Infection and Drug Resistance

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical Effectiveness of Intravenous Peramivir versus Oseltamivir for the Treatment of Influenza in Hospitalized Patients

This article was published in the following Dove Press journal:
Infection and Drug Resistance

Jin Seo Lee[1]
Mi Suk Lee[2]
Yoonseon Park[3]
Jacob Lee[4]
Eun-Jeong Joo[5]
Joong Sik Eom[6]

[1]Division of Infectious Disease, Department of Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Republic of Korea; [2]Division of Infectious Diseases, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, Republic of Korea; [3]Department of Internal Medicine, National Health Insurance Corporation Ilsan Hospital, Goyang, Republic of Korea; [4]Division of Infectious Diseases, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Republic of Korea; [5]Division of Infectious Diseases, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Division of Infectious Diseases, Department of Internal Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, Republic of Korea

Purpose: To compare the clinical efficacy between peramivir and oseltamivir in hospitalized patients with influenza.

Patients and Methods: Retrospective cohort study examined data from 542 adult patients with laboratory-confirmed seasonal influenza hospitalized in five teaching hospitals and one secondary hospital between August 2017 and May 2018. The main outcome was the defervescence rate within 3 days from the first administration of peramivir or oseltamivir. The secondary outcomes were mortality and duration of hospitalization/intensive care unit (ICU) stay.

Results: Of the 542 enrolled patients, 251 were administered the standard dose of peramivir (300 mg, single dose), 42 were administered peramivir at doses exceeding 300 mg, and 249 were administered oseltamivir (75 mg, twice daily for 5 days). There were more ICU and pneumonia cases and older patients in the peramivir group, especially the high-dose group. The Charlson comorbidity index (CCI) scores were similar among the three groups. There were no significant differences in defervescence rates within 3 days between the three groups. The mortality and duration of hospital and ICU stays also did not differ significantly. The factors associated with 30-day mortality were ICU admission, high CCI score, and pneumonia.

Conclusion: Treatment of influenza with either peramivir or oseltamivir in hospitalized adults resulted in generally similar clinical outcomes. Peramivir treatment showed good clinical response in influenza patients with pneumonia or admitted to the ICU.

Keywords: influenza, human, therapeutics, oseltamivir, administration, intravenous

Introduction

Influenza, an acute respiratory disease caused by the influenza virus, remains a major global health concern. An estimated 5–10% of adults and 20–30% of children are affected worldwide, with 250,000–500,000 deaths annually.[1] Therefore, antiviral therapy is very important for lowering the prevalence and mortality of influenza epidemics; among these therapies, oral oseltamivir and intravenous peramivir are currently mainly used.[2]

Peramivir was the first intravenous neuraminidase inhibitor (NAI) approved by the US Food and Drug Administration (FDA) for the treatment of influenza.[3] Data from randomized controlled trials have shown that peramivir is safe and well-tolerated in uncomplicated influenza, with similar or superior clinical efficacy to those of placebo and oseltamivir.[4–6] Oseltamivir and zanamivir are not easy to

Correspondence: Joong Sik Eom
Tel +82-32-460-3741
Fax +82-2-488-0119
Email helppl@gachon.ac.kr

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/IDR.S247421

administrate to severely ill patients compared to peramivir, which is injected intravenously. Peramivir has shown effectiveness in severely ill patients with influenza.[7–9] Some studies reported similar efficacies between peramivir and oseltamivir in severe influenza or influenza in high-risk patients.[10,11] In particular, hospitalized patients may be more likely to have severe clinical features with complications such as pneumonia. These patients may also have clinical benefits such as reduced mortality and shorter duration of hospital stay with anti-influenza medications.[12–15] However, there is still a lack of studies comparing the efficacy of peramivir and oseltamivir in hospitalized patients with relatively severe influenza infections.

Therefore, this study aimed to compare the clinical efficacy of peramivir with that of oseltamivir in hospitalized patients with influenza.

