Impact of Zanamivir on Antibiotic Use for Respiratory Events Following Acute Influenza in Adolescents and Adults

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Background: Influenza infections commonly lead to respiratory tract complications that result in antibiotic treatment.

Objectives: To determine frequency of respiratory events leading to antibiotic use following influenza illness in adolescents and adults, and to assess whether treatment with topical zanamivir prevents these complications.

Methods: Meta-analysis of 7 randomized, double-blind, placebo-controlled trials; 3815 mainly healthy adolescents and adults (mean age, 34 years) with an influenza-like illness of less than 2 days’ duration were randomly assigned to receive combined inhaled and intranasal zanamivir, inhaled zanamivir, or corresponding placebos. Twelve percent of enrolled subjects were high-risk patients. The main outcome was the incidence of respiratory events leading to antibiotic prescriptions in patients with proven influenza.

Results: Influenza infections were laboratory confirmed in 2499 (66%) of 3815 patients (influenza A in 88% and B in 12%). Placebo recipients developed a respiratory event leading to antibiotic use in 17% of cases, mainly for acute bronchitis or acute sinusitis. Among zanamivir-treated patients (n=1494) the incidence of respiratory events leading to the use of antimicrobials was 11% (relative risk [RR] compared with placebo, 0.69; 95% confidence interval [CI], 0.57-0.84). Intranasal and inhaled zanamivir seemed to reduce the number of upper (RR, 0.59; 95% CI, 0.36-0.97) and lower respiratory tract events (RR, 0.64; 95% CI, 0.38-1.08). Inhaled zanamivir reduced the number of lower respiratory tract events (RR, 0.60; 95% CI, 0.42-0.85), but the reduction in the number of upper respiratory tract events was not statistically significant (RR, 0.90; 95% CI, 0.63-1.27).

Conclusions: Respiratory complications or worsening of symptoms leading to antibiotic use occurred in about 17% of adolescents or adults with influenza infection. Early treatment of influenza illness with zanamivir reduced the number of these antibiotic prescriptions.

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PATIENTS AND METHODS

STUDY SELECTION

All phase II and phase III studies testing the efficacy of combined inhaled and intranasal zanamivir or intranasal zanamivir alone in the treatment of community-acquired influenza illness were considered. Our analysis included only double-blind, placebo-controlled, randomized studies performed before or during the 1997-1998 winter season and in which incidence of antibiotic prescriptions was monitored. A total of 11 phase II and/or III studies for treatment of influenza were performed; 2 pilot studies using nebulized zanamivir and 2 studies performed exclusively in Japan with different designs and databases were excluded from our analysis. Thus, 4 phase II studies11-13 and 3 phase III studies10,14,15 representing 93% of patients included in all phase II and III studies met our inclusion criteria and were included in this analysis.

PATIENTS

Patients enrolled in these studies were at least 12 years old and had an influenza-like illness with symptom duration shorter than 2 calendar days during periods of influenza virus circulation in the community. Subjects enrolled were mainly healthy adolescents and adults; only 12% were considered high-risk subjects (defined as subjects 65 years or older or those with a chronic illness, including cardiopulmonary conditions and diabetes). An influenza-like illness was defined by the presence of fever or feverishness with at least 2 additional symptoms (cough, sore throat, headache, or myalgia). Three studies required that patients have a temperature of 37.8°C or higher (>37.2°C for patients 65 years or older). For other studies, the subjective experience of feverishness was sufficient. At entry, a medical history was obtained, a physical examination was performed, and patients recorded their symptoms on a diary card. Influenza infection was documented by viral culture, antigen detection, and/or reverse transcription polymerase chain reaction for viral RNA on nasopharyngeal specimens and paired acute and convalescent serum hemagglutination-inhibition antibody assays. A positive result on at least 1 test was considered a laboratory-confirmed influenza illness. Patients were required to return for a posttreatment visit 3 days after starting treatment and for an end-of-study visit after 21 or 28 days. In all studies, investigators collected data prospectively on antibiotic use. No specific instructions were given for antibiotic indications or type, and antibiotics were prescribed when deemed necessary by investigators. For the 3 phase III trials and 2 of the phase II trials, antibiotic use for complications of influenza was prospectively defined as a secondary endpoint. For 1 trial, the investigators specifically recorded whether the patient was prescribed an antibiotic for an influenza complication. For the remaining trial, the indications for use of all antibiotics were reviewed and classified as influenza complications or other illness by a physician unaware of treatment assignments.

