Do Neuraminidase Inhibitors Prevent Influenza?

Summary

✓ Two neuraminidase inhibitors, zanamivir and oseltamivir, are well-tolerated and reduce the likelihood of contracting influenza in both healthy individuals and those who are at risk for developing complications.

✓ There is insufficient evidence to conclude that neuraminidase inhibitors reduce complications, hospitalization and death from laboratory-confirmed illness.

✓ Differences between amantadine, zanamivir and oseltamivir exist but the relative contributions of these differences to their overall effectiveness are difficult to assess due to a lack of comparative trials.

The Technology

Neuraminidase is an influenza virus enzyme that facilitates the passage of influenza virions out of infected cells and into respiratory secretions, allowing them to spread to others.¹ An improved understanding of the structure and function of neuraminidase in the 1980s led to the development of several neuraminidase inhibitors (NIs) that have been tested in human trials since the mid-1990s.

The efficacy of two NIs for influenza prevention has been investigated. Zanamivir is an inhaled preparation developed by Biota/GlaxoSmithKline under the trade name Relenza™. Oseltamivir is an oral formulation developed by Gilead/Hoffmann-La Roche under the trade name Tamiflu™.¹

Regulatory Status

Currently, neither zanamivir nor oseltamivir have been approved for the prevention (prophylaxis) of influenza in Canada. Hoffmann-La Roche has submitted an application for this indication to Health Canada for oseltamivir (Hoffmann-La Roche: personal communication, 2001 Aug 30). Both products are approved for the treatment of uncomplicated acute illness due to influenza infection.

Patient Group

Annually, individuals exhibit a collection of symptoms called clinical influenza or influenza-like illness (ILI). Physician visits for ILI can account for 3 to 6% of total outpatient visits during the influenza season.² Only a portion of patients with ILI truly have influenza infection because symptoms of ILI may be caused by other seasonal pathogens.

Two types of influenza virus, A and B, lead to seasonal epidemics. The influenza A virus occurs more frequently and produces more severe symptoms. Genetic alterations in both virus types create new viral strains and populations remain susceptible to infection.

It is known that influenza-related morbidity and mortality is primarily related to complications in individuals with chronic respiratory and cardiac disease. Mortality is most common in the elderly.³ Other individuals at risk include those with chronic renal disease, diabetes, or immunosuppression.³ Influenza-related hospitalizations are estimated to range from 0.04% to 0.1%⁴ in otherwise healthy populations and from 1.09% to 6.8%⁵ in at-risk populations. Health Canada attributes the number of deaths from influenza in Canada to be from 500 to 1,500 annually.⁵

Current Practice

Influenza prevention is accomplished through vaccination and adjunctive drug prophylaxis. Currently one drug (amantadine) is approved in Canada for prophylaxis against influenza.
Prophylaxis can be prescribed for the duration of influenza activity (i.e. seasonal prophylaxis) or after suspected exposure to influenza (i.e. post-exposure prophylaxis). Surveillance data play an important role in appropriate prescribing.

Amantadine, 100 mg, given once or twice daily for post-exposure prophylaxis will prevent one case of laboratory-confirmed ILI (LC-ILI) when administered to eight healthy adults (95% Confidence Interval (CI): 5 to 23) compared with placebo. Discontinuations due to adverse events occur in 3% (95% CI: 2% to 4%) of healthy adults. Estimates of discontinuation rates for nursing home residents range from 2% to 13.8%. Amantadine is ineffective against influenza B viruses. Amantadine-resistant influenza A viruses that remain pathogenic during epidemics have been documented. Dosage adjustments are suggested for renally impaired individuals.

Administration and Cost

Prophylaxis against naturally acquired influenza has been investigated with zanamivir 10 mg (inhaled) daily or oral oseltamivir 75 mg used once or twice daily for nine to 42 days. A dosage adjustment for oseltamivir is suggested for renally impaired individuals.

Currently, NIs are marketed for the treatment of acute infection rather than prevention. The base cost (without markup or fees) of the Relenza Diskhaler™, which contains 20 x 5 mg doses, is $3.69 per 10 mg dose. Tamiflu™ costs $4.43 per 75 mg dose.

Rate of Technology Diffusion

Prophylaxis against influenza in Canada is guided largely by annual recommendations from the National Advisory Committee on Immunization (NACI). Amantadine is recommended for use: in high risk populations during institutional outbreaks; when vaccine is either unavailable, contraindicated, or likely to be ineffective; as an adjunct to late vaccination; as a supplement to vaccination in immunocompromised patients; and for unvaccinated care providers of individuals at risk. Situations in which NIs may be appropriate (e.g. influenza B outbreaks) have been suggested by NACI. Regulatory approval combined with evidence of effectiveness compared with amantadine will likely influence recommendations surrounding the use of NIs in the future.