Patients and Methods

Patients

This retrospective cohort study examined data from patients with seasonal influenza hospitalized in five teaching hospitals and one secondary hospital between August 2017 and May 2018. All eligible patients were at least 18 years of age who had laboratory (e.g., reverse-transcriptase-polymerase chain reaction [RT-PCR] or influenza rapid antigen test) confirmed influenza A or B virus infections.

Treatment including antiviral choice was decided by the primary physicians. The patients were stratified into standard dose (300 mg, single-dose) peramivir, high-dose (exceeding 300 mg, single or multiple doses) peramivir, and oseltamivir (75 mg, twice daily for 5 days) groups. When the single dose was reduced to less than 300mg according to renal function, it was regarded as standard dose.

The use of oral or parenteral antibiotics and antipyretics was permitted at the discretion of the patient's primary physician.

Each variable was compared between the three groups and patients treated with both drugs were excluded.

This study was approved by institutional review boards of Gachon University Gil Medical Center (GBIRB2018-132), in accordance with the Declaration of Helsinki, and by the institutional review boards of other hospitals. The Committee waived the signatures of informed consents by the patients whose records were reviewed, as this was a noninterventional, observational study with data management processed anonymously.

Definitions

Influenza-like illness (ILI) was defined as the sudden onset of fever (38°C) and respiratory symptoms, as well as headache, arthralgia, or myalgia. Influenza infection was defined as patients with ILI symptoms whose nasal swab, throat swab, nasal aspirate, or sputum specimens were positive in either rapid diagnostic test kits licensed in Korea (SD Influenza Antigen kit [Standard Diagnostics, Inc., Yongin, Korea]) or RT-PCR tests. Co-morbidities were defined as the presence of one or more pre-existing major medical conditions such as malignancy, chronic lung disease, steroid or immunosuppressant use, asthma, chronic heart disease, diabetes mellitus, etc and measured according to the Charlson comorbidity index (CCI)[16] using clinical data. Pneumonia was defined as the presence of both clinical symptoms and radiographically-identified pulmonary infiltrations. Acute Physiologic and Chronic Health Evaluation (APACHE) II score, the Sequential Organ Failure Assessment (SOFA) score, partial pressure of arterial oxygen (PaO2), partial pressure of arterial carbon dioxide (PaCO2), and arterial oxygen saturation (SaO_2) was assessed to evaluate severity of illness on the day of admission.

Time from first symptom onset to first dose of peramivir/oseltamivir and durations of oseltamivir/peramivir administration were also recorded.

Defervescence was defined as the lack of a fever (≤37.5°C) for more than 24 h and the date of defervescence was defined as the first day of defervescence.

The primary outcome was defervescence within three days from the first administration of peramivir or oseltamivir. The secondary outcomes were mortality and duration of hospitalization/intensive care unit (ICU) stay.

Statistical Analysis

The means and standard deviation (SD) were calculated for continuous variables, including age, weight, duration of hospital stay, and duration of fever. Percentages were calculated for categorical variables including sex, influenza type, comorbidities, existence of symptoms, development of organ failure, and treatment modalities. Analysis of variation (ANOVA) and Fisher's exact tests were used to compare continuous and categorical variables, respectively, between the three groups. Kruskal–Wallis tests were used as an alternative to ANOVA when the data were not normally distributed.

Multivariate logistic regression was used to identify the risk factors for 30-day mortality. The multivariable models were developed using the backward stepwise method. After univariate analysis, variables with $p < 0.05$ were considered significant; variables with $p < 0.1$ were considered borderline significant and both were retained in the final multivariate prediction model. All significance testing was two tailed, and $p < 0.05$ was considered statistically significant. All analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline and Clinical Characteristics

Of 542 enrolled patients, 251 received the standard dose (300 mg, single-dose) of peramivir, 42 received peramivir doses exceeding 300 mg (high-dose), and 249 were administered oseltamivir. The distribution of the patients according to the peramivir dose administered in the high-dose group was 13 cases (31.0%) administered multiple 300-mg doses, 12 cases (28.6%) administered a single 600-mg dose, and 17 cases (40.5%) administered multiple 600-mg doses.

