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A comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and B

Naoki Kawai [a,*,d], Hideyuki Ikematsu [a,b,,d], Norio Iwaki [a], Tetsunari Maeda [a], Hideo Kanazawa [a], Takashi Kawashima [a], Osame Tanaka [a], Satoshi Yamauchi [a], Kenichi Kawamura [a], Toru Nagai [a], Satsuki Horii [a], Nobuo Hirotsu [a], Seizaburo Kashiwagi [c]**

[a] *Japan Physicians Association, Tokyo Medical Association Building 3F, 2—5 Kanda-Surugadai, Chiyoda-ku, 101-0062 Tokyo, Japan*
[b] *Department of Clinical Research, Hara-doi Hospital, Fukuoka, Japan*
[c] *Fukuoka Red Cross Blood Center, Fukuoka, Japan*

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Summary *Objective:* To compare the effectiveness of zanamivir with oseltamivir for influenza A and B.
Methods: 1113 patients with influenza A or B were enrolled in the 2006—2007 influenza season. The duration of fever (temperature, ≧37.5 °C) and the percentage of patients afebrile at 24 and 48 h after the first dose of zanamivir or oseltamivir were calculated. Virus persistence after zanamivir therapy was also evaluated.
Results: There were marginally significant differences between the duration of fever after the first dose of zanamivir (31.8 ± 18.4 h) and oseltamivir (35.5 ± 23.9 h) for influenza A ($p < 0.05$). The duration of fever after starting zanamivir therapy (35.8 ± 22.4 h) was significantly shorter than that of oseltamivir (52.7 ± 31.3 h) for influenza B ($p < 0.001$). There were no significant differences between influenza A and B in the percentage of patients afebrile at 24 or 48 h after the first inhalation of zanamivir. The reisolation rate after zanamivir therapy showed marginally significant differences between influenza A and B (<0.05). By multiple regression analysis, therapy (zanamivir or oseltamivir) was the major determinant affecting the duration of fever for influenza B.
Conclusion: Zanamivir therapy is more effective than oseltamivir for the treatment of influenza B infection.
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* Corresponding author. 4—9 Tonomachi, Gifu City 500-8116, Japan. Tel.: +81 58 245 0564; fax: +81 58 246 9057.
** Corresponding author.
E-mail addresses: nkawai@city.gifu.med.or.jp (N. Kawai), ikematsu@gray.plala.or.jp (H. Ikematsu).
[d] These two authors contributed equally to this work.

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Introduction

We previously reported that oseltamivir, a neuraminidase inhibitor, was significantly less effective for patients with influenza B than for patients with influenza A in an analysis of the duration of fever and viral persistence after oseltamivir therapy.[1–3] Recently, Sugaya et al. also reported oseltamivir to be less effective for influenza B than for influenza A.[4]

The effectiveness of zanamivir, another neuraminidase inhibitor, has been reported,[5–8] but it has not been compared fully between influenza A and influenza B, except for our recent preliminary report on a small number of patients.[9] In the preliminary study, we reported that zanamivir was effective for influenza B as well as influenza A by analyzing the percentage of patients afebrile at 24 and 48 h after the start of therapy. However, the effectiveness of zanamivir and oseltamivir for influenza B has not been compared with a large number of patients, including our previous studies. In this study, a large number of patients with influenza A and influenza B were studied individually, including both children and adults, for whom diagnosis was made using antigen detection test kits[10–12] and who were treated with zanamivir or oseltamivir. The effectiveness of zanamivir and oseltamivir for influenza A and influenza B was compared by measuring the duration of fever and the percentage of patients afebrile at 24 and 48 h after the start of therapy. Virus persistence after zanamivir therapy was also analyzed.

