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The Clinical Course of Patients with Influenza after Administration of Various Anti-influenza Drugs during the 2019-2020 Influenza Season in Osaka, Japan

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Abstract

Background

In Japan, four neuraminidase inhibitors (NAIs) and one cap-dependent endonuclease inhibitor, baloxavir marboxil (baloxavir), are currently available for treatment of influenza. We investigated prescription trends of each anti-influenza drug and the clinical course of patients with influenza who were treated with anti-influenza drugs, including baloxavir, during the 2019-2020 influenza season.

Methods

A multicenter observational study in Osaka was conducted with postcard questionnaires. Patients who were diagnosed with influenza responded to a postcard questionnaire containing questions about their background characteristic, and their body temperature. We analyzed the factors that were associated with early fever alleviation and biphasic fever, and compared the duration of fever among four anti-influenza drug groups excluding peramivir, because few patients were prescribed this drug.

Results

A total of 252 patients with influenza were enrolled and analyzed (97 patients aged <10 years, and 155 patients aged $\geqq 10$ years). Baloxavir was prescribed to three of the 97 patients aged <10 years (3.1%) and to 19 of the 155 patients aged $\geqq 10$ years (12.3%). The duration of fever in patients with influenza was not significantly different among the four groups that received oseltamivir, laninamivir, zanamivir, or baloxavir. We found no significant difference between the frequency of biphasic fever episodes and the choice of anti-influenza drugs.

Conclusions

Our study showed no significant association between baloxavir and early fever alleviation or the frequency of biphasic fever episodes. One cause may be that no statistically association was detected

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due to the decrease in the number of prescriptions of baloxavir.

Key Words: Influenza; Neuraminidase inhibitor; Baloxavir marboxil; Biphasic fever

Introduction

Influenza is an acute viral respiratory disease that is epidemic in the winter months. The seasonal epidemic of influenza is a major cause of morbidity and mortality globally, and the majority of deaths occur in the elderly. In Japan, about 10-15 million people are infected with influenza every year. Thousands of deaths occur each year due to influenza, and tens of thousands die during a pandemic[1].

Baloxavir marboxil (baloxavir) was newly released as a cap-dependent endonuclease inhibitor in March 2018 in Japan, and is now available in addition to four existing neuraminidase inhibitors (NAIs), oseltamivir, zanamivir, peramivir, and laninamivir. An international clinical trial showed that baloxavir has good therapeutic activity against influenza A and B virus infections[2,3]. A few clinical studies reported that the duration of fever in influenza patients treated with baloxavir is shorter than in those taking NAIs[4,5]. The number of baloxavir prescriptions increased explosively due to the convenience of the single oral dose and the effect; more than 5.2 million people were estimated to be prescribed baloxavir during the 2018-2019 influenza season[6]. We also reported that baloxavir was prescribed to about 40% of influenza patients[5].

On the other hand, in a clinical trial, the emergence of viruses with amino acid substitutions at position 38 of polymerase acidic protein, which reduces the susceptibility to baloxavir, occurs at a high rate, and sometimes in association with rebounds in viral titers and possibly prolongation of symptoms[2]. In October 2019, the Japanese Association for Infectious Disease and the Japan Pediatric Society suggested that doctors carefully consider the administration of baloxavir for children aged <12 years[7,8].

There are few reports which examine the clinical effects of baloxavir and compare with NAIs in clinical practice. Our objective was to investigate prescription trends of each anti-influenza drug and the clinical course of patients with influenza who were treated with anti-influenza drugs, including baloxavir, during the 2019-2020 influenza season.

Methods

Procedures

This multicenter observational study was conducted in 52 hospitals or clinics in Osaka prefecture, Japan. Physicians, pediatricians, and otorhinolaryngologists participated in this study. Patients with influenza who were diagnosed using an antigen detection kit and who were treated with an anti-influenza drug from December 1, 2019 through April 30, 2020 were enrolled. After obtaining oral informed consent from the patients or their guardians, clinicians completed the sections on age, sex, type of influenza (A or B), and the prescribed anti-influenza drug, and then handed the postcard questionnaire to the patients. Patients mailed the postcard to the Department of Respiratory Medicine, Osaka City University Graduate School of Medicine after they filled out the questionnaire.

The study protocol was approved by the Institutional Ethics Committee (Osaka City University Graduate School of Medicine, Approval No. 2019-035).

