir treatment group using an internet-based computerized randomization system (www.random.org) without a block randomization design but with an intent of 1:1 ratio. The random number generated for each consented patient was an independent event and independent by site. The randomization was not stratified by the study site. Since this study was intended to evaluate the practical feasibility of enrolling subjects for influenza therapeutic trials in the ED setting, the sample size of 50-150 subjects sample size was determined in collaboration with the funder (Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response/Biomedical Advanced Research and Development Authority) to be adequate for this pilot effort which is being conducted specifically to examine the feasibility of achieving higher recruitment rates than has historically been achieved in other clinical venues, and the ability to reliably collect useful therapeutic end-point data from an ED enrollment site.

Both oseltamivir and peramivir were dosed based on creatinine clearance (CrCl) results which was calculated using the Cockcroft Gault equation; 30 mg once daily, 30 mg twice daily or 75 mg twice daily of oseltamivir for 5 days or 100 mg, 200 mg, 600 mg of one-time IV peramivir. Both groups received the first dose of antiviral treatment in the ED following randomization. For the oseltamivir group, patients were instructed to take the remaining doses on the subsequent 4 days, either inpatient or outpatient, based on disposition from the ED attending. For the peramivir group: for patients who were discharged from the ED, no further study drug was administered; for patients admitted to the hospital from the ED, the inpatient treating provider was given the option to choose to continue administering IV peramivir, based on their clinical discretion. An investigator from the study team gave the inpatient treating provider information about the study, including information on how to continue IV peramivir at the same dose for each subsequent day for up to 4 days. If a participant remained in the hospital beyond 5 days of treatment, and the patient was symptomatically better, treatment stopped. If the patient remained hospitalized after 5 days of treatment and had not improved, the treating provider was given the option to continue IV peramivir daily for another 5-day course (with consultation as requested from a 24/7 on-call infectious disease specialist and pharmacist, to assist with decision-making). Treatment with peramivir was discontinued upon discharge from the hospital for all participants in the IV peramivir arm.

As a secondary objective, we created a repository of residual nasopharyngeal samples from ED patients with suspected influenza illness for purposes of future laboratory analysis of new assays with potential interest for characterizing patients with influenza. Specimens were collected by clinical staff at day 1 (baseline) according to standard of care practice and at day 3 (under a research protocol) using a flocked swab and universal viral transport media. Day 1 specimen was first testing for clinical purposes by Xpert Flu, and the remaining specimen was transported to, frozen and stored at the central study laboratory at JHH for future analysis. For the day 3 specimen, the entire specimen was transported to, frozen and stored at the central laboratory at JHH for future analysis (see below). The study was approved by the IRB at each of the participating institutions. This study was registered as protocol: NCT02609399 at clinicaltrials.gov.

Outcomes of antiviral treatment were measured by the validated FLU-PRO score,[18] a 32-question clinical end-point indicator (scale 1-5 for each question) from enrollment (day 1) for 14 days via patients' daily diary. Influenza disease severity was also assessed by PGIS, whereby participants rated their influenza symptoms ranging from no symptom (score 0), mild symptoms (1), moderate symptoms (2), or severe symptoms (3) at the time of enrollment, day 7 and 28.[19,20] Clinical status of the participants was evaluated by a validated 6-step Ordinal Scale (1-6) from the day of ED or hospital discharge as: return to normal activities, 1 point; discharged but not back to normal activities, 2 points; Non-ICU hospitalization, 3 points; ICU without mechanical ventilation, 4 points; ICU with mechanical ventilation/ ECMO, 5 points; and death, 6 points.[21] For any patient who was discharged where the status of back to normal activities was unknown for any particular day, the Ordinal Scale for that day was conservatively coded as “2 points”. If the patient reported returning to normal activities the previous day, and reported normal activities the day after then the Ordinal Scale was coded as “1 point”. Physical function of the participants was assessed for 14 days by daily diary

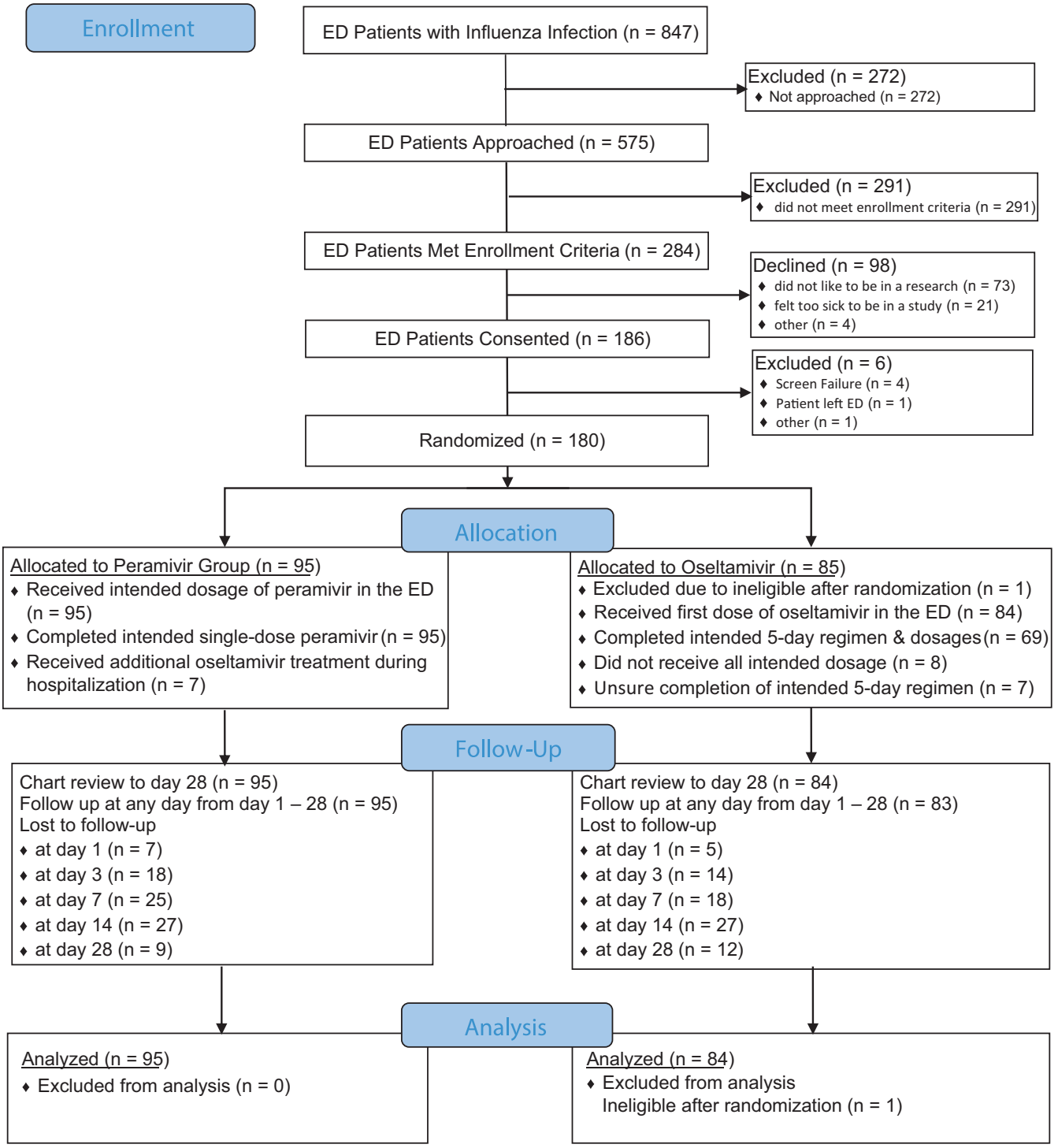


FIGURE 1 Diagram of study design and patient enrollment

reports using the Karnofsky Performance Scale, which ranges from 0 to 100, with higher scores indicating better performance status.[22] For this pilot feasibility phase of the study, all of follow-ups after the participant's discharge from the ED or hospital were conducted by study coordinators by phone.

We evaluated specimens from our biorepository for any patients in whom we were able to collect paired nasopharyngeal swab specimens (at both day 1 and 3) using a feature of the Cepheid GeneXpert® Xpress Flu/RSV real-time PCR assay which permitted us to assess the cycle threshold (C_t) values, as a semi-quantitative approach to infer influenza viral load from any particular sample. Analysis of C_t values using this approach was demonstrated previously to inversely reflect the amount of influenza viral RNA present in the sample.[23] A C_t value of 40 for influenza A or B viruses was considered as an undetectable viral load for influenza A or B virus, respectively.

TABLE 1 Characteristics of 179 emergency department patients with influenza enrolled in the influenza therapeutic study

Characteristics	Category	Total No. N = 179	Peramivir group N = 95	Oseltamivir group N = 84	*P*-value
Age (years)	18-34	43 (24.0)	22 (23.2)	21 (25.0)	.824
	35-49	45 (25.1)	25 (26.3)	20 (23.8)	
	50-64	66 (36.9)	33 (34.7)	33 (39.3)	
	≥65	25 (14.0)	15 (15.8)	10 (11.9)	
Sex	Male	73 (40.8)	37 (38.9)	36 (42.9)	.595
	Female	106 (59.2)	58 (61.1)	48 (57.1)	
Race	African American	120 (67.0)	60 (63.2)	60 (71.4)	.455[a]
	White	50 (27.9)	29 (30.5)	21 (25.0)	
	Other	9 (5.0)	6 (6.3)	3 (3.6)	
Ethnicity	Hispanic	29 (16.2)	19 (20.0)	10 (11.9)	.142
CDC-defined high risk	Intent to admit to observation unit or admission	69 (38.5)	35 (36.8)	34 (40.5)	.618
	Complications - pneumonia	12 (6.7)	3 (3.2)	9 (10.7)	.069 [a]
	Age 65 y or greater	25 (14.0)	15 (15.8)	10 (11.9)	.454
	Chronic pulmonary disease	108 (60.3)	59 (62.1)	49 (58.3)	.607
	Chronic cardiovascular disease	41 (22.9)	24 (25.3)	17 (20.2)	.425
	Chronic renal disease	8 (4.5)	4 (4.2)	4 (4.8)	1.000 [a]
	Chronic hepatic disease	23 (12.8)	12 (12.6)	11 (13.1)	.926
	Chronic hematologic disease	7 (3.9)	3 (3.2)	4 (4.8)	.708 [a]
	Chronic metabolic disease	57 (31.8)	33 (34.7)	24 (28.6)	.377
	Chronic neurologic disease	22 (12.3)	14 (14.7)	8 (9.5)	.289
	Immunosuppression	15 (8.4)	7 (7.4)	8 (9.5)	.604
	Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	NC
	Morbid obesity	25 (14.0)	13 (13.7)	12 (14.3)	.908
	Resides in nursing home	2 (1.1)	1 (1.1)	1 (1.2)	1.000 [a]
	Native American	2 (1.1)	1 (1.1)	1 (1.2)	1.000 [a]
Influenza vaccination	No vaccination	101 (56.4)	57 (60.0)	44 (52.4)	.415 [a]
	Within last 2 wk	6 (3.4)	4 (4.2)	2 (2.4)	
	More than 2 wk	72 (40.2)	34 (35.8)	38 (45.2)	
Symptoms	Subjective fever	140 (78.2)	75 (78.9)	65 (77.4)	.800
	Documented fever	71 (39.7)	33 (34.7)	38 (45.2)	.152
	Cough	168 (93.9)	90 (94.7)	78 (92.9)	.601
	Headache	113 (63.1)	62 (65.3)	51 (60.7)	.529
	Short of breath	134 (74.9)	69 (72.6)	65 (77.4)	.465
	Sore throat	89 (49.7)	50 (52.6)	39 (46.4)	.408
	Rhinorrhea	102 (57.0)	57 (60.0)	45 (53.6)	.386
	Congestion	98 (54.7)	49 (51.6)	49 (58.3)	.365
	Sinusitis	72 (40.2)	40 (42.1)	32 (38.1)	.585
Onset of symptoms	Within 2 d	79 (44.1)	39 (41.1)	40 (47.6)	.598
	3 d	46 (25.7)	27 (28.4)	19 (22.6)	
	4 d	54 (30.2)	29 (30.5)	25 (29.8)	
NEWS score	0	18 (10.1)	9 (9.5)	9 (10.7)	.165 [a]
	1-3	111 (62.0)	54 (56.8)	57 (67.9)	
	4-6	41 (22.9)	28 (29.5)	13 (15.5)	
	>6	9 (5.0)	4 (4.2)	5 (6.0)	
ED disposition	Admit	65 (36.3)	34 (35.8)	31 (36.9)	.877

Abbreviation: NC: Not calculated.

[a]Fisher's exact test.

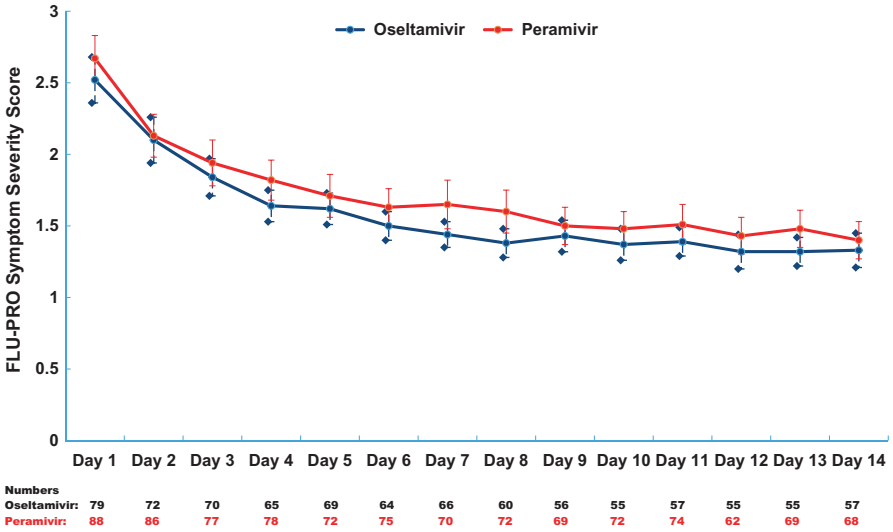


FIGURE 2 FLU-PRO symptom severity score for the 14 d of follow-up by antiviral treatment group. The blue diamonds represent the lower and upper bound of a 95% confidence interval of each point estimate of the FLU-PRO value of patients in the oseltamivir group; the red bars represent the lower and upper bound of a 95% confidence interval of each point estimate of the FLU-PRO value of patients in the peramivir group

Descriptive data analysis was performed first, followed by chi-square tests to determine the differences between the two treatment groups with regard to socio-demographic and clinical characteristics at baseline. Adherence to the assigned treatment regimen was defined as required peramivir or oseltamivir dosages that a patient received recorded in the chart (peramivir or oseltamivir group), or reported during the follow-up by the patient if he or she was discharged (oseltamivir group). Chi-square tests were then performed to determine the differences in adherence, complications, and relevant side effects between the two groups. *T* test for non-inferiority was performed to determine daily outcome measures using the original full dataset. For this, $P < .05$ indicated that the outcome of peramivir treatment was not inferior to that of oseltamivir. To examine the impact of missingness of each outcome of antiviral treatment during the follow-up, sensitivity analyses were performed. We performed the non-inferiority tests for 15 multiple-imputed datasets for each outcome of antiviral treatment by each time point, using the same approach described above. All data analyses were based on intent-to-treat analysis.

3 | RESULTS

Overall, 847 patients with laboratory-confirmed influenza were seen at the ED sites during the study period. Among them, 575 (68%) were approached by the study coordinator, 284 (49%) of those met study enrollment criteria. Among those eligible, 186 (65%) provided consent, and 180 were enrolled and randomized (Figure 1). After excluding one patient who was determined to be ineligible following enrollment, a total of 179 ED patients with influenza were analyzed, including 58 and 121 ED patients during influenza season 2015-2016 and 2016-2017, respectively. The majority were female (59%) and African American (67%) with a median and mean age of 50 years (interquartile range: 36-57 years) and 47.4 years (standard deviation: 15.0 years; range 19-80 years). The most common CDC-defined higher risk for influenza complications was chronic pulmonary disease (60.3%), followed by intent to admission (38.5%), chronic metabolic disease (31.8%), chronic cardiovascular disease (22.9%), aged of 65 years or older (14.0%), and morbid obesity (14.0%). There were 121 (67.6%) participants with more than one CDC-defined higher risk. There were more than 50% of enrollees who had onset of symptoms for more than 48 hours (n = 100, 55.9%). 135 (75%) patients were infected with influenza A virus and 44 (25%) with influenza B virus. 95 (53%) patients were randomized to the peramivir treatment arm and 84 to the oseltamivir treatment arm. There were no statistical differences between the peramivir and oseltamivir treatment groups, including co-morbidities listed by CDC (Table 1). The percentage of the influenza A virus infection was 73.7% in the peramivir group and 77.4% in the oseltamivir group ($P = .567$). The percentage of the inpatient admission in two groups was similar (peramivir: 35.8% vs 36.9%, $P = .877$). All 95 patients in the IV peramivir group received intended dosage of antiviral medication (Figure 1). On the other hand, approximately, 20% of patients who received oseltamivir did not receive the intended antiviral dosage (n = 8, 9.5%) or we did not know their adherence information (n = 7, 8.3%). There was a statistical different between two groups ($P < .001$). There were six patients in the peramivir treatment group who received peramivir in the ED and then received additional oseltamivir treatment during hospitalization. There were seven patients in the peramivir treatment group who received additional peramivir dosages during hospitalization (three with one additional dosage of peramivir, two with two, and two with four) while there was one patient in the oseltamivir treatment group who received one additional dosage of oseltamivir during hospitalization (Figure 1).

For assessment of outcome measurement, chart review was performed on all 179 participants (peramivir: 95; oseltamivir: 84) and daily follow-ups for peramivir and oseltamivir groups were obtained from 88 and 79 participants (day 1), 77 and 70 patients (day 3), 70 and 66 patients (day 7), 68 and 57 patients (day 14), and 86 and 72 patients (day 28), respectively (Figure 1). The average FLU-PRO score at baseline was similar between the two groups (peramivir: 2.67 vs oseltamivir: 2.52) and scores consistently decreased over

time for both groups (day 5: peramivir: 1.71 vs oseltamivir: 1.62; day 10: peramivir: 1.48 vs oseltamivir: 1.37; day 14: peramivir: 1.40 vs oseltamivir: 1.33; all $P < .05$ for significantly non-inferior) (Figure 2). PGIS score at baseline was also similar between the two groups (moderate or severe symptoms: peramivir: 82% vs oseltamivir: 84%) and the score decreased over time for both groups (day 7: peramivir: 27% vs oseltamivir: 18%; day 28: peramivir: 2% vs oseltamivir: 7%) (Figure 3). Regarding patient's clinical status, Ordinal Scale scores declined from day 1 to 14 for both groups (day 1 – peramivir: 3.0 vs oseltamivir: 3.0; day 7 – peramivir: 1.6 vs oseltamivir: 1.4; day 14 – peramivir: 1.3 vs oseltamivir: 1.3; all $P < .05$ for significantly non-inferior) (Figure 4). At the same time, the Karnofsky performance scale measures increased for both groups (peramivir: 58.4 vs oseltamivir: 57.0) from the high 50s at day 1, to approximately 80 at day 5 (peramivir: 77.4 vs oseltamivir: 80.0) and approximately 90 at day 14 (peramivir: 89.1 vs oseltamivir: 91.8) (Figure 5). Daily Karnofsky performance scale of the peramivir group was not inferior to that of the oseltamivir group except for at day 7 (78.5 vs 87.4) and 8 (81.1 vs 86.8). Results of sensitivity analysis showed the same results that the outcomes of peramivir group were not appreciably worse than those in oseltamivir group except for Karnofsky performance scale at day 7 (data not shown). Clinical course of the peramivir group was not inferior to that of the oseltamivir group by ED disposition (admission or discharge) evaluating by daily FLU-PRO, Ordinal Scale, PGIS score or Karnofsky performance scale except for at day 6 and 7 for hospitalized patients. Of note, there were no statistical differences in these four indicators between those with onset of symptoms greater 2 days and those less than 2 days, by treatment group, except for day 2 Ordinal Scale in oseltamivir group (onset ≤2 days: 2.7 vs >2 days: 2.5, $P = .034$).