Methods

Patients

Family doctors, pediatricians, and physicians at 27 clinics that belong to the Influenza Study Group of the Japan Physicians Association participated in the study. Patients were enrolled from 2 December 2006 through 28 May 2007. Patients who reported to any of our 27 clinics throughout Japan with influenza-like illness (manifesting such symptoms as a body temperature 37.5 °C, upper respiratory tract symptoms, and systemic symptoms) received a diagnosis of influenza A or B based on the results of commercial antigen detection kits. Among the patients with influenza confirmed by antigen detection kits, those who received zanamivir or oseltamivir within 48 h after the onset of symptoms or who did not receive an anti-influenza drug were registered in this study after providing oral informed consent. For patients with influenza, the decision on whether to administer zanamivir or oseltamivir was left to the discretion of the clinician, who considered the background and characteristics of the patient, such as the presence of other existing diseases, patient age, and patient preference.

Antigen detection test kits and virus isolation

Specimens from throat swabs, nasal swabs, or nasal aspirates were subjected to antigen detection and virus isolation. Commercial antigen detection kits based on immunochromatography (Capilia FluA + B [Alfresa Pharma Corporation], QuickVue Rapid-SP influ [DS Pharma Biomedical Co., Ltd.], BD Flu Examan [Nippon Becton Dickinson and Company.], Quick Chaser Flu A, B [Mizuho Medy Co., Ltd.]) were mainly used. Another kit based on an EIA (Influ A–B Quick ''SEIKEN'' [DENKA SEIKEN CO., LTD.]) was also used. The respective reported sensitivities and specificities of the commercial antigen detection kits based on immunochromatography or EIA in Japan are 93.9%–98% and 93.9%–100% for influenza A and 86%–91.2% and 97.6%–100% for influenza B.[13–17] No significant difference in specificity has been reported for influenza A or influenza B for either kits based on either immunochromatography or EIA.

To confirm the reliability of our diagnosis using the antigen detection kits and the effectiveness of zanamivir, virus isolation was done from the specimens of 113 patients with influenza A, 115 patients with influenza B and 11 patients with negative response in the diagnosis by antigen detection kits before and between days four and six after the start of zanamivir therapy.[3] Virus isolation was performed by standard methods using Madin-Darby canine kidney cells and PCR was used to determine influenza A/H3N2, A/H1N1 or B.[3]

Clinical outcomes

Zanamivir (10 mg for adults and for children aged five years or over) was inhaled twice per day for five days, and oseltamivir (75 mg for adults and for children who weighed 37.5 kg and 2 mg/kg for children who weighed <37.5 kg) was taken orally twice per day for five days. Patients inhaled the initial dose of zanamivir, or took the initial dose of oseltamivir at the clinic or at home and entered the time of the initial administration of the zanamivir or oseltamivir on a questionnaire that had been provided.

Age, sex, vaccination status, results of the antigen detection test kit, and the body temperature were recorded for all patients. The date and time of the onset of fever, the date and time of administration of zanamivir or oseltamivir, and the resolution of fever were recorded by the physician, patient, or an attending family member. The first time that a patient reported a fever (temperature, 37.5 °C) was defined as the time of onset. Patients were asked to measure body temperature at least three times per day (8:00 A.M., 2:00 P.M., and 8:00 P.M.). The time at which a body temperature of <37.5 °C was attained was defined as the time that the patient became afebrile and the time was recorded. The highest body temperature during the course of the disease was also recorded. As a rule, antipyretics were not administered, and in the case of emergency acetaminophen was used temporally.

All data were collected using an internet-based protocol in which the participating physicians sent their data to a central computer system based on a Pentium workstation running a Structured Query Language (SQL) database on a Web server located in a secure room at the Gifu City Medical Association. All participating doctors were given an identification number and password and were able to access the computer system via the Internet to enter data into the SQL database.[1,2,18] The time from the initial administration of oseltamivir to the resolution of fever and the duration of fever between the onset and resolution were calculated automatically in the SQL database.

In this study, to compare the effectiveness between zanamivir and oseltamivir, patients less than 5 years old were excluded from the analysis.

Statistical analysis

Student's *t*-test was used for between-group comparisons of the duration of fever. The χ^2-test was also done to compare between group differences in the percentage of afebrile patients. To address factors that might influence the duration of fever after the onset, multiple regression analysis was done. The analyzed factors were patient age, sex, type of influenza (influenza A or influenza B), treatment (zanamivir or oseltamivir), vaccination status, peak body temperature, and time to administration of the first dose after the onset of fever. A p value <0.05 was considered to be statistically significant.

