

# Current usage and effectiveness of influenza medications and factors regarding the time taken to alleviate fever based on postcard questionnaire survey

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## Abstract

**Background:** After the A/H1N1 influenza pandemic in 2009, two new drugs against the influenza virus, laninamivir and peramivir, were released in 2010 in Japan. We investigated the current usage and effectiveness of influenza medications and factors related to the time taken to alleviate fever.

**Methods:** Patients diagnosed with influenza during the 2012-2013 season in Osaka Prefecture answered a postcard questionnaire that collected data regarding their demographic characteristics, flu vaccination status, symptoms, prescribed drugs, and drug-related adverse events.

**Results:** The use of laninamivir consistently increased over the 3-year period and was prescribed at a similar rate as oseltamivir during the last year (39% and 45%, respectively). None of the neuraminidase inhibitors had a significant effect on the fever or other symptoms of influenza infection ( $P=.59$  and  $P=.70$ , respectively). Vaccinated influenza patients experienced fever for a significantly longer duration than the nonvaccinated patients ( $P=.04$ ). However, multivariate analysis showed that only influenza virus type, but not vaccination status, was related to the alleviation of fever within 2 days.

**Conclusions:** There were no significant differences of effects on fever and symptoms among neuraminidase inhibitors. Virus type was only related to the alleviation of fever.

## KEYWORDS

influenza, neuraminidase inhibitor, questionnaire-based survey, vaccine

## 1 | INTRODUCTION

Influenza infection is one of the most common viral infections on a global basis annually, especially during winter in the temperate zone. After the H1N1 influenza pandemic occurred in 2009, two new drugs against influenza infection, laninamivir and peramivir, were released in 2010 in Japan. Four varieties of neuraminidase inhibitors are typically used in Japan: oseltamivir (orally administered twice a day for

5 days), zanamivir (inhaled twice a day for 5 days), laninamivir (inhaled just once on the first day), and peramivir (intravenously administered just once on the first day or once daily for a maximum of 3 days). To investigate the status of influenza patients and their medication use, we started to conduct a survey via a postcard questionnaire in Osaka Prefecture from the 2010 to 2011 winter season. Laninamivir appeared to alleviate fever faster with fewer adverse events during the 2010-2011 season.<sup>1</sup> Laninamivir was prescribed more often than it

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inhibitors (Table 1). Regarding age, there were significant differences among the neuraminidase inhibitors, except laninamivir vs peramivir. The patients who were prescribed laninamivir and peramivir were older (mainly older than 10 years), whereas oseltamivir and zanamivir were prescribed to younger patients (mainly younger than 9 years). Fewer patients prescribed laninamivir were infected in the previous year than were those prescribed oseltamivir and zanamivir. Moreover, fewer patients prescribed laninamivir were vaccinated this year than were those prescribed zanamivir, because the patients prescribed laninamivir were older and mostly adults who have lower infection and vaccination rates than children.<sup>4</sup> Laninamivir resulted in significantly fewer adverse events than oseltamivir. There were no significant differences in sex, influenza type (A or B), vaccination during the previous year, or risk factors.

### 3.1 | Consistent increase in the use of laninamivir

Figure 2 illustrates the proportion of patients using each neuraminidase inhibitor during the 3-year period. The use of laninamivir consistently increased (22%, 38%, and 39%), whereas the use of zanamivir decreased (29%, 21%, and 12%). The proportions of laninamivir and oseltamivir were similar during the 2011-2012 (38% and 38%) and 2012-2013 (39% and 45%) seasons. Compared with oseltamivir, laninamivir was prescribed more often to older patients ( $P<.0001$ ),

as shown in Table 1. These results indicate that laninamivir was preferred for adults and oseltamivir was preferred for children. The use of oseltamivir, expressed as a proportion of all neuraminidase inhibitors, did not change over the 3 years. Peramivir was prescribed for a small proportion of patients, because all of the patients were treated in outpatient clinics for infections that were not considered severe.

### 3.2 | Neuraminidase inhibitors had similar effects on influenza infections

The time taken to alleviate fever did not differ according to which neuraminidase inhibitor was used. Although peramivir helped resolve the fever earlier, the difference was not significant ( $P=.59$ ). There were no significant differences in the duration of any other symptoms among the neuraminidase inhibitors ( $P=.70$ ) (Figure 3).

