placebo responders (69.2% vs 44.4%, respectively) than in liraglutide and placebo nonresponders (67.2% vs 39.6%, respectively). Responders had lower rates of AEs leading to withdrawal (liraglutide, 4.5%; placebo, 0.9%). In nonresponders, the figures were 17% for liraglutide vs 4.8% for placebo.

Liraglutide responders had greater improvements than nonresponders across a range of efficacy outcomes. Overall, weight loss ≥ 5% was achieved in a higher proportion of patients on liraglutide, 3 mg, with a stronger effect among responders. The rates of AEs were largely equivalent in responders and nonresponders.

A mean weight loss of 11.7% was achieved by patients who were overweight or obese without diabetes and responded to liraglutide. The weight loss responders in both treatment groups also had improved glycemic, cardiometabolic, and health-related quality-of-life outcomes. The SCALE–Obesity and Prediabetes trial showed that liraglutide is a safe and effective weight loss option in the study population.

Significant HbA_{1c} Reduction With Empagliflozin/ Linagliptin Combination

Written by Rita Buckley

One tablet of empagliflozin and linagliptin significantly reduced HbA_{1c} in patients with type 2 diabetes. Andrew J. Lewin, MD, National Research Institute, Los Angeles, California, USA, and colleagues conducted a randomized, double-blind, parallel-group, phase 3 study, the Safety and Efficacy of the Combination of Empagliflozin and Linagliptin Compared to Linagliptin Alone Over 24 Weeks in Patients With Type 2 Diabetes study [Lewin A et al. *Diabetes Care*. 2015].

Empagliflozin reduces renal glucose reabsorption, thereby increasing urinary glucose excretion. This leads to a decline in plasma glucose levels in an insulin-independent manner [Heise T et al. *Diabetes Obes Metab*. 2013]. Linagliptin prevents the inactivation of incretin peptides, such as glucagon-like peptide-1 (GLP-1), stimulates insulin release, and inhibits glucagon secretion [Gallwitz B. *Diabetes Metab Syndr Obes*. 2013]. Each drug is an FDA-approved treatment for patients with type 2 diabetes. As compared with the single agent treatment groups, those treated with the dual combination achieved lower A_{1c} levels.

Efficacy was evaluated in 667 patients who had not received antihyperglycemic therapy for ≥ 12 weeks. Their mean (standard deviation) age was 54.6 (10.2) years; mean weight was 87.9 (20.1) kg; average body mass index was 31.6 (5.6) kg/m^2; and mean HbA_{1c} level was 8.02% (0.96). Baseline characteristics were balanced between treatment groups.

Patients were randomized (1:1:1:1:1) to receive empagliflozin 25 mg/linagliptin 5 mg as a fixed-dose combination (FDC) tablet; empagliflozin 10 mg/linagliptin 5 mg as an FDC tablet; empagliflozin 25 mg; empagliflozin 10 mg; or linagliptin 5 mg for 52 weeks. The primary end point was the change from baseline in HbA_{1c} at week 24.

At week 24, reductions from baseline in HbA_{1c} were significantly greater for empagliflozin 25 mg/linagliptin 5 mg compared with linagliptin 5 mg ($P<.001$), but not compared with empagliflozin 25 mg ($P<.179$), and were significantly greater for empagliflozin 10 mg/linagliptin 5 mg compared with individual doses ($P<.001$ for both). At week 24, 55.4% of patients with baseline $HbA_{1c} \geq 7\%$ reached $HbA_{1c} < 7\%$ with empagliflozin 25 mg/linagliptin 5 mg; 62.3% did so with empagliflozin 10 mg/linagliptin 5 mg; 41.5% with empagliflozin 25 mg; 38.8% with empagliflozin 10 mg; and 32.3% with linagliptin 5 mg. Efficacy was maintained at week 52.

The proportion of patients with adverse events over this time was similar across groups (68.9% to 81.5%), with no confirmed hypoglycemic adverse events in either combination group. Empagliflozin/linagliptin was well-tolerated, with an overall safety profile similar to those of the individual drugs.

This was the first randomized controlled trial to evaluate the efficacy and safety of the initial combination of a sodium-glucose cotransporter 2 (SGLT2) inhibitor (empagliflozin) and a DPP-4 inhibitor (linagliptin) in patients with type 2 diabetes.

ATL1103 Effective in Reducing IGF-1 Levels in Patients With Acromegaly

Written by Jill Shuman

Acromegaly is a chronic disorder resulting from excessive secretion of growth hormone, with a resulting increase in the production of the hormone known as insulinlike growth factor 1 (IGF-1). ATL1103 is a second-generation antisense drug designed to silence growth hormone receptor expression, thereby reducing levels of IGF-1 in the blood. It is currently under investigation as a potential treatment for diseases associated with excessive growth hormone action, such as acromegaly [Störmann S, Schopohl J. *Expert Opin Emerg Drugs*. 2014].