Questionnaire items

Patients recorded their peak body temperature before first visiting the hospital or clinic, and their

body temperature twice a day (morning and afternoon) for 4 days from first visit. They also completed the questionnaire regarding their vaccination status this year; underlying diseases; adverse events of anti-influenza drugs such as coughing, vomiting, diarrhea, abdominal pain, abnormal behavior, and headache; and the episode of biphasic fever.

Definition of the duration of fever, fever reduction and biphasic fever

We defined the duration of fever as the time from anti-influenza drugs administration until the fever was alleviated for more than one day with no relapse thereafter. Fever reduction was defined as a temperature below 37.5℃ in patients aged <10 years or below 37.0℃ in patients aged ≧10 years[9,10]. Biphasic fever was defined as developing a fever again after alleviation of the fever for more than 1 day[11,12].

Statistical analysis

Statistical analyses were performed with JMP, ver. 10 (SAS Institute, Inc., Cary, NC, USA). The Kruskal-Wallis test followed by the Steel-Dwass test for multiple comparisons were used to compare the duration of fever with each anti-influenza drug. We conducted univariate analysis followed by multivariate analysis with logistic regression models to examine the factors (sex, age, type of influenza virus, underlying disease, vaccination status, and type of anti-influenza drug) that were associated with the alleviation of fever in 2 days after treatment with anti-influenza drugs began. Independent variables with $p < 0.20$ in univariate analysis and those reported to be associated with early fever alleviation were included in the multivariate model[11,13]. The logistic regression model was used to determine the factors (sex, age, type of influenza, underlying diseases, vaccination status, and type of anti-influenza drug) influencing the episodes of biphasic fever, and no multiplicity adjustment was performed in the analyses. To evaluate the frequency of adverse events in each anti-influenza drug, a Chi-square test was used. Three patients were prescribed peramivir, and they were excluded from statistical analyses which compared the duration of fever, examined the factors that were associated with the early fever alleviation, or biphasic fever episodes, and evaluated the frequency of adverse events.

Results

Patient characteristics

A total of 900 postcards were handed to patients with positive results on the rapid diagnostic kits. The response rate was 28.9% (260/900). Eight patients were excluded from the analyses because of incomplete questionnaire data for age, sex, type of influenza, body temperatures, or prescribed anti-influenza drug (Fig. 1). Thus, a total of 252 patients were enrolled and analyzed: 97 patients aged <10 years (Type A, 80; Type B, 17), and 155 patients aged ≧10 years (Type A, 147; Type B, 8) (Table 1). The anti-influenza drugs prescribed for the patients aged <10 years were oseltamivir for 54, laninamivir for 24, zanamivir for 17, peramivir for 0, and baloxavir for 3, and those for the patients aged ≧10 years were oseltamivir for 41, laninamivir for 77, zanamivir for 15, peramivir for 3, and baloxavir for 19. Of all patients, 51 had underlying disease (Hypertension, 10; Hyperlipidemia, 2; Diabetes mellitus, 3; Bronchial asthma, 8; Allergy, 18; Other, 20). A total of 110 patients had received the influenza vaccine this year.

Factors related to early alleviation of fever

Multivariate analysis revealed that laninamivir was significantly associated with alleviation of fever in 2 days compared to oseltamivir (odds ratio, 1.91; 95% confidence interval: 1.05-3.54; $p=0.034$)

