Comparison of the Clinical Effectiveness of Oseltamivir and Zanamivir against Influenza Virus Infection in Children

Norio Sugaya,1 Daisuke Tamura,1,a Masahiko Yamazaki,2 Masataka Ichikawa,4 Chiharu Kawakami,2 Yoshihiro Kawaoka,3,5 and Keiko Mitamura6
1Department of Pediatrics, Keiyu Hospital, and 2Yokohama City Institute of Health, Yokohama, 3Zama Children’s Clinic, Zama, 4Ichikawa Children’s Clinic, Ishiara, 5Division of Virology, Department of Microbiology and Immunology and International Center for Infectious Diseases, Institute of Medical Science, University of Tokyo, and 6Department of Pathobiological Sciences, School of Veterinary Medicine, University of Wisconsin, Madison

(See the editorial commentary by Monto on pages 346–8)

Background. We compared the clinical effectiveness of oseltamivir and zanamivir in children with influenza A (H1N1) virus, influenza A (H3N2) virus, and influenza B virus infections.

Methods. Total febrile period and the duration of fever after the start of treatment were compared between an oseltamivir-treated group (mean age, 8.9 years; range, 4.0–15.9 years) and a zanamivir-treated group (mean age, 10.0 years; range, 4.0–15.7 years) in the pediatric outpatient clinics of our hospitals. Oseltamivir was used to treat 91 children with influenza A (H3N2) infection and 24 children with influenza A (H1N1) infection. Zanamivir was used to treat 35 children with influenza A (H3N2) infection and 12 children with influenza A (H1N1) infection. Oseltamivir was also used to treat 128 children with influenza B virus infection, and zanamivir was used to treat 59 with influenza B virus infection.

Results. There was no statistically significant difference in total febrile period or duration of fever after the start of treatment between the oseltamivir-treated group and the zanamivir-treated group of children with influenza A (H1N1) (mean duration of febrile period, 2.60 days vs. 2.46 days; mean duration of fever after the start of treatment, 1.79 days vs. 1.54 days), influenza A (H3N2) (mean duration of febrile period, 2.40 days vs. 2.39 days; mean duration of fever after the start of treatment, 1.35 days vs. 1.40 days), influenza A (H1N1) (mean duration of febrile period, 2.60 days vs. 2.46 days; mean duration of fever after the start of treatment, 1.79 days vs. 1.54 days), or influenza B (mean duration of febrile period, 2.95 days vs. 2.84 days; mean duration of fever after the start of treatment, 1.86 days vs. 1.67 days). Oseltamivir was more effective against influenza A (H3N2) than against influenza A (H1N1) or influenza B.

Conclusions. Oseltamivir and zanamivir were equally effective in reducing the febrile period of children with influenza A (H1N1), influenza A (H3N2), and influenza B virus infection.

More than 70% of the total amount of oseltamivir prescribed throughout the world each year is used in Japan [1]. Most patients in Japan with an influenza-like illness are now tested with rapid diagnostic tests; when results are positive, they are treated with a neuraminidase inhibitor, usually oseltamivir [1].

Although oseltamivir is widely used in Japan, there have been several recent negative reports. First, there have been reports that oseltamivir-resistant mutants arise more frequently than should be expected. We isolated resistant influenza A (H3N2) virus from 18% of specimens obtained from young children treated with oseltamivir [2], and we isolated influenza B virus with reduced susceptibility to oseltamivir from 1.4% of specimens obtained from children treated with oseltamivir [3]. Second, we reported that oseltamivir is much less effective against influenza B virus than against influenza A (H3N2) in young children, probably because of the
low susceptibility of influenza B virus to oseltamivir [1].

Moreover, neuropsychiatric adverse reactions that may be attributable to oseltamivir have become a cause of concern in Japan [4]. Although it is unknown whether there was a causal relationship between oseltamivir treatment and patient behavior, there have been reports of 27 cases in which a patient with influenza who was being treated with oseltamivir jumped from a building: 22 of these patients were teenagers, and 6 of them died. As a result, in March 2007, the Health, Labor, and Welfare Ministry of Japan issued an emergency instruction to suspend the use of oseltamivir for the treatment of patients aged 10–19 years [5]. Accordingly, zanamivir will be prescribed widely for teenage patients with influenza.

