DRUGMonitor

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

A New Treatment for Type 2 Diabetes

Canagliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, approved by the FDA, works differently from other diabetes drugs: It blocks the kidneys from reabsorbing glucose via SGLTs, increasing glucose excretion.

In 9 double-blind clinical trials involving > 10,000 patients with type 2 diabetes, canagliflozin was studied as both a stand-alone therapy and in combination with other type 2 diabetes therapies, including metformin, sulfonylurea, pioglitazone, and insulin. The research showed reductions in A1C across subgroups, such as patients stratified by age, gender, race, and baseline body mass index.

In a placebo-controlled trial, monotherapy with canagliflozin helped more patients achieve the American Diabetes Association (ADA)-recommended A1C goal of < 7% over 26 weeks: 45% with canagliflozin 100 mg and 62% with canagliflozin 300 mg, compared with 21% on placebo ($P < .001$). Monotherapy also statistically significantly reduced systolic blood pressure, compared with placebo: – 3.3 mg Hg with canagliflozin 100 mg and – 5.0 mm Hg with canagliflozin 300 mg, vs + 0.4 mm Hg with placebo ($P < .001$). Patients on monotherapy also lost more weight: – 2.8% with 100 mg and – 3.9% with 300 mg, vs – 0.6% with placebo ($P < .001$).

In combination with metformin, canagliflozin 300 mg reduced A1C more than glimepiride by week 52, with 60% of patients reaching the ADA goal vs 56% of patients on glimepiride. Of patients on a combination of canagliflozin plus metformin and a sulfonylurea, 48% reached goal by week 52, compared with 35% of patients taking sitagliptin 100 mg.

In a 26-week placebo-controlled study, canagliflozin reduced A1C in patients with moderate renal impairment (– 0.33% with 100 mg, – 0.44% with 300 mg from baseline, vs – 0.03% with placebo). The dose of canagliflozin is limited to 100 mg/d in patients with an estimated glomerular filtration rate (eGFR) of 45 to 60 mL/min/1.73 m^2; it should not be given to patients with eGFR lower than that.

In addition to patients with moderate renal impairment, safety studies have been conducted in patients aged 55 to 80 years and those with, or at high risk for, cardiovascular disease. However, the FDA is requiring 5 postmarketing studies: a cardiovascular outcomes trial; an enhanced pharmacovigilance program to monitor for malignancies, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes; a bone safety study; and 2 pediatric studies.

The most common adverse effects of canagliflozin are vaginal yeast infection and urinary tract infection. Because canagliflozin has a diuretic effect, it can reduce intravascular volume, leading to orthostatic or postural hypotension, most commonly in the first 3 months of therapy. It is not intended for patients with type 1 diabetes, those with diabetic ketoacidosis, or those with severe kidney disease.

Sources: U.S. Food and Drug Administration. FDA approves Invokana to treat type 2 diabetes [news release]. U.S. Food and Drug Administration Website. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345848.htm. Updated March 29, 2013. Accessed May 8, 2013. Invokana [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2013.

The Problem of Chemotherapy for Oldest-Old Patients

Women aged ≥ 75 years who have stage I breast cancer have similar prospects for survival as younger women do. But when the cancer is stage II or III, it's less likely that their therapy will be adequate and appropriate, say researchers from the Swedish Cancer Institute, HealthStat Consulting Inc., and the University of Washington, all in Seattle, Washington. The study findings underscore the need to find effective treatment for those patients, the researchers say.

In the study, the researchers reviewed data from 2,329 female patients aged 65 to 94 years with breast cancer stages I to III. Of the patients, 956 (41%) were aged ≥ 75 years, and 60% of this oldest-old group had stage I tumors. Most of the patients underwent either lumpectomy with radiation (n = 698, or 73%), mastectomy with radiation (n = 108, or 11%), or mastectomy without radiation (n = 120, or 13%) for initial treatment.

Among the 716 patients who were seen by an oncologist, 106 patients (11%) were recommended chemotherapy and 88 received it. Among the 18 patients who refused adjuvant chemotherapy, 13 patients were given radiation therapy in addition to surgery.

Among the 88 patients given chemotherapy, 74 patients were given standard chemotherapy and 14 patients were given nonstandard chemotherapy due to age or comorbidity-related issues. The majority of patients receiving nonstandard chemotherapy (81%) completed therapy, but 18 patients could not tolerate standard therapy and were switched to nonstandard treatment. One patient died of causes not related to treatment.

