

Original Article

Infectious Diseases,
Microbiology & Parasitology



OPEN ACCESS

Received: Feb 3, 2018

Accepted: Apr 17, 2018

Address for Correspondence:










Woo Joo Kim, MD, PhD

Division of Infectious Diseases, Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea.
E-mail: wjkim@korea.ac.kr

© 2018 The Korean Academy of Medical Sciences.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ORCID iDs

Won Suk Choi 
<https://orcid.org/0000-0001-5874-4764>
Seong Yeol Ryu 
<https://orcid.org/0000-0002-6023-8550>
Jacob Lee 
<https://orcid.org/0000-0002-7041-065X>
Sang-Bum Hong 
<https://orcid.org/0000-0003-2737-7695>
Joong Sik Eom 
<https://orcid.org/0000-0003-2744-1159>
Jonghwan Shin 
<https://orcid.org/0000-0002-7121-2137>
Ki Ho Park 
<https://orcid.org/0000-0002-2796-7145>
Taekgeun Ohk 
<https://orcid.org/0000-0003-1005-9893>
Jin-Won Chung 
<https://orcid.org/0000-0003-4811-6056>

<https://jkms.org>

Safety and Effectiveness of Peramivir in Korean Adult Influenza Patients: Prospective Observational Study Based on Post-Marketing Surveillance Data

Won Suk Choi ¹, Seong Yeol Ryu ², Jacob Lee ³, Sang-Bum Hong ⁴,
Joong Sik Eom ⁵, Jonghwan Shin ⁶, Ki Ho Park ⁷, Taekgeun Ohk ⁸,
Jin-Won Chung ⁹, Doo Ryeon Chung ¹⁰, Dong Kee Kim ¹¹, Sang-Rok Lee ¹²,
Pill Young Kim ¹³, Shin-Woo Kim ¹⁴, Ji Yun Noh ¹, Joon Young Song ¹,
Hee Jin Cheong ¹ and Woo Joo Kim ¹

¹Division of Infectious Diseases, Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea

²Department of Infectious Diseases, Keimyung University Dongsan Medical Center, Daegu, Korea

³Division of Infectious Diseases, Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea

⁴Department of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

⁵Division of Infectious Diseases, Department of Internal Medicine, Gachon University College of Medicine, Incheon, Korea

⁶Department of Emergency Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea

⁷Kim & Park Heart & Digestive Disease Clinic, Siheung, Korea

⁸Department of Emergency Medicine, School of Medicine, Kangwon National University, Chuncheon, Korea

⁹Division of Infectious Diseases, Chung-Ang University Hospital, Seoul, Korea

¹⁰Division of Infectious Diseases, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

¹¹Songdo Green Clinic, Incheon, Korea

¹²Cheongju St. Mary's Hospital, Cheongju, Korea

¹³Kim's Internal Medicine Clinic, Daegu, Korea

¹⁴Department of Internal Medicine, School of Medicine, Kyungpook National University, Daegu, Korea

ABSTRACT

Background: The safety and clinical effectiveness data of peramivir in the real clinical field are limited. A prospective observational study was conducted based on the post-marketing surveillance data to evaluate the post-marketing safety and effectiveness of peramivir in Korean adults with seasonal influenza.

Methods: Among adults aged 20 years or older who were diagnosed with influenza A or B, patients who started peramivir within 48 hours from the initial symptoms of influenza were enrolled. All adverse events (AEs) that occurred within 7 days after administration of peramivir were checked. For the evaluation of effectiveness, changes in the severity of influenza symptoms and daily living performance were examined before and 7 days after the administration of peramivir. The date on which influenza related symptoms disappeared was checked.