Regarding patients with more than one CDC high-risk factor for an influenza complication, they did not fare worse than those with only one factor by either group in the PGIS score and the Ordinal Scale score by day. However, they reported their physical activities were worse than those with only one factor in the Karnofsky performance scale by both treatment groups in most of days followed (peramivir: day 2-11; oseltamivir: day 2-3, day 7-10, day 12-13). On the other hand, they reported their symptoms were getting much better on certain days after enrollment according to their FLU-PRO score than those with only 1 factor (peramivir: day 5, day 8-11; oseltamivir: day 2-3). Regarding the impact of medical history of chronic pulmonary diseases on the study outcomes, patients treated with oseltamivir who had chronic pulmonary diseases did not fare worse than those without chronic pulmonary diseases, according to their FLU-PRO, PGIS score, Ordinal Scale score, or the Karnofsky performance scale by day. The same trend was observed in the peramivir group, with the exception of the Karnofsky performance scale between day 2 to 7, and at day 10. Regarding the impact of medical history of metabolic diseases, there were no differences in Ordinal Scale score in either treatment group. There were also no differences in terms of inferiority in other three indicators for the majority of days patients were followed in either group (data not shown).

Among the 17 paired samples, 10 were in the oseltamivir group and seven were in the peramivir group. One patient in the oseltamivir group had an undetectable viral load at both time points, even though clinical testing by Xpert Flu at the enrollment was positive with influenza A virus. Of note, before coming to the study ED, this patient had symptoms of shortness of breath, fever and chill for 3 days and had been diagnosed with pneumonia and treated with antibiotics in another hospital the day before. This patient also tested positive for a second pathogen, respiratory syncytial virus, at the time of enrollment and with testing of aliquoted samples from day 1 and 3. Of the remaining 16 patients, influenza viral load at day 3 dropped to undetectable (ie, $C_t = 40$) in nine patients (peramivir: 3; oseltamivir: 6) (Figure 6). Of the remaining seven patients, C_t values significantly increased from day 1 to 3 in all seven patients (peramivir: 4; oseltamivir: 3). On average, the C_t values for the peramivir group and oseltamivir group were 26.3 and 27.2 at day 1, respectively and were 35.8 and 38.0 at day 3, respectively.

Influenza-related complications were similar between the two groups (peramivir: 30.5% vs oseltamivir: 21.4%). The most common complication was the requirement for oxygen supplement (peramivir: 23.2%; oseltamivir: 21.4%), followed by pneumonia (peramivir: 11.6%; oseltamivir: 14.3%) and admission to ICU (peramivir:

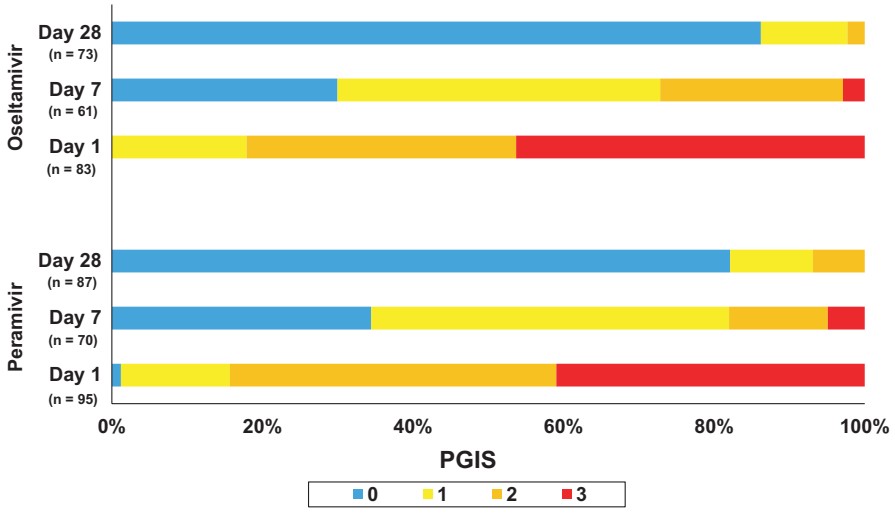


FIGURE 3 Patient global impression of severity

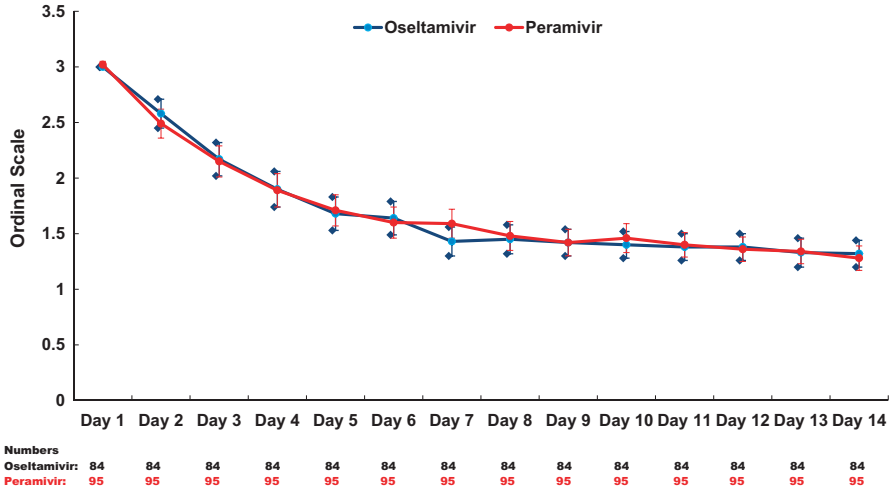


FIGURE 4 Ordinal scale for the 14 d of follow-up by antiviral treatment group. The blue diamonds represent the lower and upper bound of a 95% confidence interval of each point estimate of the Ordianl Scale of patients in the oseltamivir group; the red bars represent the lower and upper bound of a 95% confidence interval of each point estimate of the Ordianl Scale value of patients in the peramivir group

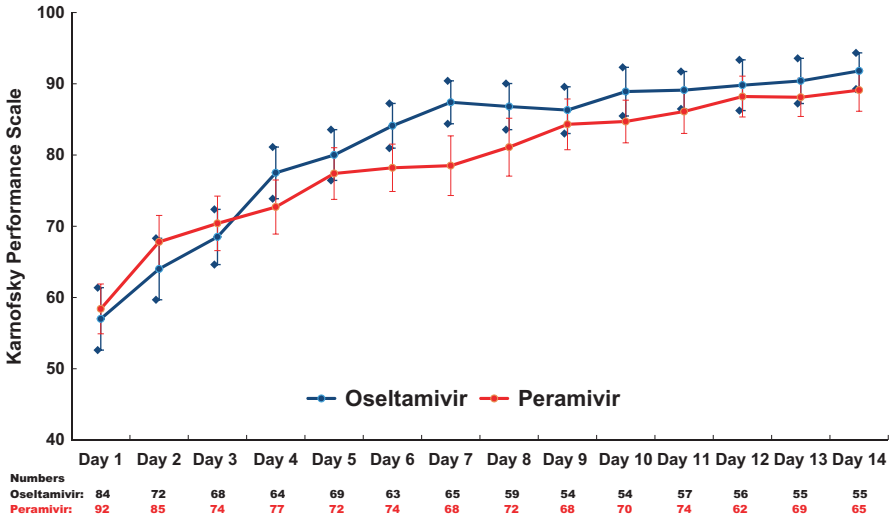


FIGURE 5 Karnofsky performance scale by day. The blue diamonds represent the lower and upper bound of a 95% confidence interval of each point estimate of the Karnofsky Performance Scale of patients in the oseltamivir group; the red bars represent the lower and upper bound of a 95% confidence interval of each point estimate of the Karnofsky Performance Scale of patients in the peramivir group

2.1%; oseltamivir: 0%). There was no difference in preventing clinical diagnosed secondary bacterial pneumonia by treatment group (peramivir: 5.3%; oseltamivir: 4.8%, $P = .878$). One patient in the IV peramivir group had a myocardial infarction but none needed extracorporeal membrane oxygenation or had a stroke. There were no deaths occurring in either group of patients during the 28-day follow-up period.

Overall, there were a total of 311 adverse events reported (peramivir: 159, oseltamivir: 152), which included 14 serious adverse events from 116 patients (peramivir: 61, oseltamivir: 55). Among them, 186 (peramivir: 90, oseltamivir: 96) or (1.04 event per patient; peramivir: 0.95; oseltamivir: 1.14) were related to the study products from 87 patients (peramivir: 43, oseltamivir: 44), but none of these were categorized as serious adverse events. The most common relevant adverse event for the peramivir group patients was diarrhea (n = 28, 31.1%), followed by insomnia (14.4%), nausea (12.2%), vomiting (11.1%) and vertigo (11.1%) while diarrhea (n = 25, 26.0%) was the leading relevant adverse event for the oseltamivir group patients, following by nausea (17.7%), vomiting (15.6%), insomnia (11.5%), and vertigo (7.3%).

4 | DISCUSSION

In this first ED-based randomized controlled influenza therapeutic clinical trial that fully enrolled, randomized, and initiated antiviral treatment intervention in EDs to compare outcomes of patients treated with IV peramivir vs a 5 day of oral oseltamivir, we found that the regimens were similar with regard to patient's self-reported relief of influenza symptoms, reduction of functional impairment, as well as the rates of adverse and severe adverse events, for influenza-infected CDC categorized "high-risk" patients. Consistent with prior peramivir vs oseltamivir randomized trials in hospitalized or outpatients, our trial in ED patients provides similar findings with regard to the clinical efficacy and safety of the use of single-dose IV peramivir.[13,15,16] To the best of our knowledge, this study provides the first evidence-based findings for use of IV peramivir in patients who present to an ED setting. As the majority of patients who are considered high risk for influenza complications receive intravenous lines as part of their ED care, the added burden of administration of IV peramivir would be unlikely to have a significant negative effect on ED staff work burden, or ED patient flow.

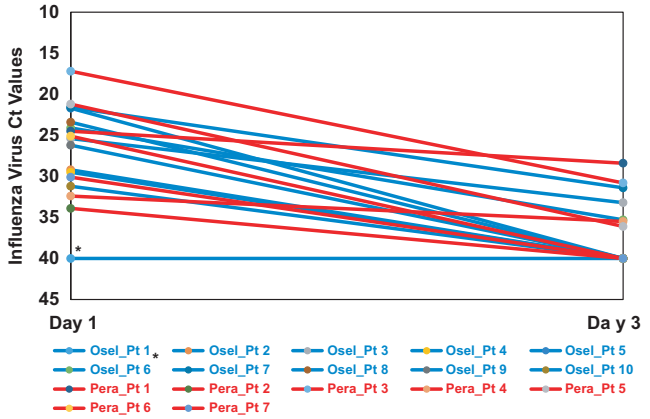


FIGURE 6 Influenza virus cycle threshold (C_t) values at day 1 and 3 among 17 influenza-infected participants by antiviral treatment group. Influenza virus cycle threshold (C_t) value, which is inversely proportional to the amount of influenza virus nucleic acid target in the sample, represents the number of cycles it takes to yield a positive value in quantitative Cepheid GeneXpert® Xpress Flu/RSV real-time PCR assay. A C_t value of 40 for influenza virus testing was considered as an undetectable viral load for influenza virus. Each red line represents specific individual participant who was in peramivir treatment group and each blue line represents participant who was in oseltamivir treatment group. * Clinical testing by Xpert Flu at the enrollment (day 1) for this patient was positive with influenza A virus. A C_t value of 40 of the aliquoted stored clinical specimen by the *Cepheid GeneXpert® Xpress Flu/RSV real-time PCR assay* indicated the possible degradation of the archived sample

In this study, we employed several validated symptom, disease severity, clinical, and physical functionality indexes to evaluate the outcomes associated with peramivir and oseltamivir treatment. All of them pointed to the same conclusion, namely that influenza symptoms were mitigated, disease severity decreased, and clinical and physical functionality improved over time with single-dose IV peramivir administered in the ED; further these outcomes were functionally similar to those observed among the group treated with a 5-day course regimen of oseltamivir. This finding, supports findings from previously observational studies conducted in non-ED studies,[13,15,16] but also provides important direct data for ED clinicians, to support consideration of single-dose treatment for influenza-infected patients at increased risk for influenza-related complications as an alternative to oral oseltamivir. Given the busy, episodic nature of the ED, and the fact that compliance with medications at the time of discharge in some ED populations may be challenging, this additional therapeutic option may be appealing to ED providers and patients. It is important to note, however, that the current costs of peramivir are 6-time higher than a 5-day course of oseltamivir.[24] Further investigations are thus warranted, taking into account issues of adherence to oseltamivir, and assessment of other factors that could be impacted by treatment compliance, including emergence of resistant strains and spread of partially treated disease in the community.

As noted above, one of the potential advantages of the use of a single-dose regimen of antiviral medication for influenza treatment, is that patients might be less likely to adhere to a multiple-day multiple dosages (eg, 5-day course of oseltamivir).[25] Our data upheld this conjecture, since approximately 20% of patients in the oseltamivir group did not adhere to the full-course of treatment; rates of non-adherence would likely be even lower in the real-world setting (where patients have to fill and pay for their own prescriptions, vs here, where subjects were provided with the actual medications at the time of enrollment). Another study in Spain also demonstrated relatively low rates of adherence to oseltamivir during both pandemic and non-pandemic influenza seasons.[26] Non-adherence is particularly concerning during influenza pandemics when the virus may be more virulent and/or more likely to spread in the population. Single-dose peramivir, the recently approved baloxavir, or recently recommended use of one-dose or two-doses intravenous zanamivir by European Medicines Agency's Panel,[27] thus provide added potential value for the population, which would be particularly important during a pandemic.

Of note, more than 50% of our enrollees reported onset of the respiratory symptoms more than 48 hours before coming to the ED, consistent with our previous study, as well as others ED-based studies.[28,29] Our results demonstrate that antiviral treatment for those with greater than 2 days of symptoms also benefit from therapy in both treatment groups since the clinical aspects of improvement by all indices measured in this study were similar regardless of duration of symptoms within or greater 48 hours. Further investigation of the impact of antiviral medication on influenza patients with longer duration of symptoms could provide additional evidence for guiding future CDC treatment recommendations regarding timing of treatment initiation (relative to symptom onset). Based on our findings here, EDs could represent an important clinical venue for conducting this type of research in the future.

One of the important features of our study is that we recruited a substantial numbers of minority influenza-infected patients to this randomized controlled trial. Approximately, two-thirds (67%) of participants were African American and 16% were Hispanic ethnicity. Studies have documented racial and ethnic disparity regarding influenza vaccination and influenza-related hospitalization.[30-34] On the other hand, little data is available in the literature related to antiviral treatment association with race/ethnicity. Only one study surveying the perceived acceptance of peramivir which was under emergency use authorizations during the 2009 H1N1 influenza pandemic, found that African American had the lowest willingness to accept the new antiviral for influenza treatment as compared to other racial/ethnic groups.[35] Notably, a previous systematic literature review on antiviral chemoprophylaxis against pandemic and seasonal influenza did not address the issue of potential differences in racial/ethnic group response to antiviral treatment.[35] Our capability to recruit a considerable number of minority patients to an influenza therapeutic randomized clinical trial provides a stepping stone for future studies and could help minimize disparities associated with antiviral treatment studies in minority populations and increase acceptance of use of antiviral among minority populations.

There are a number of limitations associated with this study. First, this study was not powered to determine the overall efficacy

of peramivir in treating high-risk ED patients with influenza, as the primary aim of the study was to determine the feasibility of conducting influenza-related therapeutic clinical trials in the ED setting. Second, the outcomes of antiviral treatment might be influenced by the virulence of influenza virus as well as its antiviral resistance level by each influenza season. However, we did not set out, to do further subtyping and/or characterization of antiviral resistance for this study. Third, even though self-reported treatment outcome measures that we used have been validated, information bias, rooted in self-reported data could have differentially occurred between the antiviral treatment groups. Fourth, some information (eg, duration and amount of antipyretic use) which might be associated the outcome of antiviral treatment was not collected during the trial. We were thus not able to assess the impact of these variables since we were not able to go back to collect that information. Fifth, our evaluation of influenza viral loads before and after administration of antivirals for this study used stored aliquoted samples, which could have suffered from degradation of the archived samples, especially for those with low viral load. Finally, it is also possible to have biases arising from missing data in the patient daily diary reports, and loss to follow-ups in this study.

In conclusion, in this ED randomized controlled clinical trial, we found the clinical and physical functionality outcomes of one-dose IV-administered peramivir was comparable to 5-day course oral oseltamivir for CDC-defined "high-risk" influenza patients. Influenza-related complications were minimal and side effects relevant to antiviral medication were mild and infrequent in both groups. While further cost-effectiveness studies are required, ED clinicians should consider the option of single-dose IV-administered peramivir for treating influenza-infected ED patients, especially those who already have intravenous lines in place.

ACKNOWLEDGEMENTS

The ED National Influenza Network Investigators:

Maricopa: Mary Mulrow, RN.

Johns Hopkins: Michele-Corinne Ako; Alaina Hergenroeder; Austin Ritter; Yewande Komolafe; Cierra Zaslowe-Dude; Ama Avornu; Eugene Ismailov; Chelsea Aika Gaviola; Ronke Adewale.

CONFLICT OF INTEREST

RER reports personal fees from Cepheid Inc, grants from Cepheid Inc, during the conduct of the study; personal fees from Roche Molecular, grants from Janssen, and grants from Cepheid, Inc, outside the submitted work. All other authors report no potential conflicts.

AUTHOR CONTRIBUTIONS

Yu-Hsiang Hsieh: Data curation (supporting); Formal analysis (lead); Investigation (supporting); Methodology (supporting); Validation (supporting); Visualization (lead); Writing-original draft (lead); Writing-review & editing (lead). Andrea Dugas: Conceptualization (equal); Data curation (lead); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Writing-review & editing (supporting). Frank LoVecchio: Data curation (supporting); Investigation (supporting); Project administration (supporting); Supervision (lead); Writing-review & editing (supporting). Breana McBryde: Data curation (supporting); Investigation (supporting); Project administration (supporting); Writing-review & editing (supporting). Erin Ricketts: Project administration (lead); Resources (supporting); Supervision (supporting); Writing-review & editing (supporting). Kathryn Shaw-Saliba: Investigation (supporting); Methodology (supporting); Supervision (supporting); Validation (supporting); Writing-review & editing (supporting). Richard E Rothman: Conceptualization (equal); Funding acquisition (lead); Investigation (lead); Methodology (lead); Project administration (lead); Resources (lead); Supervision (lead); Validation (lead); Visualization (supporting); Writing-review & editing (lead).

ETHICAL APPROVAL

Maricopa Medical Center, Phoenix, Arizona and The Johns Hopkins University School of Medicine Institutional Review Board approved the study.

Trial Registration: NCT02609399 "ED Influenza Therapeutic Pilot Study: Oseltamivir vs Peramivir".

