

## Zanamivir Reduces Respiratory Complications in Patients with Influenza

Kaiser L, Keene ON, Hammond JM, et al. Impact of zanamivir on antibiotic use for respiratory events following acute influenza in adolescents and adults. *Arch Intern Med* 2000;160:3234–40.

### Study Overview

**Objective.** To determine the frequency of respiratory events leading to antibiotic therapy following influenza-like illness, and to assess whether therapy with zanamivir can reduce these complications.

**Design.** Meta-analysis of 7 randomized, double-blinded, placebo-controlled trials.

**Setting and participants.** The trials in the meta-analysis were conducted in North America, the Southern Hemisphere, and Europe. 3815 healthy adolescents and adults were randomized to receive either inhaled and intranasal zanamivir, inhaled zanamivir alone, or corresponding placebos. Of the study subjects, 12% were considered high-risk patients. All patients had influenza-like symptoms (either fever or feverishness and at least 2 additional symptoms such as cough, sore throat, headache, or myalgia). Influenza infection was confirmed by viral culture, antigen detection, or polymerase chain reaction paired with antibody titers during the acute phase and during convalescence. Patients were seen at 5 days and at 21 or 28 days after diagnosis of influenza.

**Main outcome measures.** The main outcome was the incidence of respiratory events leading to antibiotic prescriptions in patients with confirmed influenza. Rates of hospitalization were also measured.

**Main results.** Of the patients analyzed, 2499 had laboratory-confirmed influenza and 1316 patients had unrelated influenza-like illnesses. Of patients with confirmed influenza, 1005 received placebo, 687 received inhaled and intranasal zanamivir, and 807 received inhaled zanamivir alone. 172 patients (17%) in the placebo group developed a respiratory event that required antibiotic use; 25% of these events occurred within 3 days, 50% within 5 days, and 75% within 10 days after influenza was diagnosed. Specific respiratory events included acute bronchitis (43% of cases), acute sinusitis (25%), acute pharyngitis (10%), ear infections (9%), and pneumonia (8%). 1494 zanamivir-treated patients had confirmed influenza illness; of these, 167 (11%) required antibiot-

ic treatment. The relative risk [RR] of respiratory events requiring antimicrobial treatment in zanamivir-treated patients compared with placebo was 0.69 (95% confidence interval [CI], 0.57 to 0.84;  $P < 0.001$ ), a 31% RR reduction. Absolute risk reduction was 6% (from 17% to 11%). Intranasal and inhaled zanamivir seemed to reduce the number of upper (RR, 0.59; 95% CI, 0.36 to 0.97) and lower (RR, 0.64; 95% CI, 0.38 to 1.08) respiratory tract infections. Inhaled zanamivir alone reduced the number of lower respiratory tract events (RR, 0.60; 95% CI, 0.42 to 0.85), but the reduction in upper respiratory tract events was not statistically significant (RR, 0.90; 95% CI, 0.63 to 1.27). Among the 339 total patients with confirmed influenza and respiratory illness requiring antibiotic therapy, 8 (2.4%) had to be hospitalized after starting antibiotics. Five of these hospitalizations were related to respiratory complications (eg, pneumonia, pleuritis); the other patients had non-influenza-related events.

### Conclusion

Early treatment of influenza illness with zanamivir was associated with a significant reduction in the number of antibiotic prescriptions needed to treat respiratory complications.

### Commentary

Previous research has shown that antiviral therapy with either zanamivir, amantadine, rimantadine, or oseltamivir can reduce the duration and severity of influenza [1–3]. This study by Kaiser and colleagues is one of the first to suggest that antiviral agents may reduce the rate of respiratory complications. The strength of this study lies in its use of a pool of blinded randomized controlled trials. The patient populations were similar across studies; however, few elderly or high-risk patients (12%) were included. Other studies have examined these populations, including a recent study [4] that demonstrated the cost-effectiveness of zanamivir in high-risk groups and a randomized controlled trial published this month by Murphy et al [5], which showed that zanamivir could be used safely in patients with asthma and chronic obstructive pulmonary disease (COPD). (In the latter study, a 58% reduction in antibiotic use was observed in patients treated with zanamivir.) The magnitude of effect in Kaiser and

colleagues' work was also significant. The number need to treat to prevent 1 patient from developing a respiratory illness requiring antibiotic therapy was 16 (calculated from an absolute risk reduction of 6%). One weakness of the study is the fact that diagnoses of respiratory complications were made based on clinical symptoms. This makes it difficult to determine whether symptoms were caused by bacteria or persistent viral infections, especially when 50% of the complications were diagnosed within 6 days of initial presentation. The authors acknowledged this limitation in their findings. Also, data on rates of antibiotic use among the different centers was not provided and would be interesting to know.

### Applications for Clinical Practice

This study provides strong evidence that in healthy individuals zanamivir can reduce the need for antibiotics after an episode of influenza. Other recent studies have confirmed these findings and have shown that this agent is safe for use in high-risk patients, such as those with COPD and asthma. However, further studies are needed to determine the overall cost-effectiveness of zanamivir treatment. A larger problem is that clinicians do not have a quick, rapid, cheap and

accurate test to confirm influenza diagnosis; such a test is urgently needed in order to use these antiviral medications appropriately.

### References

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