Journal of Microbiology, Immunology and Infection (2017) 50, 541–544

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Brief Communication

Safety and efficacy of anti-influenza drugs, intravenous peramivir against influenza virus infection in elderly patients with underlying disease

Kazufumi Takamatsu [a,d], Satoshi Marumo [a,c], Motonari Fukui [a], Atsuko Hata [b,c,*,d]

[a] *Department of Respiratory Medicine, Tazuke Kofukai Medical Research Institute Kitano Hospital, Japan*
[b] *Department of Pediatrics, Tazuke Kofukai Medical Research Institute Kitano Hospital, Japan*
[c] *Department of Infectious Diseases, Tazuke Kofukai Medical Research Institute Kitano Hospital, Japan*

Received 17 May 2016; received in revised form 11 November 2016; accepted 24 November 2016
Available online 26 June 2017

KEYWORDS
Aging;
Antiviral drugs;
Geriatrics;
Gerontology;
High-risk patient;
Neuraminidase inhibitor

Abstract We retrospectively analyzed data of 38 elderly patients, each with an underlying disease, to evaluate peramivir safety and efficacy. Six patients (15.8%) experienced adverse events, all tolerated. Median time from administration until the return to normal temperatures was 31.5 h (95% CI: 22.4–40.6). Results confirm intravenous peramivir's usefulness.

Introduction

The effects of influenza, an acute febrile respiratory illness caused by influenza virus, are strongest on children and elderly people worldwide. Often, life-threatening pneumonia can complicate cases in elderly people and others who are affected by disease. Reportedly, the respective relative risks (RR) of death in immunocompromised patients, those with respiratory disease, and those with renal disease are 27.7, 7.8, and 22.7. Mortality is higher among elderly people (≥65 years old) than among the general population (RR = 1.7).[1] Such high-risk patients must be treated immediately with anti-influenza drugs to prevent severe adverse outcomes. Nevertheless, inhalation and oral administration of neuraminidase inhibitors (NAIs) are difficult for elderly people. Peramivir, an anti-influenza agent

* Corresponding author. Department of Infectious Diseases, Department of Infection Control, Department of Pediatrics, Division of Infectious Diseases, Tazuke Kofukai Medical Research Institute Kitano Hospital, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480, Japan. Fax: +81 6 6312 8867.
E-mail address: a-hata@kitano-hp.or.jp (A. Hata).
[d] Kazufumi Takamatsu and Atsuko Hata contributed equally to this work.

http://dx.doi.org/10.1016/j.jmii.2016.11.006

that is administered intravenously, was first recommended during the 2014–2015 flu season by the Centers for Disease Control and Prevention (CDC) to treat influenza infection in adult patients.[2] Single administration of peramivir reportedly produces results at least as good as those of oseltamivir or zanamivir.[3–6] Administration of peramivir 600 mg/day has been recommended for high-risk patients because it is reportedly more effective for them.[7] However, earlier studies did not examine patients from elderly high-risk groups. Therefore, the safety and efficacy of peramivir in elderly high-risk groups remain unclear. This study investigates the efficacy and safety of peramivir in elderly influenza patients who were already affected by underlying diseases.

Method

Subject

This retrospective cohort study examined data of elderly patients (≥65 years) who had been hospitalized with influenza and treated with peramivir during February 2012–March 2015. Each patient had at least one underlying disease: chronic respiratory disease, chronic heart disease, diabetes mellitus, chronic kidney disease, and immunocompromised state. Data of patients meeting the criteria were extracted retrospectively from hospital charts. Influenza had been diagnosed using a rapid diagnostic test for influenza (Espline™ Influenza A&B-N kit; Fujirebio Inc., Tokyo, Japan).

The dosage for peramivir administration was chosen according to information from the package insert. The standard peramivir dosage was 300 mg/day. The increased dosage for patients with potential severity was 600 mg/day. We used the dosages explained below for patients with impaired renal function. The respective standard and increased dosages were 100 mg/day and 200 mg/day for patients with Ccr of 30–50 mL/min. They were 50 mg/day and 100 mg/day for patients with Ccr of 10–30 mL/min. All patients were febrile at the initiation of peramivir therapy. Peramivir was administered at the discretion of the physician to 5 days at most, until defervescence (body temperature $< 37\ ^{\circ}C$ for more than 12 h). The administered dosage and date were ultimately left to the discretion of each attending physician.

The ethics committee of the Tazuke Kofukai Medical Research Institute, Kitano Hospital (P15-10-012) approved the study protocol. This study, planned and conducted in accordance with guidelines outlined in the Declaration of Helsinki, was registered with the Ministry of Education, Culture, Sports, Science and Technology, Japan (UMIN000020696).