Treatment in phase II trials consisted of combined intranasal (6.4 mg, 2 or 4 times daily) and intranasal zanamivir (10 mg, 2 or 4 times daily) or intranasal zanamivir alone for 5 days. To maintain the blinding in these trials, placebo and zanamivir recipients had both intranasal sprays and drug powder in inhalation. Patients enrolled in the treatment groups in phase III trials received 10 mg of intranasal zanamivir twice daily for 5 days or corresponding placebo. The respective numbers of placebo recipients and zanamivir-treated patients enrolled in each study (as well as the route of administration) are given in Table 1.

MEASUREMENTS

The primary end point for this analysis was the occurrence of at least 1 of the following events during the follow-up period in a patient with a laboratory-confirmed influenza illness: (1) any upper or lower respiratory tract event leading to an antibiotic prescription; (2) worsening of initial symptoms leading to antibiotic prescription; or (3) an antibiotic prescribed to prevent bacterial complications. For the purpose of this analysis respiratory events were categorized under blinded conditions based on the information available in the case report forms and the recorded adverse experience reports. Upper respiratory events were defined as acute bronchitis (including tracheobronchitis, productive cough with colored sputum, or persistent cough), or pneumonia (including bronchopneumonia). When patients experienced 2 or more events, the events were included in the tabulations of complication type.

STATISTICAL ANALYSIS

The incidence of the first respiratory event leading to antibiotic use was compared between treatments using a Mantel-Haenszel test, with the analysis stratified by study. For patients experiencing more than 1 event, only the first event was considered in this analysis. Statistical tests were performed at the 2-sided 5% level of significance, and corresponding estimates of relative risks and 95% confidence intervals (CIs) were also calculated. Time to first complication was also compared using a log-rank test.

The effect of inhaled and intranasal zanamivir treatment was compared with placebo across trials that included a treatment arm of combined inhaled and intranasal drug. Similarly, inhaled zanamivir alone was compared with placebo in trials that included a treatment arm of inhaled zanamivir alone.

Interaction tests were performed to assess whether the efficacy of zanamivir varied across subgroups. These tests compared all placebo patients with all zanamivir patients using an exact test for homogeneity of odds ratios (ORs) across strata.
PATIENTS

Seven clinical trials enrolling 3815 patients met our inclusion criteria and were studied. These analyses were performed during the fall and winter seasons between 1994 and 1998 in North America, Europe, or in the Southern Hemisphere. Six of the 7 trials included a treatment arm of inhaled zanamivir, while 4 trials included a treatment arm of combined inhaled and intranasal drug. Three of the 7 trials included both of these treatment arms (Table 1). Among the 3815 patients enrolled, 2499 (66%) had a laboratory-confirmed influenza infection; 687 (27%) were randomized to receive inhaled and intranasal zanamivir; 807 (32%), inhaled zanamivir; and 1005 (40%), placebo. The mean age of patients was 34 years; 50% were male, and 12% were considered high-risk patients (suffering from a chronic illness or older than 65 years). The mean duration of influenza illness from the onset of symptoms to enrollment was 29 hours.