The patient demographic and clinical characteristics are shown in Table 1. The peramivir group, both standard dose and high-dose groups, tended to include older patients compared to the oseltamivir group (70.52±15.03 vs. 71.19±15.29 vs. 66.20±16.72, p=0.005). There were more ICU admissions (43 (17.13%) vs. 13 (30.95%) vs. 21 (8.4%), p=0.000) and pneumonia cases (89 [35.46%] vs. 27 [64.29%] vs. 36 [14.46%], p=0.000) in the peramivir group, especially in the high-dose group, while chronic heart disease (24 [9.56%] vs. 4 [9.52%] vs. 46 [18.47%], p=0.010), chronic lung disease (27 [10.76%] vs. 1 [2.38%] vs. 59 [23.69%], p<0.001), and chronic liver disease (12 [4.78%] vs. 4 [9.52%] vs. 29 [11.65%], p=0.020) were more prevalent in the oseltamivir group. However, Charlson's comorbidity index (CCI) did not differ significantly the three groups (Table 1). The duration of illness before diagnosis differed between the three groups, with the peramivir groups, especially the high-dose group, having a longer duration (days) of illness than that of the oseltamivir group (2.54±2.94 vs. 3.17±2.49 vs. 2.11 ±1.50, p=0.011).

The other clinical parameters are shown in Table 2. The baseline laboratory parameters from available patients did not differ significantly between the three groups except for Sequential Organ Failure Assessment (SOFA) score (5.11 ±3.44 vs. 8.00±3.12 vs. 4.57±3.04, p=0.032) and creatinine clearance (67.81±34.41 vs. 69.50±36.86 vs. 83.21±46.94,

Table 1 Baseline Characteristics of All Patients

Numbers (%)	Peramivir Group Standard Dose[a] (n=251)	Peramivir Group High Dose[b] (n=42)	Oseltamivir Group (n=249)	*p*
Sex, male	127 (50.6)	19 (45.24)	115 (46.18)	0.568
Age, years (mean±SD)	70.52±15.03	71.19±15.29	66.20±16.72	0.005
Influenza Type				0.016
A	143 (56.97)	21 (50)	166 (66.7)	
B	104 (41.43)	20 (47.62)	83 (33.3)	
A and B	4 (1.59)	1 (2.38)	0	
Co-morbidities				
Chronic heart disease	24 (9.56)	4 (9.52)	46 (18.47)	0.010
Chronic lung disease	27 (10.76)	1 (2.38)	59 (23.69)	<0.001
Chronic liver disease	12 (4.78)	4 (9.52)	29 (11.65)	0.020
Chronic kidney disease	36 (14.34)	2 (4.76)	26 (10.44)	0.135
Solid tumor	41 (16.33)	4 (9.52)	37 (14.86)	0.515
Hematologic malignancy	1 (0.40)	1 (2.38)	9 (3.61)	0.038
Diabetes	73 (29.08)	10 (23.81)	67 (26.91)	0.727
CCI (mean±SD)	2.00±2.28	1.48±1.76	2.10±1.98	0.212
ICU admission at baseline	43 (17.13)	13 (30.95)	21 (8.4)	0.000
Pneumonia at baseline	89 (35.46)	27 (64.29)	36 (14.46)	0.000
Time from onset to treatment initiation[c] (days, (mean±SD))	2.54±2.94	3.17±2.49	2.11±1.50	0.011

Notes: [a]300 mg, single dose; [b]exceeding 300 mg, single or multiple doses; [c]time from first symptom onset to first dose of peramivir/oseltamivir.
Abbreviations: CCI, Charlson comorbidity index; SD, standard deviation; ICU, intensive care unit.

