Pharmacology Watch

Evidence-based updates in clinical pharmacology

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FDA Committee Recommends Approval of Two New Cholesterol-lowering Drugs

Beta-blockade Use in NCS Patients

The risks and benefits of perioperative beta-blockade have been debated for decades. While the benefits are widely accepted in patients undergoing cardiac surgery, the value of perioperative beta-blockade in non-cardiac surgery (NCS) is not clear. A large retrospective observational analysis from the VA helps define which patients are candidates for beta-blockers. Patients undergoing NCS from 2008 to 2013 were evaluated (n = 314,114).

Patients were assigned a cardiovascular risk score of 0-4, with one point each for renal failure, coronary artery disease, diabetes, and surgery in a major body cavity. The endpoint was 30-day surgical mortality. Beta-blocker use was defined as a dose 8 hours pre-op to 24 hours post-op. Beta-blockade significantly lowered mortality by 37% in patients with 3-4 cardiac risk factors undergoing NCS (odds ratio [OR], 0.63; 95% confidence interval [CI], 0.43-0.93) but had no effect on patients with 1-2 risk factors. Beta-blockade increased the risk of death in patients with no risk factors undergoing NCS (OR, 1.19, 95% CI, 1.06-1.35). The authors conclude that perioperative beta-blockade appears to be beneficial for patients with high cardiac risk factors undergoing NCS, but it increased the risk of death in those with no cardiac risk factors (*JAMA Surg*, published online May 27, 2015. doi:10.1001/jamasurg.2015.86). ■

Addition of Ezetimibe to Simvastatin May Improve CV Outcomes

A new study suggests the addition of ezetimibe to simvastatin may improve cardiovascular outcomes in patients with acute coronary syndrome (ACS), although the effect is modest. More than 18,000 patients who had been hospitalized for ACS and had low-density lipoprotein (LDL) cholesterol levels < 100 mg/dL (if they were on lipid-lowering therapy) or LDL 50-125 mg/dL (if they were not on lipid-lowering therapy) were randomized to simvastatin 40 mg plus ezetimibe 10 mg or simvastatin 40 mg plus placebo.

The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, or nonfatal stroke. The median follow up was 6 years. The combination resulted in lower LDL cholesterol levels (53.7 mg/dL for the combination vs 69.5 mg/dL for simvastatin alone, $P < 0.001$). The Kaplan-Meier event rate for the primary endpoint at 7 years was 32.7% for the combination and 34.7% for simvastatin alone (absolute risk difference, 2%; hazard ratio [HR] 0.936; 95% confidence interval [CI], 0.89-0.99; $P = 0.016$). Adverse effects were similar in both groups. The authors conclude that the addition of ezetimibe to statin therapy resulted in lower LDL levels and improved cardiovascular outcomes (*N Eng J Med* published online June 3, 2015, doi:10.1056/NEJMoa1410489).

This study has generated considerable controversy, even prompting an accompanying editorial that suggests LDL-lowering goals should be examined again based on this study. Cholesterol treatment guidelines published in 2013 abandoned the "treat to target" method of cardiovascular risk control, instead focusing on the level of risk and emphasizing statin therapy as the preferred

treatment option for patients with established cardiovascular disease or hyperlipidemia. The editorialist suggests that this study "offers important new evidence in favor of the LDL hypothesis" and of the efficacy of lowering LDL by any means possible (*N Engl J Med* published online June 3, 2015. doi:10.1056/NEJMe1507041). Others argue that the dose of statin used in this study was low by current guidelines, and the incremental effect of ezetimibe was small. ■

FDA Actions

The FDA has approved two drugs for the treatment of diarrhea-predominant irritable bowel syndrome (IBS-D). Eluxadoline is a new entity that targets mu (agonist) and delta (antagonist) opioid receptors in the gut, which are thought to affect gastrointestinal (GI) motility, function, and secretion production. The drug is taken orally twice daily with food. Eluxadoline was approved on the strength of two double-blind, placebo-controlled trials of nearly 2500 patients that showed the effectiveness in reducing abdominal pain and improving stool consistency over 26 weeks. Eluxadoline is made by Patheon Pharmaceuticals and distributed by Forest Labs under the trade name Viberzi.

The agency also approved rifaximin for the treatment of IBS-D. The drug was previously approved for the treatment of travelers' diarrhea caused by *E. coli* and for the prevention of hepatic encephalopathy. For IBS-D, rifaximin is taken orally three times a day for 14 days. If symptoms recur, a 14-day course can be repeated up to two times. The drug is thought to work by changing the bacterial content of the GI tract. Approval was based on three double-blind, placebo-controlled trials, two of initial treatment and the third evaluating repeat treatment. In those studies, more patients improved with regard to abdominal pain and stool consistency compared to placebo. There is a warning that says if symptoms continue or worsen after treatment, patients should be evaluated for *C. difficile* enterocolitis. Rifaximin is marketed by Salix Pharmaceuticals as Xifaxan.

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An FDA advisory committee has recommended approval of a new drug to treat low sex drive in women. The Bone, Reproductive, and Urologic Drugs Advisory Committee to the FDA reviewed flibanserin for the treatment of hypoactive sexual desire disorder in premenopausal women and voted 18-6 to recommend approval. The drug is a 5HT type 1A receptor agonist and a 5HT type 2A antagonist, which is taken once daily at bedtime. This is the third time the drug has come to the advisory committee with concerns about safety and efficacy blocking approval previous to this review. New data presented to the group showed an increase in satisfying sexual events per month by 0.5-1 (from a baseline of 2-3 per month) compared to placebo, which was a modest but statistically significant effect. The drug is associated with syncope and hypotension — "serious safety concerns" — that will require risk mitigation strategies. Flibanserin is manufactured by Sprout Pharmaceuticals, which helped mount an "Even the Score" campaign by 24 women's groups, complaining to the FDA that there are 26 drugs approved for men with sexual dysfunction and none for women. If approved by the FDA, the drug will be marketed as Addyi.

The FDA has approved a new combination beta-agonist and anticholinergic inhaler for maintenance therapy of chronic obstructive pulmonary disease (COPD). The new agent combines tiotropium bromide with the long-acting beta2-agonist olodaterol. Tiotropium is the active ingredient in Spiriva. The combination is approved as a once-a-day inhalation for maintenance of chronic bronchitis and emphysema but not for acute deterioration of COPD or asthma. A study of 5000 patients showed that the combination was superior in improving lung function compared to tiotropium or olodaterol alone. Tiotropium/olodaterol inhalation spray is delivered in a propellant-free "Respimat" delivery system. It is marketed by Boehringer Ingelheim as Stiolto Respimat.

The FDA's Endocrinologic and Metabolic Drugs Advisory Committee has recommended the approval of two potent injectable cholesterol-lowering medications alirocumab and evolocumab, both monoclonal antibodies targeting PCSK9 (pro-protein convertase subtilisin/kexin type 9). The drugs lower LDL cholesterol (LDL-C) by up to 60%. Both will likely be approved for primary (heterozygous familial and non-familial) or mixed hyperlipidemia, statin intolerance, use in combination with a statin, patients who are not considered clinically appropriate for statins, and homozygous familial hypercholesterolemia in patients as young as 12 years of age. While both drugs are more potent than statins in lowering LDL-C, neither has been shown to lower cardiovascular outcomes, although ongoing studies are currently looking at this issue. If approved by the FDA later this summer, alirocumab will be marketed by Sanofi and Regeneron Pharmaceuticals as Praluent and evolocumab will be marketed by Amgen as Repatha. ■