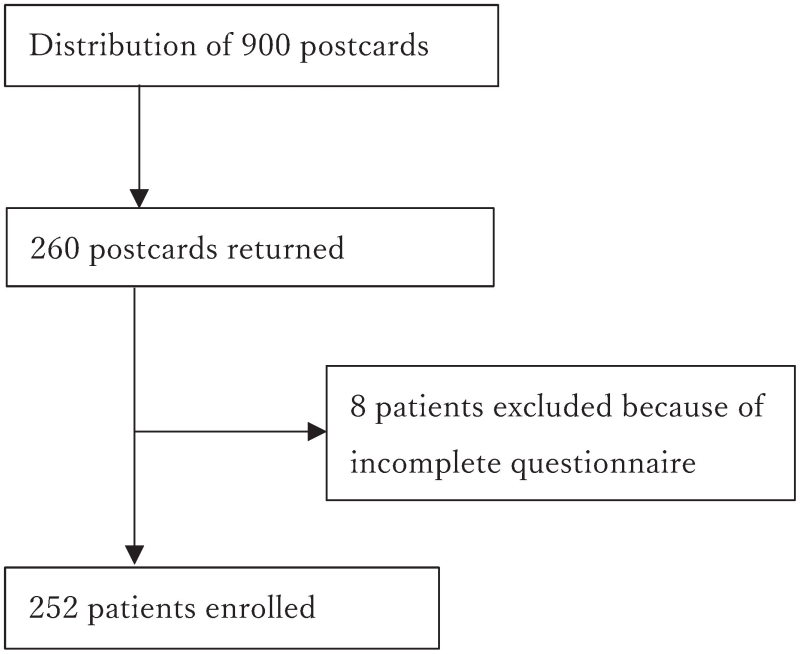

Figure 1. Flow of participants through the study. A total of 900 postcards were handed to patients with influenza. The number of postcards which were returned was 260. Eight patients were excluded from the analyses because of incomplete questionnaire data for age, sex, type of influenza, body temperatures, or prescribed anti-influenza drug. Thus, a total of 252 patients were enrolled and analyzed.

Table 1. Clinical characteristics of the study subjects

Characteristics		<10 years (n=97)	10 years≦ (n=155)	Total (n=252)
Age, Mean years±SD		6.17±2.46	31.6±20.4	21.8±20.3
Range	0-4 years	24	0	24 (9.5)
	5-9 years	73	0	73 (28.9)
	10-19 years	0	74	74 (29.4)
	20-39 years	0	14	14 (5.6)
	40-59 years	0	52	52 (20.6)
	60 years-	0	15	15 (6.0)
Gender, male/female	male	51	69	120 (47.6)
	female	46	86	132 (52.4)
Type of influenza virus	Type A	80	147	227 (90.1)
	Type B	17	8	25 (9.9)
Underlying diseases	Hypertension	0	10	10 (4.0)
	Hyperlipidemia	0	2	2 (0.7)
	Diabetes mellitus	0	3	3 (1.2)
	Bronchial asthma	2	6	8 (3.2)
	Allergy	3	15	18 (7.1)
Vaccinated this year	Yes/No/	46/48/3	64/85/6	110 (43.6) /133
	Unspecified			(52.8) /9 (3.6)
Anti-influenza drugs	Oseltamivir	53	41	94 (37.3)
	Laninamivir	24	77	101 (40.1)
	Zanamivir	17	15	32 (31.7)
	Peramivir	0	3	3 (3.0)
	Baloxavir	3	19	22 (21.8)

Data are number or proportion (%) of patients. Abbreviation: SD, standard deviation.

Table 2a. Factors influencing alleviation of fever in 2 days

Variable			Univariate analysis			Multivariate analysis		
		n/N (%)	O.R.	95% CI	p value	O.R.	95% CI	p value
Gender	Female	65/130 (50.0)	1	-	-			
	Male	72/119 (60.5)	1.53	0.93-2.54	0.096	1.58	0.94-2.65	0.08
<10 years		54/97 (55.7)	1	-	-			
≧10 years		83/152 (54.6)	0.96	0.58-1.60	0.87	0.80	0.45-1.41	0.44
Type of influenza virus	Type A	122/224 (54.5)	1	-	-			
	Type B	15/25 (60.0)	0.80	0.34-1.85	0.60	1.24	0.52-3.07	0.63
Underlying diseases	No	103/186 (55.4)	1	-	-			
	Yes	28/51 (54.9)	0.98	0.53-1.84	0.95			
Vaccinated this year	No	73/131 (55.6)	1	-	-			
	Yes	60/110 (54.5)	0.95	0.57-1.59	0.85			
Anti-influenza drug	Oseltamivir	45/94 (47.9)	1	-	-			
	Laninamivir	62/101 (61.4)	1.73	0.98-3.07	0.058	1.91	1.05-3.54	0.034
	Zanamivir	16/32 (50.0)	1.09	0.48-2.44	0.84	0.99	0.44-2.26	0.99
	Baloxavir	14/22 (63.6)	1.91	0.74-5.17	0.18	2.10	0.79-5.96	0.14

Abbreviation: O.R., odds ratio; and CI, confidence intervals.

(Table 2a).