Results

Patient characteristics

A total of 1,113 patients, 733 with influenza A and 380 with influenza B were enrolled. Of 733 patients with influenza A, 225 were treated with zanamivir and 472 with oseltamivir. 36 patients did not receive treatment with an anti-influenza drug. Of 380 patients with influenza B, 177 received zanamivir and 171 oseltamivir. 32 patients did not receive treatment with an anti-influenza drug. The demographic characteristics of the patients are summarized in Table 1.

No significant differences were shown in mean age among the patient groups treated with zanamivir, oseltamivir, and no anti-influenza drug for patients with influenza A or influenza B. The ratio of female subjects to male subjects was higher in influenza A than in influenza B, however, the ratio was not different among the zanamivir, oseltamivir and no anti-influenza drug groups, either for influenza A or influenza B. Also, no significant between-group differences were found for vaccination status among the groups treated with zanamivir, oseltamivir, and no anti-influenza drug, both for influenza A and influenza B. There were no significant differences among the zanamivir, oseltamivir, and control groups in peak body temperature, both for influenza A and influenza B.

The commercial antigen detection kits used were Capilia FluA + B in 841 cases, QuickVue Rapid-SP influ in 91 cases, BD Flu Examan in 55 cases, QuickChaser Flu A, B in 62 cases, Influ A–B Quick ''SEIKEN'' in 18 cases, and others in 46 cases.

Some patients discontinued the use of zanamivir or oseltamivir if influenza symptoms abated in less than five days (mean ± SD, 4.5 ± 0.7 days). Minor adverse reactions were observed in 18 patients treated with oseltamivir and in five patients with zanamivir. No severe adverse reactions were reported. As adverse events, any of neuro-psychiatric symptoms (hallucination, delusion, et al.) were observed in 9 patients with influenza A (4 patients before and 5 patients after starting oseltamivir therapy) and 2 patients with influenza B (1 patient after oseltamivir and 1 after zanamivir therapy).

Duration of fever from the onset

The durations of fever after the onset are shown in Table 1. The duration of fever from its onset was significantly shorter for patients with influenza A who were treated with either zanamivir or oseltamivir than in those who were not treated with an anti-influenza drug (49.7 ± 21.7 or 52.5 ± 25.6 and 75.4 ± 24.2 h, respectively; both $p < 0.001$). For patients with influenza B, the duration of fever from its onset was significantly shorter for patients who were treated with zanamivir than for those who were treated with oseltamivir or not treated with an anti-influenza drug (53.9 ± 26.4 and

Table 1 Characteristics of patients in a comparison of the effectiveness of zanamivir and oseltamivir for the treatment of influenza A and influenza B

Patient group	No. of pts.	Age, mean years ± SD	Sex, no. of patients		No. of times patient had received vaccine				Peak body temperature, mean°C ± SD	Time to the first administration of the drug after the onset, mean h ± SD	Duration of fever after the onset, mean h ± SD
			F	M	Never	Once	Twice	Unknown			
Influenza A											
Zanamivir	225	27.9 ± 16.4	122	103	164	30	29	2	38.9 ± 0.6	17.7 ± 11.3	49.7 ± 21.7[a]
Oseltamivir	472	31.6 ± 22.0	241	231	269	99	69	35	39.0 ± 0.7	16.7 ± 115	52.5 ± 25.6[a,b]
No anti-influenza drug	36	26.2 ± 20.8	21	15	22	8	6	0	39.0 ± 0.7		75.4 ± 24.2[a]
Influenza B											
Zanamivir	177	15.2 ± 10.8	82	95	113	28	34	2	38.9 ± 0.6	18.1 ± 12.1	53.9 ± 26.4[c]
Oseltamivir	171	15.5 ± 12.2	74	97	86	14	20	51	38.8 ± 0.6	16.5 ± 12.0	69.4 ± 32.9[b,c]
No anti-influenza drug	32	14.1 ± 7.0	13	19	21	3	7	1	38.9 ± 0.6		75.3 ± 27.3[c]

[a] $p < 0.001$ between zanamivir and no anti-influenza drug, or between oseltamivir and no anti-influenza drug.
[b] $p < 0.001$ between influenza A and influenza B both treated with oseltamivir.
[c] $p < 0.001$ between zanamivir and oseltamivir, or between zanamivir and no anti-influenza drug.