Since 2006, another neuraminidase inhibitor, zanamivir, has been approved in Japan for the treatment of influenza in children >5 years of age. A mixed epidemic caused by influenza A/New Caledonia/20/99 (H1N1) and influenza A/Wisconsin/67/2005 (H3N2) occurred in Japan during the 2005–2006 season [6]; during the 2006–2007 season, influenza A/Wisconsin/67/2005 (H3N2) and influenza B/Malaysia/2506/2004 (Victoria strain) were the main epidemic strains [7]. During those 2 epidemics, we compared the effectiveness of oseltamivir and zanamivir against influenza A (H1N1), influenza A (H3N2), and influenza B virus infection on the basis of the duration of the febrile period, and we monitored viral shedding after the start of neuraminidase inhibitor therapy.

**PATIENTS AND METHODS**

**Patients**

*Clinical effectiveness.* Choice of neuraminidase inhibitors was based on patients’ or parents’ wishes, in most cases. In some cases, the choice was based on patients’ clinical manifestations, such as vomiting or wheezing. We used oseltamivir to treat 115 children with influenza A in the pediatric outpatient clinic of our hospitals, and we used zanamivir to treat 47 children with influenza A. Of the 115 patients in the oseltamivir group, 91 had influenza A (H3N2) infection and 24 had influenza A (H1N1) infection. Of the 47 patients in the zanamivir group, 35 had influenza A (H3N2) infection and 12 had influenza A (H1N1) infection. We used oseltamivir to treat 128 children with influenza B, and we used zanamivir to treat 59 children with influenza B (table 1).

All of the patients arrived at our hospital with a temperature of ≥38.0°C within 48 h after the onset of a febrile illness, and all of them were tested with rapid diagnostic tests (Espline Influenza A&B-N; Fujirebio) and received a diagnosis of influenza A or influenza B before the start of oseltamivir or zanamivir therapy. The diagnoses were later confirmed by virus isolation.

Oseltamivir was prescribed in weight-based unit doses to be administered in divided doses twice per day for 5 days (weight <15 kg, 60 mg per day; weight 15–23 kg, 90 mg per day; weight 23–40 kg, 120 mg per day; weight >40 kg, 150 mg per day). Zanamivir was inhaled from a DiskHaler twice per day (total daily dose, 20 mg) for 5 days.

Parents were instructed to take their children’s temperature twice daily, in the morning and in the evening, and to record it on a fever record sheet that we prepared. The record sheet was returned to us on the day of the final visit. When a patient’s temperature decreased to 37.5°C and remained there for 2 more measurements, we considered the patient’s fever to have resolved.

*Virus isolation rate and virus shedding.* To determine the virus isolation rate of the influenza A virus, throat swab specimens were obtained on 3 occasions: before the start of neuraminidase inhibitor therapy (the first day of treatment), on the third day of treatment, and on the fifth day of treatment.

We analyzed the virus isolation rate of influenza A (H3N2) virus in 20 patients treated with oseltamivir (mean age ± SD, 6.9 ± 2.4 years; range, 4.0–13.1 years) and in 18 patients treated with zanamivir (mean age ± SD, 8.5 ± 3.0 years; range 4.0–15.0 years). We analyzed the virus isolation rate of influenza A (H1N1) virus in a group of 7 patients treated with oseltamivir (mean age ± SD, 4.7 ± 0.8 years; range, 4.0–6.6 years) and 7 patients treated with zanamivir (mean age ± SD, 7.5 ± 1.0 years; range, 6.2–8.0 years).

Virus shedding was measured as changes in infection titers in specimens from the throats of patients with influenza A (H3N2) and influenza A (H1N1) infection who were treated with oseltamivir and zanamivir. Virus infectivity titers are expressed as log10 plaque-forming units/mL.

**Methods**

*Virus isolation and titration.* Clinical specimens (throat swabs) that were found to be virus-positive by use of rapid diagnostic kits were stored at -80°C until virus isolation. Madin-Darby canine kidney cells were used for viral isolation and plaque assay. Viruses were subtyped by conventional hemagglutinin- and neuraminidase-inhibition assays.