Results: A total of 3,024 patients were enrolled for safety evaluation and 2,939 patients were for effectiveness evaluation. In the safety evaluation, 42 AEs were observed in 35 (1.16%) patients. The most common AE was fever. AEs were mostly rated as mild in severity. Serious AEs were observed in 10 patients and two of them died. However, both deaths were considered to be less relevant to peramivir. In the effectiveness evaluation, the severity of influenza symptoms decreased by 10.68 ± 4.01 points and daily living performance was

Doo Ryeon Chung 


<https://orcid.org/0000-0001-9267-101X>

Dong Kee Kim 

<https://orcid.org/0000-0002-1086-0245>

Sang-Rok Lee 


<https://orcid.org/0000-0003-0657-4657>

Pill Young Kim 

<https://orcid.org/0000-0002-9305-4301>

Shin-Woo Kim 

<https://orcid.org/0000-0002-3755-8249>

Ji Yun Noh 


<https://orcid.org/0000-0001-8541-5704>

Joon Young Song 

<https://orcid.org/0000-0002-0148-7194>

Hee Jin Cheong 

<https://orcid.org/0000-0002-2532-1463>

Woo Joo Kim 

<https://orcid.org/0000-0002-4546-3880>

Funding

This paper summarized the post-marketing surveillance study which was sponsored by Green Cross Corp., Republic of Korea from 2011 to 2016.

Disclosure

The sponsor participated in the post-marketing study design, execution, and the data collections. Although the sponsor reviewed the draft, the opinions expressed by the sponsor may not necessarily be reflected. The results of this study were presented as a poster at the 5th ISIRV-AVG conference.

Author Contributions

Conceptualization: Hong SB. Data curation: Choi WS, Kim WJ. Investigation: Choi WS, Ryu SY, Lee J, Hong SB, Eom JS, Shin J, Park KH, Ohk T, Cheong HJ, Chung DR, Kim DK, Lee SR, Kim PY, Kim SW, Noh JY, Song JY, Cheong HJ, Kim WJ. Writing - original draft: Choi WS. Writing - review & editing: Kim WJ.

improved 5.59 ± 2.16 points. Influenza related symptoms disappeared on average 3.02 ± 2.39 days after peramivir administration.

Conclusion: Peramivir showed a tolerable safety profile and acceptable effectiveness in Korean adult patients with seasonal influenza.

Keywords: Influenza; Antiviral; Peramivir; Safety; Effectiveness; Clinical Trial

INTRODUCTION

Influenza is a highly contagious acute respiratory disease caused by influenza A or B viruses. Influenza is usually accompanied by symptoms such as fever, headache, myalgia, fatigue, cough and sore throat, and usually can be recovered within 7 days. However, high-risk people like the elderly over 65 years old, pregnant women, or patients with immunocompromised diseases can have complications such as pneumonia, and can lead to death in severe cases. In the United States, more than 200,000 people are hospitalized each year for influenza.¹ In Korea, more than 23,000 people are estimated to be admitted and more than 1,200 people are estimated to die due to the influenza each year.² Influenza viruses have antigenic variations that cause not only the annual seasonal epidemic, but also pandemic every 10 to 40 years. Therefore, the antiviral agents against influenza are very important for the response to influenza pandemics as well as treatment of seasonal influenza.

Antiviral agents used for the treatment of influenza include amantadine and rimantadine classified as M2-blocker, and oseltamivir, zanamivir and peramivir classified as neuraminidase inhibitor. The M2-blocker is effective for influenza A but not for B, and it is more likely to have AEs relatively. In addition, since the current influenza A virus is resistant to M2-blocker, the use of M2-blocker is no longer recommended in the influenza treatment guidelines.^{1,3} On the other hand, influenza A and B viruses circulating currently are susceptible to neuraminidase inhibitors. Therefore, the neuraminidase inhibitor is the mainstay in the treatment of influenza now.

Peramivir is one of the neuraminidase inhibitors, and is the only intravenous formulation currently available. Peramivir has the advantage that it can be administered to patients who have difficulty in taking oral (oseltamivir) or inhaled (zanamivir) agent. The single administration is another advantage in that there is no concern about low compliance, which can decrease the risk of treatment failure or development of antiviral resistance. Peramivir was approved in Japan and Korea in 2010, and the United States in 2014.⁴ Clinical trials have shown that the effectiveness of peramivir was comparable to oseltamivir and the occurrence of AEs was relatively low.^{5,6} However, the safety and clinical efficacy data of peramivir in the real clinical field is still limited. To address this, we performed a prospective observational study to evaluate the post-marketing safety and efficacy of peramivir in adults with seasonal influenza. This study was conducted in accordance with the regulation of Korea Ministry of Food and Drug Safety (KMFDS, notice No. 2013-251).

