DRUGMonitor

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

Extended-Release Exenatide Safe With TZDs

Research has shown exenatide to be safe to use with thiazolidinediones (TZDs). Now researchers from the University of California at San Francisco in San Francisco, California; Cambridge Memorial Hospital in Cambridge, Ontario, Canada; Pharmanet/i3, Inc. in Ann Arbor, Michigan; Consultmed SRL in Iasi, Romania; and Eli Lilly and Company in Indianapolis, Indiana, say the extended-release formulation is also safe, both in exenatide-naïve patients and those switching from twice-daily treatment.

In this long-term study (open-label treatment for up to 104 or 117 weeks), patients received 2 mg exenatide once weekly while continuing a stable dosage with a TZD (rosiglitazone or pioglitazone) and metformin if applicable. Of 134 patients in the intent-to-treat (ITT) group, 44 were exenatide-naïve; 90 were switched from exenatide bid.

The drugs were generally well tolerated; adverse events (AEs) were consistent with the reported safety profile for exenatide. Overall, 80% of patients reported at least 1 AE. The most common AEs were nausea (17%) and injection-site nodule (12%). More than half were mild to moderate; 17% were characterized as severe. With regard to AEs associated with exenatide, 1 patient had mild renal failure, 1 had severe acute renal failure, and none had pancreatitis or thyroid neoplasms. No patient had TZD-related heart failure or myocardial infarction (MI) (which has led to less use of TZDs in type 2 diabetes); 4 had mild edema. Seven patients discontinued treatment due to AEs.

The researchers found no events of major hypoglycemia during the study and only a few incidents of mild hypoglycemia. They say this supports the use of the combination treatment as an option for improving glycemic control.

At 52 weeks the ITT patients saw a significant reduction in A1C (mean, –0.78%) from baseline value of 7.20%. Exenatide-naïve patients had improved A1C (mean, –1.10%), and those with prior exenatide therapy had an additional reduction from baseline (mean, –0.62%). After 2 years, the reduction was maintained, with an absolute A1C value at the endpoint of 6.73%.

Weight loss and gain was another facet of investigation. Thiazolidinediones have been associated with weight gain in patients with type 2 diabetes, whereas glucagon-like peptide-1 receptor agonists such as exenatide have been associated with weight loss. In this study, the change in weight was –2.7 kg for exenatide-naïve patients and –0.8 kg for those who switched. Exenatide-naïve patients continued to lose weight, while those who switched to once-weekly treatment maintained weight similar to that at baseline.

Norwood P, Liutkus JF, Haber H, Pintilei E, Boardman MK, Trautmann ME. *Clin Ther.* 2012;34(10):2082-2090.
doi: 10.1016/j.clinthera.2012.09.007.

Expanding the Role of Tranexamic Acid

Tranexamic acid is a lifesaver for people at high risk of bleeding to death from traumatic injuries, but it may have an even larger role to play, according to researchers from London School of Hygiene and Tropical Medicine in London, United Kingdom; University of Leicester in Leicester, United Kingdom; Guy's and St. Thomas' NHS Foundation Trust in London, United Kingdom; University of Sheffield in Sheffield, United Kingdom; Centre for Trauma Sciences, Barts and The London School of Medicine and Dentistry, Queen Mary University of London in London, United Kingdom; and the University of Oxford in Oxford, United Kingdom. Findings from their study suggest that it can help low-risk patients, too.

The researchers analyzed data from 13,273 patients in the international Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial, as well as data from the United Kingdom Trauma Audit and Research Network. They stratified patients in CRASH-2 into 4 strata of risk of mortality: < 6%, 6% to 20%, 21% to 50%, and > 50%. The patients were given either tranexamic acid (1 g over 10 min followed by 1 g over 8 h) or placebo within 3 hours of injury. The researchers examined the effects of tranexamic acid on all-cause mortality, deaths from bleeding, and thrombotic events within those 4 risk strata.

Tranexamic acid reduced the odds of death from bleeding by about 30% in each of the stratum and the odds of thrombotic events also by about 30%. Overall, 14% of patients treated with tranexamic acid died, compared with 16% of patients on placebo. In the > 50% group, 65% of treatment patients

died, compared with 70% of placebo patients. In the groups of patients who died of bleeding, 17% in the tranexamic acid > 50% group died, vs 23% in the placebo group.