Table 2 Laboratory Parameters from Available Patients

Mean±SD, n	Peramivir Group Standard Dose[a] (n=251)	Peramivir Group High Dose[b] (n=42)	Oseltamivir Group (n=249)	*p*
PaO2 (mmHg)	76.49±33.12, (128)	77.48±35.31, (21)	78.20±31.95, (102)	0.926
PaCO2 (mmHg)	37.34±9.61, (128)	34.76±7.03, (21)	35.50±10.07, (102)	0.259
SaO_2 (%)	92.39±6.54 (135)	91.41±8.49 (22)	93.22±5.64 (102)	0.396
SOFA score	5.11±3.44 (61)	8.00±3.12 (8)	4.57±3.04 (35)	0.032
APACHE II score	18.89±8.55 (18)	21.20±0.96 (5)	15.25±5.92 (32)	0.101
Creatinine clearance (mL/min)	67.81±34.41(210)	69.50±36.86(41)	83.21±46.94 (245)	0.0003

Notes: [a]300 mg, single dose; [b]exceeding 300 mg, single or multiple doses.
Abbreviations: PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of arterial carbon dioxide; SaO_2, arterial oxygen saturation; SOFA, sequential organ failure assessment; APACHE, acute physiologic and chronic health evaluation.

p=0.0003). Acute Physiology, Age and Chronic Health Evaluation (APACHE) II scores were available in a few cases and tended to be higher in the peramivir group but this difference was not statistically significant (18.89±8.55 vs. 21.20±0.96 vs. 15.25±5.92, *p*=0.101).

Clinical Outcomes

There were no significant differences in defervescence rates within three days between the single-dose and high-dose peramivir and oseltamivir groups (167 [66.53%] vs. 24 [57.14%] vs. 178 [71.49%], *p*=0.141). The durations (days) of hospital (10.65±13.84 vs. 14.12±13.75 vs. 13.28±18.12, *p*=0.129) and ICU (9.60±13.17 vs. 10.62±10.63 vs. 11.26 ±11.53, *p*=0.868) stays were also not significantly different (Table 3). No serious adverse effect was reported in any of the three groups.

The overall mortality was 7.74% (42/542) and there was no significant difference between three groups (Table 3). The factors associated with defervescence rates within three days or 30-day mortality were evaluated in all patients. Time from first symptom onset to first dose of peramivir/oseltamivir was not associated with defervescence rates (*P* =0.33). Multivariate analysis revealed that only pneumonia (OR 2.32, 95% CI (1.49–3.61), *P*=0.000) was associated with defervescence rates within three days. ICU admission (odds ratio [OR] 5.81, 95% CI (2.70–12.50), *P*=0.000), high CCI (OR 1.32, 95% CI (1.12–1.55), *P*=0.001), and pneumonia (OR 10.94, 95% CI (4.45–26.89), *P*=0.000) were associated with 30-day mortality. (Table 4).

Discussion

This study evaluated the clinical outcomes of hospitalized influenza patients administered peramivir or oseltamivir. Influenza infection can cause serious problems[17] and ICU admission.[17,18] Peramivir has been used since the 2009 pandemic to treat critically ill influenza patients.[19] Since hospitalized patients, especially critically ill patients, may have difficulty in achieving appropriate drug levels with oral oseltamivir,[20,21] intravenous peramivir can be an attractive option for clinicians. However, the few studies comparing the effectiveness of peramivir and oseltamivir in hospitalized influenza patients have reported similar efficacy[11,22]. In a study conducted in an ICU, peramivir showed similar clinical efficacy to that of oseltamivir; however, the peramivir group had significantly more patients with shock and high SOFA score.[11] A recent large prospective observational study showed that influenza related symptoms disappeared about 3 days after peramivir administration[23] and it reflected quality of life in patients with influenza infection. In this study, we

Table 3 Clinical Outcomes from All Patients

Numbers (%)	Peramivir Group Standard Dose[a] (n=251)	Peramivir Group High Dose[b] (n=42)	Oseltamivir Group (n=249)	*p*
Defervescence within 3 days	167 (66.53)	24 (57.14)	178 (71.49)	0.141
30-Day mortality	22 (8.76)	5 (11.90)	15 (6.02)	0.299
Duration of hospital stay (mean±SD)	10.65±13.84	14.12±13.75	13.28±18.12	0.129
Duration of ICU stay (mean±SD)	9.60±13.17	10.62±10.63	11.26±11.53	0.868

Notes: [a]300mg, single dose; [b]exceeding 300mg, single or multiple doses.
Abbreviations: SD, standard deviation; ICU, intensive care unit.