METHODS

Patients

This study was a single-arm, prospective, observational, cohort study conducted at 75 medical institutions in the Republic of Korea during December 2010 to August 2016. To be

enrolled in the study, patients had to meet all the following inclusion criteria: adults aged 20 years or older at enrollment, laboratory confirmation of influenza A or B, administration of peramivir within 48 hours from the initial symptoms of influenza, and obtaining a subject's written informed consent. The laboratory confirmation of influenza was performed at each medical institution with rapid antigen test (RAT), reverse transcription polymerase chain reaction (RT-PCR) or culture. Subjects with the use of peramivir out of the formal dosage recommended by KMFDS were excluded. The formal use of peramivir in Korea is to administer 300 mg once to adult influenza patients with normal renal function. The peramivir dose should be reduced for patients with impaired renal function according to their creatinine clearance. The administration of peramivir to pregnant women is generally limited due to insufficient safety data. The decision on whether to administer peramivir was based on the clinical indication by physicians of each medical institution.

Safety assessment

All AEs were checked using the prepared check sheet, which included events that occurred within 7 days after administration of peramivir. The grade and causal relationship of AEs was assessed according to the guideline of the KMFDS (notice No. 2014-97). The AEs were graded as 1 to 4 according to the severity. Severe adverse events (SAEs) were defined as important medical events that resulted in life-threatening, death, hospitalization/prolonged hospitalization, persistent or significant disability/incapacity, congenital anomaly, or other medically important situation. The causal relationship of AEs with peramivir was classified as certain, probably/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable. The causality was determined by physicians of each institution. Adverse drug reactions (ADRs) were defined as AEs for which the causality could not be ruled out as determined by physicians or sponsor.

Effectiveness assessment

The condition of the enrolled patients was checked before and 7 days after the administration of peramivir. The severity of influenza symptoms was evaluated using 0–3 scale as follows: 0, normal; 1, mild (barely noticeable); 2, moderate (bothersome); 3, severe (unbearable). The influenza symptom checked included cough, sore throat, headache, nasal congestion, febrile sense or chills, muscle or joint pain, and fatigue. Daily living performance was checked using 0–10 visual analogue scale (VAS). The date on which influenza symptoms disappeared was checked. The final effectiveness of peramivir was determined by physicians of each institution, based on the symptom and sign, as follows: effective, not effective, unable to judge.

Statistical analysis

This study was a single-arm study, so most values were described without comparisons. For the sub-analysis for estimating the difference of the safety or effectiveness according to the characteristics, the χ^2 test or the Fisher's exact test was used for categorical variables, and the t-test was used for continuous variable. Logistic regression analysis was performed to confirm the independent factors related to the AE or ADR occurrence. The factors with the statistical significance related to the AE or ADR occurrence in the univariate analysis were included in the logistic regression analysis. Comparing pre- and post-status of the influenza symptom severity and daily living performance for the effectiveness assessment was done by using Wilcoxon rank-sum test. A two-sided significance level of 5% was used throughout. The continuous variables contained the minimum and maximum statistics, the arithmetic mean, standard deviation and median, and the 95% confidence interval (CI). The categorical variables contained counts and percentages.

Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the 28 medical institutions participating this study (IRB No. of Korea University Guro Hospital: KUGH14296-001). For institutions that do not have an individual IRB, they conducted this study based on the IRB approval information from other institutions. Informed consent was obtained from all subjects when they were enrolled.

RESULTS

Characteristics of the study population

A total of 4,056 check sheets were collected during the study period. Of these, 1,032 were excluded from the analysis with the reasons as follows: 974, dosage out of the formal recommendation of KMFDS; 17, duplicated cases; 65, follow-up loss; the exclusion reasons were duplicated. As a result, a total of 3,024 subjects were included in the safety assessment. For the effectiveness assessment, a total of 2,939 subjects were included because effectiveness data was not collected from 85 subjects. The number of enrolled subjects according to the influenza seasons is shown in Fig. 1.