ORCID

Yu-Hsiang Hsieh https://orcid.org/0000-0002-1616-8014

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Disease Burden of Influenza. https://www.cdc.gov/flu/about/disease/burden.htm. Accessed February 13, 2020.
2. Simonsen L, Higgs E, Taylor R, et al. Using clinical research networks to assess severity of an emerging influenza pandemic. *Clin Infect Dis*. 2018;67(3):341-349.
3. National Center for Immunization and Respiratory Diseases (NCIRD). Past Seasons Estimated Influenza Disease Burden. https://www.cdc.gov/flu/about/disease/burden.htm. Accessed February 13, 2020.
4. Schanzer D, Schwartz B. Impact of seasonal and pandemic influenza on emergency department visits, 2003–2010, Ontario, Canada. *Acad Emerg Med*. 2013;20(4):388-397.
5. Rui P, Kang K. National Hospital Ambulatory Medical Care Survey: 2015 Emergency Department Summary Tables. https://www.cdc.gov/nchs/data/nhamcs/web_tables/2015_ed_web_tables.pdf. Accessed December 11, 2018.
6. Fiore A, Fry A, Shay D, et al. Antiviral agents for the treatment and chemoprophylaxis of influenza –- recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2011;60(1):1-24.
7. National Center for Immunization and Respiratory Diseases (NCIRD). Influenza Antiviral Medications: Summary for Clinicians. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed December 13, 2018.
8. National Center for Immunization and Respiratory Diseases (NCIRD). What You Should Know About Influenza (Flu) Antiviral Drugs. https://www.cdc.gov/flu/pdf/freeresources/updated/antiviral-factsheet-updated.pdf. Accessed December 14, 2018.
9. Hsieh Y, Chen K, Gaydos C, Rothman R, Kelen G. Antiviral prescriptions to U.S. ambulatory care visits with a diagnosis of influenza before and after high level of adamantane resistance 2005–06 season. *PLoS One*. 2010;5(1):e8945.
10. U.S. Food and Drug Administration. FDA approves new drug to treat influenza. https://www.fda.gov/NewsEvents/Newsroom/

PressAnnouncements/ucm624226.htm. Accessed December 14, 2018.
11. Gubareva L, Fry A. Baloxavir and treatment-emergent resistance: public health insights and next steps. *J Infect Dis*. 2020;221(3):337-339.
12. Takashita E, Ichikawa M, Morita H, et al. Human-to-Human Transmission of Influenza A(H3N2) virus with reduced susceptibility to Baloxavir, Japan, February 2019. *Emerg Infect Dis*. 2019;25(11):2108-2111.
13. Kohno S, Yen M, Cheong H, 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(11):5267-5276.
14. Whitley R, Laughlin A, Carson S, et al. Single dose peramivir for the treatment of acute seasonal influenza: integrated analysis of efficacy and safety from two placebo-controlled trials. *Antivir Ther*. 2015;20(7):709-719.
15. Nakamura S, Miyazaki T, Izumikawa K, et al. Efficacy and safety of intravenous peramivir compared with oseltamivir in high-risk patients infected with influenza A and B viruses: a multicenter randomized controlled study. *Open Forum Infect Dis*. 2017;4(3):ofx129.
16. de Jong M, Ison M, Monto A, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. *Clin Infect Dis*. 2014;59(12):e172-e185.
17. Wester A, Shetty A. Peramivir injection in the treatment of acute influenza: a review of the literature. *Infect Drug Resist*. 2016;9:201-214.
18. Jr P, Bacci E, Leidy N, et al. Performance of the inFLUenza Patient-Reported Outcome (FLU-PRO) diary in patients with influenza-like illness (ILI). *PLoS One*. 2018;13(3):e0194180.
19. Feinstein A. *Global Indexes and Scales*. New Haven, CT: Yale University Press, Clinimetrics; 1987.
20. Yalcin I, Bump R. Validation of two global impression questionnaires for incontinence. *Am J Obstet Gynecol*. 2003;189(1):98-101.
21. Beigel J, Tebas P, Elie-Turenne M, et al. Immune plasma for the treatment of severe influenza: an open-label, multicentre, phase 2 randomised study. *Lancet Respir Med*. 2017;5(6):500-511.
22. West H, Jin J. JAMA oncology patient page - performance status in patients with cancer. *JAMA Oncol*. 2015;1(7):998.
23. Spencer S, Chung J, Thompson M, et al. Factors associated with real-time RT-PCR cycle threshold values among medically attended influenza episodes. *J Med Virol*. 2016;88(4):719-723.
24. Antiviral drugs for treatment and prophylaxis of seasonal influenza. *Med Lett Drugs Ther*. 2019;61(1563):1-4.
25. Aldridge C. First single-dose oral antiviral shortens duration of flu symptoms. *Pharmacy Today*. 2019;25(1):14.
26. Canadell L, Martín-Loeches I, Díaz E, et al. Degree of adherence to recommended antiviral treatment during the pandemic and post-pandemic periods of influenza A(H1N1)pdm09 in 148 intensive care units in Spain. *Med Intensiva*. 2015;39(4):222-233.
27. Brown T. EMA Panel Backs Zanamivir IV for Complicated, Severe Influenza.https://www.medscape.com/viewarticle/909744.Accessed February 27, 2020.
28. Dugas A, Hsieh Y, LoVecchio F, et al. Derivation and validation of a clinical decision guideline for influenza testing in four U.S. emergency departments. *Clin Infect Dis*. 2020;70(1):49-58.
29. Havers F, Flannery B, Clippard J, et al. Use of influenza antiviral medications among outpatients at high risk for influenza-associated complications during the 2013–2014 influenza season. *Clin Infect Dis*. 2015;60(11):1677-1680.
30. Anandappa M, Boakye A, Li W, Zeng W, Rebmann T, Chang J. Racial disparities in vaccination for seasonal influenza in early childhood. *Public Health*. 2018;158:1-8.
31. Iwane M, Chaves S, Szilagyi P, et al. Disparities between black and white children in hospitalizations associated with acute respiratory illness and laboratory-confirmed influenza and respiratory syncytial virus in 3 US counties–2002-2009. *Am J Epidemiol*. 2013;177(7):656-665.
32. Vupputuri S, Rubenstein K, Derus A, Loftus B, Horberg M. Factors contributing to racial disparities in influenza vaccinations. *PLoS One*. 2019;14(4):e0213972.
33. Yoo B, Kasajima M, Phelps C, Fiscella K, Bennett N, Szilagyi P. Influenza vaccine supply and racial/ethnic disparities in vaccination among the elderly. *Am J Prev Med*. 2011;40(1):1-10.
34. Schneider E, Cleary P, Zaslavsky A, Epstein A. Racial disparity in influenza vaccination: does managed care narrow the gap between African Americans and whites? *JAMA*. 2001;286(12):1455-1460.
35. Quinn S, Hilyard K, Castaneda-Angarita N, Freimuth V. Public acceptance of peramivir during the 2009 H1N1 influenza pandemic: implications for other drugs or vaccines under emergency use authorizations. *Disaster Med Public Health Prep*. 2015;9(2):166-174.

How to cite this article: Hsieh Y-H, Dugas AF, LoVecchio F, et al. Intravenous peramivir vs oral oseltamivir in high-risk emergency department patients with influenza: Results from a pilot randomized controlled study. *Influenza Other Respi Viruses*. 2021;15:121–131. https://doi.org/10.1111/irv.12794

Original Article
Yonsei Med J 2017 Jul;58(4):778-785
https://doi.org/10.3349/ymj.2017.58.4.778
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Comparison of Efficacy of Intravenous Peramivir and Oral Oseltamivir for the Treatment of Influenza: Systematic Review and Meta-Analysis

Jonghoo Lee[1*], Ju-Hee Park[2*], Hyeyoung Jwa[1], and Yee Hyung Kim[3]

[1]Department of Internal Medicine, Jeju National University Hospital, Jeju National University School of Medicine, Jeju;
[2]Division of Pulmonary and Critical Care Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul;
[3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, Seoul, Korea.

Purpose: Peramivir is the first intravenously administered neuramidase inhibitor for immediate delivery of an effective single-dose treatment in patients with influenza. However, limited data are available on intravenous (IV) peramivir treatment compared to oral oseltamivir for these patients.

Materials and Methods: With a systematic review and meta-analysis, we compared the efficacy of IV peramivir with oral oseltamivir for treatment of patients with seasonal influenza. MEDLINE, EMBASE, and Cochrane Central Register were searched for relevant clinical trials.

Results: A total of seven trials [two randomized controlled trials (RCTs) and five non-randomized observational trials] involving 1676 patients were finally analyzed. The total number of peramivir- and oseltamivir-treated patients was 956 and 720, respectively. Overall, the time to alleviation of fever was lower in the peramivir-treated group compared with the oseltamivir-treated group [mean difference (MD), -7.17 hours; 95% confidence interval (CI) -11.00 to -3.34]. Especially, pooled analysis of observational studies (n=4) and studies of outpatients (n=4) demonstrated the superiority of the peramivir-treated group (MD, -7.83 hours; 95% CI -11.81 to -3.84 and MD, -7.71 hours; 95% CI -11.61 to -3.80, respectively). Mortality, length of hospital stay, change in virus titer 48 hours after admission, and the incidence of adverse events in these patients were not significantly different between the two groups.

Conclusion: IV peramivir therapy might reduce the time to alleviation of fever in comparison with oral oseltamivir therapy in patients with influenza; however, we could not draw clear conclusions from a meta-analysis because of the few RCTs available and methodological limitations.

Key Words: Influenza, human, peramivir, oseltamivir, fever, signs and symptoms, respiratory

Received: February 9, 2017 **Revised:** March 24, 2017
Accepted: March 27, 2017
Corresponding author: Dr. Yee Hyung Kim, Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, Kyung Hee University School of Medicine, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea.
Tel: 82-2-440-6281, Fax: 82-2-440-8150, E-mail: yhkim2007@hotmail.co.kr

*Jonghoo Lee and Ju-Hee Park contributed equally to this work.
•The authors have no financial conflicts of interest.

INTRODUCTION

Influenza viruses are important global pathogens with an estimated annual attack rate of 5–10% in adults and 20–30% in children, resulting in substantial disease incidence, hospitalization, and mortality.[1] The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommended three U.S. Food and Drug Administration (FDA)-approved influenza antiviral agents [oral oseltamivir, inhaled zanamivir, and intravenous (IV) peramivir] for the prevention and control of influenza during the 2015–2016 influenza season.[2]

Oseltamivir (F. Hoffmann-La Roche, Ltd., Basel, Switzerland) is the antiviral agent most frequently used for the treatment and prevention of influenza, and its use has increased since pandemic influenza A (H1N1) 2009. Because oseltamivir is administered via an oral route, it is often difficult to use in some cases, particularly in young children, patients with aspiration tendency, critically ill patients or patients requiring mechanical ventilation. Therefore, novel or additional effective agents are needed.[3]

Peramivir (BioCryst Pharmaceuticals Inc., Durham, NC, USA) is an antiviral agent that blocks viral growth by selectively inhibiting neuramidase (NA), an enzyme that releases viral particles from infected cells, in human influenza A and B viruses, and is administered once daily through an IV route.[3] It was licensed in Japan and South Korea in 2010.[3] In the United States, IV peramivir is still under investigation as an NA inhibitor (NAI), but it was made temporarily available in 2009 for hospitalized patients infected with pandemic influenza A (H1N1) under an Emergency Use Authorization.[4] Recent randomized controlled trials (RCTs) demonstrated that IV peramivir showed better clinical efficacy and antiviral activity than a placebo in uncomplicated influenza and was safe and well tolerated.[5,6]

Since the 2010s, several RCTs or observational studies (OBSs), comparing the clinical efficacy of peramivir with that of oseltamivir in influenza patients, have been published.[7-13] However, there is a lack of evidence regarding whether IV peramivir or oral oseltamivir should be used for initial treatment in patients with influenza. Accordingly, the purpose of the present study was to compare the clinical efficacy of these two antiviral agents through a systematic review and meta-analysis of data from clinical trials.

MATERIALS AND METHODS

Data sources and search strategy

To identify potentially relevant articles, a comprehensive search of three electronic databases (MEDLINE, EMBASE, and Cochrane Central Register) up to December 2016 was performed. The search used keywords related to peramivir: BCX-1812; RWJ 270201; oseltamivir; tamiflu; influenza; flu; H1N1; antivirals; and neuramidase inhibitors; search filters provided by SIGN (http://www.sign.ac.uk/methodology/filters.html) were used. There were no language restrictions and the search was limited to human studies. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed. In addition, we performed a manual search of the references listed in relevant review articles. As this study was a systematic review of published articles, neither informed consent nor ethics approval was required.

Inclusion criteria

A systematic review and meta-analysis were performed on studies that met the following criteria: 1) randomized controlled or observational cohort studies that treated influenza virus infection; 2) comparison of IV peramivir vs. oral oseltamivir; and 3) the presence of clinical outcomes and/or adverse events.

Study selection and data extraction

Two pulmonologists (JHL and YHK) independently retrieved potentially relevant studies and reviewed each study according to predefined criteria for eligibility, and finally extracted data. Any disagreement in the process of study selection or data extraction was resolved through consensus. A predefined form was used to extract data from each study. We used only officially published data. Primary outcomes were the time to alleviation of fever after treatment of antiviral agents. We also assessed changes in viral titer, mortality, length of hospital stay and the incidence of adverse events.

Quality assessment

As recommended by the Cochrane Collaboration, we used the Newcastle-Ottawa quality assessment scale (NOS) to assess the risk of bias in OBSs.[14] NOS uses a star system to evaluate nonrandomized OBSs in the following three domains: selection, comparability and exposure/outcome. Studies that received a star in each domain were considered to be of high quality.

The quality of RCTs was assessed using the Cochrane Handbook for Systematic Reviews of Interventions 'risk of bias' tool.[15] Risk of bias was assigned to the following domains as 'low', 'high' or 'unclear': sequence generation/allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. Agreement between reviewers was achieved through a consensus.

Statistical analysis

We analyzed data in Review Manager Software, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Random-effects models were applied. As for dichotomous variables, treatment effects were presented as risk ratios (RRs) with 95% confidence intervals (CIs) via the Mantel-Haenzel method. Statistical estimates for continuous variables were expressed as raw mean differences (MDs). The heterogeneity was assessed using I^2 statistics on a scale of 0–100%. I^2 >50% indicated a substantial level of between-study heterogeneity. If necessary, we also investigated the influence of an individual study on the overall effect estimates by removing each study in turn to explore the robustness of the pooled effect. Subgroups were analyzed as necessary. A p value <0.05 was considered statistically significant.

RESULTS

Study search

A total of 19155 published articles were initially identified through database searches. After removing duplicate articles, we screened 15554 potentially eligible articles from database searches. Of these articles, 15497 were excluded based on the title and abstract. Therefore, 57 articles remained and two potentially eligible articles were added from their reference lists. A total of 59 articles underwent full-text review. Fifty-two articles were excluded for the reasons presented in Fig. 1. Finally, a total of 7 articles were included in the current analysis.[7-13] Of these trials, two trials were RCTs and the remaining 5 trials were OBSs. All were published between 2011 and 2015. The features of the included studies are shown in Table 1. The number of patients in each trial ranged from 32 to 1091. The total number of patients in our systematic review and meta-analysis was 1676, of whom 956 were treated with IV peramivir and 720 received oral oseltamivir. Quality assessment findings of RCTs and non-randomized OBSs are demonstrated in Fig. 2 and Table 2, respectively.

Primary outcome

Fig. 3 shows the effect of IV peramivir and oral oseltamivir on the time to alleviation of influenza symptoms. Overall, a random effect model indicated that the peramivir-treated group had a significantly shorter time to alleviation of influenza symptoms or fever compared with the oseltamivir-treated group (MD, -7.17 hours; 95% CI -11.00 to -3.34; p<0.01; I^2=2%).[7-11,13] Subgroup analyses of RCTs and OBSs were performed. Although a pooled analysis of OBSs demonstrated the superiority of peramivir-treated group (MD, -7.83 hours; 95% CI -11.81 to -3.84; p<0.01; I^2=0%),[9-11,13] that of RCTs did not (MD, 5.86 hours; 95% CI -24.66 to 36.38; p=0.71; I^2=52%).[7,8] Additionally, a subgroup analysis of studies on outpatients showed that the peramivir-treated group had significantly better outcomes than the oseltamivir-treated group (MD, -7.71 hours; 95% CI -11.61 to -3.80; p<0.01; I^2=0%, respectively) in terms of the time to alleviation of fever (Fig. 4B).[8-11] However, an analysis of studies on hospitalized patients did not reveal a significant difference between groups (MD, 6.22 hours; 95% CI -24.16 to 36.60; p=0.69; I^2=50%) (Fig. 4A).[7,13]

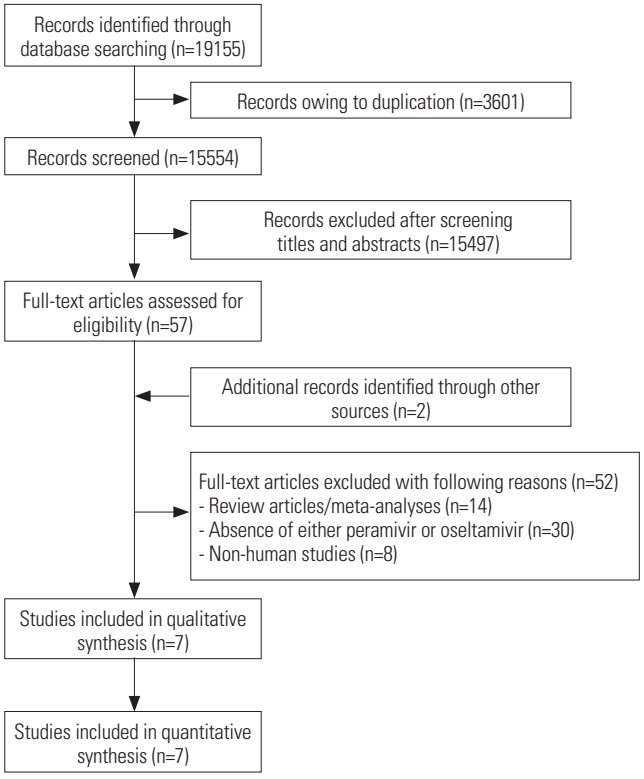


Fig. 1. Flow chart of study selection.

Secondary outcomes

Total mortality and length of hospital stay were reported in two trials, respectively.[12,13] A random effect model showed that total mortality was not significantly different between the peramivir and oseltamivir treatment groups (28.0% vs. 34.2%; RR, 0.96; 95% CI 0.55 to 1.68; p=0.90; I^2=0%) (Fig. 5A).[12,13] Length of hospital stay in the peramivir-treated group was also similar to that in the oseltamivir-treated group (MD, 0 days; 95% CI -1.19 to 1.20; p=1.00; I^2=0%) (Fig. 5B).[7,12]

We were able to retrieve data concerning the change in influenza virus titer for 48 hours after admission from two RCTs. Pooled analysis did not reveal a significant difference between the two treatment groups (MD, -0.06 $\log_{10}$ $TCID_{50}$/mL; 95% CI, -0.20 to 0.08; p=0.38; I^2=0%) (Fig. 5C).[7,8]

Adverse events

As shown in Fig. 6A, the incidence of adverse events was not significantly different between peramivir- and oseltamivir-treated groups (72.3% vs. 75.2%; RR, 1.05; 95% CI 0.77 to 1.43; p=0.76; I^2=63%).[7,8,13] Pooled estimates also revealed no significant differences in the rates of serious adverse events between the two groups (7.2% vs. 6.8%; RR, 1.06; 95% CI 0.69 to 1.63; p=0.80; I^2=0%) (Fig. 6B).[7,8]

DICUSSION

Our study showed that IV peramivir might reduce the time to alleviation of fever compared with oral oseltamivir among patients with influenza. The clinical efficacy of IV peramivir therapy was first reported in a placebo-controlled, double-blind phase II study in patients with uncomplicated seasonal influenza.[5] At both 300 and 600 mg, a single IV peramivir infusion significantly reduced the time to alleviation of symptoms for adult influenza outpatients.[5] After that, a randomized, double-blind phase III study conducted in Japan, Taiwan, and South Korea compared IV peramivir (a 300- or 600-mg single infusion) with oral oseltamivir (75 mg twice a day for 5 days) in uncomplicated cases of seasonal influenza, and demonstrated the non-inferiority of peramivir therapy to oseltamivir in terms of

https://doi.org/10.3349/ymj.2017.58.4.778

https://doi.org/10.3349/ymj.2017.58.4.778

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Study	Design	Study period	Total patients (no.)	Age (mean)	Age group	Male (%)	Treatment location	Identified influenza virus subtype	Intervention protocol	Major outcomes reported
Randomized controlled trials										
Ison, et al.[7]	Multinational, multicenter, double-blind	July 2007–September 2008	137	59.3	Adult	46.7	Hospital	A (H1N1), A (H3N2), B	5-day treatment with intravenous peramivir once daily vs. oral oseltamivir twice daily	Time to clinical stability, time to alleviation of symptoms, time to discharge, the change in influenza virus titer, adverse events
Kohno, et al.[8]	Multinational, multicenter, double-blind, double-dummy	November 2008–April 2009	1091	35.1	Adult	51.5	-	A (H1), A (H3), B	Single-dose intravenous peramivir vs. oral oseltamivir twice daily for 5 days	Time to alleviation of influenza symptoms, the change in influenza virus titer, adverse events
Observational studies										
Hikita, et al.[9]	Two-center, prospective single-arm study	February 2011–April 2011	223	6.4	Child	55.1	Outpatient clinics	A, B	Single-dose intravenous peramivir vs. other neuramidase inhibitors (oral oseltamivir twice daily for 5 days or single-dose inhaled laninamivir, or inhaled zanamivir twice daily for 5 days)	Time to alleviation of fever
Shobugawa, et al.[10]	Two-center, retrospective single-arm study	December 2010–March 2011	108	5.2	Mix	51.8	Outpatient clinics	A (H3N2)	Oral oseltamivir twice daily for 5 days or inhaled zanamivir twice daily for 5 days or a single inhaled laninamivir once, or a single intravenous peramivir once	Time to alleviation of influenza symptoms
Takemoto, et al.[11]	Multicenter, retrospective single-arm study	November 2012–March 2013	104	27.0	Mix	55.7	Outpatient clinics	A, B	Oral oseltamivir twice daily for 5 days or inhaled zanamivir twice daily for 5 days or single-dose inhaled laninamivir, or single-dose intravenous peramivir	Time to alleviation of fever
Yoo, et al.[12]	Single-center, retrospective cross-over study	December 2010–March 2014	60	68.0	Adult	55.0	Intensive care unit	A, B	Intravenous peramivir once daily for a median of 6 days vs. oral oseltamivir twice daily for a median of 5.5 days	Clinical complications, management, and clinical outcomes
Yoshino, et al.[13]	Single-center, retrospective single-arm study	October 2012–March 2013	32	75.5	Adult	56.0	Hospital	-	Single-dose intravenous peramivir vs. oral oseltamivir twice daily for 5 days	Time to defervescence and survival rate

the time to alleviation of symptoms.[8] However, due to the scarcity of clinical comparisons, we sought to determine which antiviral agent was superior through a meta-analysis of previous trials.

