J Infect Chemother 22 (2016) 677–684

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Post-marketing safety evaluation of the intravenous anti-influenza neuraminidase inhibitor peramivir: A drug-use investigation in patients with high risk factors

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ARTICLE INFO

Article history:
Received 14 May 2016
Received in revised form
1 July 2016
Accepted 9 July 2016
Available online 3 August 2016

Keywords:
Influenza
Post-marketing surveillance
Peramivir
High risk
Safety profile

ABSTRACT

Peramivir, the only injectable anti-influenza neuraminidase inhibitor medically available in Japan at present, is considered first-line treatment in patients with high risk factors for influenza exacerbation. We conducted a drug-use investigation of peramivir in inpatients with high risk factors (old age, pregnancy, and underlying disease such as chronic respiratory disease) from January 2010 to March 2013. Data of 772 patients from 124 facilities across Japan were collected; peramivir's safety in 770 patients and effectiveness in 688 patients were examined. In total, 412 adverse events were observed in 219 patients (28.4%). Of these, 155 events were adverse drug reactions (ADRs) observed in 98 patients (12.7%). Major ADRs (≥2%) were increased aspartate aminotransferase (5.1%), increased alanine aminotransferase (3.8%) and decreased white blood cell count (2.5%). Fourteen serious ADRs were observed in 12 patients (1.6%). All serious ADRs were resolved or improved except for two events for which outcomes were unknown. Multivariate analyses revealed that ADR incidences were significantly associated with these four backgrounds of patients: medical history, no influenza vaccination, renal impairment and other infection(s). With regard to its effectiveness, the median time to alleviation of both influenza symptoms and fever was 3 days, including the first day of administration, which was the same as in other previous surveillance studies. This surveillance study indicated the safety of peramivir in the treatment of influenza inpatients with high risk factors under routine clinical settings.

1. Introduction

Recent meta-analysis results have shown that treatment with anti-influenza neuraminidase inhibitor (NAI) at early disease stage (within 2 days of symptom onset) to inpatients infected by influenza A H1N1pdm09 virus results in significant reduction of mortality [1]. From these findings, early intervention with NAI can be expected to exert important efficacy in patients who require hospitalized care and may develop influenza exacerbation due to high risk factors (old age, pregnancy, and underlying disease such as chronic respiratory disease). At present, four NAIs are medically available in Japan (oseltamivir, zanamivir, peramivir and laninamivir). Of these, peramivir is the only injectable drug; reliable transfer of active ingredients during intravenous infusion should exhibit efficacy. Thus, peramivir is considered first-line treatment in patients with high risk factors who are given high dosage or administered repeatedly [2], although it is usually given as a single dose in patients whose disease conditions are relatively mild.

In fact, the efficacy/effectiveness and safety of peramivir has been reported from clinical trials [2–5] and post-marketing surveillance studies [6,7]; however, the outcome information on inpatients with high risk factors, if any, has been obtained from a limited number of patients as many were outpatients. Therefore, the efficacy and safety information of peramivir from clinical

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http://dx.doi.org/10.1016/j.jiac.2016.07.004

settings would provide better understanding for its useful intervention in inpatients with high risk factors.

We conducted a drug-use investigation of peramivir in inpatients with high risk factors from January 2010 to March 2013. This was required as a condition for approval by the Japanese Ministry of Health, Labour and Welfare (MHLW) and was conducted in compliance with the Good Post-Marketing Study Practice specified by the MHLW Ordinance No. 171 (December 20, 2004).

This paper focuses on the results from an observational drug-use investigation performed in inpatients with high risk factors under routine clinical settings for the purpose of evaluating safety and effectiveness profiles of peramivir.

2. Patients and methods

2.1. Patients

We defined the target population as inpatients with influenza infection possessing high risk factors and surveyed them from 124 facilities during the period of January 2010 to March 2013. Patients with high risk factors were defined as those with at least one of the following characteristics: being pregnant, being ≥65 years old, and suffering from an underlying disease/complication that might exacerbate influenza infection such as chronic respiratory illness/heart disease/kidney disease/liver disease, neurological/neuromuscular disorder, blood dyscrasia, diabetes mellitus, and immunosuppression associated with disease or therapy.

2.2. Dosage and administration

The standard dose of peramivir is 300 or 600 mg/day for adult and 10 mg/kg/day, not to exceed 600 mg at a time, for children, given as an I.V. infusion for ≥15 min, respectively.