Of the 3,024 subjects, 39.9% (n = 1,205) were male (Table 1). Mean age was 45.55 ± 15.30 years and 12.07% (n = 365) were adults aged 65 years or older. About one of ten subjects (10.75%, n = 325) had a history of hospitalization. Underlying diseases were present in 18.82% (n = 569) patients, and 69.74% (n = 2,109) had concomitant medication. The most common concomitant medications were anti-tussive (46.36%, n = 1,402), analgesics/antipyretics (41.57%, n = 1,257) and non-steroidal anti-inflammatory agents (38.36%, n = 1,160).

Influenza A and B accounted for 74.37% (n = 2,249) and 25.17% (n = 761), respectively. Fourteen subjects (0.46%) were diagnosed with both A and B infection. Complication of influenza was present in 9.42% (n = 285) patients, and bronchitis (6.25%, n = 189) and pneumonia (2.35%, n = 71) were most common.

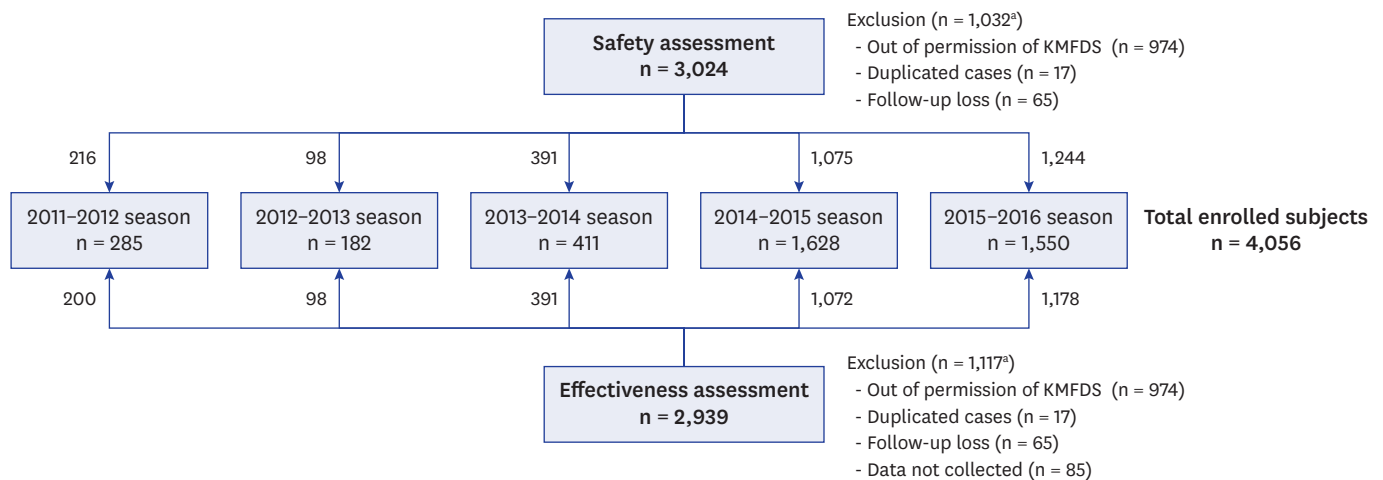


Fig. 1. The number of enrolled patients according to the influenza seasons.
 *Exclusion reasons were duplicated.

Table 1. Characteristics of the enrolled patients

Characteristics	No. of subjects
Sex, male	1,205 (39.85)
Age, yr	45.6 ± 15.3 (20–98)
Older adults (≥ 65 years)	365 (12.07)
History of hospitalization	325 (10.75)
Pregnancy among female	7 (0.38)
One or more comorbidities ^a	569 (18.82)
Cardiovascular disease	272 (8.99)
Endocrine, nutrition, or metabolic disease	188 (6.22)
Respiratory disease	123 (4.07)
Gastrointestinal or liver disease	96 (3.17)
Neoplasm	90 (2.98)
Musculoskeletal disease	55 (1.82)
Infectious disease	55 (1.82)
Genitourinary disease (including kidney disease)	44 (1.46)
Psychiatric disease	40 (1.32)
Neurologic disease	34 (1.12)
Hematologic disease	23 (0.76)
Concomitant medication, yes	2,109 (69.74)
Type of influenza	
Influenza A	2,249 (74.37)
Influenza B	761 (25.17)
Influenza A + B	14 (0.46)
Complication of influenza ^a	285 (9.42)
Sinusitis	11 (0.36)
Otitis media	1 (0.03)
Bronchitis	189 (6.25)
Pneumonia	71 (2.35)
Others	23 (0.76)

