Peramivir: Another Tool for Influenza Treatment?

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(See the article by Hernandez et al, on pages 695–706.)

During the 2009 influenza A (H1N1) (pH1N1) pandemic, young persons and groups with certain health conditions, including pregnant women, were disproportionately affected, although illnesses and influenza-related complications were seen in all age groups [1, 2]. Vaccine was not available until after the peak of the fall pH1N1 wave in the Northern Hemisphere, after the peak of pH1N1 circulation in the Southern Hemisphere, and not until early 2010 in many developing countries [3]. Thus, influenza antiviral drugs were the primary influenza-specific pharmacologic tools available to minimize severe illness and death, and there were limited treatment options for severely ill persons, especially those receiving mechanical ventilation. One year after the pandemic and as the annual influenza season looms for the Northern Hemisphere, this is a salient time to think about the tools at hand and in development to mitigate severe illness from influenza infection.

Currently, 2 classes of antiviral drugs are approved by the US Food and Drug Administration (FDA) and widely available for the treatment of influenza: neuraminidase inhibitors (NAIs) and adamantanes [4, 5]. However, only NAIs are recommended for treatment of influenza A and B because of a high level of resistance to adamantanes among influenza A viruses, including pH1N1, and because adamantanes are not effective against influenza B [4, 5]. NAIs target the influenza A and B virus neuraminidase and, by inhibiting enzyme activity, prevent the release of new virions, thereby stopping virus replication. Adamantanes target the influenza A virus M2-protein and block virus replication by inhibiting H+ flow across the M2 protein channel. Since April 2009, pH1N1 viruses have been inherently resistant to adamantanes because of the presence of asparagine at amino acid 31 in the M2 protein and, except for rare instances, are susceptible to NAIs [5–7]. Although only 2 NAIs (oral oseltamivir and inhaled zanamivir) are licensed and approved for use [4, 5], 2 investigational intravenous NAIs (peramivir and zanamivir) were available in the United States by FDA emergency investigational new drug (eIND) request from the manufacturer during the pH1N1 pandemic [8,9]. Peramivir was available in the United States by Emergency Use Authorization (EUA) from 23 October 2009 through 23 June 2010 [8, 9]. In addition, intravenous peramivir has had market authorization in Japan since January 2010 and South Korea since August 2010 and is otherwise available only through clinical trials in several countries, including the United States [9].

In this issue of Clinical Infectious Diseases, Hernandez et al [9] describe a convenience sample of 31 hospitalized patients in the United States who received peramivir under eIND during the pH1N1 pandemic. There were no specified criteria for receipt of peramivir under the eIND, but most appeared to be severely ill. Among 31 patients receiving daily intravenous peramivir for a duration of 2–15 days, none were reported to have a serious adverse event. Forty percent of patients had acute renal failure and required renal replacement therapy, and the drug was effectively cleared without any adverse events. In addition, 2 pregnant women recovered from their influenza infections and delivered healthy infants without immediate adverse events noted from either oseltamivir or peramivir; long-term follow-up of these infants would be useful. One-third of patients were children, the majority of whom were 10–17 years of age; all tolerated peramivir without significant adverse events.

The EUA required mandatory reporting of selected adverse events by clinicians to FDA via the FDA Adverse Event Reporting System (AERS) [8]. The FDA received AERS reports on 237 patients (19 children and 218 adults), from ~1250 peramivir releases under the EUA through 12 March 2010, most of whom were critically ill and with comorbidities...
Although no unusual drug-related safety signals were identified through AERS [10], similar to the reports by Hernandez et al [9], both the eIND and EUA patients were critically ill, had comorbidities, and concurrent treatments, and neither had a comparison group. Thus, the ability of these data to assess safety is limited.

Hernandez et al [9] also describe clinical parameters and outcomes of patients who were severely ill, the majority of whom received mechanical ventilation, at the time of peramivir initiation. The majority (87%) received concurrent oseltamivir, and no comparison group was available. It is unclear why clinicians chose to continue both NAIs. In addition, the authors provide no data on virologic outcomes, such as detection of virus from respiratory specimens or quantification of virus titers in serial respiratory specimens, to document virus clearance. Thus, these data cannot provide insight into the effectiveness of intravenous peramivir in severely ill persons infected with influenza.

A phase 3 randomized clinical trial (RCT) to evaluate the effectiveness of peramivir in hospitalized patients is currently underway. Until these data are available, additional information on intravenous peramivir will be useful, including adverse event information from additional patients receiving 600 mg daily for multiple days and virologic outcomes in patients receiving intravenous peramivir. Currently, data on the use of intravenous peramivir in severely ill hospitalized patients are very limited [5, 8].

There have been no RCTs to assess the efficacy of NAIs among hospitalized patients; however, RCTs in outpatients, including 1 trial with peramivir, have shown a reduction of duration of symptoms by 1–1.5 days when administered within 2 days after illness onset [5, 9]. Three observational studies of hospitalized patients with laboratory-confirmed seasonal influenza indicated a reduction in mortality and shorter duration of hospitalization with oseltamivir treatment, even when antiviral drugs were initiated >48 h after symptom onset [11–13]. Observational data from the pH1N1 pandemic also suggested that early antiviral treatment was associated with increased survival, including in pregnant women, children, and in severely ill patients [1, 14–20]. The RCT to evaluate the safety and efficacy of intravenous peramivir in hospitalized patients will be an important addition to the current evidence base.

Because almost 100% of pH1N1 viruses are inherently resistant to adamantanes [5, 7], patients with pH1N1 infection with an oseltamivir-resistant virus have limited options for treatment, especially those who are severely ill. Oseltamivir-resistant pH1N1 viruses were rarely detected during April 2009–August 2010, and among those that were, all had the H275Y mutation in the neuraminidase [5, 7]. This mutation is associated with elevated 50% inhibitory concentration (IC50) values for oseltamivir and intermediate IC50 values for peramivir. Although the clinical relevance of intermediate IC50 values is unknown and the IC50 values are below the peak of peramivir plasma concentrations (~10,000 nM), the effectiveness of peramivir in a patient with infection with a pH1N1 virus with the H275Y mutation is likely to be suboptimal. Thus, at this time, zanamivir is the preferred treatment option for patients infected with pH1N1 viruses with the H275Y mutation [5]. Although fortunately rare, viruses with resistance to 3 of 4 currently licensed antiviral agents highlight the need for new drugs with activity against influenza viruses, especially those that inhibit new virus targets, other than the M2 protein or neuraminidase.

Worldwide, annual influenza epidemics result in an estimated 3–5 million cases of severe illness and 250,000–500,000 deaths every year [21]. Vaccination is the primary tool to prevent influenza infection. However, because of suboptimal vaccination rates in developed countries, little use at all in developing countries, and because influenza vaccine effectiveness is not 100%, the need for antiviral treatment will continue for the foreseeable future. With only the NAI class of agents effective against circulating influenza virus strains and the potential threat of global circulation of oseltamivir-resistant influenza viruses, as occurred with the seasonal H1N1 viruses in 2007–2008 and 2008–2009 [5, 7], it is clear that new antiviral agents are needed. Antiviral agents that target different cellular proteins and/or drugs that are not susceptible to the same resistance mechanisms as oseltamivir are needed. Studies to evaluate the effectiveness of new antiviral agents, including peramivir, and new treatment strategies with clinical and virologic outcomes in severely ill persons are needed to inform clinical care. Without such studies, it is yet unclear how peramivir and other new influenza antiviral treatment strategies fit into our armamentarium.

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