Table 4 Multivariate Analysis of Factors Associated with 30-Day Mortality

Numbers (%)	Survivors (n=500)	Non-Survivors (n=42)	Multivariate OR (95% CI)	*p*
Age (mean±SD)	67.90±16.01	76.69±13.09		0.094
ICU admission	47(9.4)	21(50%)	5.81 (2.70–12.50)	0.000
Peramivir	266(53.2)	27(64.3)		0.377
CCI (mean±SD)	1.91±2.05	3.00±2.51	1.32 (1.12–1.55)	0.001
Pneumonia	118 (23.6)	34 (81)	10.94 (4.45–26.89)	0.000

Abbreviations: CCI, Charlson comorbidity index; SD, standard deviation; ICU, intensive care unit.

defined defervescence within 3 days as primary outcome because we thought that it is a good indicator of recovery of patient's quality of life.

The present study observed no significant differences in mortality or hospital or ICU stay durations between peramivir and oseltamivir. However, ICU admission and pneumonia, which are risk factors for mortality, were more prevalent in the peramivir group, especially in the high-dose group. The Korea Ministry of Food and Drug Safety (KMFDS) recommended the administration of a single 300-mg dose of peramivir to adult influenza patients with normal renal function during the study period.[23]

Several studies showed that 300mg IV peramivir was non-inferior to 600mg IV peramivir or oseltamivir or both.[5,24,25] Thus, in the current study, most patients treated with peramivir received a single 300-mg dose, although physicians tended to administer higher doses to more severe patients. Moreover, age, another worse prognostic factor,[11] was also higher in the peramivir group. These findings suggest the usefulness of peramivir in patients with severe influenza. Further studies are needed to determine the appropriate dose and duration in hospitalized patients with severe illness. The treatment cost of peramivir (300mg/single dose) and oseltamivir (75mg/10 capsules) were about 30–50 dollars and 13–25 dollars in Korea.

The time elapsed before the administration of antiviral medications was relatively long in this study, particularly in the high-dose peramivir group. As anti-influenza drugs are most effective when they are used within 48 hours,[5,10] this delay could have affected the clinical outcomes. Despite this, all treatment groups showed similar clinical responses, indicating that high-dose peramivir may have a clinical benefit in these patients. Some studies have suggested that hospitalized patients may have advantages from antiviral therapy starting >48 hours after symptom onset, although earlier initiation seems to be more effective.[12–14]

This study had some limitations. First, the study was a retrospective design. Therefore, severity and comorbidity were not evenly distributed between the two groups and the choice of oseltamivir or peramivir was decided by attending physicians. Moreover, laboratory parameters including severity scores such as SOFA and APACHE II could not be obtained from all patients. Although precise comparisons of clinical effectiveness between the three groups were not possible, peramivir showed similar efficacy in hospi talized patients despite the high prevalence of pneumonia and ICU admission.

Second, this study did not collect data on subjective symptoms. Because we collected only objective data considering the retrospective design, no data were available on important clinical indicators such as fever and cough, which may not accurately reflect the clinical situation. However, considering the hospitalization, we did have data on regularly checked body temperatures, which are an objective indicator to reflect improvement in influenza; thus, this method was used to accurately confirm the clinical improvement.

Conclusion

Treatment of influenza with either peramivir or oseltamivir in hospitalized adults resulted in generally similar clinical outcomes. Treatment with peramivir showed good clinical response in influenza patients with pneumonia or admitted to the ICU.

Acknowledgments

We thank BioStat. Team in D2S company for helping with statistical analysis.

Funding

This study was supported by Green Cross Corp.

Disclosure

Joong Sik Eom has received research grants from Green Cross Corp. The author reports no other conflicts of interest in this work.

