PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Stick with Two Drugs for Sicker Patients with Pneumonia

In this issue: Treating Community-Acquired Pneumonia; 4-month vs 6-month Therapy for Tuberculosis; Green Coffee Bean Study Retracted; Fecal Microbiota Transplant for *C. difficile* Infection; and FDA Actions.

Treating Community-Acquired Pneumonia

Adding a macrolide to a beta-lactam improves outcomes in patients with moderately severe community-acquired pneumonia, according to a noninferiority trial from Switzerland. In the open-label randomized trial, 580 immunocompetent adults were treated with a beta-lactam and a macrolide or a beta-lactam alone and followed for 90 days. After 7 days of treatment, clinical stability was *not* reached in 41.2% of the monotherapy group vs 33.6% of the combination group ($P = 0.07$, although the confidence interval exceeded the predefined noninferiority boundary). Patients infected with an atypical bacteria or with more severe pneumonia (Pneumonia Severity Index category IV) fared better with the combination regimen, whereas those not infected with an atypical pathogen or with lower category pneumonia did as well with monotherapy. There were more 30-day readmissions in the monotherapy arm (7.9% vs 3.1%, $P = 0.01$). Mortality, ICU admission, complications, length of stay, and recurrence of pneumonia within 90 days did not differ between the two regimens. The authors concluded that beta-lactam monotherapy was *not* noninferior in patients hospitalized for moderately severe community-acquired pneumonia. Patients infected with atypical pathogens or with more severe pneumonia had delayed clinical stability with monotherapy (*JAMA Intern Med*, published online Oct. 6, 2014. doi:10.1001/jamainternmed.2014.4887). This is somewhat confusing wording to say that single-drug therapy with a beta-lactam alone was not equivalent to dual-drug therapy with a beta-lactam and a macrolide in sicker patients with pneumonia. ■

4-months vs 6-months for Tuberculosis

In a similar study, tuberculosis treatment for 4 months including a fluoroquinolone was not as effective as standard 6-month therapy, according to three studies published in the Oct. 23 edition of the *New England Journal of Medicine*. The three regimens included either moxifloxacin or gatifloxacin in nearly 4600 patients, mostly in sub-Saharan Africa, with some patients in India, Asia, and Mexico. None of the treatment regimens met criteria for noninferiority with regard to treatment failure or relapse (*N Engl J Med* 2014;371:1577-1587, 1588-1598, 1599-1608). While more research is needed, 6 months of treatment remains the gold standard for treatment of tuberculosis. ■

Green Coffee Bean Study Retracted

The green coffee bean craze may be over after the authors of the study that launched the product have retracted their research. The original article, published in *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, suggested that green coffee bean extract could facilitate weight loss in overweight subjects. Soon after, Dr. Oz touted the supplement on his popular TV show

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. For questions and comments, please e-mail: neill.kimball@ahcmedia.com.

and the craze took off. In September, the Federal Trade Commission reviewed the study and found it "so hopelessly flawed that no reliable conclusions could be drawn from it." There were suggestions that the lead investigator altered data and switched patients from the placebo arm to the treatment arm. The journal published an official retraction on Oct. 16. In addition, Applied Food Sciences, the company that makes green coffee extract products and hired the researchers, has agreed to pay a $3.5 million fine. ■

Fecal Microbiota Transplant for CDI

If you have been involved in the care of patients with refractory *Clostridium difficile* infection, you are likely aware that fecal microbiota transplantation (FMT) is remarkably effective. Hospitals have struggled with preparation of the transplant material, often using donor stool that is prepared locally in blenders, then introduced into the colon via colonoscopy or to the small bowel via endoscopy. Now, a new study shows the promise of frozen FMT capsules that can be taken orally. In the study from Harvard, 20 patients with relapsing or refractory *C. difficile* infection received 15 FMT capsules on 2 consecutive days and were followed for 6 months. The capsules were resistant to stomach acid and were stored at -112°F until administration. Resolution of diarrhea was achieved in 14 patients (70%; 95% confidence interval [CI], 47-85%). The six non-responders were retreated and four had resolution of diarrhea, resulting in an overall 90% cure rate (95% CI, 68-98%). The number of daily bowel movements decreased from a median of five to two at day 3 and one at 8 weeks ($P < 0.001$). There were no serious adverse effects. This preliminary study provides data on rates of resolution and adverse effects in patients with recurrent *C. difficile* infections but the authors caution that larger studies are needed (*JAMA* published online Oct. 11, 2014. doi:10.1001/jama.2014.13875). It is hoped that there will soon be a commercial FMT product as pharmacy and therapeutics committees struggle to deal with the administration of stool slurries in the inpatient setting. ■

FDA Actions

The FDA has approved the first combination pill to treat patients with hepatitis C virus (HCV) genotype 1 infection. The new product contains the previously approved blockbuster sofosbuvir (Sovaldi) along with the newly approved ledipasvir. This is the first combination for the treatment of HCV genotype 1 that does not require administration with interferon or ribavirin, drugs that have significant side effects for many patients. The new combination was approved on the basis of three clinical trials of more than 1500 patients in which sustained virologic response was 94-99%, depending on the clinical setting. The drug was approved under a priority review and was designated a breakthrough therapy. Common side effects include fatigue and headache. Sofosbuvir/ledipasvir is marketed by Gilead Sciences as Harvoni. The drug is taken for 12 weeks for most patients, although treatment-experienced patients with cirrhosis require 24 weeks of therapy. The cost for 12 weeks is roughly $95,000.

As reported last month, the manufacturers of varenicline (Chantix) petitioned the FDA remove the black box warning on the drug that warns of neuropsychiatric side effects. The petition was initiated after new research suggested no increase in neuropsychiatric risks. The FDA, however, has recently elected to turn down the petition and maintain the black box warning suggesting that new research does not include all possible psychological effects. Pfizer, the drug's manufacturer, is currently doing a study on 8000 patients that compares neuropsychiatric outcomes associated with varenicline with two other smoking cessation products as well as placebo.

The FDA has approved a new combination drug for the treatment of nausea and vomiting in patients undergoing cancer chemotherapy. The oral agent combines netupitant, a newly approved NK_{1} receptor antagonist, along with the previously approved 5-HT_{3} receptor antagonist palonosetron. The combination prevents acute phase nausea (palonosetron) and delayed phase nausea (netupitant) after starting chemotherapy. Approval was based on two trials of more than 1700 cancer patients in which the drug was effective in preventing vomiting in the acute, delayed, and overall phases after the start of chemotherapy. The combination is marketed by Eisai Inc. as Akynzeo.

The FDA has approved two new drugs for the treatment of idiopathic pulmonary fibrosis. Pirfenidone acts on multiple pathways involved in scarring of lung tissue while nintedanib is a kinase inhibitor that also prevents scarring of lung tissue. Both drugs were approved under priority review as orphan products and designated as breakthrough therapy. Pirfenidone is marketed by InterMune Inc. and Roche as Esbriet and nintedanib is distributed by Boehringer Ingelheim as Ofev. Both drugs are expected to cost about $95,000 per year. ■