The researchers note that women aged ≥ 75 years are rarely included in clinical trials due to the high prevalence of comorbid conditions and increased mortality from all causes.

Also, women in this age group were more likely to refuse treatment and less likely to complete treatment because of complications. Patients who were on an initial reduced or nonstandard treatment regimen had only a 69% completion rate, and many "presumably healthier" patients starting on standard chemotherapy regimens had to be switched to a reduced regimen or stopped therapy due to complications. Even so, 28% of patients who started on standard therapy and switched to a nonstandard regimen did not complete therapy.

The researchers found that the rate of survival for patients with stage I breast cancer was "excellent," regardless of age. Most stage I patients received either no adjuvant systemic therapy or hormone-only adjuvant therapy. Many authors, the researchers note, have discussed the possibility of undertreatment for older women. In this study, women who saw an oncologist were more likely to receive adjuvant hormonal therapy. However, the researchers assume that even oncologists were loath to recommend chemotherapy for patients with higher-stage cancer because of patients' comorbidities and the "pending force of mortality from conditions other than breast cancer...."

The researchers add, however, that no patients in their study died of complications related to treatment, suggesting that "if flexibility is used, severe complications of therapy can be avoided or at least mitigated." They cite a study that found a significant portion of patients aged 65 to 78 years received intended dose intensity with manageable toxicity levels, although 24% required hospitalization for complications from treatment. The researchers emphasize the need to find safe and effective treatment that can be tolerated by older adults to bring their stage II and III disease-specific survival rates in line with those of younger patients.

Source: Kaplan HG, Malmgren JA, Atwood MK. *J Geriatr Oncol.* 2013;4(2):148-156.
doi: 10.1016/j.jgo.2012.12.007.

Clarithromycin and Cardiovascular Events

Clarithromycin, often used to treat acute exacerbations of chronic obstructive pulmonary disease (COPD) and pneumonia, may increase the risk of cardiovascular events (CEs), according to researchers from Ninewells Hospital and University of Dundee, both in Dundee; Perth Royal Infirmary in Perth; Imperial College London and Chase Farm and Barnet Hospitals NHS Trust, both in London; and Royal Infirmary of Edinburgh and University of Edinburgh, both in Edinburgh; all in the United Kingdom.

The researchers analyzed data from 2 sets of patients: 1,343 patients with COPD and 1,631 patients with community-acquired pneumonia. They classified all patients who received ≥ 1 dose of clarithromycin during their hospitalization as macrolide users and compared them with patients who did not receive any macrolide antibiotics during their admission.

During 1 year of follow-up, 268 patients with COPD and 171 patients with pneumonia were admitted to the hospital as a result of a CE. Clarithromycin nearly doubled the risk of CEs in both groups of patients. Longer courses of clarithromycin (median, 7 days) were associated with more CEs, particularly in patients with a history of coronary artery disease. Treatment of < 3 days did not carry the same risk.

Some studies have shown that clarithromycin raises the risk of CEs for a short time, during the time of administration. This study, however, is the first to show that use of clarithromycin for exacerbations of COPD and community-acquired pneumonia may be associated with excess CEs that last beyond the period of prescription, the researchers say. Although short-term events might be linked to clarithromycin proarrhythmic effects mediated through prolongation of the QT interval, this would not affect outcome after the drug is stopped, the researchers note. They suggest that clarithromycin activates macrophages, leading to an inflammatory cascade, resulting in more vulnerable plaques that over time could lead to acute coronary syndromes or sudden cardiac death by plaque rupture. That might explain, they say, why clarithromycin seems to increase CEs and mortality over the long-term. They believe the "strong association" between prolonged use of clarithromycin and CEs strengthens the case for a "true biological cause" although they acknowledge that it could also represent residual confounding by severity of illness.

The widespread use of antibiotics in COPD exacerbations is controversial, the researchers note. For one, the same bacteria are often found during exacerbations and during a stable clinical state; proving causation is difficult. Moreover, triggers other than bacterial infection, such as viruses and environmental factors, can cause "an important proportion" of acute exacerbations, the researchers note.

Macrolide antibiotics have been implicated in CEs by other studies. No evidence from controlled trials suggests that macrolides are superior to other drugs. In this study, the researchers found beta-lactam antibiotics and doxycycline were not associated with increased CEs, suggesting an effect specific to clarithromycin.

Source: Schembri S, Williamson PA, Short PM, et al. *BMJ.* 2013;346:f1235.
doi: 10.1136/bmj.f1235.

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