### 3.3 | Effect of influenza virus type on the alleviation of fever 2 days after neuraminidase inhibitor treatment

The percentages of all patients with a high fever ( $>37.0^{\circ}\text{C}$ ) according to vaccination status are shown in Figure 4. The fever duration was significantly longer in vaccinated influenza patients during the 2012-2013 season ( $P=.04$ ).

**TABLE 1** Characteristics and clinical feature of patients, compared between the 4 four neuraminidase inhibitors

	Osetamivir	Zanamivir	Laninamivir	Peramivir	P value
Number, %	108, 45%	28, 12%	95, 39%	10, 4%	
Gender					
Male/female	55/53	14/14	43/52	4/6	n.s.
Age					
Under 9 y.o.	85	17	14	0	
Over 10 y.o.	23	11	81	10	
Median (range)	5 (1-90)	8.5 (4-42)	19 (6-88)	44.5 (10-77)	$<.0001^{a,b,c,d,e}$
Type					
A/B	101/7	24/4	88/7	10/0	n.s.
Infected last year					
Yes/No/Unknown	18/88/2	11/17/0	3/92/0	0/9/1	.0003 <sup>b,d</sup>
Vaccinated last year					
Yes/No/Unknown	53/50/5	19/8/1	46/47/2	5/5/0	n.s.
Vaccinated this year					
Yes/No	63/46	21/7	42/53	6/4	.02 <sup>d</sup>
Risk factors					
Yes/No	10/98	1/27	10/85	5/5	n.s.
Adverse events					
Yes/No	25/83	4/24	6/89	2/8	.02 <sup>b</sup>

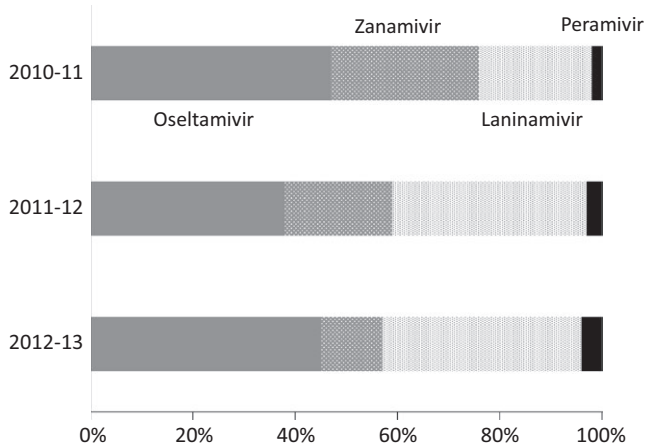
<sup>a</sup>Osetamivir vs zanamivir.

<sup>b</sup>Osetamivir vs laninamivir.

<sup>c</sup>Osetamivir vs peramivir.

<sup>d</sup>Zanamivir vs laninamivir.

<sup>e</sup>Zanamivir vs peramivir  $P<.008$  after Bonferroni correction.



**FIGURE 2** Proportion of patients using each neuraminidase inhibitor for the 3 y starting in the 2010-2011 season. Laninamivir use increased consistently each year, whereas the use of zanamivir decreased. The use of oseltamivir remained the same. Peramivir was prescribed to only a few patients

Table 2 shows the univariate and multivariate analyzes regarding the alleviation of fever within 2 days after the start of neuraminidase inhibitor treatment. In the univariate analyzes, fever was alleviated significantly earlier in patients aged  $\geq 10$  years, patients with type A virus, patients not vaccinated this year, and patients treated with laninamivir compared to oseltamivir. We performed multivariate analysis of clinically important factors to alleviate fever, such as age, virus type A or B, influenza infection last year, vaccination this year, vaccination last year, and drugs. In multivariate analysis, fever was alleviated significantly earlier only in patients with type A virus.