Patients treated with tranexamic acid had a significantly lower risk of fatal and nonfatal thrombotic events and arterial thrombotic events, although venous thrombotic events were not significantly reduced. The effects were most marked in the 21% to 50% group: Tranexamic acid patients had half the events of placebo patients (3% vs 6%). Fewer patients given tranexamic acid had an MI (23 vs 46 placebo patients) and stroke (28 vs 40).

If the effect of giving tranexamic acid within 3 hours of injury is assumed to be the same in all risk strata, the researchers say, 17% of deaths could be averted for patients in the lowest stratum, 36% and 30% for those in the middle strata, and 17% in the > 50% stratum.

Beyond the conclusion that tranexamic acid can safely be given to all trauma patients at risk for bleeding, their findings have other important clinical implications, the researchers say. The reduction in the risk of arterial events suggests that the benefits are likely to be greatest in older patients who have a higher risk of death from hemorrhage and thrombotic events, regardless of the severity of injury. Clinical concern about an increased risk of ischemic cardiac events might be "a reason to give rather than to withhold tranexamic acid." It's worth noting, the researchers add, that trials of tranexamic acid in patients undergoing cardiac surgery, a group at high risk of cardiac events, provide no evidence of any increased risk.

Estimating the risk of severe bleeding is a challenge, the researchers acknowledge, but in uncertain situations the model used in this study can offer support to consideration of tranexamic acid for patients with a risk of death > 5%.

Roberts I, Perel P, Prieto-Merino D, et al. *BMJ.* 2012;345:e5839.
doi: 10.1136/bmj.e5839.

Statins and Strokes

Do statins offer any protection against stroke? A variety of studies have suggested that they do, but their effect on mortality and functional outcome after stroke is less clear, especially in older patients. A study by researchers at Sahlgrenska University Hospital in Göteborg, Sweden; and Göteborg University in Göteborg, Sweden, offers some new evidence on whether statins help: They do, and they don't.

The study involved 799 patients (mean age, 78) with acute ischemic stroke; 183 patients were using statins before the stroke. At the 12-month follow-up visits, 67% of patients were still participating.

Statins significantly improved functional outcome at 90 days and 12 months after stroke. Patients treated with statins after hospital discharge (61%) had a significantly better neurologic outcome, compared with patients who did not receive statin treatment. One year after stroke, about 74% of patients treated with statins had a score ≤2 on the modified Rankin Scale. (A score of 0-2 corresponds favorably with independence in activities of daily living.) Only 51% of those in the nontreatment group reached the same functional level.

Prestroke statins did not significantly influence stroke severity, although the researchers found a weak trend toward lesser stroke severity. Statins also did not improve 30-day survival; 70 patients died (all-cause mortality)—55 in the hospital.

Statin treatment did not influence the rate of recurrent stroke during the first year of follow-up. But 12 months might not have been long enough to pinpoint true effects, the researchers suggest. They cite other studies that have found that significant differences in rates of recurrent stroke only began 36 months after initiation of statins.

However, statins did help with long-term survival. During the first year after stroke, 158 patients died. Survival was better among those treated with statins (hazard ratio = 0.33). Patients with A1C ≥ 6.5% benefited more from statins; survival was significantly improved.

Looking to explain the negative findings about poor 30-day survival, the researchers say any acute neuroprotective effect of statins might have been counteracted, because the patients taking statins were much sicker. Half the patients with previous statin treatment had had an ischemic stroke, half had associated cardiac pathology. The study population was elderly and "certainly frail," the researchers add. All those factors could reduce statins' effects. The researchers suggest that treatment with statins could be "a marker for disease rather than a protective factor." ●

Hjalmarsson C, Bokemark L, Manhem K, Mehlig K, Andersson B. *Am J Geriatr Pharmacother.* 2012;10(5):313-322.
doi: 10.1016/j.amjopharm.2012.09.001.

For additional online exclusive **Drug Monitor** content, go to **www.fedprac.com**