In our study, the time to alleviation of fever was considered a primary outcome when evaluating the clinical efficacy of antiviral agents for patients with influenza because it was regarded as the most important parameter in clinical studies. Although OBSs demonstrated the superiority of IV peramivir therapy with regard to fever, we could not draw concrete conclusions because the results of subgroup analysis from RCTs were ambiguous.

In addition, we compared the time to alleviation of fever according to whether patients were hospitalized or not. Although the US FDA approved peramivir as the first IV NAI for patients with uncomplicated influenza,[16] a recent placebo-controlled, double-blind RCT did not demonstrate the clinical benefit of IV peramivir in hospitalized patients with influenza.[17] No antiviral agents have been approved specifically for the treatment of influenza in hospitalized patients. In our meta-analysis, there were no statistically significant differences between treatment groups in hospitalized patients with influenza. Therefore, we could not confirm whether IV peramivir or oral olsetamivir was more effective in patients with serious influenza requiring hospitalization.

Total mortality, length of hospital stay, and changes in viral titers are key parameters of the clinical and virological effectiveness of antiviral agents. Our results revealed that these parameters did not differ between peramivir and olsetamivir treatment groups. In a RCT that enrolled 288 healthy volunteers (aged 18–45 years) intranasally inoculated with experimental influenza A or B, oral peramivir treatment at a dosage of 400 mg once daily for 5 days significantly reduced viral detection, defined by the area under the curve for nasal wash viral titers of influenza A.[18] And both 400 and 800 mg once daily for 5 days reduced viral titer of influenza B.[18] Although we evaluated changes in viral titers from base-line to 48 hours, no significant difference in virological effects was found between two groups.

In addition to clinical efficacy, adverse events are critical factors in the selection of an antiviral agent. Although we conducted a meta-analysis of adverse events using two RCT studies and one OBS,[7,8,13] the results showed no statistically significant differences in rates of any or serious adverse events between patients treated with peramivir and those treated with oselta-

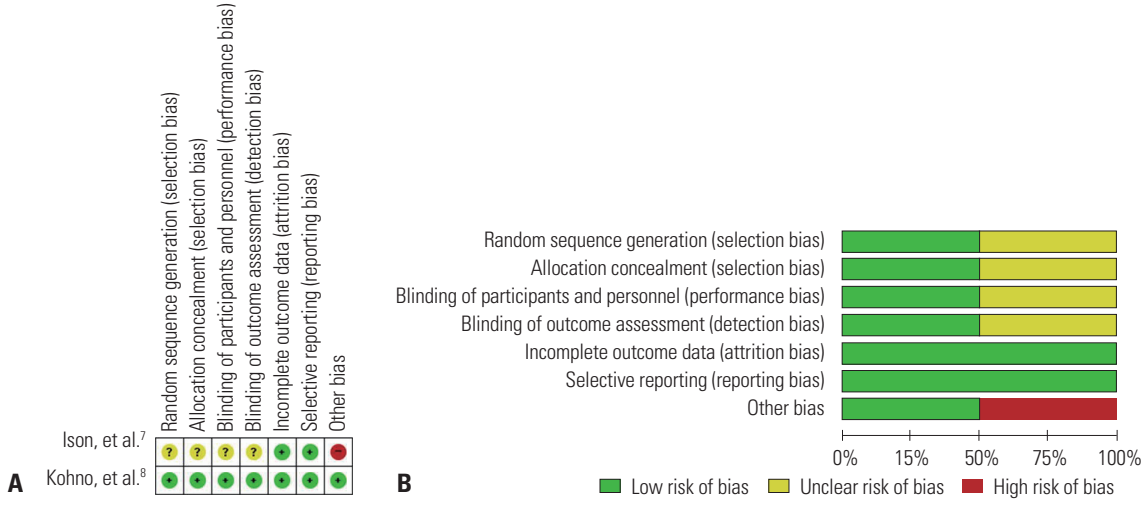


Fig. 2. Risk of bias summary (A) and risk of bias graph (B) for randomized controlled studies included in this meta-analysis.

Table 2. Risk of Bias within Non-Randomized Trials Using Newcastle-Ottawa Scale

Study	Selection				Comparability	Outcome of interest			Overall quality
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cohorts	Outcome assessment	Same methods of ascertainment for cases and controls	Non-response rate	
Hikita, et al.[9]	★	★	★	★	★	★	★	NA	High
Shobugawa, et al.[10]	★	★	★	★	★	★	★	NA	High
Takemoto, et al.[11]	★	★	★	★	★	★	★	NA	High
Yoo, et al.[12]	★	★	★	★	★	★	★	NA	High
Yoshino, et al.[13]	★	★	★	★	★	★	★	NA	High

NA, not applicable.
Studies that received a star in all three domains were judged to be of high quality. Retrospective studies were all assumed to have adequate follow-up.

https://doi.org/10.3349/ymj.2017.58.4.778

mivir. Most adverse events were mild or moderate. Pooled estimated results suggested that the incidence of severe adverse events was similar in the peramivir and oseltamivir groups (7.2% and 6.8%, p=0.08). Gastrointestinal symptoms such as diarrhea, nausea, and vomiting were the most common adverse effects in both treatment groups. The similar clinical efficacy and adverse event findings of this systematic review suggest that the choice between oseltamivir and peramivir therapy could be decided based upon the convenience of administration (IV vs. oral), the ease with which medications can be purchased, and the preference of the patient or physician. Several previous OBSs and subgroup analysis in our study showed IV peramivir to have superior efficacy in terms of the time to alleviation of fever. However, the lack of differences in total mortality rate, length of hospital stay and changes in viral titers indicate little or no difference in clinical efficacy between the two agents.

The development of influenza antiviral drug resistance in vi-

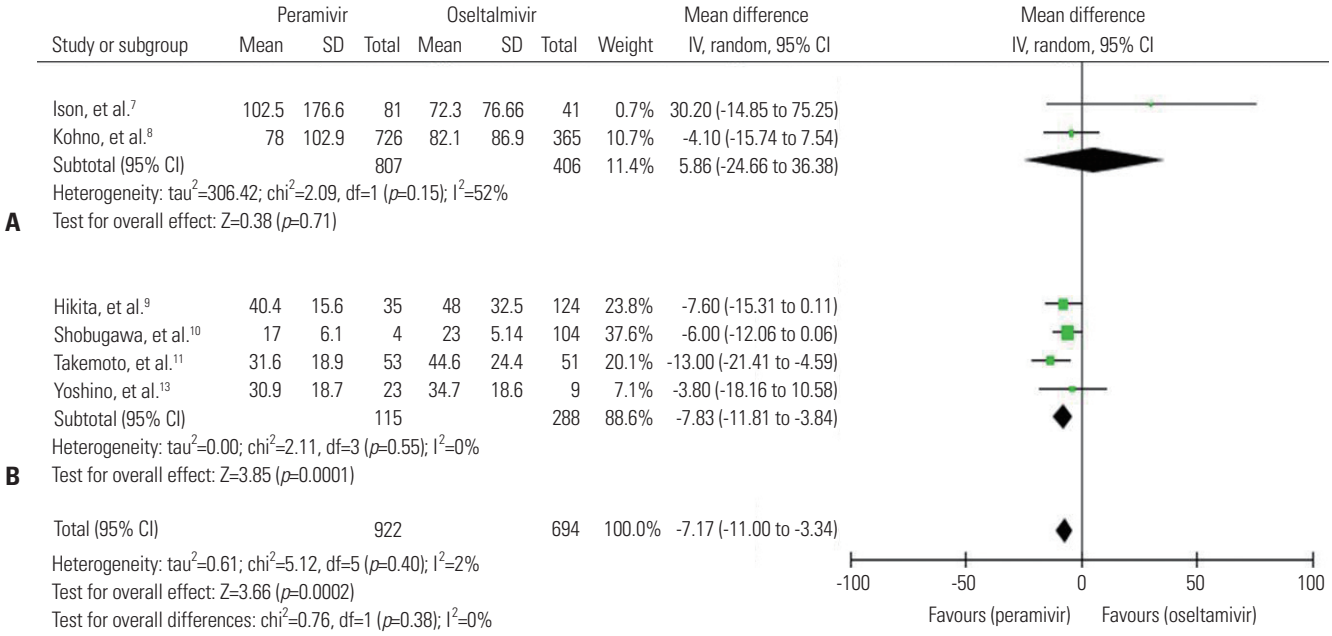


Fig. 3. Pooled adjusted risk ratio results for time to alleviation of fever among patients with influenza treated with intravenous peramivir versus oral oseltamivir in randomized controlled trials (A) and observational studies (B). SD, standard difference; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

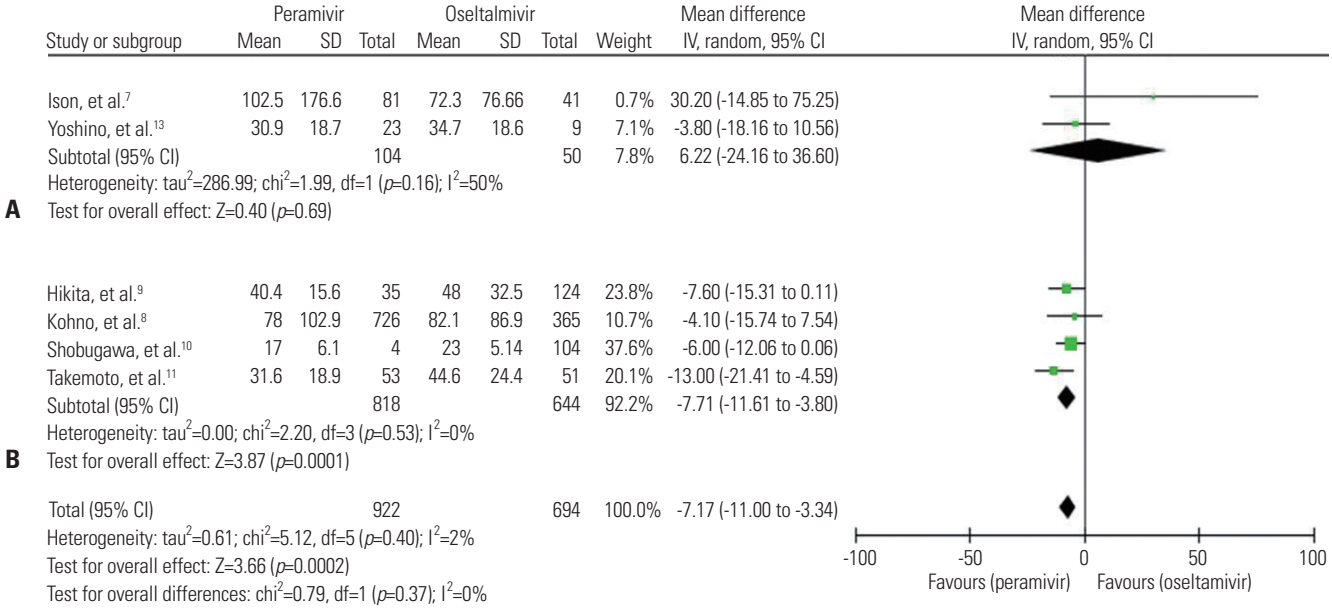
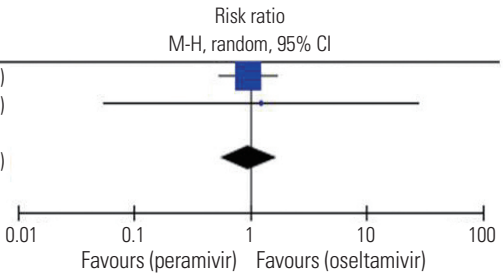


Fig. 4. Pooled adjusted risk ratio results for time to alleviation of fever with intravenous peramivir versus oral oseltamivir in inpatients (A) and outpatients (B) with influenza. SD, standard difference; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

A

Study or subgroup	Peramivir Events	Peramivir Total	Oseltamivir Events	Oseltamivir Total	Weight	Risk ratio M-H, random, 95% CI
Yoo, et al.[12]	15	34	12	26	96.8%	0.96 (0.55 to 1.68)
Yoshino, et al.[13]	1	23	0	9	3.2%	1.25 (0.06 to 28.15)
Total (95% CI)		57		35	100.0%	0.96 (0.55 to 1.68)
Total events	16		12			

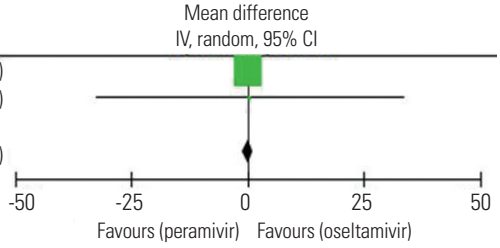
Heterogeneity: tau^2=0.00; chi^2=0.03, df=1 (p=0.87); I^2=0%
Test for overall effect: Z=0.13 (p=0.90)



B

Study or subgroup	Peramivir Mean	Peramivir SD	Peramivir Total	Oseltamivir Mean	Oseltamivir SD	Oseltamivir Total	Weight	Mean difference IV, random, 95% CI
Ison, et al.[7]	3.7	4.1	81	3.7	2.6	41	99.9%	0.00 (-1.20 to 1.20)
Yoo, et al.[12]	20.5	53.5	34	20	72.2	26	0.1%	0.50 (-32.57 to 33.57)
Total (95% CI)			115			67	100.0%	0.00 (-1.19 to 1.20)

Heterogeneity: tau^2=0.00; chi^2=0.00, df=1 (p=0.98); I^2=0%
Test for overall effect: Z=0.00 (p=1.00)



C

Study or subgroup	Peramivir Mean	Peramivir SD	Peramivir Total	Oseltamivir Mean	Oseltamivir SD	Oseltamivir Total	Weight	Mean difference IV, random, 95% CI
Ison, et al.[7]	-2.39	1	81	-2.2	1.4	41	8.4%	-0.19 (-0.67 to 0.29)
Kohno, et al.[8]	-1.09	0.86	393	-1.04	0.84	195	91.6%	-0.05 (-0.20 to 0.10)
Total (95% CI)			474			236	100.0%	-0.06 (-0.20 to 0.08)

Heterogeneity: tau^2=0.00; chi^2=0.30, df=1 (p=0.58); I^2=0%
Test for overall effect: Z=0.87 (p=0.38)

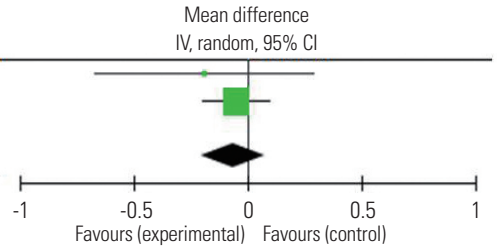
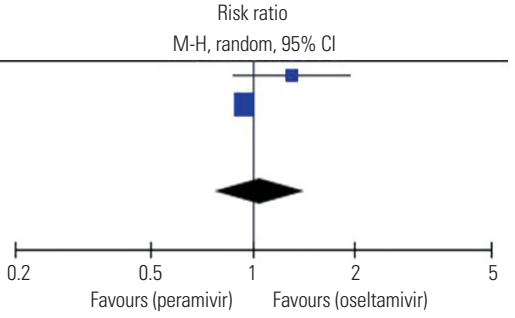


Fig. 5. Pooled adjusted odds ratio results for secondary among patients with influenza treated with intravenous peramivir versus oral oseltamivir. Mortality (A), length of hospital stay in days (B), and changes in viral titers from baseline (C) to 48 hours. M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom; SD, standard difference; IV, inverse variance.

A

Study or subgroup	Peramivir Events	Peramivir Total	Oseltamivir Events	Oseltamivir Total	Weight	Risk ratio M-H, random, 95% CI
Ison, et al.[7]	49	91	19	46	32.4%	1.30 (0.88 to 1.93)
Kohno, et al.[8]	560	728	297	365	67.6%	0.95 (0.89 to 1.01)
Yoshino, et al.[13]	0	23	0	9		Not estimable
Subtotal (95% CI)		842		420	100.0%	1.05 (0.77 to 1.43)
Total events	609		316			

Heterogeneity: tau^2=0.04; chi^2=2.70, df=1 (p=0.10); I^2=63%
Test for overall effect: Z=0.31 (p=0.76)



B

Study or subgroup	Peramivir Events	Peramivir Total	Oseltamivir Events	Oseltamivir Total	Weight	Risk ratio M-H, random, 95% CI
Ison, et al.[7]	10	91	4	46	15.4%	1.26 (0.42 to 3.81)
Kohno, et al.[8]	49	728	24	365	84.6%	1.02 (0.64 to 1.64)
Subtotal (95% CI)		819		411	100.0%	1.06 (0.69 to 1.63)
Total events	59		28			

Heterogeneity: tau^2=0.00; chi^2=0.12, df=1 (p=0.73); I^2=0%
Test for overall effect: Z=0.25 (p=0.80)

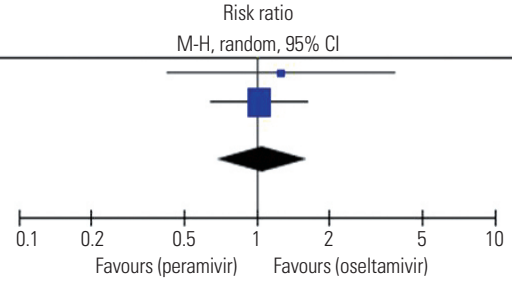


Fig. 6. Pooled analysis of adverse events among patients with influenza treated with intravenous peramivir versus oral oseltamivir. All adverse events (A) and serious adverse events (B). M-H, Mantel-Haenszel; CI, confidence interval; df, degrees of freedom.

https://doi.org/10.3349/ymj.2017.58.4.778

ruses is a major concern. Therefore, when considering which drug to choose, resistance should be considered. The H274Y mutation is associated with resistance to oseltamivir and peramivir and mutations at I222 and R292 can reduce peramivir sensitivity.[19] The incidence of resistance to oseltamivir and/or peramivir in Japan and USA during the 2013–2014 influenza season was 4.2% and 1.2% for influenza A (H1N1) pdm09, respectively. This might mean that, in spite of the low resistance rate, a particular drug could be superior to others in specific situations.

Our study has some limitations. First, since our meta-analysis considered only a small number of trials, our results should be interpreted with caution. Second, the publication bias inherent to all meta-analyses might have influenced these results. However, since the number of included trials was small, we could not estimate potential publication bias with a funnel plot for all outcomes. Third, the dosage and the duration of IV peramivir treatment varied among studies, which could affect the precision of the results. As a result, we think that additional large-scale RCTs are needed to overcome these limitations. Finally, we tried to compare the efficacy of two drugs between children and adults. We found six studies for primary outcome.[7-11,13] There are three studies for adults,[7,8,13] and one study for children.[9] The remaining two studies examined mixed group including adults and children.[10,11] Accordingly, we could not perform a meta-analysis for children group. Instead, we evaluated the time to alleviation of fever after treatment of antiviral agents on adults group.[7,8,13] Pooled estimates revealed no significant difference between two treatments (MD, -2.51 hours; 95% CI -11.88 to 6.86; p=0.60; I^2=6%).

In conclusion, our systematic review and meta-analysis suggested that IV peramivir might reduce the time to alleviation of fever among patients with influenza compared to oral oseltamivir. However, because the methodological limitations of the included trials and the scarcity of trials prevented us from drawing firm conclusions, the clinical benefit and/or superiority of IV peramivir to oral oseltamivir remains unclear in these patients. Accordingly, further large-scale RCTs are needed to establish appropriate criteria with regard to the selection of optimal NAIs for patients with influenza.

ACKNOWLEDGEMENTS

This research was supported by the 2017 scientific promotion program funded by Jeju National University.

REFERENCES

1. Vaccines against influenza WHO position paper–November 2012. Wkly Epidemiol Rec 2012;87:461-76.
2. Centers for Diseases Control and Prevention. Vaccine Recommendations of the ACIP [accessed on 2016 December 27]. Available at: https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/flu.html.
3. Wester A, Shetty AK. Peramivir injection in the treatment of acute influenza: a review of the literature. Infect Drug Resist 2016;9:201-14.
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. Kohno S, Kida H, Mizuguchi M, Shimada J; S-021812 Clinical Study Group. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. Antimicrob Agents Chemother 2010;54:4568-74.
6. Kohno S, Kida H, Mizuguchi M, Hirotsu N, Ishida T, Kadota J, et al. Intravenous peramivir for treatment of influenza A and B virus infection in high-risk patients. Antimicrob Agents Chemother 2011;55:2803-12.
7. 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.
8. 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.
9. 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.
10. Shobugawa Y, Saito R, Sato I, Kawashima T, Dapat C, Dapat IC, et al. Clinical effectiveness of neuraminidase inhibitors--oseltamivir, zanamivir, laninamivir, and peramivir--for treatment of influenza A(H3N2) and A(H1N1)pdm09 infection: an observational study in the 2010-2011 influenza season in Japan. J Infect Chemother 2012;18:858-64.
11. Takemoto Y, Asai T, Ikezoe I, Yano T, Ichikawa M, Miyagawa S, et al. Clinical effects of oseltamivir, zanamivir, laninamivir and peramivir on seasonal influenza infection in outpatients in Japan during the winter of 2012-2013. Chemotherapy 2013;59:373-8.
12. 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.
13. 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.
14. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses [accessed on 2016 December 27]. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
15. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
16. Alame MM, Massaad E, Zaraket H. Peramivir: a novel intravenous neuraminidase inhibitor for treatment of acute influenza infections. Front Microbiol 2016;7:450.
17. 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.
18. Barroso L, Treanor J, Gubareva L, Hayden FG. Efficacy and tolerability of the oral neuraminidase inhibitor peramivir in experimental human influenza: randomized, controlled trials for prophylaxis and treatment. Antivir Ther 2005;10:901-10.
19. 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.

