Short-Term Treatment with Zanamivir to Prevent Influenza: Results of a Placebo-Controlled Study

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We explored the prophylactic activity of zanamivir after presumed exposure to influenza in the community. After close contacts with index cases of influenza-like illnesses, 575 subjects were randomized in 4 treatment groups: 144 received placebo, 141 received intranasal zanamivir, 144 received inhaled zanamivir, and 146 received inhaled plus intranasal zanamivir for 5 days. Of 25 subjects (4%) who developed symptomatic influenza during the 5 days of prophylaxis, 9 (36%) were in the placebo group, 8 (32%) were in the intranasal zanamivir group (odds ratio [OR], 0.90; 95% confidence interval [CI], 0.30–2.72; P = .855), 3 (12%) were in the inhaled zanamivir group (OR, 0.27; 95% CI, 0.07–1.05; P = .058), and 5 (20%) were in the inhaled plus intranasal zanamivir group (OR, 0.52; 95% CI, 0.17–1.58; P = .247). Short-term treatment with intranasal zanamivir was ineffective. However, inhaled zanamivir treatment reduced the rate of influenza, which was 2%–3% among zanamivir recipients versus 6% among placebo recipients. Additional studies assessing a longer duration of postcontact prophylaxis are warranted.

Zanamivir is a neuraminidase inhibitor with potent activity against both influenza A and B viruses and has been shown to be effective in treating influenza in adults [1, 2]. In adults challenged intranasally with influenza A virus, treatment with zanamivir by nasal spray or drops was also 82% effective in preventing laboratory evidence of infection and 95% effective in preventing febrile illness [3]. However, the prophylactic activity of zanamivir after presumed exposure to influenza, when influenza is circulating in the community, has not been fully investigated. In addition, uncertainty exists about the main site of influenza virus acquisition and replication in naturally occurring influenza. Some observations suggest that the lower respiratory tract is the predominant site rather than the upper respiratory tract. If this suggestion is correct, treatment with inhaled zanamivir should be more effective than that with nasal sprays in preventing influenza.

We conducted a study comparing a short course of treatment with intranasal and/or inhaled zanamivir to prevent influenza in persons presumably exposed to influenza in the community.

Methods

Participants. This multicenter study was conducted during the 1995–1996 influenza season in Europe and North America. Asymptomatic subjects aged 13–65 years were eligible for study enrollment if they had been in close contact with index cases of influenza-like illnesses of no longer than 4 days’ duration. The clinical diagnosis of influenza was defined by the presence of fever (temperature, ≥37.8°C) or feverishness with at least 2 of the following symptoms: headache, myalgia, cough, and/or sore throat. Close contact was defined as living in the same household, sleeping in the same room, or being confined in the same room for an extended period. Exclusion criteria were unstable chronic illness, influenza virus vaccination, and anti-influenza treatment during the previous days. Local ethics committees approved the study, and subjects gave written informed consent.

Drug administration. Participants were randomized in a double-blind manner to 4 treatment groups: 2 intranasal sprays of zanamivir (16 mg/mL per nostril [0.1 mL per spray]) plus 2 placebo inhalations, 2 zanamivir inhalations (5 mg per inhalation) plus 2 placebo sprays per nostril, inhaled and intranasal zanamivir, and 2 placebo inhalations and 2 placebo sprays per nostril. Zanamivir or placebo was self-administered for 5 days.

Monitoring. Subjects recorded the severity (on a 6-point scale) of influenza-like symptoms, including headache, sore throat, feverishness, muscle aches, cough, nasal congestion, weakness, and loss of appetite twice daily for 10 days.

At baseline, an upper respiratory tract sample for viral culture was obtained from all subjects. Serum samples for serology were collected on days 1 and 21 and were assayed as paired samples by hemagglutination inhibition assays. Laboratory-confirmed influ-
enza was defined as a 4-fold increase in antibody level or documentation of influenza by culture or direct antigen detection.