*Plaque assay.* A modified plaque-forming assay was used [8]. Monolayer cell cultures of Madin-Darby canine kidney cells in 6 wells were infected with 10-fold serial dilution of the clinical sample. After adsorbing at 35°C in 5% carbon dioxide for 1 h, the infected cells were overlaid with 2% agarose-minimal essential medium and were incubated at 35°C in 5% carbon dioxide for 3 days. After being fixed with 10% formalin, the plaques were stained with crystal violet.

*Statistical methods.* We used Student’s t test for all statistical comparisons of mean values, and we used the χ² test to evaluate differences of fever duration in patients with influenza. Data are expressed as mean values (± SD).

Verbal informed consent was obtained from each child’s par-
Table 1. Comparison of the effectiveness of oseltamivir and zanamivir against influenza virus infection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Finding by influenza type and treatment</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
<th>Oseltamivir</th>
<th>Zanamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years ± SD (range)</td>
<td></td>
<td>6.4 ± 2.2 (4.0–12.0)</td>
<td>8.1 ± 2.1 (6.0–13.7)</td>
<td>8.0 ± 3.1 (4.0–15.9)</td>
<td>9.7 ± 3.3 (4.0–15.7)</td>
<td>9.9 ± 3.1 (4.0–15.5)</td>
<td>10.6 ± 2.8 (4.5–15.5)</td>
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<tr>
<td>Total febrile period, mean no. of days (range)</td>
<td></td>
<td>2.60 ± 0.81 (1.5–4.0)</td>
<td>2.46 ± 0.72 (1.5–3.5)</td>
<td>2.40 ± 0.81 (1.0–4.5)</td>
<td>2.39 ± 0.95 (1.0–5.5)</td>
<td>2.95 ± 1.17 (1.0–5.5)</td>
<td>2.84 ± 1.06 (1.5–5.0)</td>
</tr>
<tr>
<td>Duration of fever after the start of therapy, mean days ± SD (range)</td>
<td></td>
<td>1.79 ± 0.79 (0.5–3.5)</td>
<td>1.54 ± 0.62 (0.5–2.5)</td>
<td>1.36 ± 0.78 (0.5–4.0)</td>
<td>1.40 ± 0.75 (0.5–3.5)</td>
<td>1.86 ± 1.08 (0.5–5.0)</td>
<td>1.67 ± 1.00 (0.5–4.0)</td>
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<td>No. (%) of patients with normal body temperature</td>
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<td></td>
</tr>
<tr>
<td>Within 24 h after start of treatment</td>
<td></td>
<td>8 (33.3)</td>
<td>4 (33.3)</td>
<td>51 (56.0)</td>
<td>18 (51.4)</td>
<td>49 (38.3)</td>
<td>25 (42.4)</td>
</tr>
<tr>
<td>Within 48 h after start of treatment</td>
<td></td>
<td>19 (79.2)</td>
<td>10 (83.3)</td>
<td>85 (83.4)</td>
<td>31 (88.6)</td>
<td>91 (71.1)</td>
<td>46 (78.0)</td>
</tr>
</tbody>
</table>
ent or guardian and was recorded on the chart. Informed consent was also obtained from children >7 years of age who were able to understand the concepts and procedures of the protocol. This study was conducted with the approval of the ethics committees of our hospitals.

RESULTS

Comparison of the effectiveness of oseltamivir and zanamivir against influenza A (H3N2). There was no statistically significant difference in total febrile period or duration of fever after the start of treatment between the patients treated with oseltamivir and the patients treated with zanamivir. During the 2006–2007 epidemic, there were 8 patients with influenza A (H3N2) infection who did not receive treatment with any antiviral agents (mean age ± SD; 10.6 ± 2.6 years; range, 4.9–14.2 years), and their mean total febrile period (± SD) was 4.31 ± 2.07 days. Thus, the total febrile period was shortened by ~2 days in both the group treated with oseltamivir (P < .05) and the group treated with zanamivir (P < .05).

In both groups, the body temperature of approximately one-half of the patients returned to normal within 24 h, and in ~90%, the body temperature returned to normal within 48 h (table 1). There were no statistically significant differences in the percentages between the groups.