Table 2b showed sub-group analysis for factors influencing alleviation of fever in 2 days by age group. Laninamivir was significantly associated with alleviation of fever in 2 days compared to oseltamivir in patients aged <10 years (odds ratio, 2.93; 95% confidence interval: 1.08-8.69; p=0.035). We also analyzed the factors influencing alleviation of fever in 2 days in patients with influenza A (n=227). No statistically significant association was found between alleviation of fever in 2 days and sex, age group, underlying disease, vaccination status, or choice of anti-influenza drugs in patient with influenza A.

Duration of fever after administration of the first dose of anti-influenza drug

The duration of fever in influenza patients was not significantly different among the four groups that received oseltamivir, laninamivir, zanamivir, or baloxavir (Fig. 2). The median durations of fever in influenza patients who received each anti-influenza drug was 2.0 to 2.5 days.

Episodes of biphasic fever

Biphasic fever occurred in 10 of 249 patients (4.0%). No statistically significant association was found between the frequencies of biphasic fever and sex, age group, type of influenza, underlying disease, vaccination status, or choice of anti-influenza drugs (Table 3).

Adverse events for each anti-influenza drug

The frequency of each adverse event after administration of the anti-influenza drug is shown in Table 4. There was no statistically significant difference in the frequency of all adverse events, such as coughing, diarrhea, vomiting, abdominal pain, headache, and abnormal behavior among the four groups that received oseltamivir, laninamivir, zanamivir, or baloxavir.

Discussion

In this study, the duration of fever was not significantly different among the four groups that

Table 2b. Sub-group analysis for factors influencing alleviation of fever in 2 days by age groups

Variable		<10 years			
		n/N (%)	O.R.	95% CI	p value
Gender	Female	21/45 (46.7)	1	-	-
	Male	30/49 (61.2)	1.80	0.80-4.14	0.16
Type of influenza virus	Type A	42/80 (52.5)	1	-	-
	Type B	9/14 (64.3)	1.63	0.52-5.70	0.41
Underlying diseases	No	46/83 (55.4)	1	-	-
	Yes	6/11 (54.6)	0.97	0.27-3.59	0.96
Vaccinated this year	No	25/48 (52.1)	1	-	-
	Yes	25/44 (56.8)	1.21	0.53-2.77	0.65
Anti-influenza drug	Oseltamivir	24/53 (45.3)	1	-	-
	Laninamivir	17/24 (70.8)	2.93	1.08-8.69	0.035
	Zanamivir	10/17 (58.8)	1.73	0.58-5.41	0.33
	Baloxavir	3/3 (100.0)	-	-	-

Variable		≧10 years			
		n/N (%)	O.R.	95% CI	p value
Gender	Female	43/84 (51.2)	1	-	-
	Male	40/68 (58.8)	1.58	0.94-2.65	0.35
Type of influenza virus	Type A	80/144 (55.6)	1	-	-
	Type B	3/8 (37.5)	1.24	0.52-3.07	0.32
Underlying diseases	No	57/103 (55.3)	1	-	-
	Yes	22/40 (55.0)	0.99	0.47-2.07	0.97
Vaccinated this year	No	48/83 (57.8)	1	-	-
	Yes	33/64 (51.6)	0.78	0.40-1.50	0.45
Anti-influenza drug	Oseltamivir	21/41 (51.2)	1	-	-
	Laninamivir	45/77 (58.4)	1.34	1.05-3.54	0.45
	Zanamivir	6/15 (40.0)	0.63	0.44-2.26	0.46
	Baloxavir	11/19 (57.9)	1.31	0.79-5.96	0.63

Abbreviation: O.R., odds ratio; and CI, confidence intervals.

received oseltamivir, laninamivir, zanamivir, or baloxavir, and the frequencies of biphasic fever episodes and each adverse event in influenza patients who were treated with baloxavir was similar to that in patients treated with other anti-influenza drugs. In addition, laninamivir significantly contributed to early fever alleviation compared to oseltamivir in patients aged <10 years. The number of patients with influenza who were prescribed baloxavir decreased compared to the previous season (8.7% vs 37.5%)[5].