Data analysis. The primary end point was the proportion of subjects with symptomatic influenza during the 5-day prophylaxis period. Symptomatic influenza was defined as laboratory-confirmed influenza plus at least 2 symptoms with a severity score ≥2. Subjects with mild (severity score, <2) symptoms but confirmed influenza were considered to have mild or asymptomatic influenza. Secondary end points included the proportion of subjects with fever (temperature, ≥37.8°C) and the duration (number of days) of significant symptoms. All analyses were performed on an intention-to-treat basis by using SAS version 6.08 (SAS Institute, Cary, NC). Adjustment for multiple comparisons of confirmatory data claims of efficacy was based on improved Bonferroni adjustments. We analyzed the proportion of subjects with symptomatic influenza analyzed using Mantel-Haenszel estimates with test-based CIs and with ORs and 95% CIs stratified by center. Comparisons of baseline characteristics were performed by means of Fisher’s exact test, and age was compared by use of analysis of variance.

Sample size was calculated on the assumption that the rate of influenza would be 15% for the placebo group and 5% for the treatment groups. To obtain a power of 90% to declare any individual comparison to be significant (P < .0167), 840 subjects were planned for study enrollment.

Results

Participants. During the influenza season from November 1995 through March 1996, 575 subjects were enrolled in the study after having close contacts with subjects with influenza-like illnesses. Influenza A virus subtype H3N2 was the predominant circulating strain. The mean age of the subjects was 34 years (range, 13–77 years), and although baseline characteristics were similar in the 4 treatment groups, the proportion of smokers was higher among placebo recipients and patients treated with intranasal and inhaled zanamivir than among the 2 other treatment groups (table 1).

Outcomes. From the first day of prophylaxis until day 21, 92 (16%) of 575 subjects developed proven influenza. Influenza A occurred in 60 (65%); influenza B, in 23 (25%); and unclassified influenza, in 9 (10%). Of the 92 subjects with documented influenza, 27 (29%) were in the placebo group, 28 (30%) were in the intranasal zanamivir group, 16 (17%) were in the inhaled zanamivir group, and 21 (23%) were in the inhaled plus intranasal zanamivir group. There were 25 subjects who developed symptomatic influenza that occurred during the 5 days of prophylaxis, of whom 9 (36%) were in the placebo group, 8 (32%) were in the intranasal zanamivir group, 3 (12%) were in the inhaled zanamivir group, and 5 (20%) were in the inhaled and intranasal zanamivir group. The ORs for developing symptomatic influenza in the treatment groups versus the placebo group were as follows: 0.90 (95% CI, 0.30–2.72; P = .855, Mantel-Haenszel test stratified by center), the intranasal zanamivir group; 0.27 (95% CI, 0.07–1.05; P = .058), the inhaled zanamivir group; and 0.52 (95% CI, 0.17–1.58; P = .247), the inhaled and intranasal zanamivir group (table 2). For all participants receiving inhaled zanamivir with or without intranasal drug, the OR for developing symptomatic influenza was 0.41 (95% CI, 0.16–1.06; P = .066).

Twenty-two subjects (4%) of the enrolled study population presented with oral temperatures of ≥37.8°C during the 5 days of prophylaxis. Of these 22 subjects, 8 (36%) were in the placebo group, 7 (32%) were in the intranasal zanamivir group (OR, 0.90; 95% CI, 0.32–2.52; P = .839), 4 (18%) were in the inhaled zanamivir group (OR, 0.55; 95% CI, 0.16–1.89; P = .345), and 3 (14%) were in the inhaled and intranasal zanamivir group (OR, 0.24; 95% CI, 0.06–1.00; P = .050). The mean duration of significant influenza-like symptoms was 0.6 day for the placebo group and 0.4 day (P = .264) for the intranasal zanamivir group, 0.2 day (P = .016) for the inhaled zanamivir group, and 0.3 day (P = .024) for the intranasal and inhaled zanamivir group.