2.3. Surveillance study procedure

This surveillance study was implemented in the manner of a continuous investigation system, wherein the participating physicians were instructed to continuously complete survey forms of patients who were judged by the participating physicians as matching the target population described in "2.1. Patients" without exception until the patient number reached the requested quota (including retrospective cases). The physicians completed the survey forms, including baseline characteristics of the patients and the items related to adverse events (AEs) and effectiveness. Noting the presence/absence of the following AEs was required to ensure their detection: abnormal behavior, leukopenia/neutropenia, eosinophilia, diarrhea, nausea/vomiting, elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT), positive urine ketone bodies, anaphylactic symptoms, and psychiatric/neurological symptoms.

2.4. Safety evaluation criteria

AEs were defined as any unfavorable/unintended sign temporally associated with peramivir administration, whether or not considered related to peramivir. Adverse drug reactions (ADRs) were defined as AEs for which the causality of peramivir could not be ruled out as determined by the participating physicians or sponsor. Seriousness of AEs/ADRs was determined in accordance with the definition in the ICH-E2D guideline. ADR data were compiled according to the ICH Medical Dictionary for Regulatory Activities/J (Ver.16.1).

2.5. Effectiveness evaluation criteria

Effectiveness was evaluated as the time to alleviation of influenza symptoms and fever. The severity of influenza symptoms, including cough, sore throat, headache, nasal congestion, feverish feeling or chills, muscle or joint pain, and fatigue, were evaluated on a four-point scale as follows: normal condition, barely noticeable, bothersome, and unbearable. Symptom alleviation was considered to have occurred when all observed symptoms were scored "barely noticeable" or better. Fever alleviation was considered to have occurred when a maximum daily body temperature of <37 °C in adults (age ≥15 years) or <37.5 °C in children (age <15 years) was reached. And the time to symptom/fever alleviation was defined as the number of days from the start of peramivir administration to these endpoints.

2.6. Statistical analysis

The chi-square test was used to compare incidence rates of ADRs between categories of patient characteristics and treatment factors. For ordinal variables for which the chi-square test detected significant differences, the Cochran–Armitage test for trend was used. To assess whether the observed differences were proportional to the category order, the goodness of fit test was used. The factors showing significance in univariate analysis were further assessed as explanatory variables of a logistic regression model to determine the major factor(s) in ADRs. The response "unknown" was excluded from the data analysis. Effectiveness was assessed by first calculating the median time (days) to alleviation of influenza symptoms and fever and then obtaining Kaplan–Meier curves showing the time course of the proportion of patients remaining symptomatic. A two-sided significance level of 5% was used throughout. All of the various data analyses were performed using the SAS system (release 9.2).

3. Results

3.1. Baseline patient characteristics

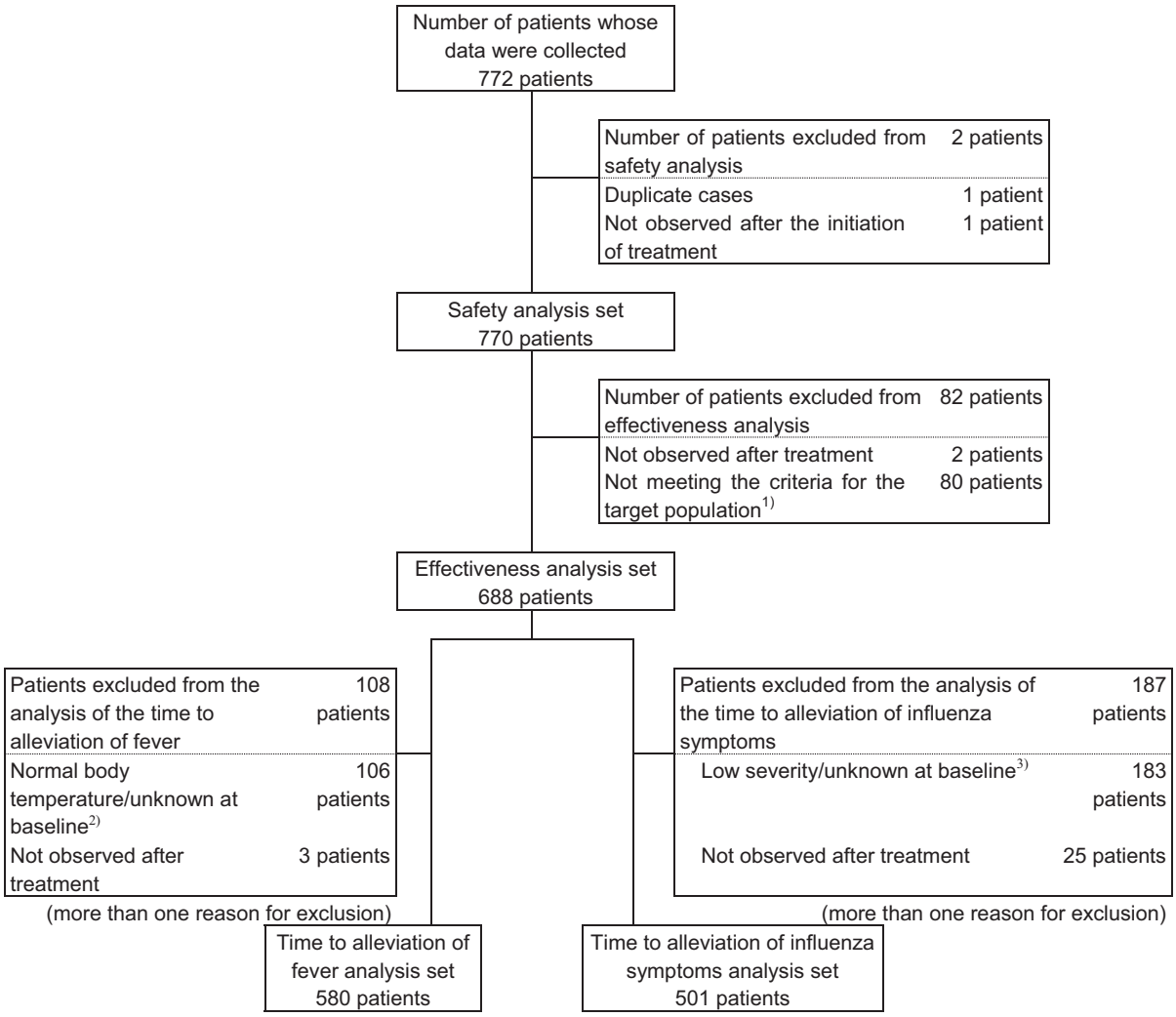
We collected data of 772 patients from 124 facilities and examined safety in 770 patients and effectiveness in 688 patients (Fig. 1).