Open Forum Infectious Diseases

MAJOR ARTICLE

Efficacy and Safety of Intravenous Peramivir Compared With Oseltamivir in High-Risk Patients Infected With Influenza A and B Viruses: A Multicenter Randomized Controlled Study

Shigeki Nakamura,[1,6] Taiga Miyazaki,[1,2] Koichi Izumikawa,[2] Hiroshi Kakeya,[3] Yutaka Saisho,[4] Katsunori Yanagihara,[5] Yoshitsugu Miyazaki,[6] Hiroshi Mukae,[1] and Shigeru Kohno[1]

[1]Department of Respiratory Diseases, Nagasaki University Hospital, [2]Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, [3]Department of Infection Control Science, Graduate School of Medicine, Osaka City University, [4]Medical Affairs, Shionogi & Co, Ltd, Osaka, [5]Department of Laboratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, and [6]Department of Chemotherapy and Mycoses, National Institute of Infectious Diseases, Tokyo, Japan

Background. Clinical studies comparing the different neuraminidase inhibitors for treatment of at-risk patients with influenza have not been performed. To optimize such treatments, we assessed the efficacy and safety of intravenous peramivir compared with oral oseltamivir in treating seasonal influenza A or B virus infection.

Methods. A multicenter, randomized, controlled clinical trial was conducted from December 2012 to May 2014 in high-risk patients infected with seasonal influenza. A total of 92 adult inpatients and outpatients with high risk factors (HRFs) were treated by either a single intravenous infusion of peramivir (600 mg) or oral administration of oseltamivir (75 mg, twice per day for 5 days).

Results. The median times to clinical stability (time to reach <37°C) were 40.0 hours (95% confidence interval [CI] = 23.3–64.5) and 37.8 hours (95% CI = 26.3–45.3) in the peramivir and oseltamivir groups, respectively; these values did not reveal a significant difference. The virus titer and change of mean total symptom scores decreased similarly with both treatments. Results of step-wise regression suggested that virus type was a significantly effective prognostic factor with respect to illness resolution. Adverse events (AEs) with peramivir and oseltamivir occurred in 2.2% (n = 1/46) and 13.0% (n = 6/46) of patients, respectively. The severity of AEs was mild in all cases except 2 patients who showed pneumonia or COPD aggravation; both were in the oseltamivir group.

Conclusions. Intravenous peramivir was effective based on the result of direct comparison with oral oseltamivir. Thus our data show that peramivir is a useful option for the treatment of influenza-infected patients with HRFs.

Keywords. high-risk patient; influenza; neuraminidase inhibitor; oseltamivir; peramivir.

Influenza virus infection remains a major global health concern. The emergence of novel influenza viruses such as A/H1N1 pdm09 virus (in the 2009 pandemic) has significantly increased hospitalizations and death rates due to lack of immune memory. The avian A/H7N9 virus may follow the same path, although the avian virus currently has a lower potential for human-to-human transmission.

Neuraminidase inhibitors (NAIs) exhibit potent inhibitory activity against neuraminidase (NA), the spike protein of influenza virus. Several recent meta-analyses [1–3] suggest that early treatment (within 48 hours after the onset of illness) with an NAI reduces the risk of hospitalization or death. The morbidity and mortality of influenza infection can be higher, particularly in high-risk populations, which include the elderly and individuals with underlying diseases (respiratory tract diseases, heart diseases, diabetes, immunodeficiency, etc) [4]. Thus, treatment with an NAI is considered essential for high-risk patients. However, this distinction in patient populations is based on an observational study, meaning that high-quality data from randomized controlled studies are lacking.

Peramivir was approved in Japan in 2010 and the compound's clinical effectiveness, especially rapid fever alleviation [5–8], has been reported since then. A previous Ph3 study (consisting of 42 high-risk patients) demonstrated that high-dose peramivir (600 mg/d, repeating dose accepted) provided significant effectiveness in decreasing the duration of influenza illness and fever alleviation compared with low-dose peramivir (300 mg/d, repeating dose accepted) [9]. In addition, several reports have indicated the efficacies of peramivir for the treatment of critically ill patients who seldom benefit from NAIs [10, 11]. In

Received 12 April 2017; editorial decision 14 June 2017; accepted 16 June 2017.

Correspondence: S. Nakamura, MD, PhD, 1-23-1 Toyama, Shinjuku-ku, Tokyo 162–8640, Japan (shigekinak@nih.go.jp).

Open Forum Infectious Diseases®

DOI: 10.1093/ofid/ofx129

animal studies, intravenous peramivir has shown robust efficacy in the treatment of lethal influenza and of secondary pneumococcal pneumonia following influenza virus infection [12–14]. Peramivir may have demonstrated efficacy in these studies due to a strong suppressive effect on the initial growth of influenza virus; notably, this compound rapidly reaches high concentrations in the plasma and upper respiratory tract during the early stages of infection [15]. That article suggested that the efficacy of NAIs may be better assessed by measuring viral clearance or alleviation of fever at earlier time points, especially in high-risk patients showing individual differences in immune response [15]. In this context, Kohno et al reported (in a Ph3 study) that peramivir showed significant earlier reduction of these endpoints at day 2, compared with oseltamivir, in patients infected by oseltamivir-resistant virus [16]. Moreover, a significant difference was observed retrospectively in several endpoints, including complications [17–19], mortality [20, 21], length of hospital stay [22], and viral shedding [23], in high-risk or hospitalized patients treated with oseltamivir compared with those not given an NAI.

However, peramivir lacks effectiveness in complicated patients. The single randomized, controlled study of intravenous peramivir in hospitalized patients was terminated for futility and failed to show efficacy [24]. Additionally, observational data from the 2009 pandemic raised concerns regarding serious adverse events in critically ill patients given peramivir [25].

We are unaware of published reports presenting comparative data for the treatment of high-risk outpatients with any pair of different NAIs. Such a study would enable determination of the superiority of either treatment. Considering that the optimal management of high-risk out- and inpatients who developed influenza has not yet been established, we planned and performed a multicenter, randomized, controlled study comparing the efficacy of 2 different systemic NAIs, peramivir and oseltamivir, in the treatment of high-risk outpatients (inpatients accepted) with influenza. We assessed the fever-alleviation time (primary endpoint) and the duration of influenza illness and the virus titer (secondary endpoints). The purpose of this study was to explore the possibility of establishing an optimal regimen for management of influenza in a high-risk patient population.

METHODS

This study was a multicenter, randomized, comparative study performed using the central registration method and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The trial was approved by the Ethics Committee of Nagasaki University. The study was conducted from December 2012 to May 2014. The clinical trial was registered with University Hospital Medical Information Network Clinical Trials as UMIN000009479. For the purposes of our study, high risk factors (HRFs) were defined as the following: age ≥65 years, chronic heart disease, chronic respiratory illness, chronic kidney disease, chronic liver disorder, diabetes mellitus, neurological disorder/neuromuscular disease, hematological disorder, or immunosuppressive conditions accompanied by diseases or requiring treatment. The target number of patients with HRFs was 100 based on the result demonstrating superiority of the high dose compared with the low dose in the previous study of peramivir in high-risk patients [9]. In our study, a total of 92 outpatients and several inpatients aged ≥20 years with influenza A or B virus infection meeting the following inclusion criteria were enrolled: (1) body temperature ≥38°C at hospital visit, (2) initiation of treatment within 48 hours from the onset of influenza illness (as indicated by at least 1 symptom), (3) positive for influenza virus by an influenza rapid diagnostic kit, and (4) having HRFs. We stopped our study early despite not achieving the target enrollment. We were conducting this clinical study for 2 influenza seasons. If we continued for an additional season, 3 seasons would cause larger bias in parallel with an increase in the variety of epidemic influenza virus appearing.

The following 7 influenza symptoms, as defined in the Influenza Symptom Severity [ISS] scale, were adopted: headache, muscle or joint pain, feverishness or chills, and fatigue as general symptoms, and cough, sore throat, and nasal stuffiness as respiratory symptoms. These symptoms were evaluated based on scores of 0–3 (0: no symptom [normal], 1: mild [barely troublesome], 2: moderate [very uncomfortable], 3: severe [intolerable]). Exclusion criteria were pregnancy, women who may become pregnant, breastfeeding women, and patients with pneumonia according to chest X-ray on admission. (Although pregnant women represent an important group at high risk for complications, we excluded this group for safety reasons.)

Using a central registration method, patients were equally randomized to receive peramivir (Rapiacta) or oseltamivir (Tamiflu) according to the respective package inserts. Peramivir was infused intravenously over 15 minutes at 600 mg once (a second infusion at >2 days later, if necessary, was permitted). Oseltamivir was administered orally at 75 mg twice a day for 5 days. All patients were checked at the respective institute for their backgrounds (including the HRFs) at the enrollment time and examined for clinical effects (such as vital signs, influenza symptom severity, complications associated with influenza, and virological examination) on days 1, 2, and 5. Chest X-ray examination and clinical laboratory tests were conducted on day 1 in all patients and on other days if required. Patients evaluated their own influenza symptoms using the ISS, and measured their own body temperature 3 times a day (morning, noon, and at the time of going to bed). It was prespecified to the patients that, if possible, body temperature was not to be assessed within the first 4 hours after taking antipyretics.

Nasopharyngeal swabs collected on days 1, 2, and 5 were used for virus typing, including subtyping, virus titration, and an NA enzyme inhibition assay. These assays and amino-acid sequence analyses were performed by LSI Medience. Infectious viral titers were calculated as $\log_{10}$ 50% tissue culture infective doses

($TCID_{50}$) per milliliter of viral transport medium according to the Spearman-Karber equation. Viral RNAs were not measured. All patients provided written informed consent before participating in the study. Each study was approved by the respective site's institutional review board before the start of the study.

The primary efficacy endpoint was the fever-alleviation time (time to reach axillary temperature of <37.0°C); in parallel with this endpoint, prognostic factors that might have affected the fever-alleviation time were determined. The secondary endpoints were (1) the duration of influenza illness, (2) the virus titer and identification of virus subtypes, (3) the occurrence of gene mutation in the influenza viruses, (4) incidence of complications associated with influenza infection, and (5) exacerbation of underlying conditions. Viral gene mutation was investigated if a noticeable increase in the half maximal inhibitory concentration (IC_{50}) value for the 4 existing NAIs (oseltamivir, peramivir, zanamivir, and laninamivir) was detected, and the difference in IC_{50} values was assessed statistically by the Kruskal-Wallis test. Safety of the drugs was evaluated by incidence of adverse events/adverse drug reactions (AEs/ADRs). Severity of the events was graded according to the Division of AIDS table, with grades 1, 2, and ≥ 3 corresponding to mild, moderate, and severe, respectively [26].

The primary efficacy analysis population was the intention-to-treat infected population, which included all of the patients receiving the study drug at least once during the study. The confidence coefficient and the significance levels were to be 0.95 and .05 (2-tailed), respectively. Kaplan-Meier curves were prepared for the fever-alleviation time and for the time to alleviation of influenza symptoms, and thereby a statistical intergroup difference was examined by using the log-rank test. Prognostic factors that might affect the fever-alleviation time were determined by the Cox proportional hazard model. For the estimation of duration of illness, the Wilcoxon rank-sum test was used after calculating the area under the curve of total symptom scores (TSSs) of influenza together with determining key statistics values by group. The key statistics values by group for IC_{50} values of each drug against a virus were calculated, followed by conducting of the Kruskal-Wallis test. The incidences of complications associated with influenza were calculated and tested by Fisher's direct probability method.

RESULTS

A total of 92 patients were enrolled from 16 medical hospitals and randomly allocated to 2 groups of equal size; all of the enrolled patients completed the study. All were patients with fever ≥38°C and visited the respective institution within 48 hours after the onset of influenza illness. Table 1 shows backgrounds of the patients who were included in safety and intention-to-treat infected populations. With the exception of the symptom score, the baseline characteristics did not significantly differ between the 2 groups. Table 1 also shows the approximately equal distribution of virus types and subtypes in the 2 groups. The majority of infections were due to influenza A/H3N2 viruses.

Figure 1 shows a Kaplan-Meier curve for the fever-alleviation time. In this analysis, 3 patients in the oseltamivir group were omitted from the clinical efficacy assessment because patient diaries (including information on body temperature) were not obtained for these subjects. Patients lacking the record of body temperature <37.0°C, irrespective of whether these patients had returned to a normal body temperature, were considered as censored. The respective medians of fever-alleviation time were 40.0 hours (95% confidence interval [CI] = 23.3–64.5) and 37.8 hours (95% CI = 26.3–45.3) in the peramivir and oseltamivir groups, respectively; these values did not exhibit a significant intergroup difference (log-rank test; $P = .69$; $\chi^2 = 0.156$). The Cox hazard analysis of the effect of the 2 NAIs showed that the 95% confidence interval for the difference between the 2 treatments ranged 0.88–2.48, indicating no significant difference between peramivir and oseltamivir. Three of 46 patients in the peramivir-treated group were administered peramivir for 2 days. Notably, this subset of 3 patients included 2 patients that were censored (as described above) and 1 patient who showed an alleviation time of 197.8 hours, a value that was onger than the median alleviation time of 37.8 hours (95% CI = 23.2–62.7) obtained from the remaining 43 patients treated with single-dose peramivir. No persistent virus was observed in the 3 patients administered peramivir for 2 days. Notably, none of the theses 3 patients harbored the H275Y mutation. Among a total of 79 patients who took antipyretics, 37 of 46 (80.4%) were treated with peramivir, and 42 of 46 (91.3%) were treated with oseltamivir. As a result, a total of 3 patients (1 and 2 subjects from peramivir- and oseltamivir-treated groups, respectively) ingested acetaminophen at approximately the same time as the alleviation time; in the other patients that ingested acetaminophen, body temperatures were measured at least 4 hours after the dose of acetaminophen was taken.

The numbers of days (mean ± SE) required for the disappearance of influenza symptoms were 5.26 ± 0.15 and 5.38 ± 0.16 days for the peramivir and the oseltamivir groups, respectively (log-rank test; $P = .65$; χ^2 value = 0.204). Table 2 shows the change of variation of the TSSs. The scores decreased over time, falling from −2.5 (peramivir) and −1.3 (oseltamivir) on day 2, to −7.1 (peramivir) and −5.9 (oseltamivir) on day 5; significant intergroup differences were not detected for this parameter. The duration of influenza illness was examined by the Wilcoxon rank-sum test. The intergroup difference of TSSs did not achieve significance ($P = .051$ at day 2). The change in infectious virus titer is shown in Figure 2. The median time for the virus titer to decrease by $<10^{1.5}$ $TCID_{50}$/mL was approximately 4 days in both groups (Kaplan-Meier method, post hoc analysis); this parameter did not reveal a statistically significant intergroup difference ($P = .51$; $\chi^2 = 0.436$). The decrease of virus

Table 1. Patient Backgrounds and High-Risk Factors at Baseline

Background Factors		Peramivir Group		Oseltamivir Group		*P* Value
		No. of Patients	%	No. of Patients	%	
No. of total patients		46	…	46	…	…
Sex	Male/Female	21/25	45.7/54.3	22/24	47.8/52.2	1.00
Age, y	No.	46		46		.42
	Mean ± SD	72.2 ± 14.1		70.1 ± 11.1		
	Median	76		72		
	Minimum to maximum	33 to 92		42 to 90		
Weight, kg	No.	45		36		.83
	Mean ± SD	55.0 ± 10.4		55.6 ± 12.3		
	Median	55		55.65		
	Minimum to maximum	36.0 to 80.5		34.2 to 88		
Height, cm	No.	43		35		.25
	Mean ± SD	155.3 ± 10.0		157.8 ± 8.9		
	Median	156		158		
	Minimum to maximum	135.7 to 174		140.6 to 174.1		
Hospitalized patients	Inpatient	7	15.2	8	17.4	1.00
Virus type	Type A	39	84.8	35	76.1	.43
	Type B	7	15.2	11	23.9	
	A + B	0	0.0	0	0.0	
Virus subtype	Type A H1N1	0	0.0	0	0.0	.76
	Type A H3N2	33	71.7	28	60.9	
	Type B	7	15.2	11	23.9	
	Type A H1N1 pdm09	5	10.9	6	13.0	
	Not detected	1	2.2	1	2.2	
Virus titer	No.	46		46		.496
	Mean ± SD	4.20 ± 2.12		4.48 ± 1.82		
	Median	4.5		4.3		
	Minimum to maximum	<1.5 to 8.5		<1.5 to 8.5		
Smoking		5	10.9	8	17.4	.38
Inoculation with influenza virus vaccine		27	58.7	19	41.3	.14
No. of patients with high-risk factors	Age ≥65 y	37	80.4	36	78.3	1.00
	Chronic heart disease	6	13.0	8	17.4	.77
	Chronic respiratory illness	18	39.1	21	45.7	.67
	Chronic kidney disease	7	15.2	4	8.7	.52
	Chronic liver disorder	8	17.4	2	4.3	.09
	Diabetes mellitus	12	26.1	10	21.7	.81
	Neurological disorder/ neuromuscular disease	0	0.0	1	2.2	1.00
	Hematological disorder	0	0.0	0	0.0	…
	Immunosuppressive conditions accompanied by diseases or requiring treatment	5	10.9	9	19.6	.38
Underlying disease/ complication		38	82.6	40	87.0	.77
Symptom score	No.	46		45		.03
	Mean ± SD	10.9 ± 2.5		9.6 ± 3.1		
	Median	10		9		
	Minimum to maximum	6 to 16		4 to 18		
	≤14	43	93.5	43	93.5	1.00
	≥15	3	6.5	2	4.3	
	Not described	0	0.0	1	2.2	
Time from onset of influenza to drug dosing, h	N	46		46		.44
	Mean ± SD	28.2 ± 16.1		25.8 ± 12.9		
	Median	24.7		23.1		
	Minimum to maximum	2.0 to 73.9		2.5 to 49.6		

Abbreviation: SD, standard deviation.

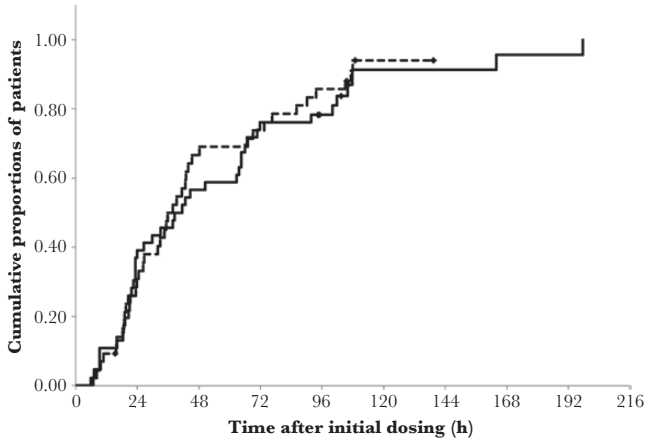


Figure 1. Kaplan-Meier survival curve for the time to fever alleviation. Solid line: peramivir group (n = 46). Dotted line: oseltamivir group (n = 43). ◆ indicates censored case (n = 4 in peramivir group; n = 4 in oseltamivir group). *P* value for the difference between treatments was .69 (log-rank test).

titer was examined by virus type and subtype, but no significant intergroup difference was detected (data not shown).

For persistent viruses sampled from 11 patients whose virus titer did not decrease to <1.5 by day 5, we assessed the IC_{50} values of the 4 NAIs. The median IC_{50} values ranged 1.3–6.7 nM; no statistically significant difference was observed among these drugs (Kruskal-Wallis test; $P = .19$). The persistent viruses associated with prolonged viral shedding were checked for the presence of known NA mutations. Notably, 2 of the 11 strains harbored H275Y mutations: both instances occurred in peramivir-treated patients. Consistent with this observation, these strains showed elevated IC_{50} values for oseltamivir (250 and 220 nM) and peramivir (18 and 17 nM), respectively. A subanalysis based on the symptoms revealed that there was no delay of healing (fever and duration of influenza illness) when comparing the 11 patients carrying persistent viruses to the remaining 78 patients (data not shown).

