TRAVEL MEDICINE ADVISOR

Your Monthly Supplement of Travel Medicine Literature

AHC Media LLC

INSIDE

Volume 21, No. 1
January 2011

Financial Disclosure:

Travel Medicine Advisor's physician editor, Frank Bia, MD, MPH, reports no financial relationships relevant to this field of study. Executive Editor Russ Underwood, and Specialty Editor Shelly Morrow Mark report no financial relationships relevant to this field of study.

To Get Flu Shots: Pregnant and Postpartum Women

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This article originally appeared in the December 2010 issue of Contraceptive Technology Update.

GET READY TO RECOMMEND FLU VACCINE TO YOUR PREGNANT AND POSTPARTUM patients. According to the Centers for Disease Control and Prevention (CDC), less than one-fourth of pregnant women in the United States were vaccinated against seasonal influenza during the 2007-08 flu season.[1]

The Advisory Committee on Immunization Practices (ACIP) is recommending that pregnant and postpartum women receive the seasonal influenza vaccine this year, even if they received 2009 H1N1 or seasonal influenza vaccine last year. Manufacturers have informed the CDC that they expect to produce approximately 160 million doses of vaccine this year, so there should be a substantial supply to cover those who wish to receive it, including pregnant women, says Tom Skinner, a CDC spokesperson.

What flu viruses are included in the seasonal vaccine for the years 2010 and 2011? The World Health Organization (WHO) in Geneva, Switzerland, has recommended that the Northern Hemisphere's 2010 and 2011 seasonal influenza vaccine contain the following three vaccine viruses: an A/California/7/2009 (H1N1)–like virus, an A/Perth/16/2009 (H3N2)–like virus, and a B/Brisbane/60/2008–like virus. The Food and Drug Administration, which determines which viruses will be used in U.S.-manufactured vaccines, has selected the same vaccine viruses. The H1N1 virus that is recommended for inclusion in the current seasonal influenza vaccine is a pandemic 2009 H1N1 virus; it is the same vaccine virus as was used in the 2009 H1N1 monovalent vaccine.

Several medical groups, including the American College of Obstetricians and Gynecologists; the Association of Women's Health, Obstetric and Neonatal Nurses; and the American College of Nurse-Midwives have joined the CDC

and the March of Dimes in emphasizing the need for immunization for pregnant and postpartum women.

Why should pregnant and postpartum women receive the seasonal influenza vaccine? Consider the following four reasons:

• Influenza is more likely to cause severe illness in pregnant women than in women who are not pregnant. Changes in the immune system, heart, and lungs during pregnancy make pregnant women more prone to severe illness from the flu.

• Risk of premature labor and delivery is heightened in pregnant women with influenza.

• Vaccination during pregnancy has been shown to protect the mother and baby (up to six months old) from lab-confirmed influenza. Influenza hospitalization rates in infants less than six months of age are more than 10 times that of older children.

• Pregnant women accounted for 5% of 2009 U.S. H1N1 influenza deaths, while only about 1% of the population was pregnant. Severe illness in postpartum women also was documented.[2]

Vaccine Is Safe

Educate pregnant and postpartum women about the importance of getting the seasonal flu shot, as well as the safety of the vaccine. Results of a cross-sectional study of 813 postpartum women during the 2009-10 flu season at the Aurora, CO-based University of Colorado Hospital indicate that many women might not be getting the message. Women in the study who chose not to receive the seasonal or H1N1 vaccine cited the following reasons: not knowledgeable about the importance of vaccination (25%), concern for effects on fetal health (18%), concern for effects on maternal health (9%), and not knowing where to obtain vaccination (9%).[3]

How can clinicians get the message across to patients? Number one: Be sure to get immunized, so you can serve as a good role model for patients, says Barbra Fisher, MD, PhD, a maternal fetal medicine fellow/instructor at the University of Colorado, Denver, and lead author of the study. Educate patients about the safety of the vaccination for mother and baby, she advocates.

Emphasize the following points about safety:

• Influenza vaccines have been given to millions of pregnant women over the last decade and have not been shown to cause harm to women or their infants.

• The flu shot can be administered to pregnant women in any trimester.

• Pregnant women should receive inactivated vaccine, which is used in the flu shot, but should not receive the live attenuated vaccine, which is used in the nasal spray.

• Postpartum women, even if breastfeeding, can receive either type of vaccine.