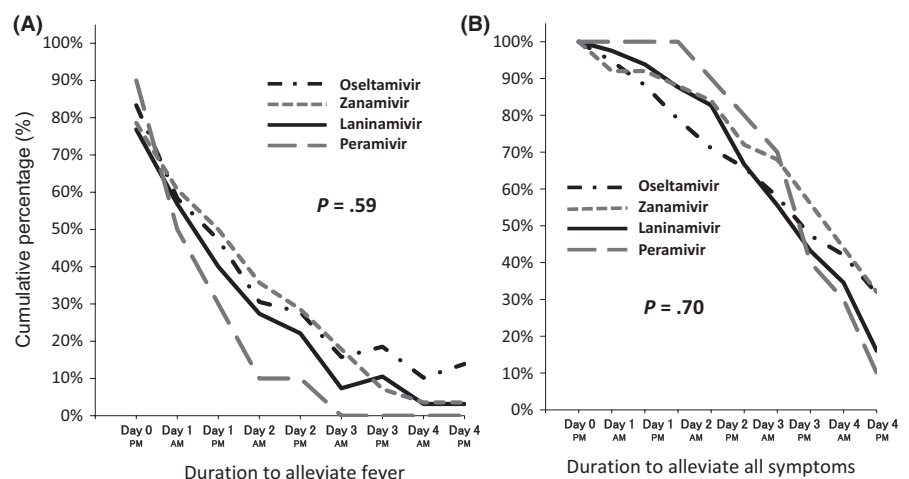
## 4 | DISCUSSION

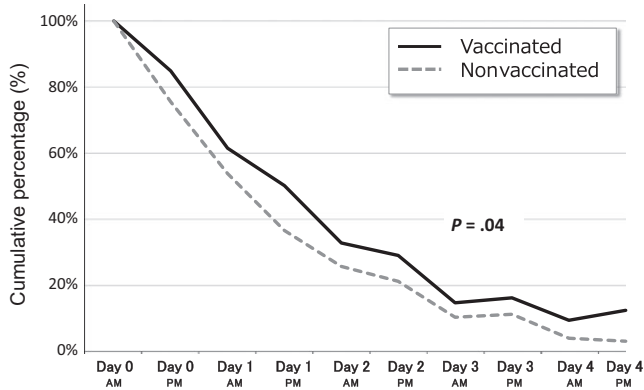
This study revealed the current usage and no significant difference of effectiveness of neuraminidase inhibitors and its effectiveness, and also only influenza virus type was related to the alleviation of fever within 2 days. We found that the only factor affecting the

alleviation of fever within 2 days after starting treatment with a neuraminidase inhibitor was influenza virus type; multivariate analysis showed that fever in patients with type A compared with type B virus infection was alleviated earlier. Many previous reports revealed patient with type A was alleviated earlier than type B after taking oseltamivir.<sup>5-7</sup> Suzuki and Ichihara reported that higher age, virus type A and lower maximum bodily temperature were related to the earlier alleviation of fever in children treated with oseltamivir.<sup>5</sup> Results of this study showed that factors, except vaccination this year, related to the time taken to alleviate fever were similar to the previous reports even in the patients treated with other neuraminidase inhibitors. The fever duration was significantly longer in vaccinated influenza patients during the 2012-2013 season. However, multivariate analysis showed there were no significant differences between vaccinated and nonvaccinated patients or among the drugs used. Vaccinated patients were significantly younger than nonvaccinated patients (vaccinated:nonvaccinated 8:14 years old [median],  $P=.03$ ), and there was no significant difference of pretreated bodily temperature between vaccinated and nonvaccinated patients (vaccinated:nonvaccinated 38.3: 38.4°C [median], n.s.). The younger vaccinated patients may lead the longer duration of fever. Otherwise, vaccinated patient with low fever might not go to hospitals because they believed to be able to avoid influenza infection by vaccination. Upon the onset of influenza, fever or other symptoms of vaccinated patients may be equivalent to those of nonvaccinated patients. They might be the reasons for that vaccination did not shorten the duration of fever in this survey.