OUTCOMES AND EFFECT OF TREATMENT

Among the 2499 patients with laboratory-confirmed influenza illness, respiratory events leading to antibiotic use occurred in 172 (7%) of 1005 placebo recipients. Twenty-five percent of these patients experienced their first events within 3 days, 50% within 5 days, and 75% within 10 days. Of the placebo recipients who presented a respiratory event leading to antibiotic prescription, 43% had acute bronchitis, 25% acute sinusitis, 10% pharyngitis, 9% ear infections, and 8% pneumonia. An additional 10% of patients received antibiotics for worsening of initial symptoms (without a specific diagnosis) or ostensibly to prevent bacterial complications.

Respiratory events leading to antibiotic use occurred in 167 (11%) of 1494 zanamivir recipients with confirmed influenza illness (RR compared with 17% placebo (0.69; 95% CI, 0.57-0.84; P < .001). This difference corresponds to a 31% reduction of antibiotic prescriptions in zanamivir recipients. Among the 1316 patients with influenzalike illness, but without confirmed influenza infection, the incidence of respiratory events leading to antibiotic prescriptions was 15% in both placebo (80/519) and zanamivir (120/797) recipients (RR, 1.0; 95% CI, 0.77-1.30; P > .9). The effect in zanamivir recipients was significantly associated with the presence of a laboratory-confirmed influenza infection (test of interaction between the influenza-positive and influenza-negative population, P = .02).

Among 339 patients with confirmed influenza and respiratory events leading to antibiotic prescriptions, 8 (2.4%) were hospitalized after initiation of study drug treatment. Five of these 8 hospitalizations were related to a respiratory event: pneumonia in 4 cases, and an acute sinusitis with pleuritis in 1. Four of these 5 patients were placebo recipients and 1 received inhaled zanamivir. The other 3 hospitalizations were for non–influenza-related events (appendicitis in 2 cases, post–antibiotic colitis in 1).

EFFECT OF ROUTE OF ADMINISTRATION

In the 4 trials that included combined inhaled and intranasal drug therapy, the incidence of respiratory events leading to antibiotic prescription was 15% in placebo recipients compared with 9% in zanamivir recipients (P = .003) (Figure 1A). In the 6 trials that included a treatment arm of inhaled zanamivir alone, this incidence of complications was 18% in placebo recipients and...
13% in zanamivir recipients (P = .006). Corresponding reductions were seen in time to first complication (Figure, P = .001 for combined inhaled and intranasal compared with placebo; P = .005 for inhaled alone compared with placebo). Of note, the rise in events around day 6 coincided with the patients’ posttreatment visits.

Combined intranasal and inhaled zanamivir seemed to reduce both upper (RR, 0.59; 95% CI, 0.36-0.97) and lower respiratory tract events (RR, 0.64; 95% CI, 0.38-1.08) (Table 2). Inhaled zanamivir treatment reduced lower respiratory tract illness (RR, 0.60; 95% CI, 0.42-0.85), but the reduction in upper respiratory tract events was smaller and not statistically significant (RR 0.90; 95% CI, 0.63-1.27) (Table 3).

### SUBGROUP ANALYSIS

We assessed whether the size of the effect was consistent across subgroups (Table 4 and Table 5). The largest differences in efficacy were for influenza subtype and patient sex. However, the P values for interaction tests comparing all zanamivir recipients with corresponding placebo recipients were P = .41 for female vs male patients and P = .72 for influenza A infection vs influenza B. Neither of these values was significant, indicating that in the studied population zanamivir effect was not limited to a subgroup of patients.

### ANTIBIOTICS

Antibiotics prescribed were penicillins in 41% of cases, macrolides in 25%, cephalosporins in 21%, tetracyclines in 9%, sulfonamides in 4%, and other (including quinolones) in 6%. There were no differences in the patterns of specific antibiotic use between zanamivir and placebo recipients.