References

1. Puig-Barbera J, Burtseva E, Yu H, et al. Influenza epidemiology and influenza vaccine effectiveness during the 2014–2015 season: annual report from the Global Influenza Hospital surveillance network. *BMC Public Health*. 2016;16(Suppl 1):757. doi:10.1186/s12889-016-3378-1
2. Alame MM, Massaad E, Zaraket H. Peramivir: a novel intravenous neuraminidase inhibitor for treatment of acute influenza infections. *Front Microbiol*. 2016;7:450. doi:10.3389/fmicb.2016.00450
3. McLaughlin MM, Skoglund EW, Ison MG. Peramivir: an intravenous neuraminidase inhibitor. *Expert Opin Pharmacother*. 2015;16 (12):1889–1900. doi:10.1517/14656566.2015.1066336
4. Kohno S, Kida H, Mizuguchi M, Shimada J. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother*. 2010;54(11):4568–4574. doi:10.1128/AAC.00474-10
5. 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. doi:10.1128/AAC.00360-11
6. 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. doi:10.1128/AAC.01718-10
7. 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(9):1209–1210. doi:10.1164/ajrccm.182.9.1209
8. Huang SF, Fung CP, Perng DW, Wang FD. Effects of corticosteroid and neuraminidase inhibitors on survival in patients with respiratory distress induced by influenza virus. *J Microbiol Immunol Infect*. 2017;50(5):586–594. doi:10.1016/j.jmii.2015.08.016
9. Yeh CY, Wang FD, Chuang YC, et al. Clinical outcomes and prognostic factors of patients with severe influenza receiving intravenous peramivir salvage therapy in intensive care units. *J Microbiol Immunol Infect*. 2018;51(6):697–704. doi:10.1016/j.jmii.2017.06.001
10. 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. doi:10.1093/ofid/ofx129
11. 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(10):1649–1655. doi:10.1002/jmv.24232
12. McGeer A, Green KA, Plevneshi A, et al. Antiviral therapy and outcomes of influenza requiring hospitalization in Ontario, Canada. *Clin Infect Dis*. 2007;45(12):1568–1575. doi:10.1086/523584
13. Murata Y, Walsh EE, Falsey AR. Pulmonary complications of interpandemic influenza A in hospitalized adults. *J Infect Dis*. 2007;195 (7):1029–1037. doi:10.1086/512160
14. Walsh EE, Cox C, Falsey AR. Clinical features of influenza A virus infection in older hospitalized persons. *J Am Geriatr Soc*. 2002;50 (9):1498–1503. doi:10.1046/j.1532-5415.2002.50404.x
15. Lee N, Chan PK, Choi KW, et al. Factors associated with early hospital discharge of adult influenza patients. *Antivir Ther*. 2007;12 (4):501–508.
16. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373–383. doi:10.1016/0021-9681(87)90171-8
17. Ortiz JR, Neuzil KM, Shay DK, et al. The burden of influenza-associated critical illness hospitalizations. *Crit Care Med*. 2014;42(11):2325–2332. doi:10.1097/CCM.0000000000000545
18. Reed C, Chaves SS, Perez A, et al. Complications among adults hospitalized with influenza: a comparison of seasonal influenza and the 2009 H1N1 pandemic. *Clin Infect Dis*. 2014;59(2):166–174. doi:10.1093/cid/ciu285
19. Birnkrant D, Cox E. The emergency use authorization of peramivir for treatment of 2009 H1N1 influenza. *N Engl J Med*. 2009;361 (23):2204–2207. doi:10.1056/NEJMp0910479
20. Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. *CMAJ*. 2010;182(4):357–363. doi:10.1503/cmaj.092127
21. Arya V, Carter WW, Robertson SM. The role of clinical pharmacology in supporting the emergency use authorization of an unapproved anti-influenza drug, peramivir. *Clin Pharmacol Ther*. 2010;88 (5):587–589. doi:10.1038/clpt.2010.187
22. 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. doi:10.3851/IMP2442
23. Choi WS, Ryu SY, Lee J, et al. Safety and effectiveness of peramivir in Korean adult influenza patients: prospective observational study based on post-marketing surveillance data. *J Korean Med Sci*. 2018;33(32):e212. doi:10.3346/jkms.2018.33.e212
24. 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. doi:10.1159/000362436
25. Yoshino Y, Seo K, Koga I, Kitazawa T, Ota YJ. Clinical efficacy of peramivir in adult patients with seasonal influenza during the winter of 2012 in Japan. *Clin Respir J*. 2015;9(2):228–232. doi:10.1111/crj.12129