Pharmacology Watch

Evidence-based updates in clinical pharmacology

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New Data Show Liraglutide Improves Renal Outcomes in Type 2 Diabetes Patients

The glucagon-like peptide 1 analogue liraglutide improves renal outcomes in type 2 diabetics, according to new data from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial. LEADER previously showed that the drug reduces the risk of cardiovascular (CV) disease, stroke, and death in type 2 diabetics. Subsequently, investigators continued the trial to study renal outcomes, too. More than 9,300 type 2 diabetics were randomized to receive liraglutide or placebo for almost four years. The primary outcome was a composite outcome of new-onset persistent macroalbuminuria, persistent doubling of the serum creatinine level, end-stage renal disease, or death due to renal disease. The outcome occurred less frequently in the liraglutide group than in the placebo group (268 of 4,668 liraglutide patients vs. 337 of 4,672 placebo patients; hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67-0.92; P = 0.003), driven primarily by less microalbuminuria. Adverse effects were no higher in the liraglutide group. The authors concluded that when added to usual care for type 2 diabetes, liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo. (*N Engl J Med* 2017;377:839-848)

Based on the LEADER trial, the FDA has approved a new indication for liraglutide: to reduce the risk of major adverse CV events, heart attack, stroke, and CV death in adults with type 2 diabetes and established CV disease. LEADER showed that a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke was reduced by 13% (P = 0.01). The absolute risk reduction was about 2% for the composite endpoint and 1.3% for death. (*N Engl J Med* 2016;375:311-322)

Canagliflozin Reduces Cardiovascular Events in Diabetic Patients

A different diabetes medication also has been shown to reduce CV events, but with some risks. Canagliflozin is a sodium-glucose cotransporter-2 (SGLT-2) inhibitor that promotes glycosuria, reducing glycemia. SGLT-2 inhibitors also reduce blood pressure, body weight, and albuminuria. The authors of the CANVAS Program examined canagliflozin regarding CV, renal, and safety outcomes in two trials that contained more than 10,000 type 2 diabetics who were at high CV risk. Participants were randomized to canagliflozin or placebo for about 3.5 years. The primary outcome (composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) was lower with canagliflozin than placebo (26.9 vs. 31.5 participants per 1,000 patient-years; HR, 0.86; 95% CI, 0.75-0.97; P < 0.001 for noninferiority; P = 0.02 for superiority). Renal benefits were not statistically significant, although there was a possible benefit regarding albuminuria, sustained 40% reduction in glomerular filtration rate, and need for renal replacement therapy or death from renal causes (HR, 0.60; 95% CI, 0.47-0.77). However, the risk for amputation was nearly doubled with canagliflozin (6.3 vs. 3.4 per 1,000 patient-years; HR, 1.97; 95% CI, 1.41-2.75), mostly at the toe and metatarsal level. The authors suggested that canagliflozin resulted in a lower risk of CV disease in type 2 diabetics who were at high

CV risk. However, there was a higher risk of amputation, which is a new finding; the mechanism is unknown. The authors recommended care in use of the drug in patients at risk for amputation. (*N Engl J Med* 2017;377:644-657)

Treating Pain and PTSD with Cannabis

Does marijuana help chronic pain or post-traumatic stress disorder (PTSD)? Two reviews funded by the VA system found a lack of evidence that plant-based cannabis helps either condition. Researchers reviewed 27 chronic pain trials. They found low-strength evidence that cannabis helps neuropathic pain, but insufficient evidence that it is effective in other pain populations. Harms include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment. (*Ann Intern Med* 2017;167:319-331)

There were no randomized trials for PTSD, but there were two systematic reviews and three observational trials. None of the studies found benefit of cannabis for PTSD. The authors noted that there are ongoing randomized trials and six other studies expected to be completed in three years regarding cannabis and PTSD. Nevertheless, there is insufficient evidence today to draw conclusions about the benefits and harms of plant-based cannabis preparations in patients with PTSD. (*Ann Intern Med* 2017;167:332-340)

FDA Actions

The FDA has approved a new fixed-dose combination for the treatment of chronic hepatitis C (HCV) infections. The combination of glecaprevir (an NS3/4A inhbitor) and pibrentasvir (an NS5A inhibitor) is taken once a day and treats all six genotypes of HCV. It is the third approved combination that treats all six HCV genotypes, after sofosbuvir/velpatasvir (Epclusa) and sofosbuvir, velpatasvir, voxilaprevir (Vosevi). It is approved for eight weeks of therapy in treatment-naïve patients and 12 weeks for those with compensated cirrhosis. Some clinical scenarios may require 16 weeks of therapy. Approval was based on studies of more than 2,300 subjects across all six HCV genotypes in whom the sustained viral response at 12 weeks (SVR12) was 93-100%. A new study shows the efficacy of the combination across all six genotypes in patients with and without cirrhosis. Treatment for 12 weeks resulted in SVR12 of 99% (*Lancet Infect Dis* 2017. doi: 10.1016/S1473-3099(17)30496-6). Glecaprevir/pibrentasvir is marketed as Mavyret. AbbVie has priced the drug significantly lower than other HCV treatments at $13,200 per month or $26,400 per eight-week treatment course.

In what the FDA calls a "historic action," the agency approved the first gene therapy available in the United States. Tisagenlecleucel is a cell-based gene therapy approved for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. Clinicians collect a patient's T cells and send them to a manufacturing center, where a technician genetically modifies the cells with a new gene that contains a chimeric antigen receptor. This new combination directs the T cells to target and kill leukemia cells that contain the CD10 antigen on their surfaces. Once the T cells are modified, clinicians infuse the mixture into the patient. Safety and efficacy was demonstrated in a trial of 63 pediatric and young adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia. The overall remission rate within three months of treatment was 83%. Side effects included cytokine release syndrome and neurologic events, both of which can be life threatening. The drug is approved with a risk evaluation and mitigation strategy. Hospitals and clinics that administer the drug must be certified. Tocilizumab recently was approved to treat cytokine release syndrome, and the FDA is requiring that all certified hospitals and clinics make it available before administering tisagenlecleucel. The FDA granted the drug priority review and breakthrough therapy designations. It is marketed as Kymriah. The cost is projected to be $475,000 for one course of treatment.

The FDA has approved a new intravenous antibiotic combination to treat adults with complicated urinary tract infections (UTIs), including pyelonephritis. The new product pairs the antibiotic meropenem with vaborbactam, which inhibits resistance mechanisms used by bacteria. It is approved to treat infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter cloacae* species complex. Safety and efficacy was shown in a study of 545 adults with complicated UTIs, which showed a cure rate of 98% for patients treated with meropenem/vaborbactam vs. 94% for patients treated with piperacillin/tazobactam. Headache, infusion site reactions, and diarrhea are the most common side effects. Meropenem/vaborbactam received priority review and was designated a qualified infectious disease product, a designation given to antibacterial products that treat serious or life-threatening infections under the Generating Antibiotic Incentives Now title of the FDA Safety and Innovation Act. Meropenem/vaborbactam is marketed as Vabomere. ■

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