Neuraminidase Inhibitors in Treatment of Influenza A

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CLINICAL CASE
Ms. Smith, a healthy 75-year-old female, presented to her family doctor’s office with a 24-hour history of fever, cough, and myalgias. She tested positive for influenza A and is requesting a prescription for oseltamivir (Tamiflu®) as she has seen multiple advertisements on television alluding to its benefits.

BACKGROUND
Typically, influenza manifests as a self-limiting upper respiratory tract infection (URTI), with symptoms of fever, cough, headache, myalgias and general malaise. Occasionally, however, serious complications develop, including viral or secondary bacterial pneumonia, myositis and central nervous system involvement. These complications can result in prolonged hospitalization and mortality. Annually, 5-10% of Canadians are infected with influenza. While children are at most risk for infection, serious illness and death occur most commonly in those greater than 65 years of age and in persons with underlying medical conditions.

Seasonal variations in the dominant circulating strains of the virus notwithstanding, influenza A/H1N1, influenza A/H3N2 and influenza B are responsible for the majority of influenza infections. Due to increasing resistance to M2 inhibitors, neuraminidase inhibitors, such as oral oseltamivir (Tamiflu®) and inhaled zanamivir (Ralenza®), are considered first line agents for seasonal influenza. These agents have both been approved by Health Canada. Current Canadian guidelines recommend considering early antiviral therapy – within 48 hours of symptom onset – for those with mild, self-limiting influenza. For patients at higher risk for adverse outcomes, such as those with comorbidities or severe illnesses requiring hospitalization, guidelines encourage continued treatment after the initial 48 hours. Typical treatment duration with neuraminidase inhibitors is 5 days, but may be longer if necessary.

RATIONALE
Results from earlier meta-analyses and Cochrane reviews on the benefits of neuraminidase inhibitors have been called into question due to concerns of publication bias and failure to validate previous results. The current review seeks to analyze a more complete set of available data, focusing on the treatment of influenza with oseltamivir.

QUESTION
Do neuraminidase inhibitors decrease symptom duration, hospitalization, and mortality associated with the influenza virus?

METHODS
Design
This is a critical review of the 2012 Cochrane study on the role of neuraminidase inhibitors for the prevention and treatment of influenza in healthy adults and children. The Cochrane study entailed a systematic review of 25 randomized controlled trials (RCT), including both published and unpublished trial results as well as the data provided to trial regulatory boards by individual study investigators. Cochrane authors used a modified CONSORT tool to aid them in the analysis.

Allocation
Greater than 75% of included RCTs were deemed to have sufficient allocation concealment, thus reducing selection bias. Allocation was considered adequate if it included a randomization code or sequentially numbered and sealed, opaque envelopes.

Blinding
Greater than 80% of included RCTs were double-blinded (both participants and study personnel), reducing performance bias. Moreover, 60% of trials were identified to have adequate blinding of outcome assessment, thus reducing detection bias.
Patients
Children and adults who were previously healthy or had chronic illnesses (excluding those with impaired immune function, such as cancer and HIV/AIDS) were included. Hospitalized patients were excluded. Two of the included studies did not specify the mean age of participants; in the remaining twenty-three studies, the age of patients ranged from 5 to 82 years. The method used to confirm the diagnosis of influenza varied between studies, ranging from laboratory confirmed influenza with serology or culture to pre-determined clinical diagnostic criteria.

Intervention
Neuraminidase inhibitors (either oral or inhaled) compared to placebo.

Outcomes
Primary outcomes included symptom relief, hospitalization/complications, and adverse effects. Secondary outcomes comprised symptom relapse following treatment completion, drug resistance, viral excretion, and mortality.

Analysis
Mean and standard deviation (SD) measures were used to estimate treatment effect. Intention-to-treat (ITT) principle was used to evaluate the effectiveness of subgroup analysis. Sensitivity analysis was conducted to assess the validity of findings.

Patient Follow-up:
Follow up periods ranged from 1-27 days post-treatment. The number of subjects lost to follow-up was not specified.

