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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Which agents should we use to treat and prevent influenza in 2006–2007?

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A: The neuraminidase inhibitors (NAIs) are the agents of choice for the treatment and prophylaxis of influenza types A and B until we have evidence that resistance to the adamantanes observed last influenza season has been reversed. Thus, amantadine (Symmetrel) and rimantadine (Flumadine) should not be used during the 2006–2007 influenza season.

Still, vaccination remains the primary measure to prevent influenza, which is responsible for a predictable annual epidemic that can become a pandemic.[1]

Use oseltamivir or zanamivir rather than amantadine or rimantadine this year

THE TROUBLE WITH ADAMANTANES

Used for the past 30 years for the treatment and chemoprophylaxis of influenza, the adamantanes amantadine and rimantadine work by inhibiting entry of the viral RNA into infected cells by blocking the viral M2 ion channel. Both are active only against influenza A. Rimantadine is preferred in the elderly, as it has far fewer adverse effects on the central nervous system.[2] Adamantanes can reduce the duration of influenza A by 1 day when started within 2 days of onset, and they are 70% to 90% protective when used preventively.

A rise in resistance observed

Resistance to the adamantanes surfaced shortly after their introduction. It is thought that this resistance occurs as a result of a single point mutation of the M2 protein. About 30% of patients receiving an adamantane can subsequently shed influenza virus resistant to these agents. More recently, resistance to these agents was documented even without prior exposure, raising concern that resistant isolates are circulating in the community.[3] Molecular cloning experiments have also shown that mutations known to confer resistance to amantadine can be detected in up to 80% of those treated with this drug.[4]

A 10-year program of worldwide surveillance noted a significant increase in amantadine resistance among influenza A (H3N2) viruses, from 0.4% in 1994 to 12.3% in 2004.[5] The degree of resistance varied significantly from country to country, with the highest frequency (74%) in China.

In several Asian countries, the adamantanes are available without a prescription and are included in various "cold and flu" remedies. In addition, the epidemic of severe acute respiratory syndrome in 2003 and the ongoing H5N1 epidemic have likely contributed to the increased use of these agents in China.

Data gathered from 26 US states showed that 91% of influenza A (H3N2) viruses, the type most frequently circulating during the last several seasons, contained a mutation that confers resistance to adamantanes.[6] This and the other data led the US Centers for Disease Control and Prevention (CDC) in January 2006 to issue a recommendation against the use of adamantanes for the treatment or prevention of influenza A in the United States.[7]

MAKING THE BEST USE OF NEURAMINIDASE INHIBITORS

In light of the CDC recommendation, an NAI, not an adamantane, should be used to treat or prevent influenza A or B for the 2006–2007 influenza season (**TABLE 1**).

*The author has indicated that he has received a grant from Roche corporation and is the primary investigator at Cleveland Clinic for a multicenter study of oseltamivir to prevent influenza in transplant patients.

TABLE 1

Neuraminidase inhibitors: Recommendations for treatment and prevention of influenza, 2006–2007

	OSELTAMIVIR (TAMIFLU)	ZANAMIVIR (RELENZA)
Formulation	Capsules or oral suspension	Powder in 5-mg blister on Rotadisk; requires Diskhaler inhalation device
Treatment dosing, adults	75 mg orally, twice a day	10 mg (two blisters) by oral inhalation, twice a day
Duration of treatment	5 days	5 days
Prophylactic dosing, adults	75 mg orally, once a day	10 mg (2 blisters) by oral inhalation, once a day
Duration of prophylaxis	10 days for family postexposure prophylaxis 2 weeks for institutional outbreak 6–8 weeks when given as seasonal prophylaxis	
Dosing adjustments	Half the dose for patients with creatinine clearance 10–30 mL/min	Not required
Adverse effects	Nausea and vomiting	Bronchospasm in patients with underlying airway disease; therefore, not recommended in these patients
Cost*	$80 for 10 capsules	$60 (5 Rotadisks with 4 powder blisters each, plus Diskhaler device)

*Cleveland Clinic formulary price, September 2006

Like the adamantanes, the NAIs zanamivir (Relenza) and oseltamivir (Tamiflu) can reduce the duration of influenza by 1 day, provided they are given early,[8] ie, within 2 days of onset. When used prophylactically, NAIs are 70% to 90% protective. Oseltamivir may be less effective in treating influenza B than influenza A.[8] No study has yet been done that was designed to detect a difference in efficacy against one type or the other. However, the prophylactic efficacy of NAIs was similar against both types of influenza in studies published to date.[9]

The recommended age range for oseltamivir is currently 1 year or older for treatment or prophylaxis; for zanamivir, the age is 5 years or older for treatment and 7 years or older for prophylaxis.

All patients experiencing potentially life-threatening illness due to influenza, regardless of their underlying health, should be treated with zanamivir or oseltamivir. I recommend doing so even if the patient presents more than 2 days after initial symptoms: since viral replication may be ongoing, a benefit should be expected. In addition, all patients with underlying medical conditions that put them at high risk for complications (eg, congestive heart failure, history of bone marrow or organ transplantation) should receive an NAI if they develop influenza.

