DRUGMonitor

Brief summaries of recent drug approvals, interactions, and adverse events

Sitagliptin's Safety

In 2007, sitagliptin was the first dipeptidyl peptidase-4 (DPP-4) inhibitor released in the U.S., but research has still not completely captured its benefits and risks. These DPP-4 inhibitors have been shown to modestly improve cardiovascular risk factors, such as triglyceride levels and blood pressure, but data have been inconsistent, say researchers from the University of Alberta in Canada, the University of Illinois College of Medicine in Peoria, and the University of Illinois at Chicago College of Pharmacy. Findings from their study can reassure clinicians about the comparative safety and effectiveness of sitagliptin, the researchers say, especially given the current controversy about other antidiabetic agents.

While sitagliptin has been widely adopted, no large comparative studies have evaluated its effectiveness on broad outcomes, such as mortality in the *real world,* the researchers say. They designed what they believe is the first population-based study of outcomes associated with sitagliptin treatment compared with other glucose-lowering agents. This retrospective study used data of 72,738 patients with diabetes who were all new users of oral antidiabetic drugs. A total of 8,032 patients (11%) had used sitagliptin, mostly as an add-on treatment with other oral agents. Follow-up lasted a mean of 2.5 years. By the end of follow-up, 14,215 patients (20%) had been hospitalized at least once, and 520 patients (1%) had died. Sitagliptin users and nonusers had similar risks for cardiovascular-related hospital admissions or all-cause mortality. Sitagliptin also was not associated with any appreciable excess risk of all-cause hospital admission or all-cause mortality in higher risk patients with ischemic heart disease or reduced kidney function.

The study underscores the comparative safety of sitagliptin and supports current guidelines about using sitagliptin as an add-on treatment. The researchers note that their results are not consistent with previous meta-analyses that have reported that sitagliptin and various other DPP-4 inhibitors, such as alogliptin, linagliptin, and saxagliptin, have been associated with statistically significant reductions in major adverse cardiac events and nonsignificant reductions in all-cause and cardiovascular death compared with other active drugs or placebo. They add that those analyses included relatively short studies and enrolled *highly selected* patients. The researchers did not observe any safety signals related to cardiovascular-related hospital admissions or death, supporting the premise that sitagliptin is safe in patients with diabetes. However, they add that sitagliptin was prescribed in their study for patients with more advanced diabetes, so any potential benefits on morbidity and mortality may have been masked by the higher baseline risk.

Consistent with previous observational studies of sitagliptin use, this study found no increased risk of acute pancreatitis. Unlike other studies, however, this one did not find any association with upper respiratory tract infections.

The results suggest differences in the use of sitagliptin with metformin vs sulfonylureas. Metformin users tended to have better glycemic control at baseline, less co-morbidity, and were less likely to use additional treatment, so the results might simply represent residual confounding, the researchers say. On the other hand, metformin-treated patients who were prescribed sitagliptin as an add-on treatment had better outcomes than did those prescribed a sulfonylurea add-on treatment.

Findings from the ongoing Trial Evaluating Cardiovascular Outcomes With Sitagliptin are not yet ready, so in the meantime, the researchers say, their observational data may provide supportive evidence of sitagliptin's safety and effectiveness.

Source: Eurich DT, Simpson S, Senthilselvan A, Asche CV, Sandhu-Minhas JK, McAlister FA. *BMJ.* 2013;346:f2267. doi: 10.1136/bmj.f2267.

New Option Approved for Hospital-Acquired Pneumonia

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection, often due to *Staphylococcus aureus (S aureus)*, particularly the methicillin-resistant form (MRSA). Until now, only vancomycin and linezolid have been recommended for treatment of HAP due to MRSA. However, vancomycin has slow bactericidal action and poor lung penetration. So the recent FDA approval of once-daily telavancin could be good news.

Telavancin is a lipoglycopeptide with potent bactericidal action against gram-positive pathogens. Its safety and effectiveness were evaluated and compared with vancomycin in 2 phase III clinical trials (Assessment of Telavancin for Treatment of Hospital Acquired Pneumonia [ATTAIN]), ATTAIN I and ATTAIN II. Patients were randomly assigned to receive intravenous (IV) telavancin 10 mg/kg every 24 hours or IV vancomycin 1 g every 12 hours for 7 to 21 days.

Telavancin therapy achieved higher cure rates (82.4% vs 80.7% with vancomycin; 95% CI: –4.3% to 7.7%).