A total of 770 patients were analyzed for safety (Table 1), including one pregnant woman, 463 elderly (≥65 years) patients (60.1%), and 765 inpatients (99.4%). Influenza A and B accounted for 663 patients (86.1%) and 82 patients (10.6%), respectively. Among the 770 patients analyzed for safety, 617 patients (80.1%) possessed at least one of underlying diseases/complications classifiable as high risk factors. These underlying diseases/complications were classified into each high risk factor as follows: chronic respiratory disease (354 patients), immunosuppression associated with disease or therapy (348 patients), neurological disorders/neuromuscular disorders (158 patients), chronic heart disease (143 patients), diabetes mellitus (110 patients), chronic kidney disease (48 patients), chronic liver disease (12 patients) and blood dyscrasias (7 patients).

3.2. Safety

3.2.1. ADR incidence and type

In total, 412 AEs occurred in 219 (28.4%) of the 770 patients. AEs with an incidence of ≥3% were increased AST (9.2%), increased ALT (7.7%), and decreased white blood cell count (4.2%). One hundred twenty-five serious AEs occurred in 77 patients (10.0%). Serious AEs with an incidence of ≥1% were decreased neutrophil count (1.4%), pneumonia (1.4%), increased AST (1.3%), decreased white blood cell



1) Patients who did not meet the criteria for the target population as described in "2.1 Patients" for reasons such as influenza virus undetected/unknown

2) Patients whose body temperatures were <37°C (<37.5°C in case of children aged <15 years) or unknown at baseline.

3) Patients whose severity of all influenza symptoms (cough, sore throat, headache, nasal congestion, feverish feeling or chills, muscle or joint pain, and fatigue) at baseline were either absent to mild or unknown, as assessed on a four-point scale [absent (normal condition), mild (barely noticeable), moderate (bothersome), and severe (unbearable)].

Fig. 1. Patient composition.

count (1.2%), increased ALT (1.0%) and increased white blood cell count (1.0%). Of the 412 AEs, 155 were reported as ADRs, and they occurred in 98 patients (12.7%; Table 2). Major ADRs (≥2%) were increased AST (5.1%), increased ALT (3.8%), and decreased white blood cell count (2.5%). Regarding the major ADRs and other related ADRs, 80 events of abnormal liver function test-related ADRs occurred in 55 patients (7.1%), and 26 events of leukopenia/neutropenia-related ADRs occurred in 23 patients (3.0%) (Table 3A). Fourteen serious ADRs occurred in 12 patients (1.6%), which included 5 cases of decreased white blood cell count, 4 cases of decreased neutrophil count, 2 cases of increased blood creatine phosphokinase, and 1 case each of viral myositis, rhabdomyolysis and increased AST.

3.2.2. Onset time and duration of ADRs

Most of the major ADRs and other related ADRs were resolved or improved within a week of onset (Table 3A). Regarding serious ADRs, apart from 2 events with unknown outcomes, all resolved or improved and there were no cases with serious outcomes of death or sequelae (Table 3B).