Concurrent Developments

Other prophylactic agents available outside of Canada include rimantadine, which is closely related to amantadine, and arbidol (a fusion inhibitor). Another NI, RWJ-270201, is currently being investigated in phase III human trials.

The Evidence

Seasonal Prophylaxis In Healthy Unvaccinated Adults:
Zanamivir: One report of a double-blind, randomized, placebo-controlled trial conducted in 1997-98 describes the efficacy of inhaled zanamivir 10 mg once daily at the start of a regional epidemic and continuing for four weeks.

Oseltamivir: Two reports of double-blind, randomized, placebo-controlled trials conducted in the U.S. (1997-98) and Japan (1998-99) describe the efficacy of oral oseltamivir 75 mg once or twice daily when given for six weeks at the start of the local influenza season. Some participants (~7%) in the Japanese study were older than 65.

Seasonal Prophylaxis In Individuals At Risk:
Zanamivir: No data are available for zanamivir.

Oseltamivir: A double-blind, placebo-controlled prophylaxis trial in a vaccinated older population (median age = 82, range = 65-96) during the 1998-99 season has been described in two abstracts and a published report. The 548 participants were occupants of residential homes or sheltered accommodation for seniors and received oseltamivir 75 mg once daily for six weeks. Complications, defined as otitis media, sinusitis, and chest infections, were significantly reduced in the oseltamivir recipients, although this reduction was not significant in those individuals who met the case definition of LC-ILI.

Post-Exposure Prophylaxis In Families:
Zanamivir: A double-blind trial randomized 337 families (two to five members) to 10 days of zanamivir 10 mg daily or placebo within 36 hours of a family member (who was treated with zanamivir 10 mg twice daily for five days) presenting with ILI.

Oseltamivir: A similar double-blind trial randomized 374 (two to nine members) families to seven days of oseltamivir 75 mg daily or placebo within 48 hours of a family member presenting with ILI.
Post-Exposure Prophylaxis In Individuals At Risk:

Zanamivir: Three open-label trials of prophylaxis in nursing homes are described in several reports.21-27 Due to limitations in the study designs, conclusions about efficacy cannot be made, however 84.4% (233/276) of pooled participants had no difficulty completing a two week course. Many trial participants suffered multiple co-morbidities.

Oseltamivir: Two Canadian open-label, non-randomized trials described in several reports investigated the use of oseltamivir in influenza outbreaks.28-29 Conclusions about efficacy cannot be made due to study design limitations, however, 97.6% (971/995) of participants were able to complete a median prophylactic course of nine days (range five to 12 days). A small number of study withdrawals, 0.9% (9/995) occurred because therapy was changed to a treatment regimen when ILI was observed within 48 hours of prophylaxis.

There is sufficient evidence to conclude NIs are well-tolerated and reduce the likelihood of contracting influenza in both healthy and individuals at risk for developing complications.

### Table 1: Number-Needed-To-Treat To Prevent One Extra Case of Laboratory-Confirmed Influenza-Like Illness

<table>
<thead>
<tr>
<th>NI Use</th>
<th>Zanamivir (95%CI)</th>
<th>Oseltamivir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal Prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy Unvaccinated</td>
<td>28 (16 to 96)</td>
<td>14 (8 to 41) to 27 (17 to 61)</td>
</tr>
<tr>
<td>Individuals at Risk:</td>
<td>–</td>
<td>25 (14 to 65)</td>
</tr>
<tr>
<td>Post-Exposure Prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy (Families)</td>
<td>18 (12 to 29)</td>
<td>15 (11 to 24)</td>
</tr>
<tr>
<td>Individuals at Risk:</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Implementation Issues

Several issues surrounding the use of NIs still exist. A reduction in complications of influenza rather than from influenza indicates the impact of NIs on more severe outcomes cannot be fully assessed. There is also insufficient evidence to assess the impact of NIs on hospitalizations and death. The importance of having conclusive evidence surrounding these benefits may affect how NIs are used in practice.

The cost of therapy to prevent one case of LC-ILI (NNT x cost of therapy) is considerable and may be prohibitive when compared with generic amantadine. However, differences in potential harm, viral resistance patterns, and spectrum of activity between NIs and amantadine exist. Assessing these differences is problematic without comparative trials and long-term NI safety data.

Differences between NIs also exist. Although zanamivir is available at a lower per treatment cost than oseltamivir, its usefulness could be limited as an inhaled preparation in the very old or those with chronic obstructive pulmonary disease.18 Conversely, nausea (Number Needed to Harm (NNH) 32; 95% CI: 21 to 68) and vomiting (NNH 89; 95% CI: 48 to 456) from oseltamivir can occur. The contribution of these differences to relative effectiveness is still unknown.

### References


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