Resistance is limited, so far

NAIs work by preventing exit of virions from infected cells, thus halting spread of infection to other respiratory epithelial cells. Resistance to NAIs was only rarely encountered during drug approval studies. But recent data from Japan, where oseltamivir is more widely used in children, show that resistant mutations arise in 18% of patients treated.[10]

Preventing serious influenza-related complications

Unfortunately, we have only limited data as to the effectiveness of any antiviral agent in preventing serious influenza-related complications, particularly in immunocompromised

patients. It is not known if the dose and duration of treatment currently approved are actually effective in this population. Also, as yet no randomized study has directly compared adamantanes and NAIs.

CURRENT INDICATIONS FOR CHEMOPROPHYLAXIS

Influenza vaccination is still the best means we have to prevent influenza. Unfortunately, it is still underused, especially in patients ages 18 to 64 with underlying high-risk medical conditions[11] (eg, congestive heart failure, bone marrow or organ transplantation, asthma, diabetes mellitus, renal dysfunction).

While chemoprophylaxis with an antiviral agent is no substitute for vaccination, it does not impair the immunologic response to vaccination, and thus has a valuable role to play.

Since antibody response to vaccination in adults takes about 2 weeks, either zanamivir or oseltamivir should be given prophylactically during any institutional outbreak to patients at high risk for influenza-related complications, as well as to their caregivers, until vaccine-related immunity develops.

An antiviral drug is no substitute for vaccination

Chemoprophylaxis with an NAI is also recommended if a person at high risk for influenza-related complications is exposed to a household member with confirmed influenza.

Finally, seasonal chemoprophylaxis with an NAI for 6 to 8 weeks can be considered for patients who are at high risk of complications (eg, those receiving immunosuppressive drugs), who are expected to have a suboptimal response to influenza vaccine, or who have a contraindication to vaccination.

The approximate retail price for a 5-day course of treatment is $60 for zanamivir and $80 for oseltamivir. The cost of seasonal chemoprophylaxis in a vaccinated population is significant and is probably not cost-effective.[12]

Hope for reemergence of adamantane-susceptible strains

Since the adamantane resistance-conferring mutation is the same worldwide, it is inferred that resistance exists in a relatively homogenous strain of influenza A (H3N2). It is thus hoped that minimizing the use of the adamantanes will result in the reemergence of susceptible strains.[13] In the interim, NAIs are our only option for the treatment and chemoprophylaxis of influenza A or B.

REFERENCES

1. **Jin XW, Mossad SB.** Avian influenza: an emerging pandemic threat. Cleve Clin J Med 2005; 72:1129–1134.
2. **Jefferson TO, Demicheli V, Deeks JJ, Rivetti D.** Amantadine and rimantadine for preventing and treating influenza A in adults. Update in Cochrane Database Systematic Reviews 2004; (3):CD001169. Update of Cochrane Database Systematic Reviews 2001; (2):CD001169. Cochrane Database of Systematic Reviews 2002; (3):CD001169.
3. **Houck P, Hemphill M, LaCroix S, Hirsh D, Cox N.** Amantadine-resistant influenza A in nursing homes. Identification of a resistant virus prior to drug use. Arch Intern Med 1995; 155:533–537.
4. **Shiraishi K, Mitamura K, Sakai-Tagawa Y, Goto H, Sugaya N, Kawaoka Y.** High frequency of resistant viruses harboring different mutations in amantadine-treated children with influenza. J Infect Dis 2003; 188:57–61.
5. **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; 366:1175–1181.
6. **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; 295:891–894.
7. **US Centers for Disease Control and Prevention (CDC).** High levels of adamantane resistance among influenza A (H3N2) viruses and interim guidelines for use of antiviral agents—United States, 2005–06 influenza season. MMWR 2006; 55:44–46.
8. **Kawai N, Ikematsu H, Iwaki N, et al.** Factors influencing the effectiveness of oseltamivir and amantadine for the treatment of influenza: a multicenter study from Japan of the 2002–2003 influenza season. Clin Infect Dis 2005; 40:1309–1316.
9. **Moscona A.** Neuraminidase inhibitors for influenza. N Engl J Med 2005; 353:1363–1373.
10. **Kiso M, Mitamura K, Sakai-Tagawa Y, et al.** Resistant influenza A viruses in children treated with oseltamivir: descriptive study. Lancet 2004; 364:759–765.
11. **US Centers for Disease Control and Prevention (CDC).** Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2006; 55(RR-10):1–48.
12. **Sturpe D, Seaton TL.** Is oral oseltamivir safe and effective for the prevention of influenza and its complications in frail elderly long-term care residents who have received influenza vaccine? J Fam Pract 2002; 51:87.
13. **Weinstock DM, Zuccotti G.** Adamantane resistance in influenza A. JAMA 2006; 295:934–936.

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