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Influenza Virus Resistance to Antiviral Agents: A Plea for Rational Use

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Abstract

Although influenza vaccine can prevent influenza virus infection, the only therapeutic options to treat influenza virus infection are antiviral agents. At the current time, nearly all influenza A/H3N2 viruses and a percentage of influenza A/H1N1 viruses are adamantane resistant, which leaves only neuraminidase inhibitors available for treatment of infection with these viruses. In December 2008, the Centers for Disease Control and Prevention released new data demonstrating that a high percentage of circulating influenza A/H1N1 viruses are now resistant to oseltamivir. In addition, oseltamivir-resistant influenza B and A/H5N1 viruses have been identified. Thus, use of monotherapy for influenza virus infection is irrational and may contribute to mutational pressure for further selection of antiviral-resistant strains. History has demonstrated that monotherapy for influenza virus infection leads to resistance, resulting in the use of a new monotherapy agent followed by resistance to that new agent and thus resulting in a background of viruses resistant to both drugs. We argue that combination antiviral therapy, new guidelines for indications for treatment, point-of-care diagnostic testing, and a universal influenza vaccination recommendation are critical to protecting the population against influenza virus and to preserving the benefits of antiviral agents.

Vaccines, antiviral agents, and personal protective nonpharmacological measures are the only tools we currently have to prevent or treat influenza virus infection. Vaccines are designed to prevent infection and its consequences, whereas antiviral agents can both prevent and treat infection. At the current time, only 2 classes of influenza antiviral agents are currently licensed in the United States—M2 ion channel inhibitors and neuraminidase inhibitors. Resistance to both M2 ion channel and neuraminidase inhibitors is usually conferred by a single point mutation in critical residues of the M2 and neuraminidase proteins, respectively [1–3]. Data demonstrate that influenza A viruses resistant to amantadine and rimantadine can emerge quickly during treatment, as early as 2–3 days after initiation of drug therapy [4]. The M2 ion channel inhibitors (amantadine and rimantadine) are ineffective against influenza B strains and, since 2003 in China and 2005 in the United States, are recognized to have extremely

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limited clinical utility because of worldwide influenza A virus resistance to these 2 drugs [1, 5].

On 12 December 2008, the Centers for Disease Control and Prevention released data showing a high level of oseltamivir resistance but susceptibility to zanamivir among nearly all influenza A/H1N1 isolates [6]. All influenza A/H1N1 isolates were susceptible to the adamantanes, whereas all influenza A/H3N2 isolates were resistant to the adamantanes. In addition, emergence of influenza B viruses with reduced susceptibility to neuraminidase inhibitors has been reported [7,8]. Thus far in the 2008–2009 influenza season, 33% of antigenically characterized influenza virus–positive specimens in the United States have been influenza A/H1N1 virus [9]. Controversy exists as to the origin of these oseltamivir-resistant influenza A/H1N1 viruses, because they are more common in countries with less use of oseltamivir (e.g., Norway and South Africa) than in other countries [10,11]. However, with rapid global travel, the emergence of resistant viruses from Asia (it is of concern that Japan has a high population use of oseltamivir and has used drug dosing regimens in children that effectively led to widespread underdosing), and a dynamic evolutionary background in which selective pressures can lead to de novo mutations, the exact origin of these variants and what led to their origin remain unclear. Of concern, however, is that these oseltamivir-resistant viruses appear fit and persistent and are transmissible from person to person [10,12].

At this point, the neuraminidase inhibitors are the sole remaining class of drugs available to prevent or treat influenza A and B virus infection. Likely because of ease of use, oseltamivir (Tamiflu; Roche) has been used preferentially over inhaled zanamivir (Relenza; GlaxoSmithKline) for prophylaxis and treatment. Oseltamivir-resistant viruses usually remain susceptible to zanamivir, because the most common neuraminidase-resistant mutational change (H274Y) affects the ability of oseltamivir, but not that of zanamivir, to bind to the active pocket adjacent to the active site of the neuraminidase enzyme [12]. Nonetheless, in conjuction with the widespread use of oseltamivir, there have been reports of resistance to this drug among influenza A/H3N2 isolates, including antiviral-resistant isolates in specimens obtained from patients not receiving treatment with oseltamivir [13,14]. In addition to resistance among seasonal influenza A/H1N1 viruses, at least 2 documented cases involving children with influenza A/H5N1 virus infection have demonstrated isolates with oseltamivir susceptibility that changed to resistance while the children were receiving oseltamivir therapy [15]. Resistance to oseltamivir has also been detected in 1%–2% of isolates obtained from adults, but it is more common among strains obtained from children, with resistant strains developing in 5%–18% of treated children [16,17].

