Pharmacology Watch

Evidence-based updates in clinical pharmacology

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New Report Raises Red Flags About Antiviral Agents and the Possibility of Liver Failure

The Institute for Safe Medication Practices (ISMP) reported on 524 cases of liver failure in the past 12 months associated with direct-acting antiviral agents for treating hepatitis C. The investigation included 24 cases of hepatitis B reactivation that were widely reported last October. But now, the ISMP has reviewed hundreds of other cases of liver failure associated with the drugs and more than 1,000 cases of severe liver injury. According to the report, 165 patients have died. All the new antivirals for hepatitis C were implicated, including sofosbuvir (Sovaldi), ledipasvir-sofosbuvir (Harvoni), and simeprevir (Olysio). Gilead Sciences suggests that approval of its drug sofosbuvir for treatment of patients with liver failure may account for some of the cases. However, the ISMP reported that the vast majority of these cases were reported by healthcare professionals to FDA's MedWatch program for adverse drug events. Further, the ISMP suggested that "Our data show the need for further investigation into the negative consequences of these expensive and important new drugs" (ismp.org/QuarterWatch/). Most experts agree that the drugs must be used with caution by those well-versed in hepatitis C treatment, but given the remarkably high cure rates, the benefits generally outweigh the risks.

Class Action Suit Accuses Pharmaceuticals of Fixing Prices

Drug prices have come under intense scrutiny, with the Trump administration promising fewer regulations and lower taxes while expecting pharmaceutical companies to lower drug prices in return. Now, a class action lawsuit accuses insulin manufacturers of fixing prices and conspiring to increase the cost of their essential medication. The manufacturers, Sanofi, Novo Nordisk, and Eli Lilly, raised insulin prices by more than 300% between 2002 and 2013 while offering large rebates to pharmacy benefit management companies. All three companies have raised prices in near identical timing. The American Diabetes Association has called for access to affordable insulin, suggesting that "millions of Americans with diabetes are paying a steep price to stay alive." Meanwhile, generic drug pricing has come under scrutiny as well. In December, the attorneys general in 20 states accused generic drug manufacturers of engaging in a price-fixing scheme to raise prices. The companies, including generic behemoths Teva and Mylan, are accused of colluding at informal gatherings and through phone and text messages. Be sure to check back with *Pharmacology Watch* and AHCMedia.com for updates on this issue.

Approved Drug Demonstrates Efficacy in Battling Potent Bacterial Infection

The monoclonal antibody bezlotoxumab targets *Clostridium difficile* toxin B. The drug was approved in October, and a new study confirms its efficacy in preventing *C. difficile* recurrence. Two double-blind, randomized, placebo-controlled trials were performed on 2,655 adults receiving oral standard-of-care antibiotics for primary or recurrent *C. difficile* infection. Participants received bezlotoxumab infusion, actoxumab (which targets *C. difficile* toxin A) along with bezlotoxumab, or placebo. (In an earlier study, researchers tried actoxumab alone but discontinued the effort after an interim analysis showed it to be of no benefit.) The primary endpoint was recurrent infection within 12 weeks after infusion in the modified intention-to-treat population. In both trials, the rate of recurrent *C. difficile* infection was significantly lower with bezlotoxumab,

17% vs. 28% in study one, and 16% vs. 26% in study two ($P < 0.001$ for both). The rates of adverse events were similar across all groups. The addition of actoxumab to bezlotoxumab did not improve efficacy. The authors concluded that bezlotoxumab was associated with a substantially lower rate of recurrent *C. difficile* infection compared to placebo with a good safety profile (*N Engl J Med* 2017;376:305-317).