Regarding the prescribed drugs, the proportion of laninamivir prescriptions consistently increased. Laninamivir is a drug that is inhaled just once. Its effects and adverse events are similar to those of other neuraminidase inhibitors, and it is also very convenient for patients, which may lead to high compliance. Laninamivir was released in Japan and several Asian countries in 2010, but it is not available in other countries. Oseltamivir tended to be prescribed to patients younger than 9 years, and laninamivir was prescribed more frequently to patients older than 10 years. Small children, especially those younger than 3 years, have difficulty inhaling laninamivir. Because oseltamivir is orally administered, it is preferred for children. However, most

**FIGURE 3** (Left) Percentage of patients with a high fever ( $>37.0^{\circ}\text{C}$ ) according to which neuraminidase inhibitor was prescribed. There were no significant differences between the groups. (Right) Length of time required to alleviate all of the symptoms according to which neuraminidase inhibitor was prescribed. There were no significant differences between the groups





**FIGURE 4** In the 2012-2013 season, vaccinated influenza patients experienced a significantly longer fever duration compared with nonvaccinated patients

patients, including adults and elderly patients, inhaled laninamivir in front of the doctor, pharmacist, or medical staff to confirm proper and complete inhalation. A previous report indicated that patients older than 3 years could inhale laninamivir properly.<sup>8</sup> Children may be able to inhale laninamivir under the observation of medical staff. As laninamivir was not released until 2010, it has not been distributed to all

doctors. The proportion of laninamivir use may further increase in the future.

All of the medications were prescribed in outpatient clinics for patients with less severe influenza infection; therefore, peramivir was prescribed to only a few patients because it is used to prevent the spread of influenza infection in clinics or hospitals during long hospital stays, and it should be infused via an intravenous drip for longer than 15 minutes. However, peramivir can also be used for more severe infections in patients who need to receive mechanical ventilation. The National Institute of Infectious Diseases of Japan reported that influenza drug resistance was not observed during the 2012-2013 season.<sup>9</sup> Before the 2009 pandemic, the A/H1N1 virus was almost entirely resistant to oseltamivir.<sup>10</sup> The 2009 pandemic erased this resistance to oseltamivir. Conducting this survey every year helps us to understand the effectiveness of anti-influenza drugs.

We used a postcard-based questionnaire in this study. The postcard return rate was only 30.5%; therefore, the sample may not be representative of all patients with influenza. The Ministry of Health, Labour and Welfare provided the number of prescriptions of neuraminidase inhibitors in 2012-2013 based on data furnished by pharmaceutical companies.<sup>11</sup> These data showed the proportions of prescribed neuraminidase inhibitors to be 45% oseltamivir, 14% zanamivir, 39%

**TABLE 2** To alleviate fever 2 d after taking medicine

Variables	n/N (%)	Univariate OR (95% CI)	P value	Multivariate OR (95%)	P value
Age					
<9	69/115 (60%)	1		1	
>10	89/115 (77%)	0.44 (0.25-0.78)	.004	0.53 (0.24-1.13)	.10
Gender					
Female	83/119 (70%)	1			
Male	74/110 (67%)	1.12 (0.64-1.96)	.69		
Type					
A	150/211 (71%)	1		1	
B	8/18 (44%)	3.07 (1.16-8.16)	.02	2.91 (1.05-8.34)	.04
Flu, last year					
Yes	18/31 (58%)	1		1	
No	139/197 (71%)	0.58 (0.27-1.26)	.16	0.66 (0.27-1.62)	.36
Vaccine, last year					
Yes	73/115 (63%)	1		1	
No	77/107 (72%)	0.68 (0.38-1.19)	.18	0.91 (0.39-2.19)	.84
Vaccine, this year					
Yes	78/124 (63%)	1		1	
No	80/106 (75%)	0.55 (0.31-0.98)	.04	0.70 (0.28-1.71)	.44
Drug					
Oseltamivir	66/106 (62%)	1		1	
Laninamivir	74/97 (76%)	0.51 (0.28-0.95)	.03	0.77 (0.34-1.72)	.52
Zanamivir	18/27 (67%)	0.83 (0.34-2.01)	.67	0.66 (0.23-1.75)	.41
Complication					
Yes	15/20 (75%)	1			
No	138/201 (69%)	1.37 (0.48-3.93)	.56		

laninamivir, and 2% peramivir, similar to our findings: 45% oseltamivir, 12% zanamivir, 39% laninamivir, and 4% peramivir. Therefore, the population of this survey might be representative suggesting the reliability of our data.