69.4 ± 32.9 or 75.3 ± 27.3 h, respectively; both $p < 0.001$). Among oseltamivir recipients, the duration of fever was significantly longer for patients with influenza B than for patients with influenza A (69.4 ± 32.9 and 52.5 ± 25.6 h, respectively; $p < 0.001$).

Duration of fever after administration of the first dose of zanamivir or oseltamivir

The durations of fever after administration of the first dose of zanamivir and oseltamivir are shown in Table 2. For patients with influenza A aged 5—10 years, no statistically significant difference in the duration of fever was shown between zanamivir and oseltamivir therapy (35.4 ± 23.2 and 30.8 ± 20.2 h, respectively). For all patients with influenza A and patients with influenza A aged >10 years, the duration of fever was significantly shorter in zanamivir therapy than in oseltamivir therapy (31.8 ± 18.4 and 35.5 ± 23.9 h; $p < 0.05$ in all patients, and 31.0 ± 17.0 and 37.1 ± 24.9; $p < 0.001$ in patients aged >10 years, respectively).

For patients with influenza B, the duration of fever was significantly shorter for patients treated with zanamivir than with oseltamivir in all patients, in patients aged 5—10 years, and in patients aged >10 years (all $p < 0.001$).

Between group comparison of patients with influenza A and influenza B for zanamivir therapy indicated marginally significant difference ($p < 0.05$) in all ages (31.8 ± 18.4 and 35.8 ± 22.4 h, respectively;) and in patients aged >10 years (31.0 ± 17.0 and 36.1 ± 20.9 h, respectively), or no significant difference in patients aged 5—10 years (35.4 ± 23.2 and 35.2 ± 25.3 h, respectively). Strongly significant difference ($p < 0.001$) for oseltamivir therapy were shown in influenza A and influenza B in all ages (35.5 ± 23.9 and 52.7 ± 31.3 h, respectively), in patients aged 5—10 years (30.8 ± 20.2 and 53.6 ± 34.3 h, respectively), and in patients aged >10 years (37.1 ± 24.9 and 52.2 ± 29.6 h, respectively).

Percentage of patients afebrile at 24 and 48 h after the first dose of zanamivir or oseltamivir

The percentage of patients afebrile after the first dose of zanamivir or oseltamivir in all age group is shown in Fig. 1. For patients with influenza A, no statistically significant differences in the percentage of patients afebrile at 24 or 48 h after the first dose of drug were shown between zanamivir and oseltamivir therapy (50.2% and 44.1%, at 24 h, or 86.7% and 83.1% at 48 h, respectively). For patients with influenza B, the percentage of patients afebrile at 24 h or 48 h after the first dose was significantly higher for patients treated with zanamivir than with oseltamivir (44.6% and 25.1% at 24 h, or 80.2% and 55.6% at 48 h, respectively; both $p < 0.001$). Between patients with influenza A and influenza B, no significant difference was found in the percentage of patients afebrile at 24 or 48 h after the start of zanamivir therapy (50.2% and 44.6% at 24 h, or 86.7% and 80.2% at 48 h, respectively). The percentage of patients afebrile at 24 or 48 h after starting oseltamivir therapy was significantly higher for influenza A than for influenza B (44.1% and 25.1% at 24 h, or 83.1% and 55.6% at 48 h, respectively; both $p < 0.001$).

Virus isolation before and after zanamivir therapy

Influenza A/H3N2 or A/H1N1 virus was isolated in 105 (95 of A/H3N2 and 10 of A/H1N1) of 113 patients with influenza A (positive predictive value, 92.9%), and influenza B virus was isolated 101 of 115 patients with influenza B (positive predictive value, 87.8%) both diagnosed by antigen detection kits before they commenced zanamivir therapy. A/H3N2 virus was also detected from six patients with negative response and one patient with influenza B in the diagnosis by antigen detection test kits.

