Implications of Antiviral Resistance of Influenza Viruses

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(See the article by Stephenson et al. on pages 389–96)

Until very recently, concern about antiviral resistance was focused on only 1 of the 2 classes of drugs licensed for prophylaxis and treatment of influenza. The adamantanes, also called M2 inhibitors because of their principal mode of antiviral action, have been used intermittently for influenza A virus infection for >40 years. Amino acid substitutions in one of several positions in the M2 protein of the virus make both amantadine and rimantadine completely ineffective. These mutations are so closely associated with high levels of drug resistance that it is unnecessary to confirm drug resistance phenotypically in 50% inhibitory concentration assays [1]. Drug-resistant strains develop in ~30% of patients treated with either adamantane, and these strains are easily transmitted [2]. Until 2003, nearly all community isolates of influenza A virus remained susceptible to the adamantanes [3]. This change likely resulted from a major increase in the overall use of amantadine that accompanied the spread of influenza A/H5N1 (influenza A/H1N1) virus. At present, in the United States, most influenza A subtype H3N2 (influenza A/H3N2) virus strains circulating are resistant to adamantanes, most influenza A subtype H1N1 (influenza A/H1N1) virus strains remain susceptible to adamantanes, and globally, resistance of influenza A/H5N1 virus to adamantanes varies by clade.

The neuraminidase inhibitors (NAIs), inhaled zanamivir and oral oseltamivir, were developed to fit into the enzymatically active pocket of the neuraminidases of influenza A and B viruses [4]. In early studies, it was observed that posttreatment resistance to both NAIs occurred far less frequently than did the documented resistance to the adamantanes. However, when detected, resistance to oseltamivir was more common than resistance to zanamivir. There was initially a debate about whether this was a result of a real difference or of sampling biases. That issue has been resolved, with drug resistance being more commonly found after oseltamivir treatment than after zanamivir treatment. Drug resistance has been detected mainly in young children, who normally shed virus for long periods and can be treated only with oseltamivir [5]. It is now clear that the molecular basis for NAI resistance is far more complicated than that for the adamantanes. Although there are several more-common subtype-specific mutations that produce high levels of drug resistance, various other mutations produce intermediate levels. Therefore, both genotypic and phenotypic studies, the latter determining 50% inhibitory concentrations, are required to fully address the issue of drug resistance [6].

Japan has been using more NAIs than the rest of the world; Japan initially used oseltamivir and currently also uses zanamivir. Several studies from Japan have examined the emergence of viral resistance to oseltamivir in infected individuals, particularly children, treated with that drug. Drug-resistant strains were demonstrated in 9 (18%) of 50 young children who were administered oseltamivir according to the Japanese dosing schedule, which is based on patient weight [7]. Of the 11 children who shed drug-resistant influenza A/H3N2 virus, 9 had strains with the Arg292Lys (R292K) mutation and 2 had strains with the Glu119Val (E119V) mutation. Strains with the former mutation are resistant to only oseltamivir; all of these children had virus with the Hys274Tyr (H274Y) mutation, which produces resistance to oseltamivir only [8].

The Japanese purely weight-based dosing schedule has been criticized, because the drug is excreted more rapidly in young children than in adults, resulting in potential underdosing. Throughout the rest of the world, a tiered weight-based dosing system is used, which in effect, involves an increased dosage, compared with the
Until 2007, it was thought that these drug-resistance mutations were not likely to become prevalent at a community level. In studies involving ferrets, the influenza A/H3N2 strains with the R292K mutation were not transmitted, and the influenza A/H1N1 strains with the H274Y mutation were transmitted but only if high levels of viral inoculum were used [14–16]. Meanwhile, no increase in the prevalence of drug-resistant viruses examined both genetically and phenotypically was recognized anywhere in the world [6]. This changed in the winter of 2007–2008 in many areas of Europe, where the H274Y mutation was frequently identified among the seasonally predominant influenza A/H1N1 isolates [17]. Paradoxically, this phenomenon did not appear to be directly related to increased use of antiviral agents. Countries with the highest prevalence of drug-resistant virus used little or no oseltamivir. In Japan, where the drug was most used, the prevalence of resistance remained low. Researchers have been attempting to determine what produced the change in the prevalence of drug resistance. The drug-resistant strains recently appeared in the Southern Hemisphere and, as the Northern Hemisphere winter has begun, they have also appeared here with high frequency.

Fortunately, the influenza A/H3N2 strains remain susceptible to both NAIs, even though they are generally resistant to the adamantanes. The influenza A/H1N1 strains produce the mildest disease overall and are rarely associated with excess mortality in defined risk groups [18]. However, H1N1 strains have been associated with complications, particularly in immunosuppressed persons [19]. With current diagnostic tests, particularly the bedside rapid tests, influenza A/H3N2 and influenza A/H1N1 subtypes cannot be distinguished. Therefore, the issue is which antiviral agents to choose if influenza A/H1N1 strains that are resistant to oseltamivir become common, because therapy must be initiated early. The effects of drug resistance will depend on the prevalence of these viruses; in most years, influenza A/H1N1 virus has not accounted for more than a small portion of isolates throughout most of the United States. Therefore, recommendations for the end of the 2007–2008 influenza season to continue use of oseltamivir in the United States for primary care were based on 4 premises: the influenza A/H3N2 strains, which occurred more frequently, were of greatest concern and are generally susceptible to oseltamivir and resistant to the adamantanes; the influenza A/H1N1 strains were of less concern than the influenza A/H3N2 strains, even though the H1N1 strains might be resistant to oseltamivir; it would be hard to identify which subtype was involved in time to make a clinical decision; and zanamivir was not commonly available. These recommendations did not apply, for example, to immunocompromised patients, for whom it would be possible to use more-specific, hospital-based diagnostic tests. Because A/H1N1 strains predominated among the type A viruses identified at the beginning of the 2008–2009 influenza season in the United States, there was a need to modify the recommendations at least on an interim basis. Zanamivir has become more available and is now an option for persons able to use an inhaled drug, because both A subtypes are susceptible to it. Alternately, combined use of an adamantane, to which A/H1N1 virus strains are susceptible, and oseltamivir, for A/H3N2 virus strains, can be considered [20]. These rather complicated interim recommendations can change as the season evolves. In the long term, a different, well-studied approach to treatment of influenza will be needed because of the problem of drug resistance. On the basis of what has been learned from the treatment of other viral infections, treatment of influenza should involve combination therapy, especially for persons who are likely to shed virus for long periods.

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References