*Note: This is a two-article spread with a shared commentary. Please scroll down for the second article.*

THERAPEUTICS

# Zanamivir speeds symptom relief in influenza

Monto AS, Fleming DM, Henry D, et al. **Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections.** J Infect Dis. 1999 Aug;180: 254-61.


## QUESTION

In patients with symptoms of influenza, what is the clinical efficacy and safety of zanamivir?

## DESIGN

Randomized {allocation concealed*}†, blinded (clinicians and patients),* placebo-controlled trial with 21-day follow-up.

## SETTING

Clinical centers in North America and Europe.

## PATIENTS

1256 patients (mean age 35 y, 66% women) who presented with symptoms of influenza of ≤ 48 hours of duration during 1 influenza season: fever and ≥ 2 of myalgia, headache, cough, or sore throat. Exclusion criteria were unstable chronic illness, receipt of other antiviral agents in the previous 7 days, inability to use inhaler devices satisfactorily, known or suspected hypersensitivity to study medication, pregnancy, lactation, or potential for pregnancy. 1182 patients (94%) completed the study.

## INTERVENTION

Patients were allocated to 5 days of treatment with zanamivir, 10 mg by oral inhalation and 6.4 mg by nasal spray 2 times/d ($n$ = 419); zanamivir (same dosages and administration routes) 4 times/d ($n$ = 415); or placebo ($n$ = 422).

## MAIN OUTCOME MEASURES

Time to alleviation of clinical symptoms, which had to be maintained for ≥ 24 hours. Secondary outcomes were mean symptom score, sleep disturbance, time to return to normal activities, and use of acetaminophen and dextromethorphan to relieve symptoms.

## MAIN RESULTS

Analysis was by intention to treat. Both regimens of zanamivir reduced the time to alleviation of clinical symptoms by 1 day less than placebo (6 vs 7 d, $P \leq 0.014$). The 2 drug groups did not differ ($P = 0.77$). In patients who entered the study within 30 hours of the onset of symptoms, symptom duration was reduced by 1 day with zanamivir 2 times/d ($P = 0.015$) and by 1.5 days with zanamivir 4 times/d ($P = 0.001$). Patients who were febrile at study entry (≥ 37.8 °C) had reduced symptom duration by 1.5 days with zanamivir 2 times/d ($P = 0.049$) and by 2 days with zanamivir 4 times/d ($P = 0.032$). In patients considered at high risk for developing complications (age ≥ 65 y or cardiovascular, respiratory, endocrine, or metabolic conditions), zanamivir 4 times/d reduced time to symptom relief by 2.8 days ($P = 0.042$), and both regimens were more effective than placebo in high-risk patients who had positive findings for influenza ($P \leq 0.016$). Zanamivir was superior to placebo in all secondary clinical outcomes. The groups did not differ for adverse events.

## CONCLUSIONS

In patients with symptoms of influenza, zanamivir given 2 or 4 times per day decreased the time to alleviation of symptoms by 1 to 1.5 days. Patients who presented early after onset of symptoms with fever ≥ 37.8 °C or who were at high risk for complications had the most benefit.


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*See Glossary.

†Information provided by author.

## COMMENTARY

Influenza remains a major cause of morbidity and mortality each year. Although vaccination is the primary method for preventing influenza, antiviral agents play an important complementary role for preventing and treating the disease.

In 1999, zanamivir and oseltamivir were approved for the treatment of influenza A and B (1). Before 1999, amantadine and rimantadine were the only antiviral agents available and were active only against influenza A viruses. Their use has been limited by side effects (especially related to the central nervous system) and the rapid emergence of resistant viruses. The neuraminidase inhibitors appear to be much less likely to induce resistance. They are also generally well tolerated, as shown in these studies by Monto and Hayden and their colleagues, although zanamivir has been reported to induce bronchospasm and oseltamivir has been associated with gastrointestinal symptoms (1).

Zanamivir and oseltamivir are effective for the treatment of influenza A or B among adults when started within 2 days of onset of symptoms. Monto and colleagues administered zanamivir by nasal spray and in its currently available form of orally inhaled powder. Duration of influenza was reduced by about 1 day, with greater benefits for patients with more severe (e.g., febrile) illness and when started within 30 hours of onset of symptoms. 2 other trials reported similar findings: Zanamivir relieved symptoms 1 to 1.5 days earlier (2, 3). Oral oseltamivir also reduces the duration of influenza illness among healthy adults by about 30 hours when started within 1.5 days of the onset of symptoms (4).

Most of the available data on the efficacy of the neuraminidase inhibitors are from healthy adults < 65 years of age. 13% of participants in the study by Monto and colleagues were high risk (age ≥ 65 y or with stable chronic medical conditions). The study findings suggested that zanamivir was also effective in this subgroup, but the sample size was too small to detect a statistically significant benefit. More data are needed to define clearly the role of the neuraminidase inhibitors in high-risk groups.