Although it is easy to perform this postcard survey and results in a low burden for doctors and patients, two biases and two limitations exist. The first bias is a doctor's bias. Doctors deciding which neuraminidase inhibitor to prescribe could lead to a prescription bias. We reported previously that there were no significant differences in sex, age distribution, or choice of prescribed drugs between our survey and the Japan Physicians Association report, which is one of the most reliable investigations of influenza in Japan.<sup>12</sup> Our findings are relevant to the clinical setting. In this survey, oseltamivir and zanamivir were prescribed to young patients, mainly younger than 9 years. Because there are many child influenza patients every year, vaccination is recommended.<sup>4</sup> The patients who received oseltamivir and zanamivir may represent patients who were vaccinated during the same year or who were infected with the influenza virus during the previous year. The second bias is a patient's bias regarding adverse events. Laninamivir resulted in fewer adverse events than other drugs; however, it was difficult to determine the accuracy of these data because the reports depended on the patients' judgment. The patients may have included influenza symptoms as adverse events or vice versa. The first limitation is the list of symptoms. Although cough is a common symptom of influenza, we assessed the symptoms of fever, sore throat, fatigue, headache, runny nose, and joint pain. For influenza patients, high fever and joint pain are the most common symptoms and were included in this study. The second limitation does not know the time of onset of influenza. We searched durations of fever after visiting hospitals or clinics; however, we did not show the onset of influenza. Kawai et al. reported the duration of fever depends on the when the first dose of oseltamivir is administered and not on the onset. They categorized the patients using oseltamivir into four groups on the basis of time from the onset of fever to the start of treatment (0-12, 13-24, 25-36, and 37-48 hours). The time to alleviate fever was similar in each group.<sup>13</sup>

## 5 | CONCLUSION

There were no significant differences of effects on fever and symptoms among neuraminidase inhibitors. Virus type was only related to the alleviation of fever.

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## CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

## REFERENCES

- Tochino Y, Fujioka M, Watanabe T, et al. A questionnaire study concerning the current status of influenza patients and their medication in Osaka Prefecture. *Jpn J Chemother*. 2012;60:541-8.
- Tochino Y, Sakazaki H, Nakajima T, et al. A questionnaire study concerning the current status of influenza patients and their medication in the 2011-12 season. *Jpn J Clin Exp Med*. 2013;90:86-90.
- Jefferson T, Jones M, Doshi P, Elizabeth A, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. *BMJ*. 2014;348:g2545.
- Nobuhara H, Watanabe Y, Miura Y. Estimated influenza vaccination rate in Japan. *Jpn Soc Public Health*. 2014;61:354-9.
- Suzuki E, Ichihara K. The course of fever following influenza virus infection in children treated with oseltamivir. *J Med Virol*. 2008;80:1065-71.
- Kawai N, Ikematsu H, Iwaki N, et al. Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from Japan of the 2002-2003 influenza season. *Clin Infect Dis*. 2005;40:1309-16.
- Sugaya N, Mitamura K, Yamazaki M, et al. Lower clinical effectiveness of oseltamivir against influenza B contrasted with influenza A infection in children. *Clin Infect Dis*. 2007;44:197-202.
- Watanabe A, Chang SC, Kim MJ, Chu DW, Ohashi Y, MARVEL Study Group. Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: a double-Blind, randomized, noninferiority clinical trial. *Clin Infect Dis*. 2010;51:1167-75.
- National Institute of Infectious Diseases, Japan. Analysis of influenza virus isolates in 2012-2013 season, Available from <http://www.nih.go.jp/niid/ja/iasr-sp/2257-related-articles/related-articles-405/4089-dj4051.html>. Accessed November 24, 2016.
- Dharan NJ, Gubareva LV, Meyer JJ, et al. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA* 2009;301:1034. e41.
- Ministry of Health, Labour and Welfare, the number of prescription of neuraminidase inhibitors in 2012-13 based on data furnished by pharmaceutical company. (in Japanese)., Available from [http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000027857\\_1\\_1.pdf](http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000027857_1_1.pdf). Accessed November 24, 2016.

12. Kawai N, Karatsu N, Ikematsu H, Kashiwagi S, Iwaki N. The manual of influenza care for the 2013-14 season. *Jpn J Phys Assoc.* 2013;28(Supplement):1-48.
13. Kawai N, Ikematsu H, Iwaki N, et al. A comparison of the effectiveness of oseltamivir for the treatment of influenza A and influenza B: a Japanese multicenter study of the 2003-2004 and 2004-2005 influenza seasons. *Clin Infect Dis.* 2006;43:439-44.

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