Importantly, the researchers say, telavancin was effective in treating patients with pneumonia due to MRSA, as well as methicillin-susceptible *S aureus*. In vitro, the researchers say, televancin is rapidly bactericidal against clinically important gram-positive bacteria, including MRSA, vancomycin-intermediate *S aureus*, and penicillin-resistant *Streptococcus pneumoniae*. Currently, telavancin is approved to treat only *S aureus*, not other bacteria that cause pneumonia, in patients who have HAP. Telavancin is also approved to treat skin and skin structure infections caused by other microorganisms, including MRSA.

More patients in the telavancin group experienced serious adverse effects (AEs) or discontinued treatment due to an AE. The incidence of most common abnormalities (anemia, abnormal serum potassium levels, and hepatic enzyme abnormalities) was similar in both groups, although patients who were treated with telavancin were more likely to have significant creatinine increases (16% vs 10%). More patients in the telavancin group with preexisting kidney problems died, compared with those treated with vancomycin. However, for most patients, any impairment in renal function had resolved or was resolving at the last follow-up visit. The researchers emphasize that a significant proportion of patients enrolled in the ATTAIN studies were critically ill.

Mortality rates were comparable between the 2 study arms except among patients who had preexisting kidney disease. In the first study, 80 patients (21.5%) treated with telavancin and 62 patients (16.6%) treated with vancomycin died (95% CI, –0.7% to 10.6%). In the second study, 70 patients (18.5%) treated with telavancin and 78 patients (20.6%) treated with vancomycin died (95% CI, –7.8% to 3.5%). The findings, which incorporated data from 1,503 patients in more than 250 sites around the world (the largest cohort to date studied for HAP), are robust and consistent across all efficacy populations, the researchers say.

According to the Food and Drug Administration, telavancin should be used to treat HAP only when alternative treatment is not available.

Sources: Rubinstein E, Lalani T, Corey GR, et al. *Clin Infect Dis.* 2011;52(1):31-40. doi: 10.1093/cid/ciq031.
U.S. Food and Drug Administration. FDA approves Vibativ for hospitalized patients with bacterial pneumonia [news release]. U.S. Food and Drug Administration Website. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm358209.htm. Updated June 24, 2013. Accessed August 26, 2013.

FDA Approves First Nonhormonal Drug for Menopause Symptoms

Hot flashes may not be life threatening, but they can be life disrupting for many women. And many women do not want to, or cannot, use hormonal treatments. But now there is an FDA-approved option: Paroxetine is the first FDA-approved nonhormonal treatment for moderate-to-severe vasomotor symptoms (hot flashes); other approved drugs contain estrogen or estrogen plus a progestin.

In 2 clinical studies of a total of 1,174 women who were having moderate-to-severe hot flashes (≥ 7 per day, or 50-60 per week), paroxetine was effective in reducing hot flashes, compared with placebo. A 12-week study found a statistically significant reduction from baseline in the frequency of symptoms at weeks 4 and 12 and a statistically significant reduction in the severity of symptoms at week 4 ($P < .01$). At weeks 4 and 12 of a 24-week study, there was a statistically significant reduction in frequency ($P < .01$ for both) and severity ($P = .04$ and $P < .01$, respectively). At 24 weeks, 48% of women saw a ≥ 50% reduction in the frequency of symptoms, compared with 36% in the placebo group.

The most common adverse effects were headache, fatigue, and nausea/vomiting. Nausea occurred primarily within the first 4 weeks of treatment and fatigue within the first week; both declined with continued therapy.

The recommended dosage (7.5 mg/d) is lower than that for treating psychiatric disorders. Although the studies excluded women with psychiatric disorders, a small number (0.3%) of women discontinued the trials due to suicidal ideation. Paroxetine, like other antidepressants, can increase the risk of suicidal thinking and behavior in young people, but there is limited information about suicidality in women who use this drug for treatment of vasomotor symptoms. The drug's label includes a warning about monitoring patients for suicidal thoughts and behaviors. The prescribing information (PI) advises discontinuing the drug in patients with worsening depression or in those who experience severe or abrupt symptoms that might be precursors to worsening depression or suicidality. The PI also suggests alerting family members and caregivers of patients being treated with paroxetine about the need to monitor for signs of agitation or unusual changes in behavior.

Additional labeled warnings include a possible reduction in the effectiveness of tamoxifen if both medications are used together, an increased risk of bleeding, and a risk of serotonin syndrome.

Sources: U.S. Food and Drug Administration. FDA approves the first non-hormonal treatment for hot flashes associated with menopause [news release]. U.S. Food and Drug Administration Website. http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm359030.htm. Updated July 2, 2013. Accessed August 26, 2013. Brisdelle [package insert]. Miami, FL: Noven Therapeutics, LLC; 2013.

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