VIEWPOINT

Treating Influenza With Neuraminidase Inhibitors
What Is the Evidence?

Janice K. Louie, MD, MPH
Division of Infectious Diseases, Department of Medicine, University of California, San Francisco.

Harry Lampiris, MD
Division of Infectious Diseases, Department of Medicine, San Francisco VA Health Care System, University of California, San Francisco.

The approaching influenza season will likely bring renewed debate about the usefulness of the neuraminidase inhibitors, a class of antiviral drugs approved for the chemoprophylaxis and treatment of influenza. The available approved formulations include oral oseltamivir (Tamiflu; Roche Pharmaceuticals), inhaled zanamivir (Relenza; GlaxoSmithKline), and intravenous peramivir (Rapivab; BioCryst Pharmaceuticals). All 3 drugs are perceived to have comparable efficacy, although because of its ease of administration, oseltamivir has been the best studied and is the most aggressively marketed and prescribed neuraminidase inhibitor in the United States and worldwide.

The utility of the neuraminidase inhibitors has been in question since their introduction in 1999, when randomized clinical trials (RCTs) sponsored by the manufacturer suggested that oseltamivir, when taken by healthy outpatients within 48 hours of symptom onset, could decrease the duration of influenza by a median of 70 hours and decrease patient-perceived severity of illness.[1] At the time, given the modest clinical benefit and the high cost (approximately $130 for a 5-day course), oseltamivir was prescribed infrequently.

In 2006, the reasons to treat patients with oseltamivir were bolstered when a Cochrane Collaboration meta-analysis concluded that early treatment also prevented lower respiratory tract infections.[2] However, this conclusion was later questioned, with critics pointing out that the review was heavily biased by inclusion of a manufacturer-sponsored meta-analysis of 10 studies, only 2 of which had been published in peer-reviewed journals. Subsequently, the Cochrane Collaboration began a 4-year quest to obtain access to the entire clinical trial data set held by Roche. The resulting analysis, published in 2014, reviewed data from 46 RCTs. This analysis found that early oseltamivir treatment decreased the duration of influenza symptoms by 17 hours in adults and 29 hours in children.[3] No benefit was found for the prevention of pneumonia, but the studies were not designed for this outcome (for example, the definitions of pneumonia did not include radiographic confirmation). Rates of influenza hospitalizations or deaths were unchanged: these events were rare in both treated and untreated groups. The overall conclusions of the 2006 and 2014 Cochrane studies were very similar.[2,3]

The conclusions of the Cochrane studies were not surprising, especially given the populations studied—the RCTs were conducted in healthy outpatient adults and children, defined as those with chronic illnesses such as asthma, diabetes, and hypertension but not those with immunosuppression as in malignant conditions or infection with human immunodeficiency virus.[2,3] Healthy outpatients are less likely than chronically ill patients to have severe influenza, so effects on morbidity and mortality would be difficult to ascertain. Virologic studies suggest a strong correlation between viral replication, clinical symptoms, and disease severity, with detection of viral nucleic acid by reverse-transcriptase polymerase chain reaction from respiratory specimens often used as an approximation for the presence of actively replicating influenza virus.[4] In healthy patients with influenza, most viral shedding occurs during the first 2 to 3 days after the onset of illness, with trends in symptom scores closely matching changes in concentrations of detected influenza virus. This short duration of viral shedding is consistent with a brief window of clinical benefit for neuraminidase inhibitors.

However, the Cochrane findings[2,3] are difficult to interpret with regard to treating patients with severe illness who are hospitalized or patients infected with novel influenza strains. Patients with influenza who are hospitalized or in intensive care typically shed virus for weeks—neuraminidase inhibitors likely have benefit because they can arrest active viral replication. Likewise, although some novel influenza viruses may have mild to moderate virulence (such as H1N1, the influenza A virus that was the most common cause of influenza in 2009), others (such as Asian avian influenza A [H5N1]) are very pathogenic and have case fatality rates that approach 50%. Viral shedding following H5N1 infection is typically active and prolonged, frequently precipitating a "cytokine storm," sepsis physiology, and multi-organ failure.[5] Early neuraminidase inhibitor drug treatment may prevent activation of the cytokine pathways that result in the storm.

In 2005, following global outbreaks of H5N1 in both poultry and people, the World Health Organization (WHO) recommended mass stockpiling of neuraminidase inhibitors so that the medication would be available to treat hospitalized and severely ill patients. The WHO relied on the available evidence—large observational studies that lacked the stringent enrollment criteria or rigorous design of RCTs. In 2009, at the onset of the H1N1 pandemic, the impact of the emerging virus on morbidity and mortality was not known—the initial news reports of young healthy adults dying in Mexico City were alarming. As a result, and with no available vaccine, the Centers for Disease Control and Prevention (CDC) and the WHO recommended widespread use of neuraminidase inhibitors. In retrospect, the 2009 H1N1 pandemic was not severe, and its lack of severity fueled the ensuing controversy about the recommendations for widespread treatment of influenza. Although the Cochrane findings added to the concern,[2,3] they may not apply to the scenario of life-threatening infections that the CDC and the WHO were initially worried about.