These events should not be surprising. Influenza A viruses are segmented RNA viruses with extraordinarily high mutational rates. Any antiviral pressure will inevitably lead to mutational changes. What is surprising is the widespread use of these drugs as monotherapy for prophylaxis and treatment. Given the biology of these viruses and the clear and increasingly worrisome evidence of rapidly evolving resistance to these drugs, such single-drug use is not rational. There is no other rapidly mutating RNA viral infection in humans that we would treat with a single drug. Such viral infections are treated with multidrug therapy in an attempt to prevent the development of viral quasi-species that are drug resistant and to avoid driving further antiviral resistance (i.e., mutational pressure) and losing the benefit of each drug. Moreover, although the risk of developing antiviral quasi-species is greater in more-persistent infections (e.g., hepatitis B virus, hepatitis C virus, and HIV infections), it nonetheless does occur in the context of large subgroups of patients who receive treatment or longer-term prophylaxis—particularly among children and immunocompromised patients who shed virus for longer periods of time and for whom transmissibility of such variants has occurred [12, 14,18–20].

To date, oseltamivir-resistant viruses are usually susceptible to zanamivir, but with the increasing resistance to oseltamivir worldwide and the increasing use of zanamivir monotherapy, it is quite possible that we may begin to see the development of zanamivir resistance. At least 2 studies have isolated influenza B viruses resistant to both oseltamivir and zanamivir [8,21]. This illustrates a dangerous and irrational therapeutic trend—the sequential use of antiviral drugs, starting one drug after the development of resistance to another drug. Such use in immunocompromised persons led to the development of dual resistance to oseltamivir and M2 ion channel inhibitors [22]. These usage and resistance patterns are particularly important in situations in which significant morbidity and mortality are likely—such as in influenza A/H5N1 virus infection or in other novel influenza virus or influenza A virus infections among immunocompromised or elderly individuals for whom prolonged treatment and the opportunity for development of antiviral resistance and transmission of resistant viruses may be more likely.

It is time to consider a more rational use of antiviral agents against influenza virus, including point-of-care testing, better algorithms for clinical use (perhaps restricting use to patients likely to develop life-threatening complications and infections), and the use of at least 2 drugs to prevent antiviral resistance from developing—ideally, using drugs with different mechanisms of action. Although the use of ≥2 agents may increase costs in the short term, the long-term clinical and economic advantages of avoiding multidrug-resistant influenza strains potentially far outweigh such concerns. For example, recognition of these issues may provide an opportunity to pursue development of a combination medication that incorporates ≥2 antiviral agents in 1 formulation. This also requires ongoing research in the development of additional influenza antiviral drugs with different mechanisms of action, such as targeting inhibition of viral attachment, polymerase inhibition, and other novel strategies. In addition, further clinical research on the efficacy and safety of a multidrug regimen is urgently needed to determine the potential for drug-drug interactions, adverse effects, efficacy, and other important outcomes. Early data involving the use of both oseltamivir and zanamivir in combination treatment, however, has demonstrated efficacy with no evidence of antiviral resistance [23,24]. A controlled clinical trial of oral rimantadine and aerosolized zanamivir versus rimantadine alone for treatment of adults with influenza virus infection complicated by serious lower respiratory tract involvement demonstrated a shorter duration of viral detection in the combination treatment group. The only antiviral-resistant isolates emerged from the rimantadine monotherapy treatment arm [25]. Pre-clinical in vitro and animal studies have also demonstrated reduced emergence of resistant influenza virus variants with the use of combination therapy [19,26].

In the meantime, given temporal and geographic changes and the shifts in antiviral drug resistance among influenza viruses, as well as rapid global travel, further research into rapid and inexpensive methods for point-of-care influenza virus subtyping is needed to provide a rational basis for therapeutic drug selection. Moreover, it would be shortsighted to lose the ability to manufacture antiviral agents to which currently circulating influenza A viruses are resistant. Over time, susceptible strains appear to reemerge, as we are beginning to see for the adamantanes. Finally, it is important to stress that the mainstay of influenza prevention remains the use of influenza vaccines. In the United States, ~85% of the population fits into a risk or occupational group that is already recommended to receive influenza vaccine. At the urging of one of us (G.A.P.), the Advisory Committee on Immunization Practices has signaled its intent to move toward a universal recommendation for all persons aged ≥6 months to receive annual influenza immunization. Current US recommendations call for routine vaccination of persons aged 6 months–18 years and persons aged ≥50 years. A universal influenza vaccination recommendation would allow influenza antiviral agents to be reserved for use for persons who cannot receive vaccine or who, despite vaccination, develop life-threatening infection (e.g., immunocompromised individuals). In support of this recommendation, a Cochrane review of

the use of influenza antiviral agents in adults concluded that only oseltamivir or zanamivir should be used and only in the case of influenza pandemics and severe epidemics [27]. At the Advisory Committee on Immunization Practices meeting on 25 February 2009, the committee adopted recommendations that essentially recommended universal vaccination, stating that "that annual influenza immunization is recommended for any adult who wants to reduce the risk of becoming ill with influenza or transmitting it to others." A policy of universal influenza vaccination would reduce the mutational pressure on influenza viruses and diminish the development of antiviral resistance, as well as prevent or at least reduce the tremendous annual morbidity and mortality burden due to influenza.

