Pharmacology Watch

Evidence-based updates in clinical pharmacology

By William T. Elliott, MD, FACP

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Report: Access to Biosimilars May Increase Access to Treatment for Cancer Patients Worldwide

A new biosimilar to trastuzumab (Herceptin) has proven effective in treating women without prior treatment for ERBB2 (HER2)-positive metastatic breast cancer. Trastuzumab is a biologic, a drug comprised of large, complex molecules derived from living organisms. Biosimilars have to demonstrate they are "highly similar" to the reference biologic product, but head-to-head studies are not required for approval. In this case, researchers performed a head-to-head study to compare the proposed trastuzumab biosimilar along with taxane to trastuzumab plus taxane in a 1:1 double-blind, randomized, parallel-group, Phase III equivalency study in 458 treatment-naïve women presenting with ERBB2-positive metastatic breast cancer. The overall response rate at 24 weeks was 69.6% for the biosimilar-based treatment vs. 64.0% for trastuzumab (overall response rate ratio, 1.09; 90% confidence interval, 0.974-1.211). At week 48, there was no statistical difference for time-to-tumor progression, progression-free survival, or overall survival. Adverse events were similar. The authors concluded that use of a proposed trastuzumab biosimilar compared with trastuzumab resulted in an equivalent overall response rate at 24 weeks (*JAMA* 2017;317:37-47). Two separate editorials lauded the findings of this study and suggested biosimilars may increase access to treatment for cancer patients worldwide.

Immobilization Affects Drug Treatment of Venous Thromboembolism

Low-molecular-weight heparin (LMWH) is not effective at preventing symptomatic venous thromboembolism (VTE) in patients who are immobilized due to leg casting or have undergone knee arthroscopy, according to a new study from the Netherlands. In two trials, 1,543 patients who underwent arthroscopy and 1,451 patients who were immobilized after casting were randomized to eight weeks of LMWH (arthroscopy) or LMWH for the full duration of immobilization (casting) in a randomized, controlled fashion. In arthroscopy patients, VTE occurred in five of the 731 patients (0.7%) in the treatment group and in three of the 720 patients (0.4%) in the control group (relative risk [RR], 1.6; 95% confidence interval [CI], 0.4-6.8). Major bleeding occurred in one patient (0.1%) in the treatment group and in one patient (0.1%) in the control group. In the casted patients, VTE occurred in 10 of the 719 patients (1.4%) in the treatment group and in 13 of the 716 patients (1.8%) in the control group (RR, 0.8; 95% CI, 0.3-1.7). No major bleeding events occurred. The authors concluded that LMWH is not effective at preventing VTE after knee arthroscopy or for patients treated during the full period of immobilization due to casting. (Published online Dec. 3, 2016, doi: 10.1056/NEJMoa1613303).

Ebola Vaccine Shows Promise

An Ebola virus vaccine tested during the recent 2013-2016 outbreak in West Africa appears to be highly effective. The vaccine, called rVSV-ZEBOV, was evaluated in more than 4,000 patients who were contacts or contacts of contacts during the recent epidemic. Researchers administered the vaccine either immediately or delayed 21 days in a randomized fashion. No

cases of Ebola occurred 10 or more days after randomization in the immediate vaccination group vs. 16 cases in the delayed vaccination group. An additional 1,700 contacts, including 200 children, also subsequently received immediate vaccination, with no cases of Ebola noted in vaccinated individuals. The authors suggested that rVSV-ZEBOV offers substantial protection against Ebola virus disease, with no cases among vaccinated individuals from day 10 after vaccination (Published online Dec. 22, 2016, doi: http://dx.doi.org/10.1016/S0140-6736(16)32621-6).

Go the Distance When Treating Otitis Media

When it comes to treating otitis media in children, longer is better, according to a new study. Researchers designed a trial to determine if five days of amoxicillin-clavulanate was non-inferior to 10 days, with the assumption that a shorter course would reduce the risk of antibiotic resistance. Researchers assigned 520 children 6-23 months of age with acute otitis media for a standard duration of 10 days or a reduced duration of five days followed by placebo for 5 days. The clinical failure rate was 34% in the shorter duration group vs. 16% for standard duration (95% confidence interval, 9-25). The mean symptom scores also were higher in the shorter duration group. There was no difference in adverse events or nasopharyngeal colonization with penicillin- nonsusceptible pathogens. The authors concluded that reduced-duration antimicrobial treatment resulted in less favorable outcomes than standard-duration treatment. Additionally, neither the rate of adverse events nor the rate of emergence of antimicrobial resistance was lower with the shorter regimen (*N Engl J Med* 2016;375:2446-2456).

FDA Actions

The FDA has removed the black box warning from varenicline (Chantix), the popular smoking cessation drug. The black box label warned of neuropsychiatric events such as depression and suicidality. But the results of a large clinical trial suggest the effects on mood are less than expected. The FDA also revised labeling for bupropion (Zyban), also used for smoking cessation. Bupropion's boxed warning no longer contains language describing serious mental health side effects, although information about the risk remains in the warnings sections of both drugs.

The FDA has approved crisaborole ointment for the treatment of moderate eczema (atopic dermatitis) in patients ≥ 2 years of age. The new ointment is a PDE-4 inhibitor, although its mechanism of action in treating atopic dermatitis is unknown. Safety and efficacy were based on two placebo-controlled trials of more than 1,500 patients suffering from mild to moderate atopic dermatitis in which the cream achieved greater response with clear or almost clear skin at 28 days. Crisaborole ointment is marketed as Eucrisa.

The FDA has approved nusinersen to treat spinal muscular atrophy (SMA) in children and adults. SMA is a rare and often fatal genetic disease that in its most severe form kills children before age 2 years. The drug is administered intrathecally several times a year. Efficacy was demonstrated in a randomized trial of 121 children presenting with infantile-onset SMA in which 40% of patients achieved improvement in motor milestones. According to the agency, a later uncontrolled trial in older children "appeared generally supportive of the clinical efficacy ...." Side effects include upper respiratory infections, lower respiratory infections, and constipation. The FDA granted this application fast track and orphan drug designation as well as priority review. Nusinersen is marketed as Spinraza. The drug has come under intense scrutiny, including an article in *The New York Times*, because of Biogen's pricing strategy, which will make the drug one of the most expensive on the market. The first year of therapy is expected to cost up to $750,000, with subsequent costs of about $375,000 per year.

The FDA has concluded that pioglitazone (Actos) may be linked to an increased risk of bladder cancer. The drug label already contains language about the risk, but the FDA is updating the warning based on an updated review. The new warning recommends that pioglitazone should not be prescribed to those suffering from active bladder cancer, and caution should be used in patients with a history of bladder cancer. Patients on pioglitazone should be warned to look for hematuria, urgency, or dysuria.

The FDA has approved a new indication for empagliflozin (Jardiance) to reduce the risk of cardiovascular death in adult patients presenting with type 2 diabetes and cardiovascular disease. Empagliflozin is an SGLT2 inhibitor that facilitates excretion of glucose through the kidney. The new indication was based on the EMPA-REG OUTCOME trial, which showed high-risk patients demonstrated a 38% relative risk reduction in rate of death compared to placebo patients. ■

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Author: **William T. Elliott, MD, FACP,** Medical Director, Pharmacy, Northern California Kaiser Permanente Assistant Clinical Professor of Medicine, University of California, San Francisco

Executive Editor: Leslie Coplin

Assistant Editor: Jonathan Springston

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Customer Service: (800) 688-2421

Email Address: jspringston@reliaslearning.com

Website: AHCMedia.com

Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.