Drugs in Pipeline Hold Promise for H1N1 Flu

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EXPERT ANALYSIS FROM A CONFERENCE ON PEDIATRIC INFECTIOUS DISEASES

VAIL, COLO. — Much needed help in treating pandemic 2009 H1N1 influenza may be on the way in the form of two promising investigational drugs that could become commercially available within the next several flu seasons.

Favipiravir and laninamivir are in phase III clinical trials abroad, where to date both appear to be performing very well, Dr. Adriana Weinberg said at the meeting sponsored by the Children's Hospital, Denver.

Favipiravir is an oral RNA polymerase inhibitor effective against both influenza A and B as well as other RNA viruses. It is in phase III testing in Japan. Importantly, it has no cross-resistance with the neuraminidase inhibitors or adamantanes.

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Laninamivir is effective against oseltamivir-resistant isolates. It is in phase III trials in Australia, where it is establishing a very favorable safety profile, according to Dr. Weinberg, professor of medicine, pediatrics, and pathology of the University of Colorado, Denver, and medical director of the clinical virology laboratory at University of Colorado Hospital.

Current treatment options for pandemic H1N1 flu are quite limited, so these two new drugs are badly needed, she added.

More than 90% of H1N1 isolates from the 2009 pandemic were resistant to adamantanes. So basically all that physicians had available early on were the oral neuraminidase inhibitor oseltamivir (Tamiflu) and the inhalation-only formulation of zanamivir (Relenza), another neuraminidase inhibitor.

These were supplemented during the pandemic by intravenous peramivir, a drug that was in phase III trials but was decreed available for use in critically ill patients as a result of an Emergency Use Authorization. The Emergency Use Authorization was terminated in June 2010. Peramivir has a resistance profile and efficacy similar to oseltamivir. Thus, its sole advantage is that it can be given intravenously. The recommended dosing is 6 mg/kg in neonates, 8 mg/kg for infants aged 31-90 days, 10 mg/kg for 91- to 180-day-olds, 12 mg/kg for children aged 181 days through 5 years, 10 mg/kg for 6- to 17-year-olds, and 600 mg for patients aged 18 years and older. The infusion is given over 30-60 minutes.

Intravenous zanamivir became available on a compassionate use basis during the pandemic. Unlike peramivir, it is effective against oseltamivir-resistant isolates.

Ribavirin is commercially available for indications other than influenza. However, it does have in vitro activity against influenza, and although it's not a very good anti-influenza drug by itself, it may have a future in combination therapy for severe pandemic H1N1 disease.

Combo therapy with neuraminidase inhibitors, ribavirin, adamantanes, and interferon was widely used for avian influenza A(H5N1), but because of the lack of controls it's hard to draw any conclusions as to whether this resulted in enhanced efficacy. In animal models, two drugs for pandemic H1N1 disease are more effective than one, regardless of the drugs tested, provided the virus is susceptible to both drugs. Results thus far are conflicting when the virus is resistant, according to Dr. Weinberg.

Oseltamivir performed well last season against pandemic H1N1. When started within 2 days following symptom onset, it reduced mortality by 50%. It also reduced the duration of symptoms. There is some evidence that if the drug is given within the first 3 days, it

reduces duration of viral shedding, which is 14 days without treatment compared with 7 days for seasonal influenza. Oseltamivir did a good job of limiting disease transmission during outbreaks in nursing homes and other closed communities.

Under an Emergency Use Authorization issued during last year's pandemic, oseltamivir became available for the treatment of patients of all ages with H1N1 flu. Recent interim data from a National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group trial suggest the best dose in infants is 3 mg/kg twice daily. In premature babies, the optimal dose appears to be 1 mg/kg twice daily (J. Infect. Dis. 2010;202:563-6).

In the middle of last year's pandemic, the World Health Organization recommended that the standard 75-mg b.i.d adult and adolescent dose of oseltamivir could be doubled in severe cases of H1N1 disease, an announcement Dr. Weinberg dismissed as "weirdness that made little sense" since the pharmacokinetics of the drug are linear up to 500 mg/dose.

"Why would you go from 75 mg to 150 and not to 300 mg/dose?" she asked. Her advice: Consider quadrupling the standard dose in severe cases.

Prophylactic administration of oseltamivir is a common inducer of resistance in immunocompetent patients, which is why the WHO recommends not using the drug for prophylaxis. Resistance also develops quickly in lung transplant recipients.

There was concern that oseltamivir resistance would spread widely through communities, but that didn't prove to be the case. All documented cases have occurred in patients on oseltamivir or in close contacts of patients treated with the drug, according to Dr. Weinberg.

Two recent animal studies reached dead opposite conclusions regarding the pathogenicity of oseltamivir-resistant H1N1 strains. One study showed the drug-resistant strains were less pathogenic than wild-type virus, whereas the other study found that the drug-resistant and wild-type viruses had similar pathogenicity. Clearly, more work is needed in this area, she noted. ■

Disclosures: *Dr. Weinberg disclosed serving as a consultant to MedImmune, Astellas, GlaxoSmithKline, and Merck.*