3.2.3. Risk factors for ADR occurrence

Table 4 shows ADR incidence by background factor. From the chi-square test, patients with "medical history present", "no influenza vaccination", "renal impairment present" and "other infection(s) present" were seen to have significantly higher ADR incidence. Significant differences were also observed between age categories. There were no significant differences between categories in terms of dose or duration of peramivir administered. Multivariate analysis results (Table 5) revealed that ADR incidences were significantly associated with these four backgrounds of patients: medical history, no influenza vaccination, renal impairment and other infection(s).

Table 1
Distribution of baseline characteristics.

Parameter	Category	Number of patients	Composition (%)
All patients		770	100.0
Gender	Male	404	52.5
	Female	366	47.5
Age	<15 years	181	23.5
	≥15 years to <65 years	125	16.2
	≥65 years	463	60.1
	Unknown	1	0.1
	Mean ± S.D. (years)	58.0 ± 32.2	
	Minimum (years)	0	
	Median (years)	73.0	
	Maximum (years)	103	
Body weight	<30 kg	155	20.1
	≥30 kg to <40 kg	89	11.6
	≥40 kg to <50 kg	128	16.6
	≥50 kg to <60 kg	133	17.3
	≥60 kg to <70 kg	91	11.8
	≥70 kg	49	6.4
	Unknown	125	16.2
	Mean ± S.D. (kg)	44.00 ± 19.40	
	Minimum (kg)	4.6	
	Median (kg)	46.10	
	Maximum (kg)	110.0	
Pregnancy (women only)	No	365	99.7
	Yes	1	0.3
Nursing (women only)	No	366	100.0
	Yes	0	0.0
Time (days) from the onset of influenza to the initiation of peramivir administration	0 day	317	41.2
	1 day	263	34.2
	2 day	90	11.7
	≥3 days	97	12.6
	Unknown	3	0.4
Virus type (test results using rapid diagnostic kits)	Type A	663	86.1
	Type B	82	10.6
	Others	10	1.3
	Unknown	15	1.9
Type A (at onset)	2009–2010	9	1.4
	2010–2011	225	33.9
	2011–2012	248	37.4
	2012–2013	181	27.3
Inpatient/outpatient	Inpatient	765	99.4
	Outpatient	5	0.6
Currently smoking	No	678	88.1
	Yes	59	7.7
	Unknown	33	4.3
Influenza vaccine	No	347	45.1
	Yes	228	29.6
	Unknown	195	25.3
Severity at baseline[a] (baseline score)	≤7	349	45.3
	8–14	228	29.6
	≥15	38	4.9
	Unknown	155	20.1
Medical history[b]	No	646	83.9
	Yes	124	16.1
Underlying diseases/ complications	No	17	2.2
	Yes	753	97.8
Hepatic impairment	No	725	94.2
	Yes	45	5.8
Renal impairment	No	710	92.2
	Yes	60	7.8
High risk factors[c] (underlying disease)	No	153	19.9
	Yes	617	80.1
Other infection(s)	No	495	64.3
	Yes	275	35.7
Allergies	No	593	77.0
	Yes	86	11.2
	Unknown	91	11.8
Highest daily body temperature (before the initiation of treatment with peramivir)	<38 °C	158	20.5
	≥38 °C to <40 °C	479	62.2
	≥40 °C	51	6.6
	Unknown	82	10.6
Serious influenza[d]	No	650	84.4
	Yes	49	6.4
	Unknown	71	9.2
Daily dose (maximum)	<300 mg	199	25.8
	≥300 mg to <600 mg	482	62.6
	≥600 mg to <1200 mg	88	11.4
	≥1200 mg	1	0.1
Number of times dosed daily (most often)	1 time	752	97.7
	≥2 times	17	2.2
	Unknown	1	0.1
Duration of treatment	1 day	577	74.9
	2 days	122	15.8
	3 days	46	6.0
	4 days	11	1.4
	≥5 days	14	1.8
Total dose	<300 mg	168	21.8
	≥300 mg to <600 mg	400	51.9
	≥600 mg to <1200 mg	154	20.0
	≥1200 mg	48	6.2
Concomitant drugs	No	46	6.0
	Yes	723	93.9
	Unknown	1	0.1

[a] Total of scores [0: absent (normal condition); 1: mild (barely noticeable); 2: moderate (bothersome); 3: severe (unbearable)] for each influenza symptom (cough, sore throat, headache, nasal congestion, feverish feeling or chills, muscle or joint pain, and fatigue) at baseline. Cases with even one missing (not described, unknown) score for any of the seven symptoms were handled as "unknown".

[b] Diseases/symptoms that were previously developed and recovered prior to peramivir administration.

[c] Underlying diseases/complications that may exacerbate influenza infections, such as chronic respiratory illness, chronic heart disease, chronic kidney disease, chronic liver disease, neurological disorders/neuromuscular disorders, blood dyscrasia, diabetes mellitus, and immunosuppression associated with disease or therapy.