Although not approved for prophylaxis, zanamivir and oseltamivir have also been shown to prevent influenza in healthy adults. Hayden and colleagues found oseltamivir given for 6 weeks was 74% effective

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# Oseltamivir once or twice daily safely prevented influenza

Hayden FG, Atmar RL, Schilling M, et al., and the Oseltamivir Study Group. **Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza.** N Engl J Med. 1999 Oct 28;341:1336-43.

### QUESTION

Is oral oseltamivir safe and effective in preventing naturally occurring influenzavirus infection?

### DESIGN

Two 6-week randomized (allocation concealed*), blinded (clinicians and patients),* placebo-controlled trials during influenza season.

### SETTING

3 centers in Virginia, 2 in Texas, and 1 in Kansas, USA.

### PARTICIPANTS

1562 persons who were 18 to 65 years of age (mean age 35 y, 63% women) and were recruited by advertisement. Exclusion criteria were influenza vaccination in the previous year, meeting ≥ 1 criterion for influenza immunization according to current (U.S.) guidelines, acute respiratory illness with fever in the previous week, pregnancy, or potential for pregnancy. 1559 participants took ≥ 1 dose of the assigned study medication and were included in the analysis (intention to treat).

### INTERVENTION

Participants were allocated to oral oseltamivir, 75 mg once ($n$ = 520) or twice ($n$ = 520) daily, or to placebo ($n$ = 519) for 6 weeks, beginning when influenzavirus activity increased at the local study sites.

### MAIN OUTCOME MEASURES

Laboratory-confirmed influenza-like illness (laboratory confirmation was culture of influenzavirus within 2 d of the onset of influenza symptoms or antibody titer on hemagglutination-inhibition testing ≥ 4 times the baseline titer or both). Adverse events were also assessed.

### MAIN RESULTS

Fewer patients receiving oseltamivir developed laboratory-confirmed influenza than did patients receiving placebo (once daily $P < 0.001$, twice daily $P = 0.001$) (Table). Rates of influenza were higher at the 3 Virginia sites than at the Texas and Kansas sites. Oseltamivir reduced influenza in Virginia (protective efficacy 82%, 95% CI 60% to 93%; $P < 0.001$) but showed no significant reduction in Texas and Kansas (protective efficacy 50%, CI –23% to 93%; $P = 0.39$). Nausea and vomiting were reported by more oseltamivir recipients than placebo recipients but did not contribute to discontinuation of treatment (Table).

### CONCLUSION

Oseltamivir once or twice daily was effective and safe in preventing influenza.

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*See Glossary.

**Oseltamivir, 75 mg once (Osel qd) or twice (Osel bid) daily, vs placebo for preventing influenza†**

| Outcomes at 6 wk | Comparison | Event rates | RRR (95% CI) | NNT (CI) |
|---|---|---|---|---|
| Laboratory-confirmed influenza-like illness | Osel qd vs placebo | 1.2% vs 4.8% | 76% (46 to 91) | 27 (17 to 59) |
| | Osel bid vs placebo | 1.3% vs 4.8% | 72% (40 to 89) | 29 (17 to 69) |
| | Combined groups vs placebo | 1.3% vs 4.8% | 74% (53 to 88) | 28 (17 to 55) |
| | | | RRI (CI) | NNH (CI) |
| Nausea | Osel qd vs placebo | 12.1% vs 7.1% | 70% (16 to 150) | 20 (12 to 70) |
| | Osel bid vs placebo | 14.6% vs 7.1% | 105% (42 to 198) | 13 (9 to 27) |
| Vomiting | Osel qd vs placebo | 2.5% vs 0.8% | 224% (12 to 840) | 58 (28 to 479) |
| | Osel bid vs placebo | 2.7% vs 0.8% | 249% (22 to 904) | 52 (26 to 267) |

†Abbreviations defined in Glossary; NNT and CI calculated from data in article; RRI and NNH calculated from data supplied by author.

## COMMENTARY

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in preventing influenza. Furthermore, a trial of a 4-week course of zanamivir in 1107 adults showed a 67% efficacy in preventing influenza and an 84% efficacy in preventing febrile influenza (5). Of note, Hayden and colleagues reported that 7 participants developed influenza within 2 weeks of completing the 6-week prophylaxis period, including 5 participants who had received oseltamivir. The neuraminidase inhibitors may protect against illness only for as long as the medication is actually taken. More data on the effectiveness of the neuraminidase inhibitors for the prevention of influenza among elderly persons, nursing-home residents, and other high-risk groups are needed.

How should the neuraminidase inhibitors be used? Immunization remains the mainstay of efforts for the prevention and control of influenza. However, antiviral agents, including the neuraminidase inhibitors, are important adjuncts to vaccination for prevention and treatment during interpandemic periods for persons who have not been vaccinated, who develop influenza even if they have been vaccinated, and who travel between May and September to areas of the world with influenza activity. Decisions about which antiviral agent to use should be based on the relative importance of spectrum of activity, side effects, risk for emergence of resistance, and cost. Given the need to start treatment within 2 days of the onset of symptoms, providers will have to develop efficient processes for accurate diagnosis and timely prescribing of these agents if they are to be used widely. The antirivals will also play an important role during the next pandemic, providing critical protection during times when sufficient supplies of vaccine may not be available.

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