Resistance to Neuraminidase Inhibitors

Raphael Dolin
Division of Viral Pathogenesis, Beth Israel Deaconess Medical Center-Harvard Medical School, Boston, Massachusetts

(See the article by Tamura et al, on pages 432–437.)

Development of resistance by a virus to the effects of an antiviral drug is a critical determinant for the selection and ultimate utility of antiviral chemotherapy, as has long been the case for resistance of other types of microbial pathogens to antibiotics. Therefore, timely and readily accessible information on resistance patterns of viruses that cause common infections, such as influenza, are of considerable interest. The report by Tamura et al [1] in this issue of Clinical Infectious Diseases adds information on the relative frequency of resistance of influenza viruses after treatment with the neuraminidase inhibitors oseltamivir and zanamivir. In comparison to antibacterial antibiotics, relatively few antiviral agents have been available against influenza. The adamantane compounds, amantadine and rimantadine, have been used for prophylaxis and treatment of influenza A for >40 years. Resistance to these compounds, although easily inducible in vitro, was relatively uncommon until the 2005–2006 influenza season, when the prevalence of resistance among influenza A/H3N2 virus isolates reached 61% in Asia and 92% in the United States [2, 3]. The reasons for this rapid emergence are unclear, but they may have been related to widespread over-the-counter use of amantadine, use of amantadine-related medications, or use of amantadine in poultry flocks [4]. Emergence of resistance to the adamantanes in some settings appears to have emerged without drug pressure. Seasonal influenza A/H1N1 viruses remained sensitive to the adamantanes until the emergence of pandemic A/H1N1 virus strains in 2009, which are largely resistant to these drugs.

In general, resistance to neuraminidase (NA) inhibitors develops less frequently than does resistance to the adamantane compounds. Reports of high rates of infection due to oseltamivir-resistant influenza viruses were uncommon until 2004 [5], but diverse sites began to report high rates of resistance to oseltamivir among influenza A/H1N1 viruses in 2006–2007. By 2008–2009, resistance to oseltamivir among seasonal A/H1N1 viruses was present worldwide [6, 7]. The emergence of resistance to oseltamivir has been noted with and without apparent drug pressure. Pandemic A/H1N1 viruses have been largely susceptible to oseltamivir, although 304 pandemic A/H1N1 isolates had been reported to be resistant to oseltamivir by the World Health Organization through August 2010 [8]. Seasonal and pandemic A/H1N1 viruses have remained generally susceptible to zanamivir, although rare infections due to zanamivir-resistant virus strains have been described, particularly among immunosuppressed patients [9].

The study by Tamura et al [1] found that resistance developed more often in children who were treated with oseltamivir (6 [8.3%] of 72 children) than in those who received zanamivir (0 of 72 children) (P = .028). The study was observational in design, involved children 4–15 years of age, and obtained specimens over 4 influenza seasons from 2005 through 2009, before the emergence of pandemic A/H1N1 virus. The study also found that zanamivir recipients shed virus for a shorter period of time than did oseltamivir recipients (ie, had fewer influenza virus isolations on days 5–7 after treatment had been begun [P = .008]). This reduction of virus shedding with zanamivir was similar to that observed by this group in infection due to A/H3N2 (but not A/H1N1) viruses in a previous study [10]. Interpretation of these findings is limited by the lack of a random, blinded allocation to treatment and by the relatively small size of the study. Along with the relatively mild nature of the illness which was observed, this limits the power to compare the clinical effects of treatment or the rates of complications in this study. Thus, the authors were unable to detect any differences in
clinical effects between oseltamivir and zanamivir treatment in their study, which is also similar to their findings in a previous study (10), nor did they observe prolonged clinical courses in the few (6) subjects who shed resistant virus.

The development of resistance to antiviral therapy remains a continuing concern in influenza, as it does for other viral infections. The data presented in the current report by Tamura et al [1] and elsewhere highlight the importance of developing strategies to reduce the likelihood of the emergence of resistance to antivirals against influenza. These strategies should be based on increased information regarding the molecular, pharmacokinetic, and physiologic basis for resistance and, ultimately, on data from rigorously conducted comparative clinical trials. A traditional approach to preventing the emergence of resistance has been the use of combinations of antibiotics, including antivirals, that are either synergistic or at least additive in activity. Of interest, a recently published randomized trial found a somewhat unanticipated result, that the combination of oseltamivir and zanamivir was less effective than oseltamivir monotherapy, both virologically and clinically, in treating A/H3N2 infection in adults [11]. Comparative antiviral studies of this type need to be confirmed and extended to include other patient populations and influenza virus subtypes. Widespread epidemiologic surveillance for influenza virus infection and for resistance patterns will continue to be needed to provide essential information for appropriate use of antivirals and for the design of clinical studies to develop and assess treatment strategies.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

References