Pharmacology Watch

Evidence-based updates in clinical pharmacology

By William T. Elliott, MD, FACP

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Top Pharmaceutical Company Suffers Blow After Major Drug Fails Phase III Trial

On Aug. 5, Bristol-Myers Squibb announced that its blockbuster checkpoint inhibitor nivolumab (Opdivo) failed a Phase III trial as monotherapy in patients with previously untreated non-small cell lung cancer (NSCLC). The drug missed its primary endpoint of progression-free survival in patients whose tumors expressed programmed death ligand 1 (PD-L1) at ≥ 5%.

Although the company did not release data from the study, it reported that it will complete a full evaluation of the CheckMate -026 data in the future. The drug is a humanized IgG4 anti-PD 1 monoclonal antibody similar to pembrolizumab (Keytruda). The drugs block a signal that prevents activated T cells from attacking cancer cells. Both drugs are approved for the treatment of a variety of cancers, including metastatic melanoma, advanced renal cell cancer, and NSCLC in patients who have not responded to previous treatment.

The failure of nivolumab as initial therapy for NSCLC is a major blow to Bristol-Myers Squibb, which saw its stock drop 16% the day of the announcement. Meanwhile, pembrolizumab reportedly has shown promising results in the same role, although results have not been published.

Report: Certain Drugs Cause, Exacerbate Heart Failure

The American Heart Association has published "Drugs That May Cause or Exacerbate Heart Failure," a comprehensive list of drugs that is readily available to healthcare providers. The list was created because heart failure (HF) patients "often have a high medication burden consisting of multiple medications and complex dosing regimens," taking an average of 6.8 medications per day with more than 10 doses per day, not including over-the-counter (OTC) medications or complementary and alternative medications (CAMS).

Drugs may worsen heart failure by a number of mechanisms: by direct myocardial toxicity; by negative inotropic, lusitropic, or chronotropic effects; by exacerbating hypertension; by delivering a high sodium load; or by drug-drug interactions that limit the beneficial effects of HF medications.

Some of the most common medications on the list include nonsteroidal anti-inflammatory drugs; COX-2 inhibitors; diabetes medications, including metformin, thiazolidinediones, and DPP-4 inhibitors (saxagliptin, sitagliptin); antiarrhythmics such as flecainide, sotalol, and dronedarone; antihypertensives such as beta-blockers and calcium channel blockers; and some antidepressants such as tricyclics antidepressants and citalopram.

The authors presented a number of recommendations for clinicians treating HF patients, including comprehensive medication reconciliation at every visit (including OTCs and CAMS), evaluating the risks and benefits of every medication at each visit, and discontinuing medications when

possible. (*Circulation* 2016;134:00–00. doi: 10.1161/CIR.0000000000000426).

Study: Knee Replacement Can Lead to Chronic Opioid Use

Total knee replacement is the surgical procedure most commonly associated with chronic opioid use in opioid-naïve patients, according to a new study.

In a retrospective analysis, researchers from Stanford compared the records of more than 640,000 opioid-naïve surgical patients to more than 18 million opioid-naïve non-surgical patients. Researchers reviewed 11 surgical procedures, including knee and hip arthroplasty, laparoscopic and open cholecystectomies, appendectomies, C-sections, sinus surgery, cataract surgery, transurethral resections of the prostate (TURP), and simple mastectomies.

Chronic opioid use was defined as filling 10 or more prescriptions or more than 120 days' supply of an opioid in the first year after surgery, excluding the first 90 postoperative days. Cataract surgery, sinus surgery, laparoscopic appendectomy, and TURP were not associated with chronic opioid use. For other procedures, C-sections had the lowest risk, while total knee replacement had the highest risk (1.41%; 95% confidence interval, 1.29%-1.53%). Men and elderly patients were at the highest risk for chronic opioid use (*JAMA Intern Med* Published online July 11, 2016. doi:10.1001/jamainternmed.2016.3298).

FDA Actions

Just in time for flu season, the FDA has approved the first generic oseltamivir (Tamiflu) to treat and prevent influenza. The drug is indicated for patients ≥ 2 weeks of age who have suffered from flu symptoms for no more than 48 hours and for prevention of the flu in patients ≥ 1 year of age. Natco Pharma and its U.S. partner, Alvogen, have the first generic approval and will be the only generic supplier for six months under a patent agreement with Roche Pharmaceuticals, the manufacturer of Tamiflu.

AstraZeneca has lost a last-ditch effort to protect its blockbuster statin rosuvastatin (Crestor) from generic competition. The company argued before a federal court that the drug had recently been approved under the Orphan Drug Act to treat children with homozygous familial hypercholesterolemia, a rare condition. AstraZeneca lost the case and was criticized for attempted abuse of the Orphan Drug Act, according to *The New York Times*. Subsequently, the FDA approved several more generic versions of rosuvastatin in early August. The drug's first generic copy was approved in May.

The FDA has approved the fifth GLP-1 agonist to treat type 2 diabetes. Lixisenatide is a once-daily injection used to improve glycemic control along with diet and exercise in type 2 diabetics. The drug previously was approved in Europe in 2013. It is not indicated for type 1 diabetes or diabetic ketoacidosis. The approval was based on 10 clinical trials consisting of 5,400 patients presenting with type 2 diabetes in which the drug was evaluated as a standalone therapy and in combination with metformin, sulfonylureas, pioglitazone, and basal insulin. Lixisenatide improved A1c levels in these trials. In 6,000 patients at risk for cardiovascular disease, lixisenatide did not increase the risk of adverse events.

The FDA has approved lifitegrast ophthalmic solution for the treatment of dry eye disease. The drug is the first of a new class of lymphocyte function-associated antigen 1(LFA-1) antagonists. Safety and efficacy was shown in four studies of more than 1,000 patients (76% female) age 19-97 years. Patients were randomized to lifitegrast or placebo twice a day for 12 weeks. Lifitegrast resulted in more improvements in both the signs and the symptoms of eye dryness than the groups treated with placebo. Lifitegrast ophthalmic solution is marketed as Xiidra. It is expected to be priced at $426 for a 30-day supply.

The FDA has approved adapalene gel 0.1% (Differin Gel) for OTC use for the treatment of acne in those ≥ 12 years of age. It represents the first retinoid to be available OTC and is the first new active ingredient for acne available OTC in nearly 30 years. The drug was originally approved in 1996. Five postmarking trials have proven safety and efficacy since 1996, also showing that consumers can understand the OTC labeling and use the product appropriately. Adapalene gel 0.1% OTC will be marketed as Differin Gel 0.1%. ■

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