In international clinical trials, the virus titer was significantly lower from the second day of administration in the baloxavir group than in the oseltamivir group[2]. Our recent report also showed that the baloxavir group had a significantly shorter duration of fever than the NAI group in those with influenza A in the 2018-2019 season[5]. However, a previous study reported the emergence of viruses with reduced susceptibility to baloxavir following baloxavir treatment, and these viruses were associated with transient rises in infectious virus titers, prolongation of virus detectability, initial

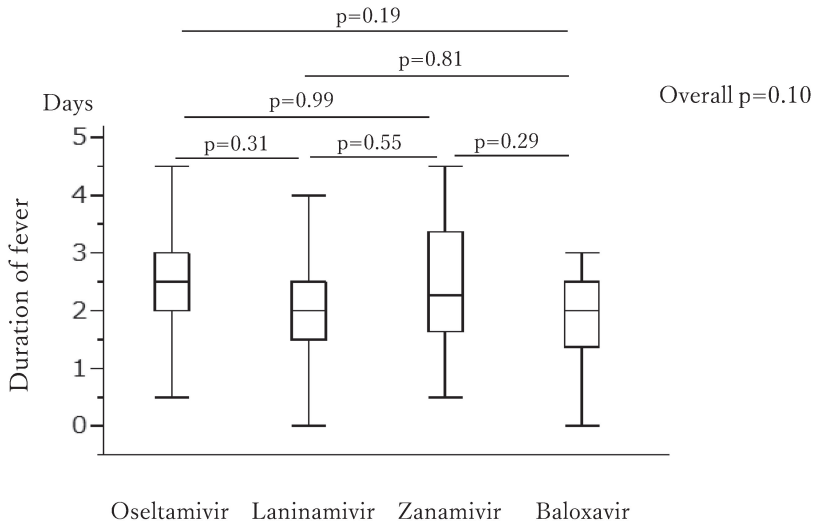

Figure 2. Comparison of the duration of fever in patients with influenza who received each anti-influenza drug. Data are the median days of fever in patients who received each anti-influenza drug; oseltamivir (median 2.5 days; interquartile range (IQR) 2.0-3.0), laninamivir (median 2.0 days; IQR 1.5-2.5), zanamivir (median 2.3 days; IQR 1.6-3.4), and baloxavir (median 2.0 days; IQR 1.4-2.5).

Table 3. Factors influencing episodes of biphasic fever according to age group, type of influenza, and anti-influenza drug

		n/N (%)	O.R.	95% CI	p value
Gender	Male	5/130	1	-	-
	Female	5/119	0.91	0.26-3.23	0.89
<10 years		4/99 (4.0)	1	-	-
≧10 years		6/155 (3.9)	0.94	0.26-3.73	0.92
Type of influenza virus	Type A	9/227 (4.0)	1	-	-
	Type B	1/25 (4.0)	1.00	0.05-5.72	0.99
Underlying diseases	No	7/186	1	-	-
	Yes	3/51	0.89	0.48-1.66	0.89
Vaccinated this year	No	3/131	1	-	-
	Yes	7/110	2.90	0.79-13.7	0.11
Anti-influenza drug	Oseltamivir	5/94 (5.3)	1	-	-
	Laninamivir	4/101 (4.0)	0.73	0.18-2.86	0.65
	Baloxavir	1/22 (4.5)	0.85	0.04-5.63	0.88

Abbreviation: O.R., odds ratio; and CI, and confidence intervals.

Table 4. Adverse events in each anti-influenza drug

	Oseltamivir (N=94)	Laninamivir (N=101)	Zanamivir (N=32)	Baloxavir (N=22)	p value
Coughing n (%)	32 (34.0)	39 (38.6)	18 (56.2)	6 (27.3)	0.10
Diarrhea n (%)	25 (26.6)	16 (15.8)	8 (25.0)	6 (27.3)	0.27
Vomiting n (%)	16 (17.0)	7 (6.9)	2 (6.3)	2 (9.1)	0.11
Abdominal pain n (%)	12 (12.77)	8 (7.92)	2 (6.25)	2 (9.1)	0.61
Headache n (%)	2 (2.1)	1 (1.0)	2 (6.3)	0 (0.0)	0.27
Abnormal behavior n (%)	3 (3.2)	2 (2.0)	0 (0.0)	0 (0.0)	0.62

delay in symptom alleviation, and uncommonly, with symptom rebound[2,3]. Our study showed no difference between the duration of fever or the frequency of biphasic fever episodes in the patients who received baloxavir and those in the patients who received oseltamivir, laninamivir, or zanamivir. Further studies will be needed to address the clinical effects of baloxavir, which contributed to shortening of the duration of fever or time to alleviation of symptoms, and the frequency of viruses with reduced susceptibility to baloxavir and their effects on clinical outcomes.