[d] Patients who had influenza encephalopathy or who were on mechanical ventilation at baseline.

After examining the reasons why these four factors increased ADR incidence, the following results were obtained. The incidence of "Investigations" was significantly higher ($p = 0.0233$) in patients who had not received influenza vaccine (37/347, 10.7%) than those who had (12/228, 5.3%). The leukopenia/neutropenia-related ADR incidence was significantly higher ($p = 0.0023$) in patients with medical history (9/124, 7.3%) than those without (14/646, 2.2%). The incidence of abnormal liver function test-related ADRs was significantly higher ($p < 0.0001$) in patients with other infections (33/275, 12.0%) than in those without (22/495, 4.4%). In the renal impairment patients, the ADR incidence of "gastrointestinal disorders" was significantly higher (<0.0001) (5/60, 8.3%) compared with patients without renal impairment (6/710, 0.8%). Especially, the incidence of "diarrhea" was higher in patients with renal impairment (3/60, 5.0%) than in those without (6/710, 0.8%). However, the cases of diarrhea that occurred in renal impairment patients were non-serious and resolved or improved by the day after onset.

3.3. Effectiveness

Fig. 2 shows Kaplan–Meier curves for the time (days) to alleviation of influenza symptoms and fever. The median time to alleviation of both influenza symptoms and fever was 3 days (including the first day of peramivir administration), and improvement was observed within 3 days in 69.4% (344/496) and 62.4% (358/574) of patients with influenza symptoms and fever, respectively.

Table 2
Incidence rates of adverse drug reactions (ADRs).

Number of patients evaluated for safety	770
Number of patients with ADRs	98
Number of ADRs	155
Incidence of ADRs	12.7%
Type of ADR	Incidence of ADRs [number (%)]
Infections and infestations	1 (0.1)
Viral myositis	1 (0.1)
Metabolism and nutrition disorders	1 (0.1)
Hypokalaemia	1 (0.1)
Psychiatric disorders	3 (0.4)
Abnormal behaviour	3 (0.4)
Gastrointestinal disorders	11 (1.4)
Constipation	1 (0.1)
Diarrhea	9 (1.2)
Nausea	1 (0.1)
Vomiting	1 (0.1)
Hepatobiliary disorders	10 (1.3)
Hepatic function abnormal	7 (0.9)
Liver disorder	3 (0.4)
Skin and subcutaneous tissue disorders	2 (0.3)
Rash	2 (0.3)
Musculoskeletal and connective tissue disorders	2 (0.3)
Arthralgia	1 (0.1)
Rhabdomyolysis	1 (0.1)
General disorders and administration site conditions	3 (0.4)
Hyperthermia	1 (0.1)
Pyrexia	2 (0.3)
Investigations	75 (9.7)
Alanine aminotransferase increased	29 (3.8)
Aspartate aminotransferase increased	39 (5.1)
Blood creatine phosphokinase increased	4 (0.5)
Blood creatinine increased	1 (0.1)
Blood lactate dehydrogenase increased	1 (0.1)
Eosinophil count increased	10 (1.3)
Gamma-glutamyltransferase increased	1 (0.1)
Neutrophil count decreased	7 (0.9)
White blood cell count decreased	19 (2.5)
Urine ketone body present	8 (1.0)
Hepatic enzyme increased	2 (0.3)

Incidence of ADRs (%) = number of patients with ADRs (events)/total number of patients evaluated for safety ×100.
Types of ADRs are shown using terms from MedDRA/J Ver.16.1.

4. Discussion

In this surveillance study, evaluation of 770 patients for safety and 688 patients for effectiveness of peramivir use under routine clinical settings was performed. Most of the patients evaluated for safety were inpatients and >60% were elderly patients and 80% possessed underlying diseases/complications classifiable as high risk factors. Further, a major proportion of the underlying diseases/complications classifiable as high risk factors were chronic respiratory disease and immunosuppression associated with disease or therapy.

The ADR incidence (12.7%) was higher than those in a previous surveillance study (4.4%) [6] and in a pediatric surveillance study (7.7%) [7]. As one of the possible explanations for the high ADR incidence, it is likely that abnormal signs were more easily detected in this surveillance study than in the other surveillance studies. Although approximately 90% of patients were outpatients in the other surveillance studies, most patients were inpatients and a large number of patients had underlying diseases/complications in this surveillance study. Thus, it seems that the patients received more careful inspection and this made abnormal signs more easily detected in this surveillance study. Indeed, the high ADR incidence was due to the increase of laboratory test-related ADRs; this supports the above explanation. Of course, as another possible explanation, it could be considered that the severity of the patient's condition influenced the ADR incidence.