Comparison of the effectiveness of oseltamivir and zanamivir against influenza A (H1N1). There was no statistically significant difference in total febrile period or the duration of fever after the start of treatment between the group treated with oseltamivir and the group treated with zanamivir. In both groups, the body temperature of one-third of the patients returned to normal within 24 h, and the body temperature of ~80% of the patients returned to normal within 48 h. The differences between the groups was not statistically significant.

Comparison of the effectiveness of oseltamivir and zanamivir against influenza B. There was no statistically significant difference in total febrile period or duration of fever after the start of treatment between the group treated with oseltamivir and the group treated with zanamivir. During the 2006–2007 epidemic, there were 47 patients with influenza B virus infection who did not receive treatment with any antiviral agents (mean age ± SD; 9.8 ± 3.0 years; range, 4.3–13.4 years), and their mean total febrile period (± SD) was 4.02 ± 1.26 days. Thus, the total febrile period was shortened by ~1 day in both the group treated with oseltamivir (P < .01) and the group treated with zanamivir (P < .01).

In both groups, body temperature returned to normal within 24 h in ~40% of patients and within 48 h in 70%–80% of patients. There were no statistically significant differences in the percentages between the groups.

Effectiveness of oseltamivir against influenza A (H1N1), influenza A (H3N2), and influenza B virus. Among the patients treated with oseltamivir, the duration of fever after the start of treatment was significantly shorter in patients with influenza A (H3N2) infection than in patients with influenza A (H1N1) infection (mean duration, 1.35 days vs. 1.79 days; P < .05) or in patients with influenza B (mean duration, 1.35 days vs. 1.86 days; P < .01) (table 1). The total febrile period was statistically significantly shorter in patients with influenza A (H3N2) virus infection than in patients with influenza B (mean duration, 2.40 days vs. 2.95 days; P < .01), and it was shorter, although the difference was not statistically significant, in patients with influenza A (H3N2) infection than in patients with influenza A (H1N1) infection (mean duration, 2.40 days vs. 2.60 days).

The percentages of patients whose temperature became normal were statistically significantly higher among patients with influenza A (H3N2) infection than among patients with influenza A (H1N1) infection (within 24 h, 56.0% vs. 33.3% [P < .05]; within 48 h, 93.4% vs. 79.2% [P < .05]) or patients with influenza B (within 24 h, 56.0% vs. 38.3% [P < .01]; within 48 h, 93.4% vs. 71.1% [P < .01]) (table 1). The total febrile period and duration of fever after the start of treatment were shorter among patients with influenza A (H1N1) infection than among patients with influenza B, although the difference was not statistically significant.

Effectiveness of zanamivir against influenza A (H1N1), influenza A (H3N2), and influenza B. Among the patients treated with zanamivir, there was no statistically significant difference between patients with influenza A (H1N1) and patients with influenza A (H3N2) with regard to total febrile period or the duration of fever after the start of treatment (table 1). However, the total febrile period was statistically significantly shorter among patients with influenza A (H3N2) infection than among patients with influenza B (2.39 days and 2.84 days, respectively; P < .05), and the duration of fever after the start of treatment was also shorter among patients with influenza A (H3N2) than among patients with influenza B, but the difference in duration of fever was not statistically significant.

There was no statistically significant difference between the patients whose temperature became normal within 24 h and those whose temperature became normal within 48 h. However, the percentages for both groups were higher for patients with influenza A (H3N2) infection than for patients with influenza A (H1N1) infection or patients with influenza B (table 1).

Influenza A (H3N2) virus isolation rate after the start of neuraminidase inhibitor therapy. On the first day of treatment, influenza A (H3N2) virus was detected in throat specimens obtained from every patient (100%). On the third day of treatment, there was no statistically significant difference between the virus isolation rate in the group treated with oseltamivir and the rate in the group treated with zanamivir. However, on the fifth day of treatment, the isolation rate in
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**Figure 1.** Virus shedding by patients with influenza A (H3N2) infection