Data are presented as means ± standard deviation (range) or number (%).

^aDuplicate counting.

Safety assessment

A total of 42 AEs was observed in 1.16% (n = 35) patients (Table 2). The most common AE was fever (0.17%, n = 5), diarrhea (0.13%, n = 4), nausea (0.10%, n = 3) and pneumonia (0.10%, n = 3). AEs were mostly rated as mild in severity (76.19%, 32/42). SAEs were observed in 10 subjects (0.33%) and two of them died. However, both deaths were attributed to pneumonia, which was less relevant to peramivir. Among the 42 AEs, only eight (19.05%) were estimated as possible causality and most (73.81%, 31/42) were assessed as unlikely. Eleven ADRs were identified in 10 patients: nausea (0.10%, n = 3), leukopenia (0.07%, n = 2), and liver function abnormality (0.07%, n = 2) were the most common ADRs.

The incidence rate of AEs of the persons 65 years or older was 3.84% (14/365 persons), which was significantly higher than persons under 65 years old (0.79%, 21/2,659) ($P < 0.001$). AEs were more common in the subjects with underlying diseases (3.87% vs. 0.53%, $P < 0.001$). Subjects with concomitant medications had more AEs than the others (1.56% vs. 0.22%, $P = 0.002$). ADRs were also more common in the subjects with concomitant medication (0.47% vs. 0%, $P = 0.038$).

The results of the logistic regression analysis of the AEs incidence showed that AEs occurred more frequently in the subjects with influenza complications (odds ratio [OR], 3.949; 95% CI, 1.877–8.308), underlying diseases (OR, 7.555; 95% CI, 3.782–15.091), or concomitant medications (OR 7.252; 95% CI, 1.737–30.274). The results of the logistic regression analysis of ADRs incidence showed that the ADRs occurred more frequently in the subjects with underlying diseases (OR, 4.153; 95% CI, 1.068–16.148).

Table 2. Incidence of AEs and ADR of peramivir

Category of AEs	AEs		ADRs	
	No. of subjects (%), [No. of events]		No. of subjects (%), [No. of events]	
Gastrointestinal disorder	12 (0.40), [13]		5 (0.17), [5]	
Diarrhea	4 (0.13), [4]		1 (0.03), [1]	
Nausea	3 (0.10), [3]		3 (0.10), [3]	
Constipation	2 (0.07), [2]		-	
Stomatitis	1 (0.03), [1]		-	
Abdominal pain	1 (0.03), [1]		-	
Upper abdominal pain	1 (0.03), [1]		1 (0.03), [1]	
Indigestion	1 (0.03), [1]		-	
Infection	5 (0.17), [5]		1 (0.03), [1]	
Pneumonia	3 (0.10), [3]		1 (0.03), [1]	
Herpes simplex	1 (0.03), [1]		-	
Skin and soft tissue infection	1 (0.03), [1]		-	
Administration reaction	5 (0.17), [5]		-	
Fever	5 (0.17), [5]		-	
Respiratory disorder	4 (0.13), [4]		-	
Rhinorrhea	2 (0.07), [2]		-	
Hemoptysis	1 (0.03), [1]		-	
Pulmonary embolism	1 (0.03), [1]		-	
Hematologic disorder	3 (0.10), [3]		2 (0.07), [2]	
Leukopenia	2 (0.07), [2]		2 (0.07), [2]	
Neutropenia	1 (0.03), [1]		-	
Musculoskeletal disorder	2 (0.07), [2]		-	
Chest muscular pain	1 (0.03), [1]		-	
Rhabdomyolysis	1 (0.03), [1]		-	
Metabolic and nutrition disorder	2 (0.07), [2]		1 (0.03), [1]	
Anorexia	1 (0.03), [1]		1 (0.03), [1]	
Hypokalemia	1 (0.03), [1]		-	
Neurologic disorder	1 (0.03), [1]		-	
Sensory loss	1 (0.03), [1]		-	
Laboratory abnormality	2 (0.07), [2]		2 (0.07), [2]	
LFT abnormality	2 (0.07), [2]		2 (0.07), [2]	
Skin and soft tissue disorder	2 (0.07), [2]		-	
Itching sense	1 (0.03), [1]		-	
Drug eruption	1 (0.03), [1]		-	
Vascular disorder	1 (0.03), [2]		-	
Hypertension	1 (0.03), [1]		-	
Hypotension	1 (0.03), [1]		-	
Cardiac disorder	1 (0.03), [1]		-	
Tachycardia	1 (0.03), [1]		-	
Total	35 (1.16), [42]		10 (0.33), [11]	