We have shown no difference between the frequency of adverse events after administration of the anti-influenza drug. Abdominal symptoms such as vomiting, diarrhea, and abdominal pain in patients who were treated with oseltamivir were previously reported as adverse events and bronchospasm after inhalation of laninamivir or zanamivir were also reported as adverse events[9,14,15]. However, it is difficult to accurately evaluate abdominal symptoms, coughing, and others as adverse events of anti-influenza drugs because they also occur with the symptoms of influenza. The frequency of adverse events after administration of baloxavir was similar to that of other influenza drugs. Because baloxavir is still a new drug, further studies on adverse events of baloxavir are needed in the future.

We have shown that laninamivir significantly contributed to early fever alleviation compared to oseltamivir in patients aged <10 years. We also found that all patients aged ≦4 years were prescribed laninamivir with a nebulizer. Laninamivir is not sold overseas, because the time to alleviation of symptoms in patients treated with laninamivir was not significantly different from that in patients who received a placebo in a phase Ⅱ trial, although the drug is effective in reducing the virus[16]. However, in Japan, some previous reports have shown that laninamivir has a similar efficacy and safety as oseltamivir for the treatment of influenza[10,17,18]. Because laninamivir is a single-dose inhalation drug that has an advantage over oseltamivir for medication adherence especially in children who frequently refuse to take an oral drug, it may be significantly associated with early fever reduction in patients aged <10 years. Nebulizers were used for inhaling laninamivir beginning in October 2019 in addition to a dry powder inhaler. We consider that nebulized administration of laninamivir can be widely prescribed to infants and elderly patients who may have difficulty using a dry powder inhaler.

The number of patients who were prescribed baloxavir was significantly reduced in our survey of the 2019-2020 season compared to the 2018-2019 season[5], similar to national trends in Japan[19]. We consider that one cause of the decrease in the number of prescriptions of baloxavir is the suggestions from the Japanese Association for Infectious Diseases and the Japan Pediatric Society based on some reports of the emergence of viruses with reduced susceptibility to baloxavir in children and their human-to-human transmission[7,8,20,21]. The decrease in the number of prescriptions of baloxavir may have affected the results in our study. The frequency and odds ratio of alleviation of fever in 2 days in patients who were prescribed baloxavir was higher than those in patients who were prescribed laninamivir, however no significant difference could be detected due to the small number of prescriptions of baloxavir.

Some limitations of this study should be recognized. First, the response rate of the postcard questionnaires was not high. Therefore, the sample may not be representative of all patients with influenza. The proportion of our patients who were in their 20's and 30's was lower than that in the data from the Ministry of Health, Labour and Welfare (MHLW) (5.5% vs 16.1%). However, the proportion of patients aged 5-9 years and 10-14 years was higher than those in the MHLW data

(53.2% vs 38.7%). The proportions of the other age groups in our subjects were similar to those in the MHLW data[22]. We suggest that the working populations who were in their 20's and 30's may not return many postcards because they didn't have enough time to answer and mail the postcard questionnaire. Second, the answers including body temperature were self-reported data, and the reliability of the answer is a limitation. Third, the use of antipyretics was not considered, and the duration of fever may shorter than the actual one. Based on the above limitations, we should consider adding or modifying questionnaire items and other questionnaire methods such as an online survey for the further development of the study in the future. Fourth, this study was an observational study, not a randomized controlled study. The selection of the anti-influenza drug was at the discretion of each physician, introducing invisible selection bias. Making an accurate comparison of the effects of each anti-influenza drug may be difficult, because their prescription numbers were different. Fifth, we could not confirm the influenza subtype in this study. For the 2019-2020 season, the National Institute of Infectious Disease reported that more than 90% of the influenza subtype was type A (H1N1 pdm09), which almost constituted an epidemic[23].

In conclusion, our study showed no significant association between baloxavir and early fever alleviation or the frequency of biphasic fever episodes that have been reported in the previous study. One cause may be that no statistically association was detected due to the decrease in the number of prescriptions of baloxavir. Further studies will need to address the clinical effects of baloxavir, which contributes to the shortening of the duration of fever or the time to alleviation of symptoms, and the association between baloxavir and biphasic fever episodes. Because epidemic influenza virus subtypes change from season to season, annual influenza surveys are also important for investigating the appropriate use and efficacy of anti-influenza drugs.

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