

PHARMACOTHERAPY NEWSLETTER

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June 22, 2009

Volume 1; Issue 23

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Question: Is oseltamivir (Tamiflu®) effective if administered greater than 48 hours after the onset of flu-like symptoms caused by swine-origin influenza A (H1N1) viral infection?

Answer: As the swine-origin influenza type A (H1N1) virus spreads across the globe, more patients will qualify for treatment with the neuraminidase inhibitor, oseltamivir (Tamiflu®). For information on how oseltamivir works to prevent and treat the current H1N1 virus, please refer to the Pharmacotherapy Newsletter from May 4, 2009.¹ The Centers for Disease Control and Prevention (CDC) currently recommends that clinicians initiate oseltamivir therapy within 48 hours of symptom onset.² However, many patients are not able or simply do not present to their health care provider within this window of time. How effective is oseltamivir in patients who have been experiencing flu-like symptoms for greater than 48 hours?

There are limited data regarding this topic. In addition, the data reflect the use of oseltamivir in the context of the seasonal flu virus not the current swine-origin influenza A (H1N1) virus. However, the CDC does comment on its use in patients who have had symptoms longer than 48 hours.² The CDC essentially states that if it is determined by a physician that a patient should be treated with oseltamivir, then the full treatment course with a neuraminidase inhibitor should be started even it has been greater than 48 hours.² This recommendation is based in part on Infectious Diseases Society of America's (IDSA) influenza guidelines. This report states that, "persons who require hospitalization for laboratory-confirmed influenza, whose positive laboratory test result for influenza is from a specimen obtained >48 h after the onset of illness may also benefit from treatment" and is graded as a B-II recommendation. A B-II recommendation is defined as moderate strength evidence to support a recommendation for or against use derived from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time-series; or from dramatic results from uncontrolled experiments.³

This recommendation is based on a prospective cohort study conducted by the Toronto Invasive Bacterial Diseases Network to assess the impact of antiviral therapy on outcomes of patients hospitalized with influenza in Ontario, Canada from January 2005 through May 2006. The primary outcome was mortality within 15 days of symptom onset. Patients were diagnosed with influenza by enzyme immunoassay (EIA), direct fluorescent antigen detection, and/or culture. Logistic regression models were used to adjust for covariates that might be confounders affecting the effect of antiviral therapy on mortality.⁴

Outcomes of 322 adult patients (15-99 years of age) were evaluated; 103 patients received oseltamivir compared to 219 patients who did not receive oseltamivir therapy.⁴ Those patients in the oseltamivir arm were given 75 mg by mouth twice a day for 5 days or an equivalent adjusted dose for renal insufficiency. This study is important because it did treat some patients with symptom onset beyond the 48 hours. For all patients, the 15 day mortality rate was 3.9% (4/103) in the oseltamivir arm and 10% (22/219) in control arm, odds ratio (OR) 0.36 (95% CI, 0.12-1.1), p=0.08. Based on these results, 16 patients would have to be treated to prevent 1 death. How did patients do when starting oseltamivir 48 hours after symptom onset?

For patients who received oseltamivir after 48 hours of symptoms onset, the OR for oseltamivir associated mortality was 0.24 (0.05-1.14).⁴ The main finding was that some patients appeared to benefit from antiviral

therapy initiated >48 hours after symptom onset; however, results were not statistically significant, possibly due to limited power. Why do some patients seem to benefit from therapy initiated >48 hours from symptom onset?

In the aforementioned study, 75% of patients had an underlying chronic condition such as cancer, diabetes, renal or pulmonary diseases. It appears that in patients with healthy immune systems, viral replication and viral load starts decreasing up to 48 hours after symptom onset.⁵ In patients with compromised immune systems the viral load clearance may be delayed, which may explain a benefit from antiviral therapy after 48 hour symptom onset in patients with chronic disease states.^{6,7}

While this data suggests some patients may benefit from initiating oseltamivir treatment beyond the 48 hour window, it is important to remember that it does not include patients with the current strains of the influenza A (H1N1) virus. Fortunately, the current H1N1 strain does not appear to be as virulent or deadly as the H1N1 strain from the 1918 pandemic that killed so many people worldwide.⁸ However, the H1N1 strain from the 1918 pandemic also started out slow but ended up escalating to kill over 25 million people. The ideal scenario is for oseltamivir to be administered within 48 hours of symptom onset, especially if the current H1N1 strain were to take a turn for the worse.