AE = adverse event, ADR = adverse drug reaction, LFT = liver function test.

Safety assessment in special groups

Seven pregnant women were included in the study, but no AE was identified. Forty-six patients with underlying liver disease were included in the study. Among them, pneumonia was detected in 2.17% (1/46, 1 subject) as an AE, but there was no ADR. Four patients with underlying kidney disease were included in the study, but no AE was identified.

Effectiveness assessment

After administration of peramivir, the severity of influenza symptoms decreased by 10.68 ± 4.01 points and the daily living performance was improved by 5.59 ± 2.16 points (Table 3). In both effectiveness assessments, pre- and post-treatment differences were statistically significant ($P < 0.001$).

In the sub-analysis of the changes of the severity of influenza symptoms, the females showed more decrease than the males (10.83 ± 3.88 vs. 10.44 ± 4.20 , $P = 0.028$). Adults younger than 65 years showed more decrease than the older adults (10.95 ± 3.84 vs. 8.56 ± 4.61 , $P < 0.001$). Subjects with influenza complication showed less decrease than those without complication (9.29 ± 3.49 vs. 10.83 ± 4.04 , $P < 0.001$). Subjects with underlying diseases showed less decrease than the others (8.40 ± 4.72 vs. 11.19 ± 3.64 , $P < 0.001$). In the sub-analysis of the changes of the daily living performance, there was no statistically significant difference according to the subjects' characteristics.

Influenza-related symptoms disappeared on average 3.02 ± 2.39 days after peramivir administration (median 2.00 days, range 0–32 days). The persons 65 years or older took more days to lose influenza symptoms than the younger persons (3.55 ± 2.80 vs. 2.95 ± 2.32 , $P < 0.001$). Subjects with underlying diseases took more days than the others (3.82 ± 2.68 vs. 2.83 ± 2.28 , $P < 0.001$). Subjects with influenza B took more days than those with influenza A (3.17 ± 2.31 vs. 2.96 ± 2.41 , $P < 0.001$).

The results of the final effectiveness assessment as follows: effective, 97.96% (2,879/2,939); unable to judge, 1.02% (30/2,939); not done, 0.75% (22/2,939); and no effective, 0.27% (8/2,939).

DISCUSSION

Peramivir has been approved for emergency use during the A/H1N1pdm09 pandemic prior to formal licensing.⁷ At that time, peramivir was usually used as a salvage treatment in severe patients who had no effect on oseltamivir. There were a few reports on the safety and effectiveness during emergency use and the results were acceptable for clinical use.⁸⁻¹⁰ After that, the result of the phase III clinical trial was reported and the peramivir with once daily regimen showed acceptable safety and effectiveness compared to the 5-day regimen of oral oseltamivir.⁵ However, since peramivir was approved only in a few countries, such as Japan, Korea, and the United States, safety and effectiveness data in clinical use was relatively limited. Most of the studies were conducted in Japan and showed similar effectiveness and safety compared with oseltamivir.¹¹⁻¹³ There are two clinical studies of peramivir in Korea that are searchable through PubMed. One study compared the clinical effectiveness of oral oseltamivir and intravenous peramivir in patients with severe influenza.¹⁴ Both antiviral agents showed similar clinical effectiveness. Another study was a meta-analysis, not a direct clinical study.¹⁵ Although this study was conducted as a post-marketing surveillance, it has strength in terms of a prospective clinical study with more than 3,000 subjects during various influenza seasons. It is also meaningful in that the safety and effectiveness of peramivir are evaluated with a variety of subjects including healthy adults, the elderly and patients with chronic diseases.

