High-Dose Oseltamivir Appears Safe for Some

BY DOUG BRUNK

SAN FRANCISCO — The antiviral drug oseltamivir was well tolerated by healthy adults in doses up to 450 mg twice daily, results from a randomized, multicenter, double-blind trial showed.

Oseltamivir (Tamiflu) is Food and Drug Administration–approved for use in adults at a treatment of 75 mg twice daily for 5 days, but "there are some questions about whether or not you might need a higher dose if you a have higher viral load or a more virulent virus," Regina Dutkowski, Ph.D., said in an interview during a poster session at the annual meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy.

Dr. Dutkowski, medical director in virology at Hoffmann-LaRoche Inc., Nutley, N.J., and her associates studied 391 healthy adult volunteers aged 18-65 years from nine medical centers and randomized them to the following twice-daily dosing regimens of oseltamivir for 5 days: placebo (100), 75 mg (95), 225 mg (97), and 450 mg (99). The volunteers were required to be in good general health with normal vital signs, laboratory tests, and electrocardiograms; and have a body mass index within 40% of accepted normal values. Women were required to comprise at least 40% of the study population. The mean age of patients was 34 years, 53% were female, and 81% were white.

All doses of oseltamivir were well tolerated. Headache was the most common adverse event and occurred in 20% of the placebo group, 17% of the 75-mg group, 24% of the 225-mg group, and 23% of the 450-mg group.

Gastrointestinal events, dizziness, and sensations of heat or hot flushes also were observed and appeared to be dose related. For example, nausea occurred in 8% of the placebo group, 8% of the 75-mg group, 26% of the 225-mg group, and 31% of the 450-mg group; vomiting occurred in 2% of the placebo group, 3% of the 75-mg group, 7% of the 225-mg group, and 16% of the 450-mg group, while feelings of heat or hot flushes occurred in 0% of the placebo group, 2% of the 75-mg group, 3% of the 225-mg group, and 5% of the 450-mg group.

'There are some questions about whether or not you might need a higher dose if you a have higher viral load or a more virulent virus.'

"The safety data from this study are reassuring because they support the known profile that indicates that GI events are associated with the drug," Dr. Dutkowski said. "What we see here are increases in GI events, but they're not limiting."

Only four patients withdrew from the trial because of adverse events: two in the placebo group (one case of dermatitis and one mistaken case of QT prolongation) and two in the 225-mg group (one case of urticaria and one case of pruritus).

No apparent effects on cardiac or laboratory parameters were observed.

Hoffmann-La Roche Inc. sponsored the study. ■

Early Treatment Advised for Pregnant Women With the Flu

BY MITCHEL L. ZOLER

Pregnant women with suspected or confirmed influenza should get early treatment with either oseltamivir or zanamivir, the Centers for Disease Control and Prevention said in updated recommendations.

Treatment should start "as early as possible," and "should not wait for laboratory confirmation of influenza," said the detailed recommendations (www.cdc.gov/h1n1flu/pregnancy/antiviral_messages.htm). The e-document also cited oseltamivir as the "preferred" agent because of its systemic absorption. The recommended dosage for treating infection was the standard amount of 75 mg b.i.d., taken for 5 days.

The CDC recommendations explained that pregnant women are at higher risk for severe complications and death from influenza, including both pandemic influenza A(H1N1) and seasonal flu. "The available risk-benefit data indicate pregnant women with suspected or confirmed influenza should receive prompt antiviral therapy. Pregnancy should not be considered a contraindication to oseltamivir or zanamivir use." The agency said treatment should start within 48 hours of illness onset, and that laboratory confirmation isn't needed because a negative result from a rapid test doesn't rule out influenza.

"Since rapid access to antiviral medications is essential, health care providers who care for pregnant women should develop methods to ensure that treatment can be started quickly after symptom onset," the recommendations said. This means telling pregnant women about the signs and symptoms of flu and alerting them to the need for early treatment. It also requires physicians to ensure that their pregnant patients have rapid access to telephone consultation and clinical evaluation. The CDC advised physicians to "consider empiric treatment of pregnant women based on telephone contact" when hospitalization isn't needed to cut delays before starting treatment.