These 102 patients with influenza A/H3N2, 10 patients with influenza A/H1N1 and 101 patients with influenza B

Table 2 Duration of fever after administration of the first dose of zanamivir or oseltamivir for patients aged 5—10 years or over 10 years old with influenza A or influenza B

	Influenza A		Influenza B		*p* between influenza A and influenza B
	No. of patients	Duration of fever, mean h ± SD	No. of patients	Duration of fever, mean h ± SD	
All ages					
Zanamivir	225	31.8 ± 18.4	177	35.8 ± 22.4	<0.05
Oseltamivir	472	35.5 ± 23.9	171	52.7 ± 31.3	<0.001
p (*)		<0.05		<0.001	
5—10 years					
Zanamivir	43	35.4 ± 23.2	56	35.2 ± 25.3	NS
Oseltamivir	120	30.8 ± 20.2	58	53.6 ± 34.3	<0.001
p (*)		NS		<0.001	
>10 years					
Zanamivir	182	31.0 ± 17.0	121	36.1 ± 20.9	<0.05
Oseltamivir	352	37.1 ± 24.9	113	52.2 ± 29.6	<0.001
p (*)		<0.001		<0.001	

p (*): a *p* value between zanamivir and oseltamivir therapy in patients with influenza A or influenza B.

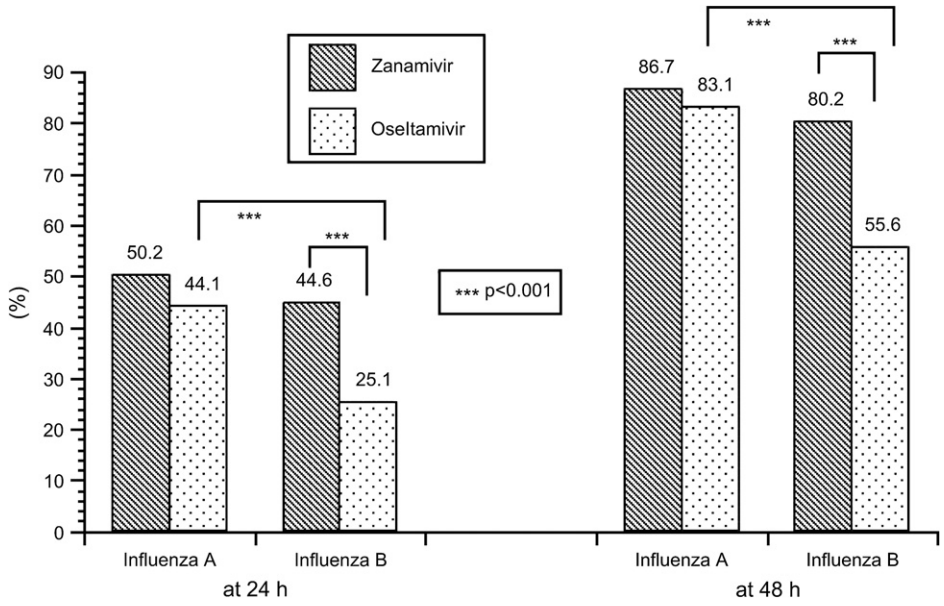

Figure 1 The percentage of patients afebrile at 24 h and 48 h after the first dose of zanamivir or oseltamivir for patients with influenza A or influenza B.

underwent virus isolation between days four and six (mean ± SD, 4.8 ± 0.6 days) after the start of zanamivir therapy. The reisolation rate of each virus in each age group is listed in Table 3. In patients aged 5—10 years old, there was no significant difference in the reisolation rate between influenza A (A/H3N2 or A/H1N1, 47.1%) and influenza B (36.1%). The reisolation rate in patients aged >10 years and in all patients was significantly higher for influenza B (20% and 25.5%) than for influenza A (6.3% and 12.5%, respectively; $p < 0.01$ and $p < 0.05$, respectively).

The reisolation rate was significantly higher in patients aged 5—10 years than in patients aged >10 years for influenza A ($p < 0.001$).