RESULTS
A total of 25 RCTs were included for analysis. An additional 42 studies did not meet the inclusion criteria, and were thus excluded from the study. Notably, all of the included studies were sponsored by manufacturers of neuraminidase inhibitors. Median time to resolution of influenza symptoms was 160 hours (range 125 to 192 hours) in the placebo groups and was reduced by 21 hours in the oseltamivir group (P<0.001, 95% Confidence Interval [CI] -29.5 to -12.5 hours). There was no significant difference in hospitalizations between the oseltamivir and placebo groups (OR 0.95; 95% CI 0.57-1.61). Unfortunately, the data available to the Cochrane Collaboration lacked the necessary detail to accurately assess the effect of oseltamivir on complications of influenza, including mortality.

COMMENTARY
While oseltamivir significantly shortened symptom duration in those with influenza, these results must be interpreted with caution. Despite multiple attempts, investigators were unsuccessful at obtaining complete study reports for all trials and resolving data discrepancies from the manufacturers, thus potentiating the risk of publication bias.

Considering the burden of disease associated with influenza, Canadian guidelines recommend the use of oseltamivir for the treatment of influenza in certain populations and settings (see Box 1). Unfortunately, the quality of evidence supporting the use of oseltamivir is controversial given previously identified and significant publication biases. Moreover, difficulty in obtaining unpublished trial information limited a more comprehensive review of the efficacy of neuraminidase inhibitors.

BOX 1. Canadian Guidelines Relevant to the Clinical Scenario

- Initiate NI treatment as rapidly as possible after illness onset
- Healthy patients with mild influenza are unlikely to benefit from NI therapy initiated more than 48 hours after symptom onset
- Antiviral therapy should be initiated even if illness onset is greater than 48 hours if the illness is severe enough to require hospitalization
- Treatment should routinely be 5 days

Earlier evidence includes a meta-analysis of 10 trials, which was conducted in 2003 by Kaiser et al (2003). The authors concluded that the use of oseltamivir in the treatment of influenza reduced antibiotic utilization and lower respiratory tract complications in both healthy adults and those with underlying comorbidities. This paper is frequently cited as the source for recommendations for oseltamivir use and its conferred benefits. The meta-analysis was not based on a systematic review, however, and 8 of the trials included in the study remain unpublished, with study data unavailable for independent analysis. Additionally, in spite of the conclusions drawn in this study, it did not show a statistically significant decrease in the frequency of hospitalization.

In an effort to circumvent publication bias, Jefferson et al (2009) attempted to review unpublished RCTs that were excluded from the Kaiser meta-analysis, of the role of neuraminidase inhibitors on influenza outcomes. The authors did find a modest reduction in symptom severity and duration with oseltamivir compared with placebo. This review of unpublished data in the most recent Cochrane Collaboration by Jefferson et al (2012) again shows a significant reduction in symptom duration with the use of neuraminidase inhibitors, which may help guide clinical practice.

In addition to RCTs, the benefit of neuraminidase inhibitors is noted through several observational studies. Hsu et al (2012) conducted a systematic review of 72 observational studies and noted a reduction in hospitalization (OR 0.52, 95% CI 0.33-0.81), ICU admissions due to respiratory failures (OR 0.22, 95% CI 0.15-0.33) as well as mortality (OR 0.33, 95% CI 0.12-0.86), when oseltamivir is administered within 48 hours of symptom onset. This review also
A study by Hayden et al. (1999) demonstrated that headache occurred in 39-47% of treated patients. Review of unpublished data from Japanese regulatory documents revealed an OR of 1.37 (95% CI 1.06-1.76) for neuropsychiatric events associated with treatment dose oseltamivir compared with placebo (p<0.014). This information had not been previously reported in the literature until the most recent Cochrane review.

**BOTTOM LINE**

Both RCT and observational data has consistently shown that oseltamivir reduces the duration of influenza symptoms by less than one day in low risk individuals with mild disease. The clinical benefit of this small decrease in symptom duration is questionable, not least in part due to previously identified publication biases. Additional randomized, placebo controlled trials are warranted to examine the clinical risks and benefits of oseltamivir in healthy patients with laboratory proven influenza to help guide physicians in their treatment practices. Given the current evidence, we currently recommend oseltamivir for the treatment of laboratory confirmed influenza in otherwise previously healthy patients. Physicians should however inform their patients of the limited evidence regarding the clinical efficacy of the drug and its possible adverse effects. Although the side effect profile has not been captured thoroughly in clinical trials, post-marketing data have not indicated any significant concerns about the safety of oseltamivir or zanamivir.

**REFERENCES**