Comparing First-line Treatments for *C. Difficile* Infections

In a related story, vancomycin and metronidazole are both used as first-line treatment for *C. difficile* infections (CDI), but vancomycin may be superior in reducing 30-day mortality, according to a new study. In a retrospective, propensity-matched cohort study evaluating patients presenting with CDI from the VA system, more than 47,000 patients (96% men) were evaluated. Initial treatment was 95.6% with metronidazole and 4.4% vancomycin. The 2,068 vancomycin patients were case-matched with more than 8,000 metronidazole patients for the evaluation. There was no difference in the risk of recurrence between patients treated with vancomycin vs. those treated with metronidazole. However, those treated with vancomycin were less likely to die across all severity cohorts (relative risk [RR], 0.86; 95% confidence interval [CI], 0.74-0.98). No difference in mortality was observed in patients with mild disease, but vancomycin significantly reduced the risk of all-cause, 30-day mortality in patients suffering from severe CDI (adjusted RR, 0.79; 95% CI, 0.65-0.97; adjusted risk difference, -0.04; 95% CI, -0.007 to -0.01). The authors concluded that although the recurrence rates were similar among patients treated with vancomycin and metronidazole, the risk of 30-day mortality was reduced in patients treated with vancomycin, especially for those suffering from severe CDI. Although metronidazole generally is recommended as first-line therapy, these findings may justify use of vancomycin, especially in sicker patients (*JAMA Intern Med*. Published online Feb. 6, 2017. doi:10.1001/jamainternmed.2016.9045).

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Promising Treatment for Multiple Sclerosis Closer to Approval

Ocrelizumab may be closer to approval for the treatment of progressive multiple sclerosis based on the recently published results of two studies. Ocrelizumab is a humanized monoclonal antibody that selectively depletes CD20-expressing B cells. In the first study, 732 patients with primary progressive multiple sclerosis were randomized 2:1 to receive intravenous ocrelizumab or placebo every 24 weeks for at least 120 weeks and until a pre-specified number of confirmed disability progression events occurred. The percentage of patients with 12-week confirmed disability progression (primary endpoint) was 32.9% with ocrelizumab vs. 39.3% with placebo (hazard ratio [HR], 0.76; 95% CI, 0.59-0.98; $P = 0.03$). At 24 weeks, the percentages were 29.6% vs. 35.7%, respectively (HR, 0.75; 95% CI, 0.58-0.98; $P = 0.04$). At week 120, performance measures had improved with ocrelizumab (25-foot walk test) as well as the total volume of brain lesions on MRI. Side effects with ocrelizumab included infusion-related reactions, URIs, and oral herpes. The rate of neoplasm was 2.3% in the ocrelizumab group vs 0.8% with placebo (*N Engl J Med* 2017;376:209-220). The second study compared ocrelizumab to interferon beta-1a in patients presenting with relapsing multiple sclerosis. In two identical studies, 1,656 patients were randomized to ocrelizumab 600 mg intravenously every 24 weeks or subcutaneous interferon beta-1a 44 mcg three times weekly for 96 weeks. The annualized relapse rate was lower with ocrelizumab in both trials (0.16 vs. 0.29; $P < 0.001$ for both). The percentage of patients with disability progression at 12 and 24 weeks was better with ocrelizumab, as were MRI findings. Serious infections were lower with ocrelizumab compared to interferon, while neoplasms occurred in 0.5% patients treated with ocrelizumab vs. 0.2% of those treated with interferon beta-1a. Both the placebo-controlled trial and the head-to-head study confirm the efficacy of ocrelizumab. However, further safety studies are required, especially regarding the rate of neoplasm (*N Engl J Med* 2017;376:221-234). The FDA has granted the manufacturer of ocrelizumab Breakthrough Therapy designation, which allows for an expedited review process.

FDA Action

The FDA has approved a second cyclase-C agonist for the treatment of chronic idiopathic constipation. Plecanatide is a once-a-day tablet that stimulates fluid movement in the gut and facilitates defecation. It follows linaclotide (Linzess), which was approved in 2012 for the same indication, although linaclotide also was approved for irritable bowel syndrome with constipation. Plecanatide was approved on the strength of two 12-week, placebo-controlled trials in 1,775 adults suffering from chronic idiopathic constipation, defined by less than three defecations per week for at least the previous three months, as well as other constipation-related symptoms. Plecanatide resulted in improved frequency of complete spontaneous bowel movements compared to placebo as well as improvements in stool frequency, consistency, and straining. The most common side effect was diarrhea. Plecanatide is marketed as Trulance. ■