**Figure 2.** Changes in virus shedding by patients with influenza A (H1N1) infection

<table>
<thead>
<tr>
<th>Influenza virus and treatment</th>
<th>Patient age, mean years ± SD (range)</th>
<th>Proportion (%) of patients with virus isolation on third day of treatment</th>
<th>Proportion (%) of patients with virus isolation on fifth day of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (H3N2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>6.9 ± 2.4 (4.1–13.1)</td>
<td>10/16 (62.5)</td>
<td>7/17 (41.2)</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>8.5 ± 3.0 (4.2–15.0)</td>
<td>10/17 (58.8)</td>
<td>1/16 (6.3)</td>
</tr>
<tr>
<td>A (H1N1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>4.7 ± 0.8 (4.0–6.6)</td>
<td>7/7 (100)</td>
<td>2/6 (33.3)</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>7.5 ± 1.0 (6.2–8.0)</td>
<td>5/7 (71.4)</td>
<td>3/7 (42.9)</td>
</tr>
</tbody>
</table>

Influenza A (H1N1) virus isolation rate after the start of neuraminidase inhibitor therapy. Influenza A (H1N1) virus persisted in throat specimens obtained from a high percentage of the patients after the start of treatment, although the total number of patients was small. Even on the fifth day of treatment, the isolation rate was 30%–40% in both the group treated with oseltamivir and the group treated with zanamivir (table 2).

Changes in virus shedding by patients with influenza A (H3N2) infection. Before neuraminidase inhibitor therapy was initiated (i.e., on day 1), mean infection titer (± SD) was similar—4.23 ± 0.67 in the group treated with oseltamivir (20 patients) and 4.10 ± 0.98 in the group treated with zanamivir (18 patients) (figure 1). After the start of therapy, the virus titers of the specimens from both treatment groups decreased rapidly. On the third day of treatment, the mean virus titers (± SD) in the group treated with oseltamivir (15 patients) and the group treated with zanamivir (17 patients) were almost the same (1.21 ± 1.17 vs. 1.20 ± 1.25, respectively). On the fifth day of treatment, the group treated with oseltamivir (17 patients) had a statistically significantly higher infection titer than did the group treated with zanamivir (16 patients) (0.76 ± 1.08 vs. 0.07 ± 0.29; P < .05). On the fifth day of treatment, 15 of the 16 patients in the group treated with zanamivir did not shed viruses.

Changes in virus shedding by patients with influenza A (H1N1) infection. Before neuraminidase inhibitor therapy was initiated (i.e., on day 1), mean virus infectivity (± SD) was 4.25 ± 0.58 in the oseltamivir group (7 patients) and was 3.80 ± 0.93 in the group treated with zanamivir (7 patients). After the start of treatment, there was no statistically significant difference between the group treated with oseltamivir and the group treated with zanamivir (mean virus infectivity ± SD on the third day of treatment, 1.56 ± 1.02 [7 patients] vs. 1.77 ± 1.77 [6 patients]; mean virus infectivity ± SD on the fifth day of treatment, 1.18 ± 0.10 [6 patients] vs. 1.39 ± 0.18 [7 patients]) (figure 2).

DISCUSSION

To our knowledge, this is the first study to compare the clinical effectiveness of oseltamivir with that of zanamivir against influenza virus infection in children. The comparison between the oseltamivir-treated group and the zanamivir-treated group in this study confirmed that both neuraminidase inhibitors—oseltamivir and zanamivir—are equally effective in reducing the febrile period of children with influenza A (H1N1), influenza A (H3N2), and influenza B infection (table 1). However, the results showed that oseltamivir had lower clinical effectiveness against influenza A (H1N1) than against influenza A (H3N2). Among patients with influenza A who were treated with oseltamivir, the duration of fever after the start of treatment was significantly longer for patients with influenza A (H1N1) infection, and the percentage of patients who became afebrile was statistically significantly lower for the patients with influenza A (H1N1) infection (table 1). These results were obtained in a double-blind fashion; the diagnosis of influenza A was based on the results of rapid diagnostic tests, so neither the patients nor the pediatricians knew whether the patients had influenza A (H1N1) or influenza A (H3N2) infection.
We have reported elsewhere the finding that oseltamivir is less effective against influenza B infection than it is against influenza A (H3N2) infection [1], and lower effectiveness of oseltamivir against influenza B was confirmed in the present study (table 1). Thus, the present study demonstrated that oseltamivir is clinically more effective against influenza A (H3N2) infection than it is against influenza A (H1N1) or influenza B virus infection. No statistically significant difference was found between oseltamivir’s effectiveness against influenza A (H1N1) infection and its effectiveness against influenza B.