Prognostic factors that might affect the fever-alleviation time were examined using the Cox proportional hazard model, to which all of the prognostic factors were inputted. The result of variable selection by the step-wise method confirmed that antiviral agent, virus type, sex, chronic cardiac disease, and chronic liver disorder were possible effective prognostic factors (a significance level of 0.2 to allow a variable into the model and to stay in the model), with respective hazard ratios of 1.461, 0.449, 1.518, 1.579, and 2.091 (Table 3).

The incidence of complications associated with influenza also was examined as a secondary endpoint. Only 4 of 46 (8.7%) peramivir-treated patients and 6 of 46 (13.0%) oseltamivir-treated patients developed complications associated with influenza; these values did not demonstrate a significant intergroup difference (Fisher's direct probability test; $P = .74$). Notably, the exacerbation of underlying conditions and complications did not lead to discontinuation from the study. Hypertension and bronchial asthma gave the most incidences of aggravation (peramivir: n = 3 each; oseltamivir: n = 4 each). The safety of both drugs was examined by monitoring the appearance of AEs/ADRs. The severity of AEs was mild in all cases, with the exception of 1 case each of pneumonia and COPD aggravation. Both of these events occurred in the oseltamivir-treated group and were of moderate severity (Table 4). Adverse drug reactions in the oseltamivir group consisted of 1 case each of hepatic functional

Table 2. Change of Variation of Total Symptom Scores

Time	Treatment Group	No. of Subject	Mean ± SD	Median	Minimum	Maximum	*P* Value (Wilcoxon rank sum test)
Day 2	Peramivir	46	−2.5 ± 3.5	−2	−9	6	.051
	Oseltamivir	45	−1.3 ± 2.2	−1	−5	4	
Day 3	Peramivir	46	−4.2 ± 3.6	−5	−12	5	.09
	Oseltamivir	45	−3.0 ± 3.2	−4	−9	5	
Day 4	Peramivir	46	−5.5 ± 3.8	−6	−12	6	.22
	Oseltamivir	45	−4.3 ± 4.2	−5	−10	6	
Day 5	Peramivir	46	−7.1 ± 3.6	−8	−12	5	.22
	Oseltamivir	45	−5.9 ± 4.3	−7	−13	5	

Variation on each day was calculated using total symptom score on day 1 as standard. Fundamental statistics were calculated by regarding the variation as a continuous quantity. The test was carried out by day without considering multiplicity.

Abbreviation: SD, standard deviation.

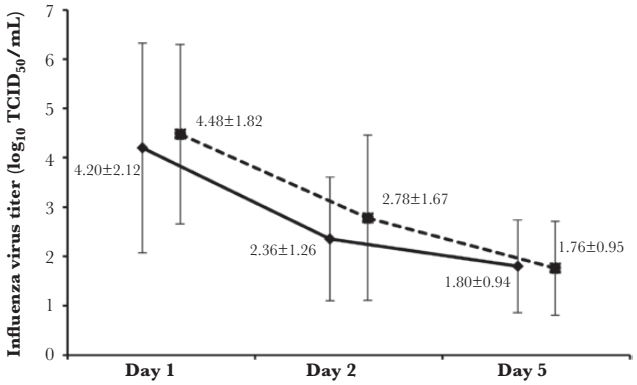


Figure 2. Time course of virus titers in peramivir and oseltamivir dose groups. Solid line: peramivir group. Dotted line: oseltamivir group. The error bars represent standard deviation. Abbreviation: $TCID_{50}$, 50% tissue culture infective dose.

abnormality, diarrhea, and decrease in white blood cell count; no ADRs were reported in the peramivir group. The case of pneumonia (in the oseltamivir-treated group) was not thought to be related to the administered medication; this patient recovered on day 10.

DISCUSSION

As described in previous reports [9, 17, 18], duration of influenza illness is apparently longer in influenza patients with >1 HRFs than in otherwise healthy patients [16, 27]. In our study's investigation of prognostic factors, the step-wise method identified virus type as one of the covariates for fever-alleviation time (Table 3). Vaccination status did not affect treatment outcome, contrary to our expectation. The median durations of influenza illness observed in the peramivir- and oseltamivir-treated groups in our study were approximately 5 days, values that are consistent with those previously reported for high-risk cases treated with oseltamivir [17, 18]. The median fever-alleviation time in our study was approximately 40 hours, a value similar to that reported in other studies [9, 17]. Thus, the results obtained in our study were not notably different from those obtained in other studies with high-risk patients.

In the previous Ph3 study, no significant intergroup difference was observed for any of these endpoints when comparing groups treated with peramivir (intravenous) or oseltamivir (oral). These results contrasted with our expectations, which were based on the fact that the intravenous administration of peramivir yields higher exposure at an earlier stage of infection, possibly leading to more efficient inhibition of the viral NA during the exponential phase of viral replication [15]. It was previously reported that 600 mg (repeating dose accepted) of peramivir showed significantly higher efficacies regarding duration of influenza illness and time to return to normal body temperature compared with 300 mg (repeating dose accepted) in a study with high-risk patients [9]. The medians of the duration of influenza illness and the time to return to normal body temperature with 600 mg were 42.3 hours (90% CI = 30.0–82.7) and 37.6 hours (90% CI = 22.3–46.8), respectively. In our study, which also used a 600-mg dose, medians of the 2 endpoints were 5 days (95% CI = 5–5 days) and 40.0 hours (95% CI = 23.3–64.5), respectively.

Table 3. Prognostic Factors that May Affect the Fever-Alleviation Time

Variable	HR (95% CI)	*P* Value
Antiviral agent (peramivir/oseltamivir)	1.461 (0.887–2.408)	.14
Virus type (type A/type B)	0.449 (0.239–0.843)	.01
Sex (male/female)	1.518 (0.950–2.425)	.08
Chronic cardiac disease (no/yes)	1.579 (0.835–2.986)	.16
Chronic liver disorders (no/yes)	2.091 (0.974–4.487)	.06

Results were obtained by using a Cox proportional hazard model that incorporated all of the prognostic factors, with the exception of the 5 factors in the table; these excepted factors instead were examined by variable selection using a stepwise method (a significance level of .2 to allow a variable into the model and to stay in the model).Abbreviations: CI, confidence interval; HR, hazard ratio.

Although comparable data were obtained for the fever-alleviation times, the 2 studies resulted in distinctively different median times for duration of influenza illness. This difference in results can be attributed to the different dose regimens used in the 2 studies. Specifically, in the former study, peramivir was administered repeatedly (for >2 days) to 16 of 19 patients, whereas in our study, peramivir was administered only once in almost all of the cases (single dose in 43 of 46 patients; 2 doses in 3 of 46 patients). As a second reason for the difference, the enrollees in the 2 studies exhibited distinct backgrounds. For instance, approximately 26% and 80% of the peramivir-treated groups were aged ≥65 years in the previous high-risk study and in our study, respectively. Moreover, our study enrolled patients with a wider variety and number of HRFs than those enrolled in the former study. The increased median age and larger number of HRFs in our study presumably yielded a larger variance of immune response and clinical presentation. In other words, the sample size for patients with a large variety of HRFs in our study likely was smaller than that for otherwise healthy patients generally required to demonstrate a significant difference in clinical efficacy. A significant difference between 2 drugs may be demonstrated by limiting the number of HRF(s) to the one(s) expected to exhibit smaller variances of response and clinical presentation (eg, diabetes mellitus). Meanwhile, in our study the changes in the TSSs in the peramivir-treated patients tended to be more favorable than those in the oseltamivir-treated patients, especially on day 2 ($P \geq .05$) (shown in Table 2), whereas there were no significant differences in efficacy between the 2 drugs. These results indicated that despite such limitations, our data provide some valuable information that can contribute to strategies for the treatment of influenza-infected patients with HRFs.

In conclusion, our results suggest that administration of peramivir as a single (or twice in 2 exceptional cases) 600-mg intravenous dose displayed no significant difference in efficacy

Table 4. Occurrences of Adverse Events (Adverse Drug Reactions), Influenza-Associated Complications, and Exacerbation of Underlying Disease

		Peramivir Group (n = 46)		Oseltamivir Group (n = 46)	
		No. of Cases	%	No. of Cases	%
AEs (ADRs)	Pneumonia	0	0	1[a] (0)	2.2
	Pneumonia/bronchial asthma attack	1(0)	2.2	0	0
	COPD exacerbation /nausea	0	0	1[a](0)	2.2
	Liver dysfunction	0	0	2 (1)	4.3 (2.2)
	Diarrhea	0	0	1 (1)	2.2 (2.2)
	Decrease WBC counts	0	0	1 (1)	2.2 (2.2)
	Total	1 (0)	2.2	6 (3)	13.0 (8.7)
Influenza-associated complications	Pneumonia	1	2.2	2	4.3
	Bronchitis	0	0	1	2.2
	Bronchial asthma attack	2	4.3	2	4.3
	Others	1	2.2	1	2.2
	Total	4	8.7	6	13.0
Exacerbation of underlying diseases	Total	4	8.7	7	15.2

Abbreviations: ADRs, adverse drug reactions; AEs, adverse events; COPD, chronic obstructive pulmonary disease; WBC, white blood cell.

[a]Severities of pneumonia and COPD exacerbation were moderate in the indicated case. Severities were mild in all other cases.

compared with oseltamivir administered orally at a dose of 75 mg twice a day for 5 days, which has been already established as a standard treatment. Thus, our data show that peramivir is 1 useful option for the treatment of influenza-infected patients with HRFs.

Acknowledgments

This study was conducted by the multiple sites described below. We thank the representatives of the following institutions for their cooperation in the completion of this study: Internal Medicine, Kawamura Clinic: Sumio Kawamura; Tomonaga Internal Medicine Clinic: Akimitsu Tomonaga; Onitsuka Naika Shokaki Hospital: Yasunori Onitsuka; Department of Internal Medicine, Kouseikai Hospital: Yasumasa Dotsu; Department of Respiratory Organs, Izumikawa Hospital: Kinichi Izumikawa; Department of Respiratory Organs, Isahaya Health Insurance General Hospital: Yuichi Inoue; Department of Respiratory Organs, The Sasebo Municipal Hospital: Yuichi Fukuda; Internal Medicine, Shigeno Hospital: Yoshiteru Shigeno; Department of Internal Medicine, Senju Clinic: Jun Araki; Department of Respiratory Medicine, Hokusho Central Hospital: Yasuhito Higashiyama; Department of Internal Medicine, Nagasaki Harbor Medical Center City Hospital: Naofumi Suyama; Department of Respiratory Medicine, National Hospital Organization Ureshino Medical Center: Eisuke Sasaki; Department of Respiratory Medicine, The Japanese Red Cross Nagasaki Genbaku Hospital: Koji Hashiguchi; Department of Respiratory Medicine, The Japanese Red Cross Nagasaki Genbaku Isahaya Hospital: Kiyoyasu Fukushima; Department of Internal Medicine, Irifune Clinic: Kenji Irifune.

Financial support. This work was supported by Shionogi & Co, Ltd

Potential conflicts of interest. S. K. receives honoraria from Shionogi & Co, Ltd for delivering promotional lectures on infectious diseases and is an adviser to Shionogi & Co, Ltd, which develops anti-influenza drugs. K. Y. declares that he has served as an investigator in a study conducted by Shionogi & Co, Ltd and receives honoraria from Shionogi & Co, Ltd, for delivering promotional lectures. Y. S. is an employee of Shionogi & Co, Ltd. K. I. received a research grant from Shionogi & Co, Ltd. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Muthuri SG, MyIes PR, Venkatesan S, et al. Impact of neuraminidase inhibitor treatment on outcomes of public health Importance during the 2009–2010 influenza A(H1N1) pandemic: a systematic review and meta-analysis in hospitalized patients. J Infect Dis. **2013**;207:553–63.
2. Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med. **2013**;7:76–81.
3. Muthuri SG, Venkatesan S, Myles PR, et al; PRIDE Consortium Investigators. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med. **2014**;2:395–404.
4. World Health Organization. *WHO Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses*. Geneva, Switzerland: World Health Organization; 2010. http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf
5. Hikita T, Hikita H, Hikita F, et al. Clinical effectiveness of peramivir in comparison with other neuraminidase inhibitors in pediatric influenza patients. Int J Pediatr. **2012**;2012:834181.
6. Shobugawa Y, Saito R, Sato I, et al. Clinical effectiveness of neuraminidase inhibitors—oseltamivir, zanamivir, laninamivir, and peramivir—for treatment of influenza A(H3N2) and A(HINl) pdm09 infection: an observational study in the 2010–2011 influenza season in Japan. J Infect Chemother. **2012**;18:858–64.
7. Takemoto Y, Asai T, Ikezoe I, et al. Clinical effects of oseltamivir, zanamivir, laninamivir and peramivir on seasonal influenza infection in outpatients in Japan during the winter of 2012–2013. Chemotherapy. **2013**;59:373–8.
8. Sugaya N, Sakai-Tagawa Y, Bamba M, et al. Comparison between virus shedding and fever duration after treating children with pandemic A H1N1/09 and children with A H3N2 with a neuraminidase inhibitor. Antivir Ther. **2015**;20:49–55.
9. Kohno S, Kida H, Mizuguchi M, et al; S-021812 Clinical Study Group. Intravenous peramivir for treatment of influenza A and B virus infection in high-risk patients. Antimicrob Agents Chemother. **2011**;55:2803–12.
10. Nasu T, Ogawa D, Wada J, Makino H. Peramivir for severe influenza infection in a patient with diabetic nephropathy. Am J Respir Crit Care Med. **2010**;182:1209–10.
11. Hung S-F, Fung C-P, Perng D-W, Wang F-D. Effects of corticosteroid and neuraminidase inhibitors on survival in patients with respiratory distress induced by influenza virus. J Microbiol Immunol Infect. **2015**. http://dx.doi.org/10.1016/j.jmii.2015.08.016
12. Boltz DA, Ilyushina NA, Arnold CS, et al. Intramuscularly administered neuraminidase inhibitor peramivir is effective against lethal H5N1 influenza virus in mice. Antiviral Res. **2008**;80:150–7.
13. Tanaka A, Nakamura S, Seki M, et al. The effect of intravenous peramivir, compared with oral oseltamivir, on the outcome of post-influenza pneumococcal pneumonia in mice. Antivir Ther. **2015**;20:11–9.

14. Kitano M, Kodama M, Itoh Y, et al. Efficacy of repeated intravenous infection of peramivir against influenza A (H1N1) 2009 virus injection in immunosuppressed mice. Antimicrob Agents Chemother. **2013**;57:2286–94.
15. Saisho Y, Ishibashi T, Fukuyama H, et al. Pharmacokinetics and safety of intravenous peramivir, neuraminidase inhibitor of influenza virus, in healthy Japanese subjects. Antivir Ther. **2016**; doi:10.3851/IMP3104.
16. Kohno S, Yen MY, Cheong HJ, et al; S-021812 Clinical Study Group. 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.
17. Singh S, Barghoorn J, Bagdonas A, et al. Clinical benefits with oseltamivir in treating influenza in adult populations: results of a pooled and subgroup analysis. Clin Drug Investig. **2003**;23:561–9.
18. Dutkowski R. Oseltamivir in seasonal influenza: cumulative experience in low- and high-risk patients. J Antimicrob Chemother. **2010**;65:ii11–ii24.
19. Patrick M, Sebstian LJ. Influenza infection and COPD. Int J Chron Obstruct Pulmon Dis. **2007**;2:55–64.
20. McGeer A, Green KA, Plevneshi A, et al; Toronto Invasive Bacterial Diseases Network. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. Clin Infect Dis. **2007**;45:1568–75.
21. Lee N, Choi KW, Chan PK, et al. Outcomes of adults hospitalised with severe influenza. Thorax. **2010**;65:510–5.
22. Coffin SE, Leckerman K, Keren R, et al. Oseltamivir shortens hospital stays of critically ill children hospitalized with seasonal influenza: a retrospective cohort study. Pediatr Infect Dis J. **2011**;30:962–6.
23. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis. **2009**;200:492–500.
24. de Jong MD, Ison MG, Monto AS, et al. Evaluation of intravenous peramivir for treatment of influenza in hospitalized patients. Clin Infect Dis. **2014**;59:e172–85.
25. Louie JK, Yang S, Yen C, et al. Use of intravenous peramivir for treatment of severe influenza A(H1N1)pdm09. PLoS One. **2012**;7:e40261.
26. Division of Acquired Immunodeficiency Syndrome, NIAID, NIH. Division of AIDS table for grading the severity of adult and pediatric adverse events. http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf. Accessed December 2004.
27. Kohno S, Kida H, Mizuguchi M, Shimada J; S-021812 Clinical Study Group. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. Antimicrob Agents Chemother. **2010**;54:4568–74.

Received: 11 March 2020 | Accepted: 29 June 2020

DOI: 10.1111/irv.12788

ORIGINAL ARTICLE

WILEY

Effect of peramivir on respiratory symptom improvement in patients with influenza virus infection and pre-existing chronic respiratory disease: Findings of a randomized, open-label study

Motokazu Kato[1] | Yutaka Saisho[2] | Hiroshi Tanaka[3] | Takuma Bando[4]

[1]Chest Disease Clinical and Research Institute, Kishiwada City Hospital, Osaka, Japan

[2]Shionogi & Co., Ltd., Osaka, Japan

[3]Sapporo Cough Asthma and Allergy Center, Sapporo, Japan

[4]Bando Internal Medicine Clinic, Hakusan, Ishikawa, Japan

Correspondence
Yutaka Saisho, Shionogi & Co., Ltd., 12F, Hankyu Terminal Bldg., 1-4 Shibata 1-Chome, Kita-ku, Osaka 530-0012, Japan.
Email: yutaka.saisho@shionogi.co.jp

Present address
Motokazu Kato, Respiratory Institute, Kamei Hospital, Osaka, Japan

Funding information
Shionogi & Co., Ltd.

Abstract

Background: The efficacy of neuraminidase inhibitors on improvement of respiratory symptoms triggered by influenza in patients with pre-existing chronic respiratory diseases is unknown.

Methods: This 2-week, randomized, open-label study evaluated intravenous peramivir 600 mg on two consecutive days (peramivir-repeat), peramivir 300 mg single dose (peramivir-single), and oral oseltamivir 75 mg twice daily for 5 days in patients with confirmed influenza and chronic respiratory diseases. Patients recorded symptom scores daily. The primary endpoint of cumulative area of time vs symptoms (CATVS) was expressed as an index value of area under the curve vs time of the total score of cough, sore throat, and nasal congestion from baseline to 2 weeks.

Results: Of 214 randomized patients, 209 (56% female, 77% aged <65 years, 94% outpatients, 91% bronchial asthma, 62% influenza A) received ≥1 dose of study drug. Mean (standard deviation) CATVS was similar for peramivir-repeat (782.78 [487.17]) vs peramivir-single (717.35 [347.55]; $P = .4371$), and for peramivir-repeat vs oseltamivir (856.34 [404.99]; $P = 1.00$). However, CATVS was significantly shorter for peramivir-single vs oseltamivir, with an estimated treatment difference (TD) of −145.07 (95% confidence interval: −284.57, −5.56; $P = .0416$). In subgroup analyses, CATVS was significantly shorter for peramivir-single vs oseltamivir among patients with influenza A (TD: −206.31 [−383.86, −28.76]; $P = .0231$), bronchial asthma (TD: −156.57 [−300.22, −12.92]; $P = .0328$), baseline respiratory severity score <5 (TD: −265.32 [−470.42, −60.21]; $P = .0120$), and age <65 (TD: −184.30 [−345.08, −23.52]; $P = .0249$).

Conclusions: In patients with chronic respiratory diseases, peramivir-single was not significantly different from peramivir-repeat and was more effective than oseltamivir at alleviating respiratory symptoms.

KEYWORDS

asthma, cough, influenza A virus, influenza B virus, neuraminidase, peramivir, pulmonary diseases, chronic obstructive; signs and symptoms, respiratory

1 | INTRODUCTION

Influenza is a potentially life-threatening illness associated with seasonal epidemics that result in significant societal disruption and morbidity.[1,2] Progression of infection to the lower respiratory tract can prove fatal, particularly in patients with chronic respiratory diseases such as bronchial asthma, chronic bronchitis, and chronic obstructive pulmonary disease (COPD).[3,4] Susceptible individuals have a high risk of acute respiratory distress syndrome, which is typically triggered by influenza A infection.[3]

Antiviral treatment with a neuraminidase inhibitor (NAI) can bring clinical benefits, including clearing virus, alleviating symptoms, reducing transmission,[5] and potentially improving survival.[1,6] NAI efficacy has been explored predominantly in patients with uncomplicated seasonal influenza.[7-11] Among these agents, intravenous peramivir, including a single-dose 300 mg regimen, showed more rapid symptom alleviation compared with placebo[11] and other NAIs.[8-10] However, further data are needed for high-risk patients with chronic respiratory diseases that can be aggravated by influenza, leading to delayed recovery from influenza symptoms.[12,13]

A phase III trial previously investigated intravenous peramivir 300 or 600 mg/d for 1-5 days as needed in high-risk patients.[14] The median duration of influenza illness was 114.4 and 42.3 hours in the 300 and 600 mg groups, respectively (hazard ratio: 0.497; 90% confidence interval [CI], 0.251-0.984). In a post hoc analysis, the effect of peramivir on symptom alleviation was assessed using an index value for area under the curve (AUC) vs time based on the changing total scores of cough, sore throat, and nasal congestion (M. Kato, Y. Saisho, H. Tanaka, T. Bando, unpublished results). Peramivir 600 mg appeared to be more effective than peramivir 300 mg, with the former demonstrating a higher reduction from baseline in total symptoms at 2 weeks.

