PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

New Hepatitis C Combination Approved

The hepatitis C wars have escalated with the approval of a new four-drug oral combination to treat hepatitis C virus (HCV) genotype 1 infection. The combination contains three new drugs — ombitasvir, paritaprevir and dasabuvir — as well as the previously approved ritonavir, a CYP3A inhibitor, to boost the levels of paritaprevir. The drug is approved for use in patients with HCV infections, including those with cirrhosis. It can be used with or without ribavirin, but it is not recommended in those with decompensated cirrhosis. The combination was evaluated in six clinical trials of more than 2300 patients with HCV infection with and without cirrhosis, showing 91-100% sustained viral response (SVR) rate after 12 weeks of treatment. The new combination is marketed by AbbVie Inc as Viekira Pak. The approval comes 2 months after the approval of Gilead's combination HCV drug, Harvoni, which boasts similar SVR rates. Harvoni is also an all-oral regimen for 12 weeks, and like VIekira Pak, is an interferon-free regimen. It appears that AbbVie and Gilead may be locked in a price war, with both drugs costing from $85,000 to $95,000 per treatment course. Health plans and PBMs are already maneuvering for best pricing. In late December, Express Scripts announced an exclusive contract with AbbVie to make Viekira Pak, their drug of choice, for HCV genotype 1 patients.

The popular pain reliever tramadol is associated with hypoglycemia, according to a new study from the United Kingdom. In a nested case-control analysis conducted in the United Kingdom, tramadol was compared to codeine for non-cancer pain between 1998 and 2012. Cases of hypoglycemia were matched with up to 10 controls on age, sex, and duration of follow-up, in a study that included more than 330,000 patients. Compared to codeine, tramadol use was associated with an increased risk of hospitalization for hypoglycemia (odds ratio [OR], 1.52; 95% confidence interval [CI], 1.09-2.10), particularly in the first 30 days of use (OR, 2.61; 95% CI, 1.61-4.23). This was confirmed in both cohort and case-crossover analyses. The authors conclude that initiation of tramadol therapy is associated with an increased risk of hypoglycemia requiring hospitalization (*JAMA Int Med*, published online Dec 8, 2014, doi:10.1001/jamainternmed.2014.6512). This study is important because the use of tramadol has increased in the past few years. The drug is a weak opioid analgesic that was only recently placed in schedule IV. Tramadol has been viewed by some physicians as an option to hydrocodone, which was moved from schedule III to the more restrictive schedule II in August. Tramadol has been reported to cause hypoglycemia in those with no known risk factors in up to 40% of cases.

Use caution when prescribing clarithromycin with all statins. That according to an observational study from Canada. Clarithromycin has been shown to increase the toxicity of statins metabolized by CYP3A4, but even statins that are not metabolized by CYP3A4 are implicated in a new study. These include rosuvastatin (Crestor), fluvastatin (Lescol) and pravastatin (Pravachol). The study looked at Canadian health care databases and compared the use of clarithromycin

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(which also not only inhibits CYP3A4, but also inhibits liver enzymes that help metabolize all statins) with azithromycin (which does inhibit statin metabolism). Compared to use with azithromycin, use of clarithromycin, plus one of the three statins, increased the risk of hospitalization for kidney injury (relative risk [RR], 1.65; CI, 1.31-2.09), admission with hyperkalemia (RR, 2.17; CI, 1.22-3.86), rhabdomyolysis (RR, 2.27; CI, 0.86-5.96), and all-cause mortality (RR, 1.43; CI, 1.15-1.76). The incidence of these outcomes was small, with an absolute increase of less than 1%, still statistically significant (*CMAJ* published online December 22, 2014, doi:10.1503/cmaj.140950). The FDA has recommended use of non-CYP3A4 metabolized statins as safer alternative when taken with a CYP3A4 inhibitor, but as this study points out, all statins may cause risk. ■

FDA Actions

The FDA has approved the first IV drug to treat influenza. Peramivir is a neuraminidase inhibitor similar to oseltamivir (Tamiflu) and zanamivir (Relenza). Peramivir is administered as a single 600 mg IV dose. The drug was approved on the strength of a single trial of nearly 300 patients with flu who received peramivir 600 mg, 300 mg, or placebo. If given within 48 hours of the onset of symptoms, the 600 mg dose alleviated flu symptoms 21 hours sooner than placebo, although efficacy could not be established in seriously ill patients requiring hospitalization. The most common side effect is diarrhea, although there was also a higher incidence of hallucinations and delirium in patients with flu. Peramivir is marked by BioCryst Pharmaceuticals as "Rapivab."

The FDA has approved a new 9-valent HPV vaccine (Gardasil 9) for the prevention of human papillomavirus infections. The previous Gardasil vaccine protected against four strains of the virus. The new vaccine has the potential to prevent 90% of cervical, vulvar, vaginal, and anal cancers. The 9-valent vaccine is approved for females ages 9-26 and males ages 9-15. Gardasil 9 was approved based on a study of about 14,000 females in the target ages who received either Gardasil or Gardasil 9. The newer vaccine is 97% effective in preventing cervical, vulvar, and vaginal cancers caused by the additional HPV types not covered in the older vaccine, and was as effective as the older vaccine in protecting against the four shared HPV types. The vaccine is administered as three shots at zero, 2, and 6 months. Gardasil 9 is manufactured by Merck Sharp & Dohme Corp.

The FDA has approved liraglutide for the new indication of chronic weight management, in addition to a reduced-calorie diet and physical activity. The drug, which is a GLP-1 receptor agonist, is already approved for treatment of type 2 diabetes under the trade name Victoza, but at a lower dose. The drug was approved for weight loss based on clinical trials of about 4,800 obese and overweight patients, showing that patients given liraglutide lost between 3.7-5% of body weight depending on the clinical setting, with diabetic patients losing the least weight. The drug is given as a once a week subcutaneous injection. As with all drugs in this class, liraglutide comes with a boxed warning regarding an increased incidence of thyroid tumors seen in rodent studies. Serious side effects include pancreatitis, gallbladder disease, renal impairment, suicidal ideation, and elevated heart rate. Liraglutide is marketed Novo Nordisk as Saxenda.

The FDA has approved the fourth new antibacterial drug for 2014 with the approval of the combination drug ceftolozane/tazobactam. Ceftolozand is an antipseudomonal cephalosporin, while tazobactam is a beta-lactamase inhibitor. The combination is approved to treat complicated intra-abdominal infections and complicated urinary tract infections. In clinical trials, the combination (with metronidazole) was found to be non-inferior to meropenem for complicated abdominal infections, and noninferior to levofloxacin for complicated urinary tract infections. Ceftolozane/tazobactam is marketed by Cubist Pharmaceutical as Zerbaxa. The drug was approved as a Qualified Infectious Disease Product and given expedited review, qualifying the drug for an additional 5 years of marketing exclusivity.

Alcon Laboratories has received approval to market a new otic fluoroquinolone suspension for the treatment of acute otitis media. Finafloxacin otic suspension treats infections caused by *Pseudomonas aeruginosa*- and *Staphylococcus aureus*-causing infection of the outer ear and ear canal. Alcon will market finafloxacin otic as "Xtoro"overseas. It is not clear when Alcon plans on marketing the product in this country. ■