### COMMENT

Our results showed that in a largely healthy population of ambulatory adolescents and adults developing acute...
Table 4. Patients With Proven Influenza Illness and Treated With Combined Inhaled and Intranasal Drug: Incidence of Respiratory Complications Leading to Antibiotic Prescriptions According to Risk Groups*  

<table>
<thead>
<tr>
<th>Subgroup Characteristic</th>
<th>Placebo Intranasal and Inhaled†</th>
<th>Zanamivir Intranasal and Inhaled</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With influenza A‡</td>
<td>62/380 (16)</td>
<td>52/604 (9)</td>
<td>0.54 (0.38-0.77)</td>
</tr>
<tr>
<td>With influenza B§</td>
<td>6/59 (10)</td>
<td>8/74 (11)</td>
<td>1.10 (0.44-2.75)</td>
</tr>
<tr>
<td>Males</td>
<td>24/220 (11)</td>
<td>25/334 (7)</td>
<td>0.71 (0.42-1.21)</td>
</tr>
<tr>
<td>Females</td>
<td>44/227 (19)</td>
<td>37/335 (10)</td>
<td>0.56 (0.37-0.84)</td>
</tr>
<tr>
<td>Aged 50 or over</td>
<td>9/57 (16)</td>
<td>10/85 (12)</td>
<td>0.84 (0.38-1.87)</td>
</tr>
<tr>
<td>Aged less than 50</td>
<td>59/390 (15)</td>
<td>52/602 (9)</td>
<td>0.58 (0.41-0.83)</td>
</tr>
<tr>
<td>Smokers (current)</td>
<td>13/104 (13)</td>
<td>13/168 (8)</td>
<td>0.71 (0.36-1.41)</td>
</tr>
<tr>
<td>Non smokers</td>
<td>55/534 (16)</td>
<td>49/519 (9)</td>
<td>0.60 (0.41-0.86)</td>
</tr>
<tr>
<td>Vaccinated§</td>
<td>3/9 (33)</td>
<td>1/10 (10)</td>
<td>0.30 (0.04-2.28)</td>
</tr>
<tr>
<td>Not vaccinated§</td>
<td>54/349 (15)</td>
<td>54/589 (9)</td>
<td>0.63 (0.44-0.90)</td>
</tr>
<tr>
<td>High-risk patients</td>
<td>9/57 (16)</td>
<td>10/70 (14)</td>
<td>0.89 (0.39-2.05)</td>
</tr>
<tr>
<td>Non–high-risk patients</td>
<td>59/390 (15)</td>
<td>52/617 (8)</td>
<td>0.58 (0.41-0.83)</td>
</tr>
<tr>
<td>Baseline temperature ≥38.3°C</td>
<td>22/126 (17)</td>
<td>17/186 (9)</td>
<td>0.51 (0.28-0.91)</td>
</tr>
<tr>
<td>Baseline temperature &lt;38.3°C</td>
<td>46/320 (14)</td>
<td>44/495 (9)</td>
<td>0.65 (0.44-0.97)</td>
</tr>
<tr>
<td>Duration of symptoms ≤24 h</td>
<td>27/170 (16)</td>
<td>24/262 (9)</td>
<td>0.60 (0.36-0.99)</td>
</tr>
<tr>
<td>Duration of symptoms &gt;24 h</td>
<td>41/277 (15)</td>
<td>38/425 (9)</td>
<td>0.62 (0.40-0.94)</td>
</tr>
<tr>
<td>All patients</td>
<td>68/447 (15)</td>
<td>62/887 (9)</td>
<td>0.61 (0.44-0.85)</td>
</tr>
</tbody>
</table>

* Unless otherwise indicated, data are number of subjects/number of subjects in subgroup (percentage). RR indicates relative risk; CI, confidence interval.  
† Placebo recipients from the 4 trials that included a treatment arm of intranasal and inhaled zanamivir.  
‡ Seventeen patients had undetermined subtype.  
§ Patients in Hayden et al12 were nonvaccinated.  
¶ Baseline temperature missing for 7 patients.  
* Duration of symptoms not collected in hours in Lalezari et al.14  
# P = .003.