Table 3. Change of the severity of influenza symptoms and the daily living performance after the administration of peramivir

Characteristics	The severity of influenza symptom				The daily living performance			
	No.	Average \pm SD	Median	Range	No.	Average \pm SD	Median	Range
Before	2,758	12.61 \pm 4.39	13.00	0.00–21.00	2,712	3.47 \pm 2.08	3.00	0.00–10.00
After	2,638	2.12 \pm 2.27	2.00	0.00–17.00	2,619	9.04 \pm 1.46	10.00	0.00–10.00
Change	2,634	-10.68 \pm 4.01	-11.00	-21.00–3.00	2,613	5.59 \pm 2.16	6.00	-8.00–10.00
Rate of change	2,633	-84.11 \pm 16.19	-86.67	-100.00–42.86	2,558	257.08 \pm 225.82	200.00	-100.00–900.00
P value			< 0.001				< 0.001	

SD = standard deviation.

Compared with the phase III clinical trial⁵ and the post-marketing surveillance conducted in Japan,¹¹⁻¹³ the incidence of AEs identified in this study was much lower. This may be due to differences in the characteristics of the population, or due to the differences in the subjects' perception of the AEs. However, there was no difference in that most AEs were mild and the SAE was rare.

In this study, AEs of peramivir were found to be more frequent in subjects with influenza complications, underlying diseases, or concomitant medications. This is thought to be due to the underlying condition of subjects rather than the peramivir drug itself.

Two deaths were identified during this study. One case was a patient admitted to the emergency room accompanied by influenza and severe pneumonia, and died two days after receiving peramivir. Another case was a patient with alcoholic liver disease, non-Hodgkin's lymphoma, cardiomyopathy and diabetes mellitus, and died two days after receiving peramivir with severe pneumonia. In both cases, the death was possibly related to complicated pneumonia following influenza rather than the AE of peramivir. However, since the peramivir is likely to be administered to severe patients due to the possibility of intravenous use, a large-scale prospective study will be needed to analyze the effectiveness of peramivir compared to other antiviral agents in patients with severe influenza.

Seven pregnant women were included in this study. Peramivir is generally not recommended for pregnant women in the guideline due to the insufficient safety data.³ The pregnant women were monitored until the birth results to be confirmed, and there was no specific problem related to the birth. However, the results of this study are not enough to confirm the safety of peramivir in pregnant women. Therefore, it cannot be recommended to pregnant women with this data. Additional research and data collection will be needed to confirm the safety of peramivir during pregnancy.

The effectiveness of peramivir was confirmed by a significant improvement in influenza symptom severity and daily living performance before and after administration of peramivir. However, since this study was a single-arm study in which placebo or other antiviral agents were not used as a control group, it was impossible to confirm the efficacy compared to the placebo or other antiviral agents. Sub-analysis showed better effectiveness in patients with young age, without influenza complication, or without underlying disease. This result is considered to reflect the underlying condition of subjects rather than the pharmacodynamic properties of peramivir. It is not clear why the influenza symptom severity was significantly improved in females compared to males. One of the possible explanations is that men are likely to state symptoms with narrow spectrum due to cultural factors. It is not clear why the symptom of influenza B disappeared later than influenza A. Further studies will be required to evaluate the effectiveness of peramivir in each type of influenza virus.

