PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

More Advances in Hepatitis C Treatment

In this issue: Costs of hepatitis C drugs expected to rise; Truvada to prevent HIV infection; and FDA actions.

Costs of HCV drugs expected to rise

Advances in the treatment of hepatitis C virus (HCV) are occurring at breakneck speed, with new drugs and new drug combinations showing astounding cure rates, but coupled with astounding price tags. No sooner was sofosbuvir approved and marketed at a cost of $84,000 per treatment course, that new drug combinations started emerging, some containing sofosbuvir. The importance of these drugs is demonstrated by a few statistics — as many as 170 million people are infected with HCV worldwide, including 3.2 million Americans. It is the most common cause of liver-related death and liver transplant in the United States, and HCV recently passed HIV as a cause of death in this country. But the pace of research into treatment is impressive. In the last 2 months, six studies were published in the *New England Journal of Medicine* evaluating new drug regimens. Three of them looked at sofosbuvir/ledipasvir alone or in combination with ribavirin for treatment of genotype 1 hepatitis C. Ledipasvir is an unapproved NS5A inhibitor. The combination offers the advantage of an all oral, short-course, interferon-free regimen. Both in previously treated and untreated patients, sustained virologic responses were at least 94% with no additional benefit from ribavirin. There was a very low discontinuation rate with all regimens (*N Engl J Med* 2014;370:1483-1493, 1879-1888, 1889-1898). Sofosbuvir plus ribavirin was also shown to be highly effective for treating HCV genotypes 2 and 3 (*N Engl J Med* published online May 4, 2014, doi: 10.1056/NEJMoa1316145). Finally, two studies looked at a new highly active, interferon-free regimen of a new protease inhibitor with ritonavir (ABT-450/r), the NS5A inhibitor ombitasvir, and the nonnucleoside polymerase inhibitor dasabuvir with ribavirin in patients with HCV genotype 1. Sustained virologic response rates were 95% or higher in both untreated and previously treated individuals after 12 weeks. This regimen was also well tolerated with a low discontinuation rate (*N Engl J Med* 2014;370:1594-1603, 1604-1614). This is very promising news, except for the cost of treatment, which is also expected to escalate. As one editorialist puts it "The predicted costs of the new oral antiviral agents are as breathtaking as their effectiveness" (*N Engl J Med* 2014;370:1552-1553.) ■

Truvada to prevent HIV infection

The CDC is now recommending Truvada (emtricitabine and tenofir) daily to prevent HIV infection in high-risk adults. In a new guideline titled "Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014)," experts from the CDC define at-risk individuals who are candidates for pre-exposure prophylaxis. This includes men who have sex with men who are not in a monogamous relationship and who engage in unprotected anal intercourse, heterosexually active adults with multiple partners who do

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not use condoms on a regular basis, any adult in an ongoing relationship with an HIV-positive partner, injection drug users who share needles or who are at risk of sexual acquisition of HIV, and others. The dose of Truvada is one pill a day — the same dose given to treat HIV infection in adults. Patients on prophylaxis should be HIV negative before starting the drug and should be tested every 3 months. The recommendation is based on several studies, including international studies that were done on at-risk populations such as all the risk groups mentioned above, which showed that the drug can reduce the rate of HIV infection by more than 90%. Truvada costs about $15,000 per year. The drug is manufactured by Gilead Sciences — the same company that makes the hepatitis C drug sofosbuvir. ■

FDA actions

The FDA has approved vorapaxar, a first in class oral antiplatelet agent to reduce the risk for myocardial infarction (MI), stroke, cardiovascular death, and revascularizttion in patients with a history of MI or peripheral artery disease. The drug is a protease-activated receptor-1 antagonist that prevents platelet aggregation. Vorapaxar increases the risk of bleeding and is contraindicated in patients who have had a stroke, transient ischemic attack, or intracranial bleeding. The drug was approved on the basis of one study that showed that it resulted in a 1.6% lower absolute risk of MI, stroke, or cardiovascular death over 3 years (9.5% vs 7.9%) but with a higher risk of bleeding. Vorapaxar is made by Merck and will be marketed as Zontivity.

The FDA is planning on investigating generic versions of extended-release metoprolol (Toprol XL). The investigation is the result of nearly 3500 adverse incident reports in the last 6 years, including lack of effectiveness and troublesome side effects. The FDA will assess whether generics are chemically the same as the branded product. There are also questions about the efforts to copy the delayed-release capsule of the original. The generics in question are manufactured in India and the United States.

The FDA has approved omega-3-carboxylic acids as an adjunct to diet to treat severe hypertriglyceridemia (levels ≥ 500 mg/dL). The product is the first omega-3 in free fatty acid form that allows dosing to be as few as two capsules once a day. This product joins two other prescription omega-3 supplements on the market for the same indication. The new omega-3 product is manufactured by AstraZeneca and marketed as Epanova.

The FDA has completed a safety evaluation of dabigatran (Pradaxa) in 134,000 Medicare patients, comparing the drug to warfarin in patients being treated for stroke prevention with atrial fibrillation. The study looked at the risk of ischemic or embolic stroke, brain hemorrhage, major gastrointestinal (GI) bleeding, MI, and death in patients ≥ 65 years of age. Compared to warfarin, dabigatran was associated with a 20% lower risk of embolic stroke, 66% lower risk of brain hemorrhage, and 14% lower death rate, although there was a 28% higher risk of GI bleeding. The MI risk was similar. These findings are similar to those of clinical trials that led to the drug's approval (RE-LY). As a result, the FDA considers dabigatran to have a favorable benefit-to-risk profile and is not recommending any labeling changes.

The FDA is requiring labeling changes for eszopiclone (Lunesta) that would lower the starting dose from 2 mg to 1 mg at bedtime for both men and women. Data show that the higher initial dose may result in blood levels the next morning that are high enough to impair activities that require alertness, including driving. The 1 mg dose can be increased to 2 mg or even 3 mg if needed. The change is partially the result of a study of 91 healthy younger adults which showed that compared to placebo, eszopiclone 3 mg was associated with severe next-morning psychomotor and memory impairment in both men and women 7.5 hours after taking the drug, and the effects can last as long as 11 hours. The patients were generally unaware they were impaired. This is the second "z-drug" dose reduction — last year the FDA recommended a similar dose reduction for zolpidem (Ambien, Ambien CR).

The FDA has approved a new GLP-1 agonist for the treatment of adults with type 2 diabetes. Albiglutide is approved for monotherapy or in combination with existing treatment options, including metformin, glimepiride, pioglitazone, or insulin. The drug's approval was based on eight clinical trials of more than 2000 patients with type 2 diabetes that showed a modest improvement in HbA1c levels. The drug comes with a boxed warning regarding thyroid tumors. Albiglutide is marketed by GlaxoSmithKline as Tanzeum. ■