Also, talk about potential complications for pregnant women who contract influenza, says Fisher. Explain that the best way to avoid those complications is become vaccinated, she states. ■

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Travel Medicine Advisor (ISSN # 1930-0867) is published monthly by AHC Media LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (404) 262-7436. Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Travel Medicine Advisor,*** PO Box 740059, Atlanta, GA 30374-9815.

Subscription Information: Customer Service: (800) 688-2421 or fax (800) 284-3291. Hours of operation: 8:30am-6pm Monday-Thursday; 8:30am-4:30pm Friday ET. Email: customerservice @ahcmedia.com Website: www.ahcmedia.com. Subscription rates: USA, one year (12 issues) $449. Add $17.95 for shipping & handling. Outside U.S., add $30 per year, total prepaid in U.S. funds. Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

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Rotavirus Vaccine and Intussusception: Rarely, at Least in Some Places

ABSTRACT & COMMENTARY

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This article originally appeared in the December 2010 issue of Infectious Disease Alert.

Synopsis: *Recent post-marketing surveillance from Mexico and Australia has identified a very low but increased risk of intussusception following rotavirus vaccination with Rotarix, especially following the first dose.*

Source: Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases: Statement regarding Rotarix and RotaTeq rotavirus vaccine that intussusception. Issued November 3, 2010 at http://www.cdc.gov/vaccines/vpd-vac/rotavirus/intussusception-studies-acip.html, accessed November 12, 2010.

POST-MARKETING SURVEILLANCE OUTSIDE THE UNITED states of the two FDA-licensed rotavirus vaccines, RotaTeq (Merck, licensed in 2006) and Rotarix (GSK Biologicals, licensed in 2008), have identified a very low but increased risk (1 case/100,000 vaccinated infants) of intussusception following Rotarix vaccination. On Sept. 22, 2010, the FDA approved a label change for Rotarix based on data from Mexico. Analysis of one population in Mexico revealed clustering of 18 hospitalizations for intussusception in the 1-7 days following the first dose of Rotarix. This rate is 4-5 times higher than in later periods after vaccination, after adjusting for age. A second analysis of a different population in Mexico revealed a possible 1.8-fold increased risk of intussusception in the 30 days following the first dose of Rotarix, with the clustering of cases in the first week after vaccination. No increased risk was identified in the post-marketing surveillance studies of Rotarix in Brazil. Other post-marketing surveillance studies in Australia identified a few cases of intussusception that suggest the possibility of an increased risk of intussusception in the first week after vaccination with either Rotarix or RotaTeq vaccines.

Pre-licensure trials for Rotarix and RotaTeq vaccines each involved more than 60,000 participants and showed no increased risk for intussusception. More than 27 million doses of RotaTeq and more than 2.7 million doses of Rotarix have been distributed in United States. Postmarketing surveillance and studies have not identified an increased risk of intussusception in the United States, including a new study of 800,000 total doses of RotaTeq vaccine conducted in response to this new information, though a risk as low as that reported with Rotarix in Mexico cannot be excluded by these analyses.

■ COMMENTARY

A previous rotavirus vaccine, RotaShield, was withdrawn from the market because post-marketing surveillance revealed an association with intussusception (1 case/10,000 vaccinated infants). From that experience, the risk for this adverse event was specifically included in the design and evaluation of pre-licensure trials for each of the two current vaccines; an association with intussusception was not observed. The risk continues to be monitored by post-marketing surveillance in the United States and many other countries.

The impact of rotavirus vaccine in the United States has been significant. Hospitalization and emergency department care of infants and children with rotavirus disease have decreased by about 85%, with an estimated 40,000-60,000 fewer gastroenteritis-related hospitalizations annually among children less than 5 years of age. The proven benefit of rotavirus vaccination is significantly greater than the very small risk of intussusception that

may result from rotavirus vaccine. The role of wild-type rotavirus causing intussusception remains unsettled. The CDC continues to recommend both Rotarix and RotaTeq vaccines to prevent severe rotavirus disease in United States. ■

FDA Tentatively Approves Fixed-dose Lamivudine/ zidovudine

Editor Melinda Young, Senior Managing Editor Gary Evans, and Executive Editor Coles McKagen report no relationships with companies related to this field of study. Physician Reviewer Morris Harper, MD, AAHIVS, Vice President, Chief Medical Officer, HIV/AIDS & Hepatitis Associates, Waynesburg, PA, reports consulting work with Agouron Pharmaceuticals, Gilead Sciences, Abbott Pharmaceuticals, GlaxoSmithKline, and Bristol-Myers Squibb. Nurse Planner Kay Ball, RN, PhD, MSA, CNOR, FAAN Perioperative Consultant/Educator, K & D Medical, Lewis Center, OH, is a consultant and stockholder with Steris Corp. and is on the speaker's bureau for the Association of periOperative Nurses.