Multiple regression analysis

For influenza A and B, the type of influenza ($p = 1.1 \times 10^{-11}$), zanamivir or oseltamivir ($p = 0.0010$), patient age ($p = 3.8 \times 10^{-5}$), time from onset of fever to administration of zanamivir or oseltamivir ($p = 2.2 \times 10^{-38}$), and the peak body temperature ($p = 1.4 \times 10^{-7}$) were found to be independent factors that affect the duration of fever after the onset. For influenza A, patient age ($p = 0.00035$), time from the onset of fever to administration of zanamivir or oseltamivir ($p = 2.5 \times 10^{-29}$) and the peak body temperature ($p = 5.7 \times 10^{-5}$) were found to be independent factors. For influenza B, zanamivir or oseltamivir ($p = 8.7 \times 10^{-5}$), patient age ($p = 0.0070$), time from the onset of fever to administration of zanamivir or oseltamivir ($p = 7.9 \times 10^{-12}$), and the peak body temperature ($p = 0.00048$) were found to be independent factors. No significant relationship to duration of fever after the onset was shown for sex or vaccination status.

Discussion

We have reported in our analyses of the duration of fever calculated in days (2002—2003 season) and in hours (2003—2004 and 2004—2005 seasons)[1,2] that oseltamivir therapy was possibly less beneficial for influenza B than for influenza A. In this study, both the duration of fever from the first dose of oseltamivir and the duration from the onset of fever were significantly longer for patients with influenza B than for patients with influenza A in the 2006—2007 season. These results suggested that oseltamivir therapy is less beneficial for influenza B than for influenza A.

In our preliminary study, zanamivir treatment was equally effective for both influenza A and influenza B with regard to the percentage of patients afebrile at 24 and 48 h in a small number of patients.[9] In this study, duration of

Table 3 Reisolation rates of influenza A/H3N2, influenza A/H1N1 and influenza B viruses after zanamivir therapy

	A/H3N2	A/H1N1	A (A/H3N2 or A/H1N1)	B	*p* between influenza A and influenza B
All ages	11.8% (12/102)	20% (2/10)	12.5% (14/112)	25.5% (26/101)	<0.05
5—10 years	50% (7/14)	33.3% (1/3)	47.1% (8/17)	36.1% (13/36)	NS
>10 years	5.7% (5/88)	14.3% (1/7)	6.3% (6/95)	20% (13/65)	<0.01
p (*)	<0.001	NS	<0.001	NS	

p (*): a *p* value between patients aged 5—10 years and over 10 years.

fever from the first inhalation of zanamivir was almost equal (5—10 years) or slightly longer (>10 years or all ages) for patients with influenza B than for patients with influenza A in the 2006—2007 season. There was no significant difference in the duration of fever from the onset or the percentage of patients afebrile at 24 h or 48 h between influenza A and influenza B in all ages. Therefore, the difference in the effectiveness of zanamivir for influenza A and influenza B is considered to be minimal.

In this study, we also performed virus isolation before and after zanamivir therapy and calculated the reisolation rates of influenza A/H3N2, A/H1N1 and B viruses. The reisolation rate of the influenza B virus was almost equal to that of the influenza A virus in patients aged 5—10 years and significantly higher than influenza A in patients >10 years. These findings coincided with the results of the duration of fever from the first inhalation of zanamivir obtained in this study.

The reisolation rate was higher in both of influenza A and influenza B in patients aged 5—10 years. The rate become significantly lower and the duration of fever after zanamivir therapy tended to become shorter in children over 10 years and in adults than in children aged 5—10 years for influenza A. However, the reisolation rate and the duration of fever did not become lower or shorter in children over 10 years or adults for influenza B. This may be because of the immaturity of the immune system in children less than 11 years against both influenza A and B or because there was no or little prior exposure to influenza B in children over 10 years or adults, not only in children under 11 years.

In this study, the reisolation rate after oseltamivir therapy was not analyzed. However, reisolation rate in patients with influenza B of each age group was as follows in our previous study performed in 2003—2004 and 2004 and 2005 seasons; 57.1% in 0—6 years, 69.2% in 7—15 years, 15.4% in 16—64 years, 42.9% in over 64 years and 33.3% in all age groups.[3] Therefore reisolation rate in patients with influenza B seemed to be lower in zanamivir therapy than in oseltamivir therapy.