The primary objective of this study was to compare peramivir 600 mg repeat dose (1200 mg total dose) with peramivir 300 mg single dose and oseltamivir 75 mg twice daily in patients with influenza A or B infection and chronic respiratory diseases. The study also compared the effect of peramivir 300 mg single dose with oseltamivir. Secondary objectives reported here include changes in respiratory symptom scores over time, virus titer, and safety; additional outcomes will be reported separately.

2 | METHODS

2.1 | Study design

This was a 2-week, multicenter, randomized, open-label study to evaluate intravenous peramivir 600 mg repeat dose, intravenous peramivir 300 mg single dose, or oral oseltamivir 75 mg twice-daily treatment in patients with confirmed influenza A or B together with concomitant bronchial asthma, COPD, or pulmonary fibrosis. The study was conducted between October 2017 and February 2019, encompassing two influenza seasons, across 50 sites in Japan. The study was conducted in accordance with the Declaration of Helsinki and, from October 2017 through December 2018, Ethical Guidelines for Medical and Health Research Involving Human Subjects. The study was a specified clinical trial as defined by the revised 2017 Clinical Trials Act and, therefore, from January 2019 through study completion, followed the guidelines set forth in the Act. The protocol was reviewed and approved by local ethical review boards and, in January 2019, by the clinical research board of Nippon Medical University, as per the Act. Patients gave written informed consent. The study was registered at the UMIN-CTR Clinical Trials Registry (https://www.umin.ac.jp/ctr/index.htm, identifier: UMIN000030118) and at the Japan Registry of Clinical Trials (https://jrct.niph.go.jp/en-latest-detail/jRCTs031180322, identifier: jRCTs031180322).

Enrollment occurred within 48 hours from influenza onset defined as an initial ≥1°C increase in axillary body temperature above normal or worsening of ≥1 systemic or respiratory symptom compared with normal. All patients had ≥4 clinic visits (Figure 1). During a screening visit, influenza diagnosis was confirmed using the rapid antigen test. Patients were instructed in the use of a daily diary to record influenza symptom scores and temperature. A COPD assessment test (CAT) was conducted together with oxygen saturation and respiratory function testing. Patients were assigned to treatment, and the study drug was administered. Patients assigned to peramivir 600 mg repeat dose had an additional visit to receive the repeat treatment on Day 2. Adverse events (AEs) were monitored throughout the 14-day study period.

2.2 | Study population

Eligible patients were male or female inpatients or outpatients diagnosed with influenza aged 16-79 years, with those aged 16-19 years requiring consent from a legal guardian. Other key inclusion criteria were the following: a total symptom score for cough, sore throat, and nasal congestion of ≥3 including a score of ≥1 for cough, and ≥1 systemic symptom that scored ≥2 for headache, muscle or joint pain, heat or chills, or fatigue; nasal or throat swab with a positive rapid influenza test; maximum axillary temperature ≥37.5°C for ≥12 hours before screening; and receiving treatment for bronchial asthma, pulmonary fibrosis, or COPD. Key exclusion criteria were the following: concomitant infectious disease requiring treatment with a systemic antibacterial, antifungal, or antiviral drug; history of convulsions or other neurological symptoms within the past 2 years; chronic respiratory failure requiring management on a mechanical ventilator; diabetes with glycated hemoglobin A1c >10% within 4 weeks prior to screening; previous treatment with an NAI, amantadine hydrochloride, or baloxavir marboxil within the previous 7 days; cardiovascular disease requiring hospitalization, and other serious diseases requiring treatment, including congestive heart failure, central nervous system diseases, metabolic diseases, malignancies, renal dialysis, and transplantation within the previous 12 months.

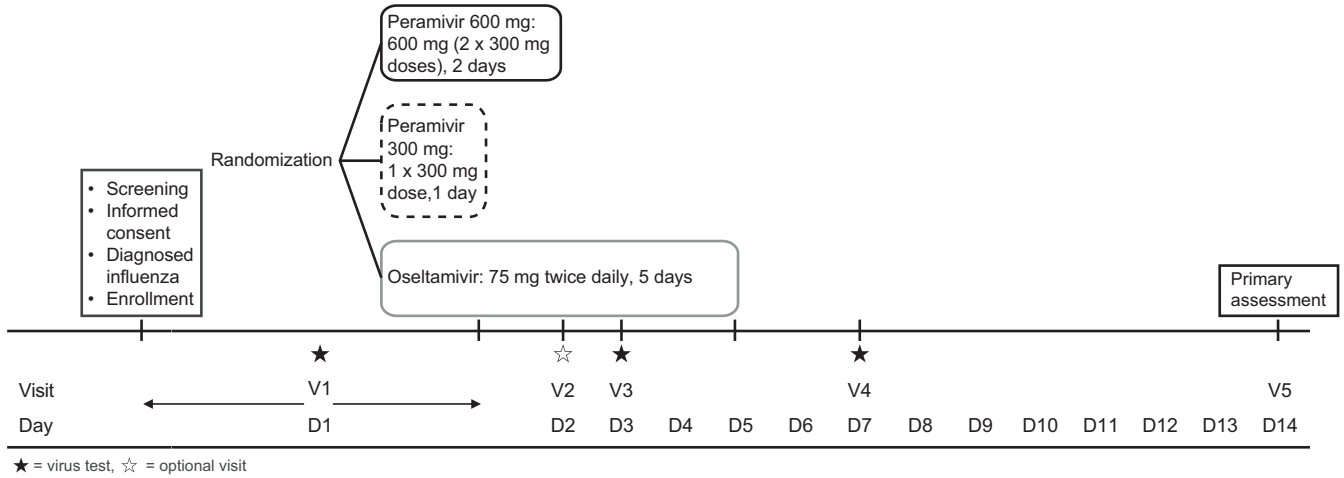


FIGURE 1 Study design. Screening visit (Day 1): patient consent, evaluation of patient demographics and clinical characteristics, physical examination, axillary body temperature, assessment of influenza symptoms, nasal cavity evaluation and throat swab, and confirmation of influenza using the rapid antigen test. Day 2: patients assigned to peramivir 600 mg received repeat treatment; if available, patients in any arm had physical examination and virus test. Day 3: physical examination, virus testing, and CAT, oxygen saturation, and respiratory function assessments in all patients, and clinical examination in patients in the two peramivir groups. Day 7: physical examination, virus testing, and testing for CAT, oxygen saturation, and respiratory function in all patients; clinical examination in patients in the oseltamivir arm. Day 14: physical examination, clinical examination (where possible), CAT, oxygen saturation, and respiratory function assessments in all patients. Patients were instructed to record their axillary body temperature four times per day on Days 1-3 and twice per day from Day 4, and to record their influenza symptom scores twice per day on Days 1-7, then once daily from Day 8. CAT, chronic obstructive pulmonary disease assessment test

2.3 | Randomization and treatment

Patients were randomized (1:1:1) to peramivir 600 mg repeat dose administered as two 300 mg intravenous infusions on two consecutive days (ie, 1200 mg total dose), peramivir 300 mg single dose administered as a single 300 mg infusion, or oral oseltamivir 75 mg twice daily for 5 days (Figure 1). Infusion time was 15-75 minutes for peramivir 600 mg repeat dose and 15-45 minutes for peramivir 300 mg single dose. Randomization was conducted using the minimization method, stratified by total score of respiratory symptoms (≥5, <5) and underlying respiratory disease (bronchial asthma, COPD, or pulmonary fibrosis). Concomitant drugs (except topical medicines) such as antivirals, antifungals, antipyretics (except acetaminophen), general cold drugs, antihistaminic drugs, immunosuppressive drugs, Chinese medicine for influenza virus, and investigational drugs were not permitted. Patients could take a chemical mediator release inhibitor or leukotriene receptor antagonist as an alternative to antihistaminic drugs.

2.4 | Outcome measures

The primary efficacy endpoint was "cumulative area of time vs symptoms" (CATVS) expressed as an index AUC of the total score of three respiratory symptoms (cough, sore throat, and nasal congestion) for 2 weeks (from Visit 1 [baseline] to Visit 5 [Day 14]). Influenza symptom severity was assessed using seven items including the three respiratory symptoms and four systemic symptoms (headache, muscle or joint pain, feverishness or chills, and fatigue) by patient diary. Symptom severity was scored as 0 (no symptoms), 1 (mild), 2 (moderate), or 3 (severe). Secondary efficacy endpoints were mean change from baseline over Visits 2-5 in the total score of three respiratory symptoms, and mean change from baseline over Visits 2, 3, and 4 in virus titer, expressed as median 50% tissue culture infectious dose ($TCID_{50}$) per mL. Nasal or throat swabs were sent to a central laboratory for viral titer measurement (LSI Medience Corporation). Safety assessments included the frequency of treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), and discontinuations due to TEAEs.

2.5 | Statistical analysis

The planned sample size of 70 patients per treatment group was based on an estimate of 64 patients per group needed to provide 80% power to detect a difference between treatments with a two-sided significance level of .05. Assumptions were further based on the results of a post hoc analysis of a phase III study of high-risk patients,[14] which showed a difference in index AUC for the total scores of cough, sore throat, and nasal congestion between peramivir 600 mg/d and peramivir 300 mg/d of 11.5; the standard deviation of each treatment group was 24.0. Oseltamivir was assumed to have the same effect on index AUC as peramivir 300 mg/d.

The primary efficacy analyses were conducted using the intent-to-treat (ITT) population, which included all randomized patients who received ≥1 dose of study drug and were eligible for efficacy analysis. The primary efficacy endpoint was analyzed using analysis of covariance with the weighted Holm method for multiplicity adjustment (with two-sided significance level of .05 split into .04

TABLE 1 Baseline demographics and disease characteristics (safety analysis set)

Characteristic	Peramivir 600 mg N = 70	Peramivir 300 mg N = 67	Oseltamivir N = 72	*P*-value
Age				
<65 y	51 (72.9)	54 (80.6)	56 (77.8)	.5747[a]
≥65 y	19 (27.1)	13 (19.4)	16 (22.2)	
Sex				
Male	35 (50.0)	30 (44.8)	28 (38.9)	.4030[a]
Female	35 (50.0)	37 (55.2)	44 (61.1)	
Smoking status				
Never	46 (65.7)	43 (64.2)	45 (62.5)	.9414[b]
Former smoker	15 (21.4)	13 (19.4)	23 (31.9)	
Current smoker	9 (12.9)	11 (16.4)	4 (5.6)	
Hospitalization				
Inpatient	3 (4.3)	7 (10.4)	2 (2.8)	.1508[a]
Outpatient	67 (95.7)	60 (89.6)	70 (97.2)	
Type of influenza				
A virus	42 (60.0)	42 (62.7)	46 (63.9)	.9049[a]
B virus	28 (40.0)	25 (37.3)	26 (36.1)	
Influenza time of onset				
≤12 h	15 (21.4)	10 (14.9)	9 (12.5)	.5892[b]
>12 to ≤24 h	29 (41.4)	27 (40.3)	32 (44.4)	
>24 to ≤36 h	9 (12.9)	12 (17.9)	17 (23.6)	
>36 to ≤48 h	15 (21.4)	16 (23.9)	9 (12.5)	
>48 h	1 (1.4)	1 (1.5)	2 (2.8)	
Unknown	1 (1.4)	1 (1.5)	3 (4.2)	
Chronic respiratory disease				
COPD	5 (7.1)	4 (6.0)	6 (8.3)	.9903[c]
Bronchial asthma	64 (91.4)	62 (92.5)	65 (90.3)	
Pulmonary fibrosis	1 (1.4)	1 (1.5)	1 (1.4)	
Total score of three respiratory symptoms				
≥5 score	45 (64.3)	44 (65.7)	44 (61.1)	.8443[a]
<5 score	25 (35.7)	23 (34.3)	28 (38.9)	
Body temperature				

(Continues)

TABLE 1 (Continued)

Characteristic	Peramivir 600 mg N = 70	Peramivir 300 mg N = 67	Oseltamivir N = 72	*P*-value
<37°C	0 (0.0)	0 (0.0)	0 (0.0)	.1503[b]
≥37°C to <38°C	21 (30.0)	30 (44.8)	33 (45.8)	
≥38°C to <39°C	37 (52.9)	30 (44.8)	26 (36.1)	
≥39°C to <40°C	10 (14.3)	7 (10.4)	11 (15.3)	
≥40°C	2 (2.9)	0 (0.0)	2 (2.8)	
Influenza vaccine in the past 6 mo				
No	44 (62.9)	43 (64.2)	43 (59.7)	.8609[a]
Yes	26 (37.1)	24 (35.8)	29 (40.3)	
History of influenza ever				
No	62 (88.6)	63 (94.0)	69 (95.8)	.2746[a]
Yes	8 (11.4)	4 (6.0)	3 (4.2)	
Concomitant illness				
Pneumonia	0 (0.0)	2 (3.0)	2 (2.8)	.4688[a]
Bronchitis	0 (0.0)	2 (3.0)	1 (1.4)	.3175[a]
Otitis media	0 (0.0)	0 (0.0)	0 (0.0)	-
Sinusitis	2 (2.9)	3 (4.5)	3 (4.2)	.9084[a]
Prior non-drug treatment[d]				
No	54 (77.1)	54 (80.6)	56 (77.8)	.9115[a]
Yes	16 (22.9)	13 (19.4)	16 (22.2)	
Prior drugs[d]				
No	3 (4.3)	4 (6.0)	4 (5.6)	.9291[a]
Yes	67 (95.7)	63 (94.0)	68 (94.4)	

Note: All values are n (%).

COPD, chronic obstructive pulmonary disease.

[a]Fisher's exact test.

[b]Kruskal-Wallis test.

[c]Pearson's chi-squared test.

[d]For influenza or chronic respiratory disease.

TABLE 2 Cumulative area of time vs symptoms expressed as an index value for area under the curve of the total score of cough, sore throat, and nasal congestion from the start of study drug administration to 2 wk post-administration (ITT population)

Variable	n	Mean	SD	Min	Median	Max
Peramivir 600 mg	70	782.78	487.17	64.4	771.60	2296.3
Peramivir 300 mg	66	717.35	347.55	47.8	684.49	1625.8
Oseltamivir	72	856.34	404.99	85.7	859.32	1856.4

	Estimated difference between 2 groups	SE	95% CI	*P*-value
Peramivir 600 mg vs peramivir 300 mg	66.70	71.16	−73.62, 207.02	.4371[a]
Peramivir 600 mg vs oseltamivir	−78.36	69.64	−215.69, 58.96	1.0000[a]
Peramivir 300 mg vs oseltamivir	−145.07	70.75	−284.57, −5.56	.0416[b]

CI, confidence interval; ITT, intent-to-treat; Max, maximum; Min, minimum; SD, standard deviation; SE, standard error.

[a]Adjusted *P*-value by weighted Holm method.

[b]Non-adjusted *P*-value.

and .01, respectively, for comparisons of peramivir 600 mg repeat dose with peramivir 300 mg single dose and with oseltamivir), AUC of the total score of three respiratory symptoms over 2 weeks as response variable, and total score at baseline and chronic respiratory disease as covariates. The comparison between peramivir 300 mg and oseltamivir was a secondary analysis. A subgroup analysis was conducted according to influenza virus type, chronic respiratory disease, severity of three respiratory symptoms (<5, ≥5), and age (<65 years, ≥65 years).

A secondary efficacy analysis of all pairwise comparisons was conducted. In the ITT population, the between-group difference in the mean change from baseline in total score of the three respiratory symptoms every 24 hours was analyzed using a linear model with intra-patient correlations between time points. The model included groups, time points, interaction between groups and time points, and chronic respiratory disease as explanatory variables with unstructured intra-patient correlation. The degrees of freedom were adjusted using Kenward and Roger approximation. Safety analyses were conducted using the safety analysis set (SAS), which included all patients who received ≥1 dose of study drug. TEAEs were categorized by system organ class and preferred term (Medical Dictionary for Regulatory Activities, version 22.0). No multiplicity adjustment was conducted except for the primary efficacy analysis. Analyses were conducted using SAS software version 9.3 (SAS Institute).

3 | RESULTS

3.1 | Demographic and baseline clinical characteristics

Of 214 patients randomized, 209 received ≥1 dose of study drug and comprised the SAS (Figure S1). Screening data before obtaining consent were not available, but the major reason for patient ineligibility was not having a body temperature ≥37.5°C during the previous 12 hours. In the peramivir 600 mg repeat-dose arm, one patient who withdrew consent was not included in the safety or ITT analyses. In the peramivir 300 mg single-dose arm, four patients (two without written consent, one who withdrew consent, and one who required a prohibited drug) were not included in the SAS; in addition, one patient who received the allocated treatment was not included in the ITT population because they did not have a body temperature ≥37.5°C within 12 hours before screening and therefore did not meet this inclusion criterion. Patient demographics and baseline clinical characteristics were well balanced between treatment arms, with no significant differences (Table 1). Most patients were outpatients, aged <65 years, never smokers, with comorbid bronchial asthma, a total score of three respiratory symptoms ≥5, and a predominance of infection by influenza A.

3.2 | Primary outcome measure

3.2.1 | Peramivir 600 mg repeat-dose vs peramivir 300 mg single-dose treatment (primary analysis)

There was no difference between peramivir 600 mg repeat dose and 300 mg single dose with respect to the primary outcome of CATVS (Table 2). The mean index AUC of 782.78 for peramivir 600 mg repeat dose equated to an estimated between-group treatment difference (TD) relative to peramivir 300 mg single dose of 66.70 (95% CI: −73.62, 207.02; $P = .4371$). Similarly, there was no difference between peramivir 600 mg repeat dose and oseltamivir, with an estimated between-group TD of −78.36 (95% CI: −215.69, 58.96; $P = 1.0000$).

3.2.2 | Peramivir 300 mg single-dose vs oseltamivir treatment

Cumulative area of time vs symptoms was significantly shorter for peramivir 300 mg single dose compared with oseltamivir (Table 2).

The mean index AUC of 717.35 for peramivir 300 mg equated to an estimated between-group TD relative to oseltamivir of −145.07 (95% CI: −284.57, −5.56; $P = .0416$), indicating shorter time to symptom resolution.