In conclusion, continued use of antiviral monotherapy against influenza virus is unwise and dangerous. More discussion and more research on the feasibility of multidrug therapy, the development of new classes of antiviral drugs, point-of-care diagnostic testing, and better treatment algorithms for determining who should receive treatment, as a well as a universal recommendation for influenza vaccination, are urgently needed.

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References

1. Bright RA, Medina MJ, Xu X, et al. Incidence of adamantane resistance among influenza A (H3N2) viruses isolated worldwide from 1994 to 2005: a cause for concern. Lancet 2005;366:1175–81. [PubMed: 16198766]
2. Gubareva LV, Kaiser L, Hayden FG. Influenza virus neuraminidase inhibitors. Lancet 2000;355:827–35. [PubMed: 10711940]
3. Hay, A. Amantadine and rimantadine—mechanisms. In: Richman, DD., editor. Antiviral drug resistance. Chichester, United Kingdom: John Wiley & Sons; 1996. p. 43-58.
4. Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine. Curr Top Microbiol Immunol 1992;176:119–30. [PubMed: 1600749]
5. Bright RA, Shay DK, Shu B, Cox NJ, Klimov AI. Adamantane resistance among influenza A viruses isolated early during the 2005–2006 influenza season in the United States. JAMA 2006;295:891–4. [PubMed: 16456087]
6. Centers for Disease Control and Prevention. Update: influenza activity—United States, September 28–November 29, 2008. MMWR Morb Mortal Wkly Rep 2008;57:1329–32. [PubMed: 19078922]
7. Hatakeyama S, Sugaya N, Ito M, et al. Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors. JAMA 2007;297:1435–42. [PubMed: 17405969]
8. Hurt AC, Iannello P, Jachno K, et al. Neuraminidase inhibitor-resistant and -sensitive influenza B viruses isolated from an untreated human patient. Antimicrob Agents Chemother 2006;50:1872–4. [PubMed: 16641465]
9. Centers for Disease Control and Prevention. Flu activity & surveillance. [Accessed 20 February 2009]. Available at: http://www.cdc.gov/flu/weekly/fluactivity.htm
10. Hauge SH, Dudman S, Borgen K, Lackenby A, Hungnes O. Oseltamivir-resistant influenza viruses A (H1N1), Norway, 2007–08. Emerg Infect Dis 2009;15:155–62. [PubMed: 19193257]
11. Lackenby A, Hungnes O, Dudman SG, et al. Emergence of resistance to oseltamivir among influenza A(H1N1) viruses in Europe. Euro Surveill 2008;13:8026.
12. Stephenson I, Democratis J, Lackenby A, et al. Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. Clin Infect Dis 2009;48:389–96. [PubMed: 19133796]
13. Sheu TG, Deyde VM, Okomo-Adhiambo M, et al. Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008. Antimicrob Agents Chemother 2008;52:3284–92. [PubMed: 18625765]

14. Aoki FY, Boivin G, Roberts N. Influenza virus susceptibility and resistance to oseltamivir. Antivir Ther 2007;12:603–16. [PubMed: 17944268]
15. de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med 2005;353:2667–72. [PubMed: 16371632]
16. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001;20:127–33. [PubMed: 11224828]
17. Kiso M, Mitamura K, Sakai-Tagawa Y, et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 2004;364:759–65. [PubMed: 15337401]
18. de Jong MD, Tran TT, Truong HK, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med 2005;353:2667–72. [PubMed: 16371632]
19. Hayden F. Developing new antiviral agents for influenza treatment: what does the future hold? Clin Infect Dis 2009;48(Suppl 1):S3–13. [PubMed: 19067613]
20. Monto AS. Implications of antiviral resistance of influenza viruses. Clin Infect Dis 2009;48:397–9. [PubMed: 19586376]
21. Escuret V, Frobert E, Bouscambert-Duchamp M, et al. Detection of human influenza A (H1N1) and B strains with reduced sensitivity to neuraminidase inhibitors. J Clin Virol 2008;41:25–8. [PubMed: 18055253]
22. Ison MG, Gubareva LV, Atmar RL, Treanor J, Hayden FG. Recovery of drug-resistant influenza virus from immunocompromised patients: a case series. J Infect Dis 2006;193:760–4. [PubMed: 16479508]
23. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. N Engl J Med 2000;343:1282–9. [PubMed: 11058672]
24. Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without postexposure prophylaxis. J Infect Dis 2004;189:440–9. [PubMed: 14745701]
25. Ison MG, Gnann JW Jr, Nagy-Agren S, et al. Safety and efficacy of nebulized zanamivir in hospitalized patients with serious influenza. Antivir Ther 2003;8:183–90. [PubMed: 12924534]
26. Ilyushina NA, Bovin NV, Webster RG, Govorkova EA. Combination chemotherapy, a potential strategy for reducing the emergence of drug-resistant influenza A variants. Antiviral Res 2006;70:121–31. [PubMed: 16516984]
27. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pietrantonj C, Rivetti A. Antivirals for influenza in healthy adults: systematic review. Lancet 2006;367:303–13. [PubMed: 16443037]