Cass et al. studied zanamivir deposition in the respiratory tract by pharmacoscintigraphy and reported that local concentrations of zanamivir that result from oral inhalation via the Diskhaler are estimated to be >10 μmol/L throughout the respiratory tract, well in excess of the concentrations observed to inhibit influenza virus neuraminidases by 50% (0.64—7.9 nmol/L).[19] Therefore, in patients with influenza treated with zanamivir, both viral concentration and local concentration of zanamivir are high in the respiratory system, and the effectiveness of zanamivir may be reinforced.

In multiple regression analysis performed for patients with influenza A or B treated with zanamivir or oseltamivir, the duration of fever after the onset was significantly longer in patients with influenza B, in patients who started treatment later, in patients with a high peak body temperature, and in elderly patients. For influenza B, duration of fever was significantly longer in oseltamivir therapy, elderly patients, and patients with a high peak body temperature. We reported in our previous studies that early administration of oseltamivir increases the benefits of influenza treatment, as mentioned by Aoki et al. and Gillissen et al.[20,21] In this study, we confirmed the benefits of early treatment with zanamivir or oseltamivir. Duration of fever from the onset was longer in patients with influenza A treated with zanamivir or oseltamivir over 64 years (51.0 ± 23.4 h in patients less than 65 years and 61.0 ± 35.5 h in patients 65 years or over). A higher peak body temperature may reflect higher viral replication. Also, an association between increased viral number and higher cytokine levels has been reported elsewhere.[22,23]

The ratio of female subjects to male subjects was higher in influenza A and lower in influenza B in this study. In patients with influenza A, the ratio of female for the number of patients in each age group was 44.8% in 5—10 years, 41.0% in 11—20 years and 58.0% in over 20 years groups. And in patients with influenza B, the ratio of female was 43.4% in 5—10 years, 42.3% in 11—20 years and 57.8% in over 20 years. Therefore the ratio of female in each age group was not different between influenza A and B, and was higher in adults aged over 20 years than children less than 21 years. In the 2006—2007 season, influenza B was prevalent in children and influenza A was prevalent in adults, and the ratio of female was higher in influenza A than in influenza B. The large ratio of female in adults was possibly caused by the transmission from family members, especially from children to mother proposed by Hirotsu et al.[24]

In Japan, neuro-psychiatric symptoms possibly caused by oseltamivir therapy have recently been of major concern recently. In this study, neuro-psychiatric symptoms were observed in nine patients with influenza A and two patients with influenza B, however, these symptoms was appeared in four patients before starting oseltamivir therapy. And it seemed to be difficult to establish a cause and effect relationship between oseltamivir or zanamivir therapy without further study. However, neuro-psychiatric symptom observed in this study was not severe and recovered soon.

There is a limit to the findings of our study in that it was performed in a general practice setting and not in the context of a rigorous clinical protocol. By the recent development of antigen detection test kits, it has been easily possible to differentiate influenza A and B. Therefore the decision to use zanamivir or oseltamivir was made by the physician after he knew whether the patient was Influenza A or Influenza B and not simply influenza positive. However, this limitation should not be sufficient to invalidate our findings.

In conclusion, zanamivir is more effective than oseltamivir for the treatment of influenza B. Zanamivir is the most effective neuraminidase inhibitor for the treatment of influenza B in children over four years and adults.

The influenza study group of the Japan Physicians Association: Hideo Kanazawa, Hiroshi Ukai, Ietaka Sato, Ken-ichi Doniwa, Kenichi Kawamura, Ken Takayasu, Kunio Kondou, Mari Wakimoto, Mami Imoto, Midori Yoshimura, Naoki Kawai, Nobuo Hirotsu, Norio Iwaki, Osame Tanaka, Satsuki Horii, Satoshi Yamauchi, Seio Tamai, Shinro Matsuura, Tadashi Ogawa, Takashi Kimura, Takeshi Shigematsu, Tetsunari Maeda, Toku Takahashi, Tomoyuki Harada, Toru Nagai, Tuyoshi Okayama and Yasuhito Yamanishi.

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