Endpoint

Safety was evaluated according to the type, severity, causality, and incidence of adverse events. Symptoms were extracted from medical records. Patients underwent blood examinations regularly. Oxygen saturation and electrocardiographic data were monitored until the medical state settled. The Division of AIDS (DAIDS) table for grading adverse event severity was used for rating severity: grade 1, mild; grade 2, moderate; and grade 3, severe.

Efficacy was evaluated according to the time from administration to return to normal temperatures. Severe complications (pneumonia, bronchitis, meningitis, otitis media, and paranasal sinusitis) and hospital mortality were also evaluated. To judge defervescence, body temperature was recorded every 8 h. General status was evaluated using Eastern Cooperative Oncology Group performance status (ECOG PS).

Statistics

Median values were used to assess the endpoint of the duration of administration to return to normal temperatures. Comparison between the two groups was made using a Mann–Whitney *U* test. All statistical tests were applied to assess two-tailed significance for $p < 0.05$. Software was used for analyses (Statmate IV; ATMS Co. Ltd., Tokyo, Japan).

Results

Patient characteristics

Table 1 shows characteristics of the patients (median age, 80 years old; 66–101 yr). The influenza virus types, as determined using the influenza virus simple kit, were type A in 31 cases (82%) and type B in 7 cases (18%). Although 25 patients were administered the standard dosage of peramivir, 13 patients were administered double the dosage because of their potentially severe condition. No patient was admitted to the intensive care unit.

Safety

Adverse events that were plainly influenced by peramivir occurred in 18.4% of all subjects (7/38 cases). Table 2 presents results of the adverse events: two cases of appetite loss, one of diarrhea, wobble, rash, thrombocytopenia ($9.9 \times 10^4/\mu L$), and creatinine kinase elevation (567 U/L). The possibility cannot be denied that these adverse events were symptoms of the influenza infection itself or that they resulted from the influence of new drugs other than peramivir. All adverse events were mild (grade 1) or moderate (grade 2) as judged by the severity grading of the DAIDS table. In the standard dosage group, two patients experienced moderate anorexia. All others were mild adverse events. No gastrointestinal adverse event or neutropenia occurred.

Efficacy

The median time from administration to return to normal temperatures of all patients was 31.5 h (95% confidence interval (CI): 22.4–40.6 h). The median time from administration to return to normal temperature in 25 patients treated with the standard dosage was 27 h (95% CI: 19.6–34.5 h). It was 41 h (95% CI: 19.8–62.2 h) in patients

Table 1 Background characteristics of patients.

	Total	Standard dosage	Increased dosage
Total	38	25	13
Sex male/female	15/23	9/16	6/7
Age (yr) [median]	80	80	82
BMI	20.65	19.6	20.8
Influenza type			
A/B	31/7	21/4	10/3
Performance status			
0/1/2/3/4	8/13/10/6/1	6/7/7/4/1	2/6/3/2/0
SOFA (mean)	1.5 (0–15)	1 (0–4)	3 (1–15)
Hospital stay (mean)	14 (3–155)	14 (3–118)	16 (8–155)
Administration duration			
1 day	33	23	10
2 day	5	2	3
Underlying disease			
Chronic respiratory disease	27	20	7
Chronic heart disease	10	5	5
Diabetes mellitus	9	5	4
Chronic kidney disease	17	6	11
Immunocompromised state			
Before[a]	4	3	1
After[b]	19	13	6

[a] Use of immunosuppressive agents before influenza virus infection.
[b] Use of immunosuppressive agents after influenza virus infection.
Performance status: 0, fully active; 1, restricted in physically strenuous activity; 2, ambulatory and capable of all selfcare but unable to carry out any work activities; 3, capable of only limited selfcare; 4, completely disabled.

treated with the increased dosage. No significant difference was found between the standard administration dosage and increased dosage ($p = 0.11$). Hospital mortality was 5.3% (2/38 cases).

Two patients died during this study. One patient with idiopathic pneumonia, who was diagnosed with influenza at our hospital, had consulted us because of fever. The patient's fever subsided 47 h after peramivir administration, but pneumothorax and carbon dioxide narcosis developed thereafter. He died on hospital day 9. Another patient, positive for aspergillus antibodies after earlier treatment for aspergillosis, came to our hospital with fever, cough, and sputum. He was diagnosed as having influenza. His fever subsided 39 h after peramivir administration. He died two months after hospitalization because of the progression of pulmonary aspergillosis. The two cases were regarded as unrelated to adverse effects of peramivir.