Regarding the major ADRs of abnormal liver function test-related and leukopenia/neutropenia-related events in this surveillance study, these ADRs are known to occur in a proportion of inpatients with influenza [8]. Furthermore, there are some reports suggesting that treatment with NAIs was not associated with hepatotoxicity or neutropenia [9,10]. Taken together, it is possible that these ADRs were related with the infection of influenza itself.

Serious ADRs observed in this surveillance study were leukopenia/neutropenia-related events (decreased white blood cell count, decreased neutrophil count), muscular-related events (increased blood creatine phosphokinase, viral myositis, rhabdomyolysis) and abnormal liver function test-related events (increased AST). All of these ADRs appear to be consequences of influenza infection because muscular-related events are also well known to be caused by influenza infection itself, although the causal relationship between peramivir and these ADRs could not be denied, of course. Among patients with serious ADRs, most of them were resolved or improved within two weeks and there were no cases with a problematic outcome such as death or sequelae.

From the results of multivariate analysis, four factors such as other infection(s), medical history, no influenza vaccination and renal impairment were suggested to be significantly related to the occurrence of ADRs. Regarding patients with other infections,

Table 3A
Time of onset, outcome, and time until "resolved or improved" by type of major ADRs and other related ADRs.

Type of ADR		Number of events	Time of onset			Outcome						Time until resolved or improved			
			1 to 3 days	4 to 7 days	≥8 days	Resolved	Improved	Not resolved	Resolved but with sequela	Death	Unknown	0 to 3 days	4 to 7 days	8 to 14 days	≥15 days
Abnormal liver function tests related ADRs	Aspartate aminotransferase increased	39	25	12	2	25	8	1			5	12	11	8	2
	Alanine aminotransferase increased	29	12	14	3	21	5				3	5	11	7	3
	Hepatic function abnormal	7	4	2	1	5					2		2	1	2
	Liver disorder	3	2	1		3						1	1	1	
	Hepatic enzyme increased	2	1	1		1		1					1		
Leukopenia/neutropenia related ADRs	White blood cell count decreased	19	9	10		15	2				2	5	5	4	3
	Neutrophil count decreased	7	2	5		6	1					2	2	2	1

Table 3B
Time of onset, outcome, and time until "resolved or improved" by type of serious ADRs.

Type of ADR	Number of serious events	Time of onset			Outcome						Time until resolved or improved			
		1 to 3 days	4 to 7 days	≥8 days	Resolved	Improved	Not resolved	Resolved but with sequela	Death	Unknown	0 to 3 days	4 to 7 days	8 to 14 days	≥15 days
White blood cell count decreased	5	5			4					1		1	2	1
Neutrophil count decreased	4	1	3		3	1					1	1	1	1
Blood creatine phosphokinase increased	2	1	1			1				1		1		
Viral myositis	1	1			1							1		
Rhabdomyolysis	1	1			1								1	
Aspartate aminotransferase increased	1			1	1							1		

Table 4
Risk factors for the occurrence of ADRs.