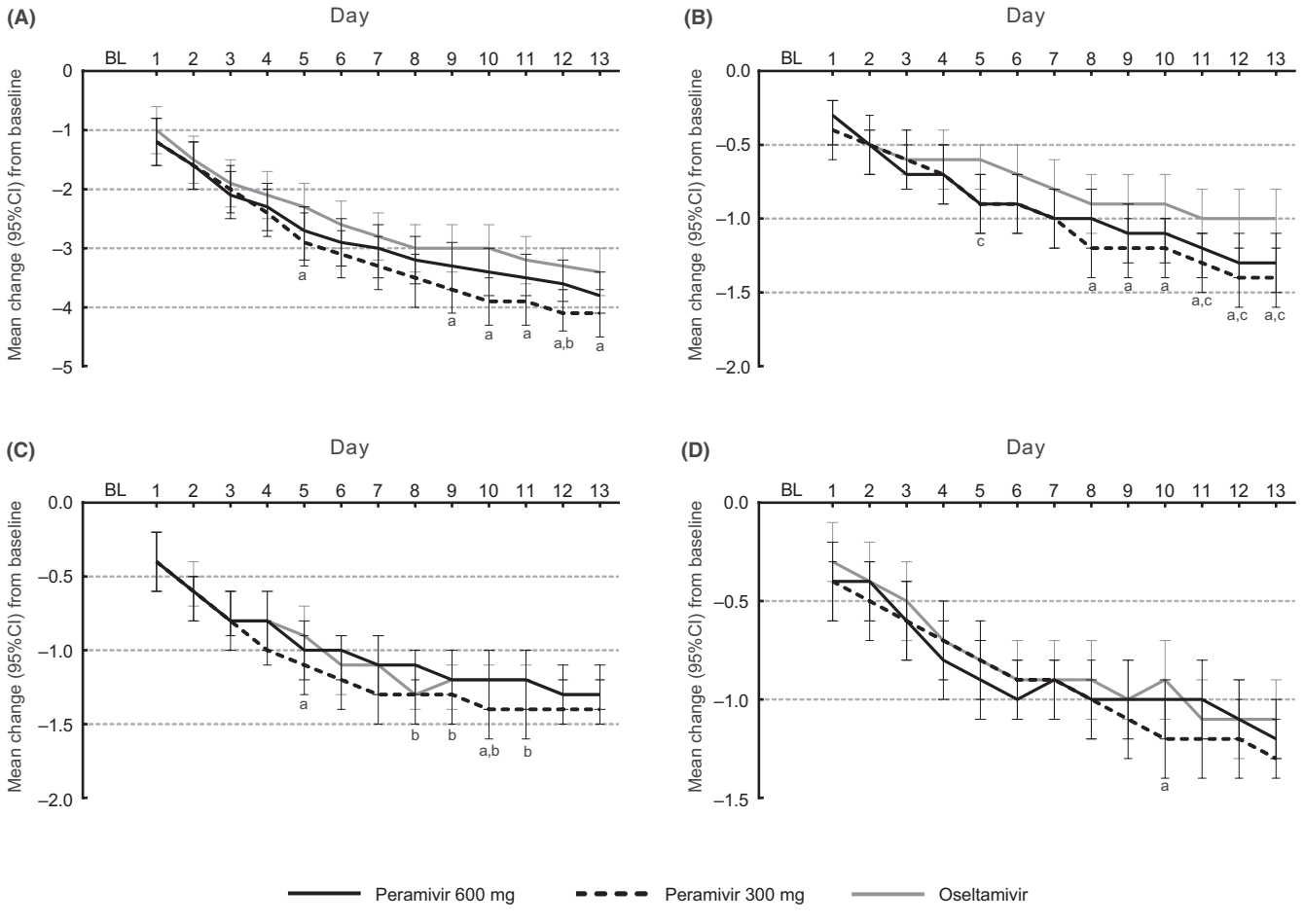
3.2.3 | Subgroup analyses

Compared with peramivir 600 mg repeat dose or oseltamivir, treatment with peramivir 300 mg single dose was associated with shorter CATVS across a range of subgroups, including virus type, those with bronchial asthma or pulmonary fibrosis, symptom severity score <5 or ≥5, and age <65 years (Table S1). The estimated TD was significant for the comparison between peramivir 300 mg single dose and oseltamivir among patients with influenza A (TD: −206.31; 95% CI: −383.86, −28.76; $P = .0231$), but not for patients with influenza B where CATVS was similar for all three arms. The estimated TD was also significant for the comparison between peramivir 300 mg single dose and oseltamivir among patients with bronchial asthma (TD: −156.57; 95% CI: −300.22, −12.92; $P = .0328$), those with a baseline total respiratory symptom severity score <5 (TD: −265.32; 95% CI: −470.42, −60.21; $P = .0120$), and for patients <65 years old (TD: −184.30; 95% CI: −345.08, −23.52; $P = .0249$). In each case, the TD indicated a shorter CATVS for peramivir 300 mg single dose. Additionally, the estimated TD was significant for the comparison between peramivir 600 mg repeat dose and oseltamivir for patients with a baseline total respiratory symptom score <5 (TD: −261.22; 95% CI: −459.30, −63.15; $P = .0105$).

3.3 | Secondary outcome measures

3.3.1 | Changes in symptoms

Peramivir 300 mg single dose was associated with significantly greater decreases from baseline in total symptom score compared with both oseltamivir (Day 5 and Days 9-13) and peramivir 600 mg repeat dose (Day 12) (Figure 2A). Compared with oseltamivir, cough scores decreased significantly more with both peramivir 300 mg single dose (Days 8-13) and peramivir 600 mg repeat dose (Day 5 and



$P<0.05$: [a]peramivir 300 mg vs oseltamivir, [b]peramivir 300 mg vs peramivir 600 mg, [c]peramivir 600 mg vs oseltamivir

FIGURE 2 Overall mean change from baseline in score of three respiratory symptoms to Day 13: (A) total score, (B) cough, (C) sore throat, and (D) nasal congestion. Values are mean and 95% CI (ITT population). BL, baseline; CI, confidence interval; ITT, intent-to-treat. [a]$P < 0.05$ (peramivir 300 mg vs oseltamivir). [b]$P < 0.05$ (peramivir 300 mg vs peramivir 600 mg). [c]$P < 0.05$ (peramivir 600 mg vs oseltamivir)

Days 11-13) (Figure 2B). Decreases in sore throat scores were significantly greater with peramivir 300 mg single dose than with oseltamivir (Days 5 and 10) and peramivir 600 mg repeat dose (Days 8-11) (Figure 2C). Decreases in nasal congestion score were similar in the three groups, except for a greater decrease with peramivir 300 mg single dose compared with oseltamivir on Day 10 (Figure 2D).

3.3.2 | Virus titer

The reduction in symptom score was associated with a decrease in viral titer at Days 2, 3, and 7 (Figure 3). At Day 3 following completion of dosing in the two peramivir arms but not oseltamivir, the mean (standard deviation) reduction from baseline in virus titer (expressed as $\log_{10}TCID_{50}$/mL) was −3.74 (2.45) for peramivir 600 mg repeat dose, −3.49 (2.34) for peramivir 300 mg single dose, and −3.08 (2.23) for oseltamivir.

In a subanalysis of viral titer by influenza type, patients with influenza A had a more rapid reduction in viral titer vs those with influenza B (data not shown). Among patients with influenza A, peramivir 300 mg single dose compared with peramivir 600 mg repeat dose was associated with a significantly greater reduction in viral titer at Day 2 ($P = .0268$), and peramivir 600 mg repeat dose compared with oseltamivir was associated with a significantly greater reduction in viral titer at Day 3 ($P = .0313$). There were no differences in viral titer between the three arms at Day 7.

3.4 | Safety and tolerability measures

Treatment with peramivir 600 mg repeat dose, peramivir 300 mg single dose, or oseltamivir was well tolerated (Table S2). The incidence of any TEAEs was higher among patients treated with peramivir 600 mg repeat dose (25.7%) compared with either peramivir 300 mg single dose (13.4%) or oseltamivir (13.9%). However, the only TEAEs that occurred in ≥2 patients in any arm were diarrhea, hepatic function abnormal, vomiting, and decreased appetite. Three patients experienced SAEs: one patient each with vomiting and pneumonia in the peramivir 600 mg repeat-dose arm, and one patient with pneumococcal pneumonia in the peramivir 300 mg single-dose arm.

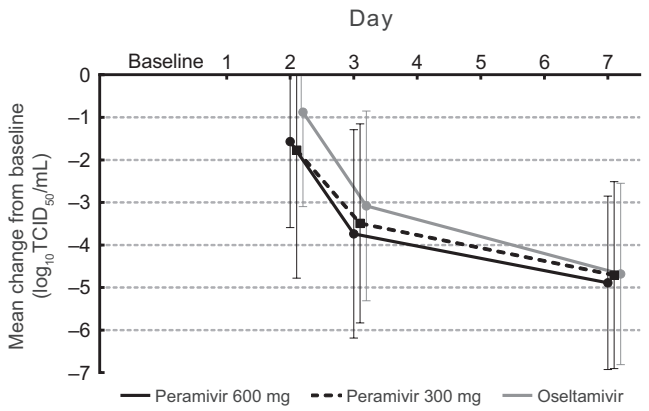


FIGURE 3 Overall change from baseline of virus titer at Days 2, 3, and 7 (ITT population). Values are mean and SD. Mean (SD) baseline values were 5.63 (2.04), 5.38 (2.21), and 5.44 (2.13) $\log_{10}TCID_{50}$/mL in the peramivir 600 mg, peramivir 300 mg, and oseltamivir groups, respectively. ITT, intent-to-treat; SD, standard deviation; $TCID_{50}$, 50% tissue culture infectious dose

4 | DISCUSSION

This is the first prospective, randomized, head-to-head study of oseltamivir and peramivir 600 mg repeat-dose and 300 mg single-dose regimens in high-risk patients with chronic respiratory diseases. The findings showed that in patients with respiratory diseases, predominantly bronchial asthma, there was no difference between the peramivir dose arms in CATVS. However, treatment with peramivir 300 mg single dose compared with oseltamivir was associated with a significant reduction in CATVS, suggestive of a shorter cumulative time with symptoms for patients treated with single-dose peramivir. Considering individual respiratory symptoms, the reduction from baseline in cough symptom score was significantly greater for patients treated with peramivir 300 mg single dose or peramivir 600 mg repeat dose compared with oseltamivir. Among patients with influenza A, peramivir 300 mg single dose was associated with a shorter CATVS than oseltamivir. Compared with oseltamivir, peramivir 300 mg single dose was also associated with a shorter time to resolution of respiratory symptoms for patients with bronchial asthma, those aged <65 years, and patients with a baseline total respiratory symptom score of <5. Further, NAI treatment was well tolerated irrespective of treatment. Collectively, these findings suggest that peramivir 300 mg single dose is effective and well tolerated in high-risk patients with chronic respiratory diseases and is able to reduce the duration of influenza symptoms compared with oseltamivir. These results also support previous evidence that, owing to the rapid increase in plasma concentration after administration,[15] peramivir reduces virus levels more quickly than oseltamivir[8] and independently of immune status.[6]

Previous head-to-head trials of NAIs have focused on the general patient population receiving treatment for acute uncomplicated seasonal influenza.[7,8,16,17] Studies of patients with high-risk features have also been conducted,[14,18-22] including with peramivir 300 or 600 mg/d administered for 1-5 days (mostly 1-2 days) as needed.[14] This latter trial included patients with diabetes and chronic respiratory diseases and showed a shorter median duration of influenza for patients who received peramivir 600 mg/d compared with 300 mg/d.[14] However, the sample size was small. Another study directly compared intravenous peramivir 600 mg single dose (a second dose was necessary in three of 46 patients) with oseltamivir 75 mg twice daily for 5 days in high-risk patients with influenza A or B infection.[19] Changes in mean total symptom scores and virus titer were similar between treatments, whereas peramivir 600 mg single dose was somewhat better tolerated. The present study adds to these findings in that it establishes either

peramivir 300 mg single dose or 600 mg repeat dose as an effective antiviral option in patients with chronic respiratory diseases. In particular, peramivir 300 mg single dose offered greater efficacy than oseltamivir in patients with bronchial asthma and influenza A. Although a potential benefit for the 600 mg repeat-dose regimen could not be established, with the 300 mg single-dose regimen providing significant antiviral effect and symptom reduction, the former regimen may be more appropriate for the inpatient setting. Thus, it is relevant that the majority of patients treated in this study were outpatients. Our findings also confirm the safety of intravenous peramivir in patients with high-risk features, with overall safety consistent with post-marketing safety evaluations of peramivir.[18]

In addition to providing superior symptom relief overall, peramivir 300 mg single dose also had an impact on cough. Influenza symptoms are triggered in response to upper airway infection, damage to the respiratory epithelium, and the subsequent host immune response.[23] Peramivir's mechanism of action is explained by its potent inhibition of influenza neuraminidase enzyme, with prolonged binding compared with either oseltamivir or zanamivir.[24] Given peramivir's effect on cough was superior to oseltamivir, this indicates that its strong antiviral effect may reduce damage to the airway epithelium leading to earlier alleviation of symptoms. Viruses such as influenza are implicated in the majority of asthma and COPD exacerbations.[25] The diminished cough associated with peramivir in the present context may reflect reductions in virus-associated epithelial activation and degeneration, which stimulate persistent cough through mechanisms involving inflammatory mediators[26] and stimulation of C-fibers,[27] respectively.

4.1 | Study strengths and limitations

This study permitted robust comparison between peramivir and oseltamivir while minimizing the potential for selection bias through randomization. The inclusion of high-risk patients, for whom NAI head-to-head data are limited, expanded the understanding of peramivir's efficacy beyond patients with uncomplicated influenza to include high-risk patients who are likely to benefit most from NAI treatment. As an open-label study, there was the potential for selection bias related to the inability to conceal treatment allocation. Blinded outcome assessment was not undertaken as it would have required a double-blind, double-dummy design. The inclusion of a control group through which to compare treatment outcomes in patients with and without chronic respiratory diseases would have strengthened the study. Outcome assessment depended on subjective self-reports of respiratory symptoms, which may have resulted in detection bias as patients receiving in-clinic intravenous treatment may have viewed symptom resolution more positively than patients taking oral treatment. The peramivir 600 mg repeat-dose regimen required a clinic visit on the second day, which potentially affected patients' subsequent recovery. Regardless, intravenous peramivir even for the 600 mg repeat-dose regimen achieved at least comparable results to oseltamivir and showed superiority in some measures, suggesting that this was not a study limitation.

5 | CONCLUSION

In the main analysis, there were no significant differences in CATVS between peramivir 600 mg repeat dose and either peramivir 300 mg single dose or oseltamivir. Secondary analysis showed a significant difference between peramivir 300 mg single dose and oseltamivir. Significant differences between peramivir and oseltamivir were seen for several secondary endpoints, including changes in respiratory symptoms (especially cough). Differential effects of peramivir and oseltamivir on other outcomes, including the COPD Assessment Test, will be reported elsewhere.

ACKNOWLEDGEMENTS

This study was sponsored by Shionogi & Co., Ltd., manufacturer/licensee of peramivir. Shionogi & Co., Ltd. was involved in the study design, data collection, and interpretation of results. The authors would like to thank EP-CRSU Co., Ltd. for statistical analysis. Medical writing assistance was provided by Rebecca Lew, PhD, CMPP, of ProScribe—Envision Pharma Group, and was funded by Shionogi & Co., Ltd. ProScribe's services complied with international guidelines for Good Publication Practice (GPP3).

CONFLICT OF INTEREST

MK is a steering committee member for AstraZeneca K.K., Nippon Boehringer Ingelheim Co., Ltd, GlaxoSmithKline K.K., and Shionogi & Co., Ltd., and has given lectures for AstraZeneca K.K., Nippon Boehringer Ingelheim Co., Ltd., GlaxoSmithKline K.K., Novartis Pharma K.K., Sanofi K.K., and Shionogi & Co., Ltd. YS is an employee of Shionogi & Co., Ltd. HT has received speaker honoraria from GlaxoSmithKline K.K., Kyorin Pharmaceutical Co., Ltd., AstraZeneca K.K., Shionogi & Co., Ltd., Meiji Seika Pharma Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Sanofi K.K., Novartis Pharma K.K., Hisamitsu Pharmaceutical Co., Inc., and TEIJIN Pharma Limited. TB is an executive director of Japan Physicians Association and has received study funding support from Shionogi & Co., Ltd. and Daiichi Sankyo Co., Ltd.

AUTHOR CONTRIBUTIONS

MK: Study design; principal investigator. YS: Study design; statistical analysis (interpretation of analyses conducted by EP-CRSU Co., Ltd). HT: Data collection; co-investigator. TB: Data collection; co-investigator. All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript.

ORCID

Yutaka Saisho https://orcid.org/0000-0002-4387-2699

REFERENCES

1. Chow EJ, Doyle JD, Uyeki TM. Influenza virus-related critical illness: prevention, diagnosis, treatment. *Crit Care*. 2019;23(1):214.
2. Singh S, Barghoorn J, Bagdonas A, et al. Clinical benefits with oseltamivir in treating influenza in adult populations: results of a pooled and subgroup analysis. *Clin Drug Investig*. 2003;23(9):561-569.
3. Kalil AC, Thomas PG. Influenza virus-related critical illness: pathophysiology and epidemiology. *Crit Care*. 2019;23(1):258.
4. Lin JT, Yu XZ, Cui DJ, et al. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. *Curr Med Res Opin*. 2006;22(1):75-82.
5. Hirotsu N, Saisho Y, Hasegawa T. The effect of neuraminidase inhibitors on household transmission in Japanese patients with influenza A and B infection: a prospective, observational study. *Influenza Other Respir Viruses*. 2019;13(2):123-132.
6. Hirotsu N, Saisho Y, Hasegawa T, Kitano M, Shishido T. Antibody dynamics in Japanese paediatric patients with influenza A infection treated with neuraminidase inhibitors in a randomised trial. *Sci Rep*. 2019;9(1):11891.
7. Kohno S, Yen MY, Cheong HJ, 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(11):5267-5276.
8. Hirotsu N, Saisho Y, Hasegawa T, Shishido T. Clinical and virologic effects of four neuraminidase inhibitors in influenza A virus-infected children (aged 4–12 years): an open-label, randomized study in Japan. *Expert Rev Anti Infect Ther*. 2018;16(2):173-182.
9. Shobugawa Y, Saito R, Sato I, et al. Clinical effectiveness of neuraminidase inhibitors–oseltamivir, zanamivir, laninamivir, and peramivir–for treatment of influenza A(H3N2) and A(H1N1)pdm09 infection: an observational study in the 2010–2011 influenza season in Japan. *J Infect Chemother*. 2012;18(6):858-864.
10. Takemoto Y, Asai T, Ikezoe I, et al. Clinical effects of oseltamivir, zanamivir, laninamivir and peramivir on seasonal influenza infection in outpatients in Japan during the winter of 2012–2013. *Chemotherapy*. 2013;59(5):373-378.
11. Whitley R, Laughlin A, Carson S, et al. Single dose peramivir for the treatment of acute seasonal influenza: integrated analysis of efficacy and safety from two placebo-controlled trials. *Antivir Ther*. 2015;20(7):709-719.
12. Talbot HK. Influenza in older adults. *Infect Dis Clin North Am*. 2017;31(4):757-766.
13. Yamaya M. Virus infection-induced bronchial asthma exacerbation. *Pulm Med*. 2012;2012:834826.
14. Kohno S, Kida H, Mizuguchi M, et al. Intravenous peramivir for treatment of influenza A and B virus infection in high-risk patients. *Antimicrob Agents Chemother*. 2011;55(6):2803-2812.
15. Saisho Y, Ishibashi T, Fukuyama H, Fukase H, Shimada J. Pharmacokinetics and safety of intravenous peramivir, neuraminidase inhibitor of influenza virus, in healthy Japanese subjects. *Antivir Ther*. 2017;22(4):313-323.
16. Ison MG, Hui DS, Clezy K, 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(5):651-661.
17. Lee J, Park JH, Jwa H, Kim YH. Comparison of efficacy of intravenous peramivir and oral oseltamivir for the treatment of influenza: systematic review and meta-analysis. *Yonsei Med J*. 2017;58(4):778-785.
18. Komeda T, Ishii S, Itoh Y, Sanekata M, Yoshikawa T, Shimada J. Postmarketing safety evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir: a drug-use investigation in patients with high risk factors. *J Infect Chemother*. 2016;22(10):677-684.
19. Nakamura S, Miyazaki T, Izumikawa K, et al. Efficacy and safety of intravenous peramivir compared with oseltamivir in high-risk patients infected with influenza A and B viruses: a multicenter randomized controlled study. *Open Forum Infect Dis*. 2017;4(3):ofx129.
20. Takamatsu K, Marumo S, Fukui M, Hata A. Safety and efficacy of anti-influenza drugs, intravenous peramivir against influenza virus infection in elderly patients with underlying disease. *J Microbiol Immunol Infect*. 2017;50(4):541-544.
21. Venkatesan S, Myles PR, Leonardi-Bee J, et al. Impact of outpatient neuraminidase inhibitor treatment in patients infected with influenza A(H1N1)pdm09 at high risk of hospitalization: an individual participant data metaanalysis. *Clin Infect Dis*. 2017;64(10):1328-1334.
22. Watanabe A. A randomized double-blind controlled study of laninamivir compared with oseltamivir for the treatment of influenza in patients with chronic respiratory diseases. *J Infect Chemother*. 2013;19(1):89-97.
23. Eccles R. Understanding the symptoms of the common cold and influenza. *Lancet Infect Dis*. 2005;5(11):718-725.
24. Bantia S, Arnold CS, Parker CD, Upshaw R, Chand P. Anti-influenza virus activity of peramivir in mice with single intramuscular injection. *Antiviral Res*. 2006;69(1):39-45.
25. Kurai D, Saraya T, Ishii H, Takizawa H. Virus-induced exacerbations in asthma and COPD. *Front Microbiol*. 2013;4:293.
26. Gon Y, Hashimoto S. Role of airway epithelial barrier dysfunction in pathogenesis of asthma. *Allergol Int*. 2018;67(1):12-17.
27. Canning BJ, Chang AB, Bolser DC, et al. Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report. *Chest*. 2014;146(6):1633-1648.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Kato M, Saisho Y, Tanaka H, Bando T. Effect of peramivir on respiratory symptom improvement in patients with influenza virus infection and pre-existing chronic respiratory disease: Findings of a randomized, open-label study. *Influenza Other Respi Viruses*. 2021;15:132–141. https://doi.org/10.1111/irv.12788