This article originally appeared in the December 2010 issue of AIDS Alert.

On Oct. 18, 2010, the FDA granted tentative approval to fixed-dose combination lamivudine/zidovudine tablets, 150 mg/300 mg, indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults. The product is manufactured by Strides Arcolab Limited of Bangalore, India. The application was reviewed under expedited review provisions for the President's Emergency Plan for AIDS Relief (PEPFAR).

Combination products such as this one can decrease pill burden and may result in improved dosing compliance for HIV-infected individuals.

"Tentative approval" means that FDA has concluded that a drug product meets all required quality, safety and efficacy standards, but is not presently eligible for final approval for marketing in the United States because of existing patents and/or exclusivity rights. However, tentative approval does make the product eligible for purchase and use outside the United States under PEPFAR.

As with all generic applications, FDA conducts an onsite inspection of each manufacturing facility, and of the facilities performing the bioequivalence studies, to evaluate the ability of the manufacturer to produce a quality product and to assess the quality of the bioequivalence data supporting the application prior to granting approval or tentative approval to these applications.

This is a generic formulation of Combivir tablets, 150 mg/300 mg, a product of VIIV Healthcare Company, which is subject to patent protection in the United States.

A list of all Approved and Tentatively Approved Antiretrovirals in Association with the President's Emergency Plan is available on the FDA website. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Rivaroxaban: Another Warfarin Replacement

In this issue: Rivaroxaban may be dabigatran's first competitor; a new way to measure non-adherence to medication therapy; FDA Actions.

Another Warfarin Replacement on Horizon

Just as Boehringer Ingelheim begins marketing dabigatran (Pradaxa®) as a replacement for warfarin, a competitor drug may be on the horizon. As reported at the American Heart Association (AHA) meetings in November, rivaroxaban, an oral drug factor Xa inhibitor, is as effective as warfarin at preventing stroke and blood clots in patients with nonvalvular atrial fibrillation.

The ROCKET AF study (Stroke Prevention Using the Oral Direct Factor Xa Inhibitor Rivaroxaban Compared With Warfarin in Patients with Nonvalvular Atrial Fibrillation) looked at more than 14,000 patients with atrial fibrillation. Patients were randomized to warfarin or rivaroxaban (20 mg/day). The time in therapeutic range for warfarin was 57.8%. With a primary endpoint of stroke and non-CNS systemic embolism, rivaroxaban was associated with a rate of 1.71 events per 100 patient-years vs 2.16 for warfarin (P = 0.015 for superiority and P < 0.001 for non-inferiority). On an intention to treat (ITT) basis, event rates were 2.12 for rivaroxaban vs 2.42 for warfarin (P = 0.117). There were 55 intracranial bleeds with rivaroxaban compared with 84 with warfarin (P = 0.019). Rivaroxiban also showed numerically fewer MIs (0.91 vs 1.12 per 100 person-years; P = 0.12). All-cause mortality was 1.87 in the rivaroxaban group vs 2.21 in the warfarin group (P = 0.073). In the ITT analysis, mortality was 4.52 vs 4.91 (P = 0.152), respectively.

This study (presented at the American Heart Association Scientific Sessions; Chicago, IL; Nov. 15, 2010) was the seventh Phase III trial in the development of rivaroxaban, with other studies evaluating the drug for prevention and treatment of venous thromboembolism, indications that Bayer and Johnson & Johnson have already filed with the FDA. It is also expected that a new drug application will be filed soon for the prevention of stroke in patients with nonvalvular atrial fibrillation. Like dabigatran, rivaroxaban requires no monitoring and has few drug interactions. Rivaroxaban has the advantage of being dosed once a day compared to twice-daily dosing for dabigatran. ■

Non-adherence: A New Way to Measure

A new study examines drug adherence in an interesting way — by looking at the rate of prescriptions abandoned at the pharmacy. Traditional non-adherence studies have looked at refill rates, pill counting, and patient reports of medication use. But prescriptions abandoned at the pharmacy represent a potential opportunity to intervene and improve adherence at the very onset of the prescribing process.