The debate about the role of neuraminidase inhibitors continued well into the 2014-2015 influenza sea-

Corresponding Author: Janice K. Louie, MD, MPH, Division of Infectious Diseases, Department of Medicine, University of California, San Francisco, 513 Parnassus Ave, San Francisco, CA 94143 (Janice.Louie@ucsf.edu).

Copyright 2015 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Medical College of Wisconsin User on 01/06/2020

son, when release of the most recent Cochrane results coincided with strong messages from the CDC recommending antiviral treatment in high-risk or severely ill patients with seasonal influenza.[6] In the fall of 2014, public health officials were concerned about a severe influenza season; one reason was a poor match between components of the northern hemisphere influenza vaccine and circulating influenza strains. The evidence suggesting benefit for treating high-risk or severely ill patients has in large part been based on data from observational retrospective studies published following the 2009 pandemic and has continued to grow. Many of these studies have shown that morbidity and mortality are reduced in hospitalized and critically ill patients, and that the "window of benefit" for starting treatment is significantly longer than would have been anticipated from the RCTs performed in healthy outpatients.[7,8] Data from the observational studies have also identified previously unrecognized populations at risk for severe disease (such as patients with morbid obesity) and confirmed that pregnant women, young children, and the elderly are all at high risk.[8]

Finally, in contrast to the findings of the Cochrane meta-analyses,[2,3] which was based on summary data from the RCTs, an individual patient data meta-analysis found a decreased risk of lower respiratory tract infection and hospitalization with early oseltamivir treatment.[9] The study, published in 2015, was funded by an unrestricted grant from Roche Pharmaceuticals to a foundation; the authors stated that neither the company nor the foundation had any role in the analysis, interpretation, or reporting of data, or in the decision to submit the manuscript for publication. Of the four authors, one reported receiving fees from Roche and another company outside the submitted work, and another reported receiving travel funding from Roche.[9]

In conclusion, the available evidence suggests that the effect of neuraminidase inhibitors on morbidity and mortality from influenza depends on the population being treated and the setting. The findings from the Cochrane reviews are important,[2,3] but the trials were performed with a specific population (healthy outpatients) and a different outcome (duration of symptoms rather than assessment of pneumonia or mortality) in mind. Because the CDC and WHO have formally endorsed treatment with neuraminidase inhibitor drugs in high-risk or severely ill patients with seasonal influenza, it is unlikely that RCTs in such populations will be performed, as such trials would raise ethical concerns.[10,11] Although the evidence to treat high-risk or hospitalized patients is inadequate and does not meet the highest level of evidence (RCTs have not been performed in these populations to confirm clinical benefits), the available observational data suggest benefit, especially in hospitalized patients. When influenza is circulating in the community, early treatment with a neuraminidase inhibitor should be emphasized for outpatients with risk factors for severe disease, such as pregnant women, the elderly, young children, people who are immunocompromised, and for those with severe or progressively worsening illness. Likewise, hospitalized patients with clinical signs and symptoms suggestive of influenza should be treated promptly. In both settings, treatment should not be delayed for the results of influenza testing. Rapid influenza diagnostic tests may have poor sensitivity; therefore, even if the results of a rapid influenza diagnostic test are negative, patients meeting the listed criteria should be treated when the clinical suspicion of influenza is high. These recommendations are consistent with those of both the CDC and the Infectious Disease Society of America.[8,11]

ARTICLE INFORMATION

Published Online: October 19, 2015. doi:10.1001/jamainternmed.2015.5747.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Treanor JJ, Hayden FG, Vrooman PS, et al; US Oral Neuraminidase Study Group. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. *JAMA*. 2000;283(8):1016-1024.

2. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev*. 2006;(3):CD001265.

3. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev*. 2014;4:CD008965.

4. Fielding JE, Kelly HA, Mercer GN, Glass K. Systematic review of influenza A(H1N1)pdm09 virus shedding: duration is affected by severity, but not age. *Influenza Other Respir Viruses*. 2014;8(2):142-150.

5. Uyeki TM. Human infection with highly pathogenic avian influenza A (H5N1) virus: review of clinical issues. *Clin Infect Dis*. 2009;49(2):279-290.

6. Centers for Disease Control and Prevention (CDC). Seasonal influenza communications to health care providers: antiviral letter to providers. http://www.cdc.gov/flu/pdf/professionals/antiviral-letter-providers-2014-2015.pdf. Accessed September 9, 2015.

7. Muthuri SG, Venkatesan S, Myles PR, et al; PRIDE Consortium Investigators. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med*. 2014;2(5):395-404.

8. Centers for Disease Control and Prevention (CDC). Recommendations of the Advisory Committee on Immunization Practices (ACIP): Information for Health Care Professionals. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed May 14, 2015.

9. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet*. 2015;385(9979):1729-1737.

10. World Health Organization. WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses: revised February 2010. http://www.who.int/csr/resources/publications/swineflu/h1n1_guidelines_pharmaceutical_mngt.pdf. Accessed June 24, 2015.

11. Infectious Disease Society of America. Statement by the Infectious Disease Society of America (IDSA) on the recent publication on "Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children": April 2014. http://www.idsociety.org/Influenza_Statement.aspx. Accessed May 14, 2015.

Copyright 2015 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Medical College of Wisconsin User on 01/06/2020