Parameter	Category	Incidence of ADRs (%)	p value
All patients		12.7 (98/770)	–
Gender	Male	12.1 (49/404)	p1 = 0.6006
	Female	13.4 (49/366)	
Age	<15 years	7.2 (13/181)	p1 = 0.0396*
	≥15 years to <65 years	15.2 (19/125)	p2 = 0.0333*
	≥65 years	14.0 (65/463)	p3 = 0.1652
	Unknown	100.0 (1/1)	
Body weight	<30 kg	9.0 (14/155)	p1 = 0.1653
	≥30 kg to <40 kg	16.9 (15/89)	
	≥40 kg to <50 kg	14.8 (19/128)	
	≥50 kg to <60 kg	7.5 (10/133)	
	≥60 kg to <70 kg	15.4 (14/91)	
	≥70 kg	14.3 (7/49)	
	Unknown	15.2 (19/125)	
Pregnancy (women only)	No	13.4 (49/365)	p1 = 0.6938
	Yes	0.0 (0/1)	
Nursing (women only)	No	13.4 (49/366)	–
	Yes	–	
Time (days) from the onset of influenza to the initiation of peramivir administration	0 day	10.4 (33/317)	p1 = 0.1908
	1 day	16.0 (42/263)	
	2 days	14.4 (13/90)	
	≥3 days	10.3 (10/97)	
	Unknown	0.0 (0/3)	
Virus type (test results using rapid diagnostic kits)	Type A	13.7 (91/663)	p1 = 0.1968
	Type B	8.5 (7/82)	
	Others	0.0 (0/10)	
	Unknown	0.0 (0/15)	
Type A (at onset)	2009–2010	22.2 (2/9)	p1 = 0.7155
	2010–2011	13.3 (30/225)	
	2011–2012	12.5 (31/248)	
	2012–2013	15.5 (28/181)	
Inpatient/outpatient	Inpatient	12.7 (97/765)	p1 = 0.6245
	Outpatient	20.0 (1/5)	
Currently smoking	No	12.1 (82/678)	p1 = 0.1462
	Yes	18.6 (11/59)	
	Unknown	15.2 (5/33)	
Influenza vaccine	No	13.5 (47/347)	p1 = 0.0142*
	Yes	7.0 (16/228)	
	Unknown	17.9 (35/195)	
Severity at baseline (baseline score)	≤7	11.5 (40/349)	p1 = 0.2322
	8–14	13.2 (30/228)	
	≥15	21.1 (8/38)	
	Unknown	12.9 (20/155)	
Medical history	No	11.6 (75/646)	p1 = 0.0337*
	Yes	18.5 (23/124)	
Underlying disease/ complications	No	5.9 (1/17)	p1 = 0.3918
	Yes	12.9 (97/753)	
Hepatic impairment	No	12.6 (91/725)	p1 = 0.5574
	Yes	15.6 (7/45)	
Renal impairment	No	11.8 (84/710)	p1 = 0.0103*
	Yes	23.3 (14/60)	
High risk factors (underlying disease)	No	9.8 (15/153)	p1 = 0.2255
	Yes	13.5 (83/617)	
Other infection(s)	No	10.1 (50/495)	p1 = 0.0033*
	Yes	17.5 (48/275)	
Allergies	No	12.3 (73/593)	p1 = 0.2622
	Yes	8.1 (7/86)	
	Unknown	19.8 (18/91)	
Highest daily body temperature (before the start of treatment with peramivir)	<38 °C	12.7 (20/158)	p1 = 0.9554
	≥38 °C to <40 °C	13.6 (65/479)	
	≥40 °C	13.7 (7/51)	
	Unknown	7.3 (6/82)	
Serious influenza	No	13.2 (86/650)	p1 = 0.8339
	Yes	14.3 (7/49)	
	Unknown	7.0 (5/71)	
Daily dose (maximum)	<300 mg	10.6 (21/199)	p1 = 0.2151
	≥300 mg to <600 mg	12.4 (60/482)	
	≥600 mg to <1200 mg	19.3 (17/88)	
	≥1200 mg	0.0 (0/1)	
Number of times dosed daily (most often)	1 time	12.9 (97/752)	p1 = 0.3909
	≥2 times	5.9 (1/17)	
	Unknown	0.0 (0/1)	
Duration of treatment	1 day	12.5 (72/577)	p1 = 0.5156
	2 days	11.5 (14/122)	
	3 day	13.0 (6/46)	
	4 days	27.3 (3/11)	
	≥5 days	21.4 (3/14)	
Total dose	<300 mg	9.5 (16/168)	p1 = 0.1235
	≥300 mg to <600 mg	11.8 (47/400)	
	≥600 mg to <1200 mg	17.5 (27/154)	
	≥1200 mg	16.7 (8/48)	
Concomitant drugs	No	8.7 (4/46)	p1 = 0.3958
	Yes	13.0 (94/723)	
	Unknown	0.0 (0/1)	

Incidence of ADRs (%) = number of patients with ADR/total number of patients evaluated for safety × 100.
*: $p < 0.05$.
p1: χ^2 test, p2: Cochran–Armitage test, p3: Goodness of fit.

since abnormal liver function test-related ADRs occurred with high frequency, detailed examination of the type of other infection(s) in 33 abnormal liver function test-related ADR cases was performed. Of the 33 ADR cases, 32 cases had pneumonia/bronchitis and the remaining 1 case had bacteraemia. It was considered that an exacerbated physical condition due to pneumonia/bronchitis and/or drugs such as antibiotics for treatment of these infections could possibly have an influence on the liver function test values. As the incidence of leukopenia/neutropenia-related ADRs was found to be high in patients with medical history, the medical history of 9 leukopenia/neutropenia-related ADR cases was examined in detail. However, no common disease was observed in these 9 cases.

Unlike patients in relatively good condition, the administration of peramivir in high doses and/or in a repeated manner would likely occur in inpatients with high risk factors. Indeed, 88 patients were administered 600 mg and 193 patients were given repeated doses. However, the categories of peramivir dose or duration of

Table 5
Multivariate analysis to find risk factors.