Tolerance. Adverse events considered as possibly drug-related occurred in 25 placebo recipients (17%) and 14–19% of zanamivir recipients (23 [16%] of the intranasal recipients, 27 [19%] of the inhaled recipients, and 20 [14%] in the intranasal and inhaled recipients). Reported adverse events were primarily headaches, nasal signs or symptoms, fatigue, and throat discomfort. These events did not differ across groups.

Discussion

After presumed exposure to influenza virus, the rate of symptomatic influenza was only 6% for the placebo group during the 5-day follow-up period. The frequency was also 6% for the subjects receiving intranasal zanamivir, which failed to show any protective benefit. In contrast, for the 2 groups receiving inhaled zanamivir, the rate of influenza was approximately one-half that for the placebo group, ranging from 2% to 3% (although none of the primary treatment comparisons were statistically significant). Secondary end points, specifically fewer episodes and occurrence of influenza-like symptoms, also occurred less frequently in the inhaled zanamivir groups.

<p>| Table 1. Baseline characteristics of subjects given placebo or zanamivir prophylaxis for influenza. |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 144)</th>
<th>Intranasal (n = 141)</th>
<th>Inhaled (n = 144)</th>
<th>Intranasal and inhaled (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in y (mean (range))</td>
<td>34 (13–77)</td>
<td>35 (14–70)</td>
<td>34 (13–70)</td>
<td>34 (14–68)</td>
</tr>
<tr>
<td>Male</td>
<td>57 (40)</td>
<td>60 (45)</td>
<td>56 (39)</td>
<td>59 (40)</td>
</tr>
<tr>
<td>Female</td>
<td>87 (60)</td>
<td>81 (57)</td>
<td>88 (61)</td>
<td>87 (60)</td>
</tr>
<tr>
<td>Associated condition</td>
<td>92 (64)</td>
<td>99 (70)</td>
<td>101 (70)</td>
<td>100 (68)</td>
</tr>
<tr>
<td>Concurrent medication</td>
<td>81 (56)</td>
<td>86 (61)</td>
<td>80 (56)</td>
<td>83 (57)</td>
</tr>
<tr>
<td>Current tobacco use</td>
<td>43 (30)</td>
<td>26 (18)</td>
<td>22 (15)</td>
<td>40 (27)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of subjects.
Our results only suggest that zanamivir is effective in preventing influenza virus illness; they do not provide the proof. However, 2 recent studies [4, 5] have demonstrated that administration of neuraminidase inhibitors for 4- to 6-week periods is effective as prophylaxis. During community influenza activity, once daily inhaled zanamivir for 4 weeks demonstrated 67% efficacy in preventing symptomatic infection and 84% efficacy in preventing influenza-associated fever [4]. Oseltamivir (GS4104), another new neuraminidase inhibitor, when used orally once daily for 6 weeks showed an overall protective efficacy of 76% in preventing influenza [5]. These observations strongly suggest that the absence of a statistically significant protective effect of zanamivir in our study was due to lack of power. Our study did not enroll the targeted member of contacts, and the 6% event rate for the placebo group was lower than assumed. Our observations also suggest that 5 days of prophylaxis may not be long enough for postexposure prophylaxis when influenza is circulating in the community.

An interesting finding in this study was the difference in protection between intranasal zanamivir and inhaled zanamivir. These results suggest that preventing influenza requires distribution of the drug in the lower respiratory tract and are consistent with the hypothesis that most cases of naturally occurring influenza are initiated in the pharynx or in the lower respiratory tract [6]. These results corroborate those of a study of intranasal IFNs, which provided partial protection against influenza after intranasal viral inoculation in experimentally exposed volunteers but were ineffective in preventing natural influenza [7].

Five days of inhaled zanamivir prophylaxis was well tolerated and decreased the frequency of influenza in contacts by ~60%. However, 4 weeks of prophylaxis during the influenza season may be impractical, and new studies assessing longer durations of postcontact prophylaxis are warranted.

References