More than 1,000 subjects were excluded from the analysis. Of those, 357 had no laboratory confirmation of influenza infection. However, in the current guidelines for the use of influenza antiviral agents, high-risk patients are recommended to receive empirical antiviral agents during influenza epidemics without laboratory confirmation of influenza virus infection. Supplementary analysis was performed with the data of excluded subjects. Among the 950 subjects with sufficient data, the incidence of AE was 2.53% (24/950), the incidence of ADR was 0.32% (3/950), and the incidence of SAE was 0.42% (4/950). There was no significant difference compared to the subjects included in the main analysis.

This study has some limitations. Because this study was conducted according to the regulation of the Republic of Korea, research design and data collection were limited in comparison with other clinical studies. This was a single-arm study that cannot compare the safety and effectiveness with placebo or other antiviral agents. The number of excluded subjects was relatively large, which was about 25% of the total enrolled subjects. The data of children was excluded from the analysis because peramivir is approved only for adults in Korea.

In conclusion, peramivir was confirmed to have a tolerable safety profile and acceptable effectiveness in Korean adult patients with seasonal influenza, which was similar to those of previous clinical studies.

REFERENCES

1. Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM, 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.
[PUBMED](#)
2. Choi WS, Cowling BJ, Noh JY, Song JY, Wie SH, Lee JS, et al. Disease burden of 2013-2014 seasonal influenza in adults in Korea. *PLoS One* 2017;12(3):e0172012.
[PUBMED](#) | [CROSSREF](#)
3. Choi WS, Lee J, Lee HY, Baek JH, Kim YK, Kee SY, et al. Clinical practice guideline for antiviral treatment and chemoprophylaxis of seasonal influenza. *Infect Chemother* 2012;44(4):233-49.
[CROSSREF](#)
4. Alame MM, Massaad E, Zaraket H. Peramivir: a novel intravenous neuraminidase inhibitor for treatment of acute influenza infections. *Front Microbiol* 2016;7:450.
[PUBMED](#) | [CROSSREF](#)
5. 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(11):5267-76.
[PUBMED](#) | [CROSSREF](#)
6. 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(5):651-61.
[PUBMED](#) | [CROSSREF](#)
7. Birnkrant D, Cox E. The Emergency Use Authorization of peramivir for treatment of 2009 H1N1 influenza. *N Engl J Med* 2009;361(23):2204-7.
[PUBMED](#) | [CROSSREF](#)
8. Hernandez JE, Adiga R, Armstrong R, Bazan J, Bonilla H, Bradley J, et al. Clinical experience in adults and children treated with intravenous peramivir for 2009 influenza A (H1N1) under an Emergency IND program in the United States. *Clin Infect Dis* 2011;52(6):695-706.
[PUBMED](#) | [CROSSREF](#)
9. Louie JK, Yang S, Yen C, Acosta M, Schechter R, Uyeki TM. Use of intravenous peramivir for treatment of severe influenza A(H1N1)pdm09. *PLoS One* 2012;7(6):e40261.
[PUBMED](#) | [CROSSREF](#)
10. Sorbello A, Jones SC, Carter W, Struble K, Boucher R, Truffa M, et al. Emergency use authorization for intravenous peramivir: evaluation of safety in the treatment of hospitalized patients infected with 2009 H1N1 influenza A virus. *Clin Infect Dis* 2012;55(1):1-7.
[PUBMED](#) | [CROSSREF](#)
11. Komeda T, Ishii S, Itoh Y, Ariyasu Y, Sanekata M, Yoshikawa T, et al. Post-marketing safety and effectiveness evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir (I): a drug use investigation. *J Infect Chemother* 2014;20(11):689-95.
[PUBMED](#) | [CROSSREF](#)
12. Komeda T, Ishii S, Itoh Y, Ariyasu Y, Sanekata M, Yoshikawa T, et al. Post-marketing safety and effectiveness evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir. II: a pediatric drug use investigation. *J Infect Chemother* 2015;21(3):194-201.
[PUBMED](#) | [CROSSREF](#)

13. Komeda T, Ishii S, Itoh Y, Sanekata M, Yoshikawa T, Shimada J. Post-marketing 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):677-84.
[PUBMED](#) | [CROSSREF](#)
14. 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):1649-55.
[PUBMED](#) | [CROSSREF](#)
15. 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):778-85.
[PUBMED](#) | [CROSSREF](#)