Parameter	Category	Number of evaluated patients	Number of patients with ADRs	Incidence of ADRs (%)	Estimate	Standard error	Odds ratio (95% CI)	p value
Analysis set		574	62	10.8				
Intercept					−3.201	0.451		<0.0001*
Age	<15 years	131	6	4.6	–	–	–	–
	≥15 years to <65 years	102	15	14.7	1.003	0.514	2.726 (0.996, 7.461)	0.0508
	≥65 years	341	41	12.0	0.694	0.463	2.002 (0.808, 4.959)	0.1336
Influenza vaccine	No	346	46	13.3	–	–	–	–
	Yes	228	16	7.0	−0.685	0.313	0.504 (0.273, 0.931)	0.0286*
Medical history	No	488	45	9.2	–	–	–	–
	Yes	86	17	19.8	0.885	0.331	2.423 (1.267, 4.636)	0.0075*
Other infection(s)	No	391	30	7.7	–	–	–	–
	Yes	183	32	17.5	0.979	0.284	2.663 (1.527, 4.643)	0.0006*
Renal impairment	No	530	52	9.8	–	–	–	–
	Yes	44	10	22.7	0.900	0.409	2.459 (1.104, 5.475)	0.0277*

CI, confidence interval.
*$p < 0.05$.

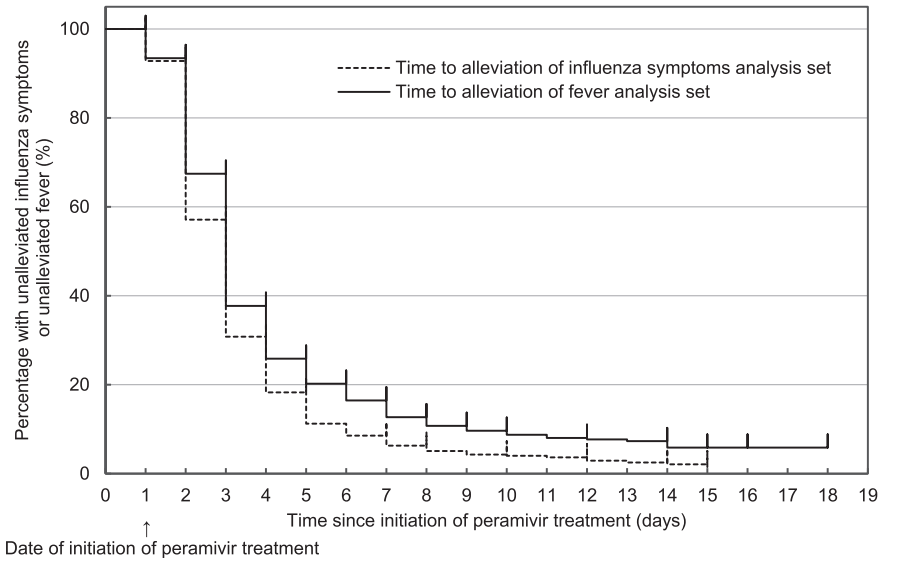


Fig. 2. Kaplan–Meier curves of time to alleviation of influenza symptoms and of fever.

administration were not observed to be factors related to ADR incidence in this surveillance study.

With regard to the effectiveness, the median number of days to fever alleviation and influenza symptom alleviation was 3 days, which was similar to that found in other previous surveillance studies [6,7], although the observation conditions of patients are thought to differ.

This surveillance study has some limitations. It could not be denied that the surveillance study procedure might introduce bias into the safety evaluation because this surveillance study was conducted in an open-labeled manner and the participating physicians could determine AEs as ADRs. Actually, some AEs supposed to be caused by influenza infection itself were included in the ADRs. On the other hand, the incidence of laboratory test-related ADR might be underestimated. Because, in this surveillance study, laboratory tests were measured as needed under routine clinical settings and it was not confirmed whether each laboratory test was measured or not, the exact number of patients whose laboratory tests were measured could not be determined. Thus, applying all of the 770 patients to the denominator for calculation of the laboratory test-related ADR incidence might make the estimation of the incidence lower. However, taking into consideration that most patients were inpatients in this surveillance, it was supposed that laboratory tests were measured in most patients and the degree of lower estimation was small, if any. Regarding effectiveness evaluation, the efficacy of peramivir could not be clearly demonstrated because this surveillance study was conducted without control. However, taking the fact that the median time to alleviation of both influenza symptoms and fever was 3 days which was consistent with previous surveillance studies [6,7] into consideration, it is suggested that the peramivir was effective even in patients with high risk factors.

This surveillance study indicated the safety of peramivir in the treatment of influenza inpatients with high risk factors under routine clinical settings and this surveillance study would support the implementation of proper use of peramivir in patients with high risk factors.

Conflict of interest

JS is employed as a counselor for Shionogi & Co., Ltd. All other authors were from Shionogi & Co., Ltd.

Acknowledgments

We would like to thank the 124 medical facilities and their physicians for participating in this investigation and providing valuable data. This survey was conducted with a grant from Shionogi & Co., Ltd. (Osaka, Japan).

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