(PW Pharmacother Newsl 2009;1(23):1-4.) ©2009 Pharmacology Weekly, Inc.

Take Home Points:

- There is limited evidence demonstrating the benefit of initiating oseltamivir therapy >48 hours after symptom onset from seasonal flu in hospitalized patients. No data exists for the current H1N1 virus.
- The Infectious Disease Society of America influenza guidelines recommend initiation of oseltamivir therapy in hospitalized patients if symptoms have been present for >48 hours. This is considered a B-II level of evidence.
- Ideally, oseltamivir should be started within 48 hours of symptom onset to maximize survival and symptom duration benefits.
- In patients with projected delayed viral clearance (i.e., immunocompromised states), initiating oseltamivir >48 hours after symptom onset may be beneficial in reducing mortality and decreasing symptom duration.

Considerations for Clinicians Based on Setting:

Outpatient Setting:

Since many patients will initially present to the clinic, emergency department, and/or physician's office with complaints of the flu, clinicians in the outpatient setting will likely be initially triaging patients and making the determination for the need for prophylaxis, treatment and/or hospital admission. Due to potential issues related to the availability of oseltamivir, clinicians should try to accurately determine who is likely to have the flu and require treatment and/or prophylaxis. The symptoms of the flu include: fever (generally greater than 100°F), chills, headache, dry cough, achy joints, and GI distress (including nausea /vomiting and even diarrhea). If a patient has a high likelihood of having the flu, it is preferable to start oseltamivir within 48 hours of onset of symptoms and prophylaxis for family members or close contacts. See the [CDC website](#) for more information.

Inpatient Setting:

The same information from the outpatient setting should apply to the inpatient setting as well. If oseltamivir treatment was initiated prior to admission, it should be continued in the hospital for at least 5 days (total treatment regimen) per the current CDC recommendations. Prophylaxis of family members or other close contacts should also be given consideration. See the [CDC website](#) for more information.

Important Counseling Bullet Point(s):

- It would be critical for clinicians to counsel their patients to start the medication without delay upon being given a valid prescription and to complete the entire course whether it is being used for prophylaxis or treatment. In addition, it would be advisable to counsel them on mechanisms to prevent further exposure to the public or close contacts should they have the current strain of H1N1 virus. These include: covering their mouths appropriately when coughing and sneezing, washing their hands routinely and using an alcohol based hand sanitizer, staying at home for at least 7 days, getting plenty of rest, and drinking appropriate fluids to prevent dehydration to name a few.

Medical/Legal Consideration(s):

- There were no cases identified in the 2008 edition of LexisNexis' Drugs in Litigation regarding oseltamivir, Tamiflu® or products liability claims against the drug manufacturer, and Pharmacology Weekly's legal counsel has not identified any such cases to date.⁹ Nevertheless, because of the risk which has now been clearly identified by the CDC and World Health Organization, it would be prudent to document in the medical chart that the patient has been appropriately screened for the current H1N1 strain and advised of precautions to prevent its spread and/or contraction. In addition, if prophylaxis and/or treatment are offered to the patient, documentation of the need to start the medication without delay and to complete the entire course would be important to also include in the medical chart.

Test Questions for CE:

Which of the following outcomes is potentially improved in some patients with oseltamivir initiation >48 hours after symptom onset for seasonal flu?

- a. Hospital length stay
- b. Quality of life
- c. Mortality
- d. Pain level

What is a proposed mechanism for why some patients respond to oseltamivir > 48 hours after symptom onset?

- a. Patient's underlying immunocompromised states can have decreases in viral clearance
- b. Patient's healthy immune system decreases viral clearance
- c. Patient's decreased metabolism of oseltamivir
- d. Increased viral susceptibility to oseltamivir

What level of evidence is the Infectious Disease Society of America's current recommendation regarding the administration of oseltamivir >48 hours after symptom onset for seasonal flu?

- a. A-II
- b. C-I
- c. B-I
- d. B-II

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Disclosures of Conflict of Interest: None

Issue Citation:

Bar SA, Herrington JD, Busti AJ, Lehew DS, Nuzum DS, Daves BJ, McKeever GC. Is oseltamivir (Tamiflu®) effective if administered greater than 48 hours after the onset of flu-like symptoms from the swine-origin influenza A (H1N1) viral infection? PW Pharmacother News 2009;1(23):1-4.

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