Table 5. Patients With Proven Influenza Illness and Treated With Inhaled Drug: Incidence of Respiratory Complications Leading to Antibiotic Prescriptions According to Risk Groups  

<table>
<thead>
<tr>
<th>Subgroup Characteristic</th>
<th>Placebo†</th>
<th>Zanamivir Inhaled</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With influenza A‡</td>
<td>117/651 (18)</td>
<td>87/691 (13)</td>
<td>0.71 (0.55-0.91)</td>
</tr>
<tr>
<td>With influenza B§</td>
<td>22/108 (20)</td>
<td>18/112 (16)</td>
<td>0.77 (0.45-1.34)</td>
</tr>
<tr>
<td>Males</td>
<td>59/378 (16)</td>
<td>56/437 (13)</td>
<td>0.81 (0.58-1.13)</td>
</tr>
<tr>
<td>Females</td>
<td>80/380 (21)</td>
<td>49/370 (13)</td>
<td>0.65 (0.47-0.90)</td>
</tr>
<tr>
<td>Aged 50 or over</td>
<td>34/146 (23)</td>
<td>23/117 (20)</td>
<td>0.86 (0.54-1.38)</td>
</tr>
<tr>
<td>Aged less than 50</td>
<td>105/619 (17)</td>
<td>82/660 (12)</td>
<td>0.71 (0.49-0.92)</td>
</tr>
<tr>
<td>Smokers (current)</td>
<td>10/63 (17)</td>
<td>5/15 (3)</td>
<td>0.77 (0.40-1.52)</td>
</tr>
<tr>
<td>Non smokers</td>
<td>109/599 (18)</td>
<td>79/624 (13)</td>
<td>0.70 (0.54-0.91)</td>
</tr>
<tr>
<td>Vaccinated§</td>
<td>3/12 (2)</td>
<td>1/3 (1)</td>
<td>0.50 (0.28-0.89)</td>
</tr>
<tr>
<td>Not vaccinated§</td>
<td>97/623 (16)</td>
<td>86/660 (13)</td>
<td>0.72 (0.56-0.93)</td>
</tr>
<tr>
<td>High-risk patients</td>
<td>110/687 (16)</td>
<td>92/718 (13)</td>
<td>0.75 (0.58-0.96)</td>
</tr>
<tr>
<td>Non–high-risk patients</td>
<td>139/765 (18)</td>
<td>105/807 (13)</td>
<td>0.72 (0.57-0.91)</td>
</tr>
</tbody>
</table>

* Unless otherwise indicated, data are number of subjects/number of subjects in subgroup (percentage).  
† Placebo recipients from the 4 trials that included a treatment arm of intranasal and inhaled zanamivir.  
‡ Ten patients had undetermined subtype.  
§ Patients in Hayden et al12 were nonvaccinated.  
¶ Baseline temperature missing for 7 patients.  
‖ Duration of symptoms not collected in hours in Lalezari et al.14  
# P = .006.

Influenza, the rate of physician-diagnosed respiratory events leading to antibiotic prescriptions was about 17%. Approximately half of these events occurred within the 6 days after the onset of influenza symptoms and were most commonly acute bronchitis and acute sinusitis. Our results also indicate that in mainly healthy adolescent and adult patients, treatment of laboratory-confirmed influenza illness with either combined intranasal and inhaled or inhaled zanamivir alone reduces respiratory events leading to antibiotic use; antibiotic prescriptions were 28% lower in inhaled zanamivir recipients compared with placebo recipients.

This study represents the first demonstration in a large population of patients with influenza that early antiviral therapy can reduce physician-diagnosed complications and associated antibiotic use. Of note, in our population the mean duration after the onset of symptoms was approximately 29 hours, and all patients were included within 2 days. Therefore, efficacy has only been established when zanamivir is administered early in the course of the disease. Also of note, only a minority (12%) of our subjects had comorbidities or were older than 65 years; further studies are necessary in such high-risk populations.