Zanamivir has been reported to be equally effective against influenza A and influenza B [9]. However, we found a statistically significantly shorter total febrile period in patients with influenza A (H3N2) infection than in patients with influenza B infection (table 1). Zanamivir is probably less effective against influenza B than it is against influenza A (H3N1) infection, as is the case with oseltamivir. Zanamivir was also less effective against influenza A (H1N1) infection than it was against influenza A (H3N2) infection, although the difference was not statistically significant (table 1).

The effectiveness of neuraminidase inhibitors is basically determined by the susceptibility (IC50) of influenza viruses [1]. Our results for the clinical effectiveness of oseltamivir apparently reflect the reported oseltamivir IC50 values for influenza viruses: 0.3 nmol/L for influenza A (H3N2) [2], 0.66 nmol/L [10] and 1.34 nmol/L [11] for influenza A (H1N1), and 75.4 nmol/L for influenza B [1].

Although there have been small differences in the reported susceptibility (IC50) of influenza A (H1N1) virus to zanamivir—for example, 0.37 nmol/L [10] and 0.92 nmol/L [11] for influenza A (H1N1) virus and 1.6 nmol/L [3] for influenza A (H3N2) virus—because the concentration of zanamivir in the respiratory tract is much higher [12], differences in IC50 values may not be evident. On the other hand, there was a significant difference in the total febrile period between patients with influenza A (H3N2) infection and patients with influenza B, probably because of much lower susceptibility of influenza B virus to zanamivir (10.1 nmol/L) [3].

The isolation rate of influenza A (H3N2) virus from the throat on the fifth day of treatment was statistically significantly higher in the oseltamivir-treated group than in the zanamivir-treated group (43.8% vs. 6.3%), suggesting that zanamivir is more effective than oseltamivir in clearing influenza A (H3N2) virus from the respiratory tract. Because influenza A (H3N2) virus is more susceptible to oseltamivir than to zanamivir (0.3 nmol/L [2] vs. 1.6 nmol/L [3]), the difference in isolation rate of influenza A (H3N2) virus between the oseltamivir-treated group and the zanamivir-treated group is probably attributable to the higher concentration of zanamivir in the respiratory tract [12].

It is unknown whether the influenza viruses at such low infection titers as 0.76 plaque-forming units/mL in the oseltamivir-treated group on the fifth day of treatment are capable of causing infection in others (figure 1). However, prolonged viral shedding is an indispensable factor for induction of resistance to oseltamivir, because oseltamivir-resistant strains emerge 3–5 days after the start of therapy [2, 3]. Even on the fifth day of treatment, influenza A (H3N2) virus was isolated from throat specimens obtained from 41.2% of the oseltamivir-treated patients in this study, whereas most subjects in the zanamivir-treated group had no virus isolated from throat specimens on day 5. We found that influenza A (H3N2) developed resistance to oseltamivir easily. In contrast, we did not detect influenza A (H3N2) viruses that were resistant to zanamivir. A detailed analysis of strains that are resistant to oseltamivir and zanamivir will be reported elsewhere.

There was no statistically significant difference in the isolation rate of influenza A (H1N1) virus between the oseltamivir-treated group and the zanamivir-treated group (table 2), and viral shedding persisted in both groups, which possibly led to resistance or lower susceptibility to both neuraminidase inhibitors (figure 2). Because of the small number of patients, more data will be needed before the clinical implications of this finding become clear.

In conclusion, we compared the clinical effectiveness of oseltamivir and zanamivir in children with influenza and found that both neuraminidase inhibitors were equally effective in reducing the febrile period in influenza A (H1N1), influenza A (H3N2), and influenza B virus infection.

Acknowledgments

Potential conflicts of interest. N.S. has received a travel grant from Roche to attend meetings on avian influenza, has received a speaker’s honorarium from Daiichi Sankyo, and is currently conducting studies evaluating compounds from Daiichi Sankyo. Y.K. is a recipient of speakers’ honoraria for scientific presentations from Chugai Pharmaceutical, Novarlis, Daiichi Sankyo, Toyama Chemical, and Wyeth; is conducting studies evaluating compounds from Daiichi Sankyo; and is cofounder of FluGen. All other authors: no conflicts.

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References