Researchers used the CVS pharmacy database to evaluate more than 10 million prescriptions

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filled by more than 5 million patients. The overall abandonment rate was 3.27%, although nearly half of those were eventually filled by the same drug or a similar drug within 30 days. Not surprisingly, patients were least likely to abandon opiate prescriptions, and were most likely to abandon expensive prescriptions. Prescriptions with a copayment of $40-$50 and those with a copayment of more than $50 were 3.4 times and 4.68 times more likely to be abandoned, respectively, than prescriptions with no copayment ($P <$ 0.001 for both comparisons). New users of medications were more likely to abandon prescriptions than prevalent users, and prescriptions that were delivered to the pharmacy electronically were 1.64 times more likely to be abandoned than those that were not electronic ($P < 0.001$); however, they were unable to determine whether written prescriptions were never delivered to the pharmacy by patients.

The authors concluded that prescription abandonment represents an important opportunity to intervene and improve adherence (*Ann Intern Med* 2010;153:633-640). An accompanying editorial points out that the rate of abandonment in this study was actually quite low. Others studies have suggested that 17%-20% of patients do not pick up new prescriptions, and 8% of patients' prescriptions are denied by health plans. Physicians and pharmacists are urged to remain mindful that costs are an important barrier to adherence and that lower cost alternatives should be prescribed "whenever feasible" (*Ann Intern Med* 2010;153:680-681). ■

FDA Actions

The FDA has asked the manufacturers of propoxyphene-containing pain medications (Darvon®, Darvocet®, and generics) to withdraw them from the market. The withdrawal is based on new data showing the drugs are associated with serious and fatal heart arrhythmias. Health care professionals are advised to stop prescribing propoxyphene and patients are asked to contact their health care providers to discuss switching to other pain medications. Propoxyphene has been the target of consumer groups for more than 30 years because of evidence of poor efficacy in treating pain and a high level of side effects including falls. ■

The FDA has approved duloxetine (Cymbalta®) for the treatment of chronic musculoskeletal pain. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, was previously approved for treating depression, generalized anxiety disorder, diabetic neuropathy, and fibromyalgia. The new indication for musculoskeletal pain includes low back pain and osteoarthritis. The expanded indication was based on the results of four double-blind, placebo-controlled trials, which showed that patients treated with duloxetine had significantly greater pain reduction than those patients treated with placebo. Duloxetine is marketed by Eli Lilly and Company. ■

The FDA has approved lurasidone for the treatment of schizophrenia in adults. The drug is classified as an atypical antipsychotic, and like other drugs in this class, carries a boxed warning regarding an increased risk of death associated with off-label use to treat behavioral problems in older adults with dementia. Common adverse reactions include drowsiness, feelings of restlessness, nausea, agitation, and Parkinsonian symptoms such as bradykinesia, tremor, and muscle stiffness. Lurasidone will be marketed by Sunovion Pharmaceuticals as Latuda™. ■

The FDA has approved a new injectable cephalosporin, ceftaroline, to treat community-acquired bacterial pneumonia (CABP) and bacterial skin infections, including those caused by methicillin-resistant *Staphylococcus aureus*. Ceftaroline was approved based on data from four studies that showed the drug to be as effective as ceftriaxone for the treatment of CABP and as effective as vancomycin plus aztreonam for the treatment of acute bacterial skin and skin structure infections. The recommended dose for patients with normal renal function is 600 mg given as a one-hour IV infusion every 12 hours. Ceftaroline is marketed by Forest Laboratories as Telflaro™. ■

The FDA's Vaccines and Related Biological Products Advisory Committee has recommended an expanded indication for Gardasil®, Merck's quadravalent human papillomavirus vaccine to prevent anal intraepithelial neoplasia and anal cancer in males and females ages 9-26. The approval was based on a phase III double-blind, placebo-controlled trial in which more than 4000 males were randomized to receive the three-dose vaccine or placebo. There was a significant reduction in the rate of anal intraepithelial neoplasia or anal cancer, especially in men who have sex with men. The vaccine is already approved for prevention of genital warts and cervical, vulvar, and vaginal cancer in females ages 9-26 and prevention of genital warts in males ages 9-26. ■