Table 2 Adverse events related to peramivir.

Adverse events [no. (%)]	All	Standard dosage	Increased dosage
Total	7 (18.4)	6 (15.8)	1 (2.6)
Anorexia	2 (5.3)	2 (5.3)[a]	0 (0)
Rash	1 (2.6)	1 (2.6)	0 (0)
Diarrhea	1 (2.6)	1 (2.6)	0 (0)
Wobble	1 (2.6)	1 (2.6)	0 (0)
Thrombocytopenia	1 (2.6)	1 (2.6)	0 (0)
Creatinine kinase elevation	1 (2.6)	0 (0)	1 (2.6)

[a] Grade 2 (moderate). All the other was grade 1 (mild).

Discussion

This retrospective cohort study evaluated the safety and efficacy of peramivir in 38 elderly patients who were hospitalized with influenza. The patients were of a high-risk group, as classified by the CDC, having one or more comorbidities. Few and mild adverse events occurred.

This study produced important findings. First, peramivir is safe for high-risk, elderly patients. Several reports have described examinations of the efficacy and safety of NAIs in high-risk patients.[9] Nevertheless, no report has described a study demonstrating the efficacy of NAIs solely for elderly people. This report is therefore the first of a study evaluating the safety of peramivir for elderly people. Second, the adverse events of the double-dosage group were not numerous, even compared with the standard dosage group. Typically, adverse events of NAIs are mild in healthy adults. Adverse events of peramivir are well tolerated in healthy adults and high-risk patients.[7,9] The present study found few adverse events of peramivir. In fact, the results were similarly mild to those of healthy adults reported earlier.[7–9] Some adverse events were explainable as symptoms of the influenza virus infection itself. Third, the time for the increased dosage group to return to a normal temperature tended to be longer than that of the normal dosage group.[7] Of 13 patients who received high doses, 8 were affected by pneumonia or bronchiolitis secondary to influenza virus infection. However, 9 of the 25 patients who received the standard dose were affected by pneumonia and/or bronchiolitis. The SOFA score of the increased dosage group tended to be higher than that of the standard dosage group. Apparently, the time to normal

temperature was related to the percentage of influenza-related complications and severity.

This study has some limitations. First, the symptoms and adverse events were obtained retroactively from medical-record-based information. The adverse events might be fewer than those of previous reports. Second, the possibility exists that the time to return to normal temperature was affected by the administration of immunosuppressive drugs such as corticosteroids. Corticosteroid therapy has insufficient effectiveness for influenza infection.[10] Of the patients, 11% were administered immunosuppressive drugs for underlying disease before influenza infection. Half of the patients were administered intravenous corticosteroids for 3—7 day bronchial asthma attack, or acute exacerbation of chronic obstructive pulmonary disease after influenza infection. Another report described that 24.3% of high-risk patients had used immunosuppressive drugs with peramivir.[7] The patients administered immunosuppressive agents in this study were fewer than those administered immunosuppressive agents in the earlier study.

In conclusion, results show that intravenous peramivir is acceptable and effective at a standard dosage in elderly patients with underlying diseases. Double doses of peramivir exhibited similar efficacy to that of the standard dose, but adverse events were not more frequent.

Disclosure statement

The authors have no conflict of interest in relation to this study.

References

1. Van Kerkhove MD, Vandemaise KA, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donnelly CA, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS Med* 2011;**8**:e1001053.
2. *Influenza antiviral medications: summary for clinicians*. 2016. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm [Accessed 26 May 2016].
3. Ison MG, Hui DS, Glezy 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. *Antiviral Ther* 2016;**18**:651—61.
4. 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.
5. 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.
6. Gubareva LV, Webster RG, Hayden FG. Comparison of the activities of zanamivir, oseltamivir, and RWJ-270201 against clinical isolates of influenza virus and neuraminidase inhibitor-resistant variants. *Antimicrob Agents Chemother* 2001;**45**:3403—8.
7. 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.
8. Burch J, Paulden M, Coti S, Stock C, Corbett M, Welton NJ, et al. Antiviral drugs for the treatment of influenza: a systematic review and economic evaluation. *Health Technol Assess* 2009;**13**:1—265. iii—iv.
9. Kohno S, Kida H, Mizuguchi M. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother* 2010;**54**:4568—74.
10. Rodrigo C, Leonaldi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev* 2016;**7**. 3:CD010406, http://dx.doi.org/10.1002/14651858.CD010406.pub2.