The recommendations also called for considering an antiviral regimen for postexposure prophylaxis in pregnant women following contact with someone likely infectious with influenza. The drug of choice for prophylaxis may be zanamivir because of its limited systemic absorption. The suggested regimen was two 5-mg inhalations (10 mg total) once daily for 10 days. But zanamivir can produce respiratory complications. For women at risk for respiratory problems, oseltamivir is a reasonable alternative, given as 75 mg once daily for 10 days. As of mid-September, most pandemic H1N1 influenza viruses are susceptible to both drugs, the CDC said. Treatment after signs and symptoms of influenza appear was advised as an alternative to chemoprophylaxis.

Although people infected with influenza do not always have fever, a recent series of pregnant women infected by pandemic H1N1 influenza showed fever in 97% (the next most common symptoms were cough, in 94%, and rhinorrhea, in 59%). Fever in pregnant women needs treatment because it appears to pose a risk to the fetus. Acetaminophen appears to be the best option for treatment of fever. ■

194 Million H1N1 Vaccine Doses

Virus *from page 1*

tients with symptomatic flu who were culture positive for the pandemic virus. In this group, eight (19%) remained culture positive 8 days after their symptom onset. In contrast, all patients with seasonal flu are routinely culture negative a week after symptom onset. "We can say that H1N1 appears to be shed longer [than seasonal flu] but not much longer," said Dr. De Serres, who also is professor of epidemiology at Laval University, Quebec. All 43 H1N1 patients in the study were culture negative 10 days after symptom onset.

Another 57 family members of these cases had concurrent flulike symptoms, but all 57 were culture negative the first time they were tested. Adding these 57 to the first 43 produced a total of 100 patients apparently infected with H1N1, of whom 8 were culture positive a week after their illness began, establishing a minimum 8% rate for the persistence of H1N1 shedding beyond a week of infection. The rate might even be a bit greater because all of the family members may not have been infected with H1N1.

Dr. De Serres cautioned that the findings don't mean that all eight patients remained contagious at day 8. Contagion requires more than just shedding live virus; it also requires transmission of an adequate virus dose. The study didn't look at the amount of virus shed on day 8. People who shed live virus "may potentially be contagious; we're not saying they are contagious," Dr. De Serres said.

Vaccine against pandemic influenza A(H1N1) were on track to reach providers early this month, a Centers for Disease Control and Prevention official said at a meeting of the National Vaccine Advisory Committee.

This timetable applies to the vaccines that received approval from the Food and Drug Administration last month, said Dr. Jay Butler, who heads the H1N1 vaccine implementation program for the CDC in Atlanta. (See related stories on p. 5).

The U.S. government has arranged to purchase 194 million H1N1 vaccine doses, which will be supplied to the U.S. public at no charge for the vaccine (although there will be charges for ancillary materials), said Dr. Robin Robinson from the Biomedical Advanced Research and Development Authority of the Department of Health and Human Services in Washington.

Dr. Anne Schuchat, director of the CDC's National Center for Immunization and Respiratory Diseases, said that during the first 2 weeks of September, 4% of visits to CDC sentinel providers of outpatient or emergency department care were for flu-like illness. That rate is as high as that seen in February 2009, the most recent peak of seasonal influenza in the United States. At press time, the spike of flu cases had been most dramatic in states located in the southeastern United States.

Dr. Schuchat's data also showed that U.S. cases of H1N1 infection never disappeared over the summer, although the reported cases of flu-like illness were down compared with the prior H1N1 peak last April and May. Current assessment of the virus indicates that the strain circulating in early September is not genetically different or any more virulent than the strain that circulated last spring.

Based on recent data on immunogenicity, the new H1N1 vaccine will be administered to people aged 10 and older as a single dose. Children younger than 10 are slated to receive two doses regardless of their immunization history.

Other notable features of the H1N1 infection pattern have been higher than usual infection rates in people aged 5-17 and 18-49, and the unexpected finding that morbidly obese people were among those at increased risk for infection. The highest hospitalization rates for H1N1 infections have been in patients younger than 5, followed by those aged 5-24.

The threat of H1N1 infection in young adults aged 18-24 has created a new target for immunization messages, said Dr. Kris Sheedy, communications director for the CDC's National Center for Immunization and Respiratory Diseases.

Until safety data from broad field use are available, the CDC will need to rely on the fact that the new H1N1 vaccines were made by the same methods that have been applied in past years to produce hundreds of millions of doses of seasonal flu vaccine, Dr. Schuchat said. This record of safety should be balanced against the clear health risk that H1N1 presents, a comparison that should convince most people to get immunized. ■