The beneficial effect of inhaled zanamivir was observed mainly in patients presenting with symptoms consistent with lower respiratory tract events. This suggests that zanamivir effect was mainly directed to the lower respiratory tract. The addition of intranasal zanamivir treatment to inhaled zanamivir therapy was not associated with additional overall clinical benefit. However, intranasal zanamivir treatment reduces viral replication in the nasopharynx, whereas inhaled zanamivir does not; and we observed a lower incidence of upper respiratory tract events in subjects receiving intranasal zanamivir.
In previous studies exploring the role of zanamivir given intranasally in experimental human influenza, the incidence of middle ear abnormalities was decreased in zanamivir recipients. The rate of otitis media was low in our adult population, and no specific effect on this complication occurred. However, otitis media is a frequent event and the leading cause of antibiotic prescriptions in young children. Whether the addition of intranasal zanamivir could be associated with additional benefit should be investigated in appropriate studies comparing intranasal plus inhaled zanamivir to inhaled zanamivir treatment alone in young children.

Our conclusions have some limitations. The diagnosis of respiratory complications was based mainly on clinical examinations, and we did not provide additional bacteriological or radiological data. It is possible that in some cases, symptoms leading to antibiotic prescriptions were attributable to persisting influenza rather than bacterial complications. We cannot precisely state the proportion of respiratory complications of viral origin alone or of bacterial origin alone or in combination with viral. In addition, the conclusions on the effect of route of administration on the different types of respiratory complications (ie, upper or lower respiratory tract events) are limited by the lack of accuracy of the clinical diagnosis. However, these limitations are a common dilemma in daily practice, where additional investigations in patients with respiratory diseases are limited and antibiotics are generally prescribed on the basis of clinical findings only. Of note, our results are also supported by recent trials performed with another neuraminidase inhibitor, oral oseltamivir (or GS4104), in patients with community-acquired influenza. In these studies, a significant reduction of respiratory complications leading to antibiotic prescriptions also occurred. Another limitation of our study is that we enrolled a limited number of high-risk persons.

It has been well documented that influenza virus infections initiate production of various proinflammatory cytokines, including interferon α, interferon γ, interleukin (IL) 6, and IL-8. These cytokines are implicated in recruitment of inflammatory cells and contribute to disease expression. Their role in the pathogenesis of secondary complications is not well understood, but in adults experimentally infected with influenza A virus, IL-6, IL-8, and tumor necrosis factor α peak in nasal washes on day 4 or 5 after the initial infection. Recent studies found that intravenous zanamivir or oral oseltamivir administration significantly reduces viral replication, proinflammatory cytokine levels in nasal lavages, and illness during experimental human influenza. Oral rimantadine therapy also decreased virus titers, levels of IL-8, and severity of symptoms. These results suggest that early antiviral treatment of influenza infection decreases levels of inflammatory mediators and thus could decrease complications promoted by these mediators. However, no direct studies characterizing the effect of antiviral therapy on such mediators in natural influenza have been reported.

Findings of subgroup analyses do not suggest that the beneficial effect of zanamivir on respiratory events leading to antibiotic use was limited to a subgroup of patients. A trend toward a greater effect was observed in patients with influenza A infection compared with those with influenza B, but the number of patients with influenza B was smaller, which limits our conclusions. The higher incidence of antibiotic prescriptions initially observed in female patients compared with males was not confirmed by further analysis. In trials performed with zanamivir, no sex differences occurred in other measures of clinical efficacy. This finding is likely attributable to chance, although differences in utilization of health care resources, physician diagnosis, or actual risk of complication could account for the difference.

Our study is the first comprehensive survey of influenza complications in previously healthy adolescent and adult patients with laboratory-documented influenza illness. We determined that approximately 1 of 6 of the placebo recipients eventually received an antibiotic prescription, mainly for secondary events such as acute bronchitis or acute sinusitis, and less often for worsening of initial symptoms. Half of these apparent complications occurred within approximately 6 days after the onset of symptoms. Our results showed that early therapy with neuraminidase inhibitors reduces clinical events leading to antibiotic prescriptions following this viral respiratory infection.

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