Peter J. Trainer, MD, The Christie National Health Service Foundation Trust, Manchester, United Kingdom, reported primary efficacy results from the phase 2 clinical trial of ATL1103 in patients with acromegaly [2012-003147-30]. The ATL1103 phase 2 trial was a randomized, open-label, multicenter, parallel group study

of the safety, tolerability, pharmacokinetics, and efficacy of 2 subcutaneous dosing regimens of ATL1103 in 26 adult patients in the United Kingdom, France, Spain, and Australia. Patients were required to have active acromegaly, defined as an IGF-1 level > 130% of the upper limits of normal. In addition, patients had to undergo a washout from long-acting somatostatin agonists (4 months) and dopamine agonists (6-8 weeks). Patients were excluded if they had a tumor within 3 mm of the optic chiasm or had undergone pituitary surgery within 3 months or radiotherapy within 1 year.

Over a period of 13 weeks, patients were randomized to 2 groups. One group (n = 13) received the injection of 200 mg 3 times in the first week and 200 mg once weekly thereafter; the second group (n = 13) received 200 mg 3 times in the first week and 200 mg twice weekly thereafter. The primary end point was the percent change in IGF-1 at week 14. Pharmacokinetics and safety were also measured. At baseline, patients in the 200 mg once weekly group were younger (mean age, 48 ± 14 vs 53 ± 17) and had greater weight (97 ± 20 vs 85 ± 25) than those in the 200 mg twice weekly group. However, both groups had a similar number of male patients (5 vs 6), patients who had prior radiotherapy (5 vs 6), and those who had prior surgery (13 vs 12).

Only patients who received ATL1103 200 mg twice weekly showed a statistically significant reduction in IGF-1 levels at week 14 compared with baseline. Specifically, in the 200 mg twice weekly group, mean IGF-1 levels reduced by 26% from about 600 ng/mL at baseline to nearly 400 ng/mL at week 14 ($P < .0001$), whereas in the 200 mg once weekly group, mean IGF-1 levels were about 500 ng/mL at baseline, with a nonsignificant reduction at week 14. IGF-1 levels normalized in 1 patient in both groups at week 14. Mathematical modeling of the dose curve for the higher dose of ATL1103 suggests that the maximum reduction of IGF-1 would be seen at 17 or 21 weeks if the patients had been treated for that long.

There were no significant changes in 2 secondary outcomes among patients on either dose, including signs and symptoms and the global Acromegaly Quality of Life score. Patient ring size was reduced significantly in the higher dose group ($P = .01$).

The 2 most frequent treatment-emergent events included injection site reactions and headache. One patient in each group withdrew from the study and there were 4 serious adverse events, none of which were thought to be drug related. No patient reported flulike symptoms, which are a recognized side effect in drugs of this class.

Prof Trainer concluded that for many patients with acromegaly, a larger dose of ATL1103 taken over a longer period of time will likely be well tolerated and able to produce improved disease control.

Increased TSH Levels Do Not Affect Safety, Efficacy in Refractory Thyroid Cancer

Written by Emma Hitt Nichols, PhD

Increased thyroid-stimulating hormone (TSH) levels due to lenvatinib treatment in patients with radioactive iodine 131 (^{131}I)-refractory differentiated thyroid cancer (DTC) were not associated with differences in overall safety, efficacy, or lenvatinib exposure, based on measurement of worst postbaseline TSH levels.

Steven I. Sherman, MD, University of Texas MD Anderson Cancer Center, Houston, Texas, USA, presented data from an exploratory analysis of the SELECT trial [Schlumberger M et al. *N Engl J Med.* 2015], a randomized phase 3 trial of lenvatinib in ^{131}I-refractory DTC demonstrating significantly improved progression-free survival (PFS) and response rates compared with placebo. The purpose of this exploratory analysis was to evaluate the effect of thyroid abnormalities on the outcomes observed in the SELECT trial.

Lenvatinib is a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptors 1 through 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor α, ret proto-oncogenes, and stem-cell receptors [Okamoto K et al. *Cancer Lett.* 2013; Matsui J et al. *Int J Cancer.* 2008]. A common side effect of tyrosine kinase inhibitors with multiple targets is hypothyroidism [Rini B et al. *J Natl Cancer Inst.* 2007] and exacerbation of postsurgical hypothyroidism [Brose MS et al. *Lancet.* 2014; Elisei R et al. *J Clin Oncol.* 2013], which may be associated with response to therapy [Kust D et al. *Anticancer Res.* 2014; Schmidinger M et al. *Cancer*. 2011].

In the double-blind, phase 3 SELECT trial, 392 adult patients with ^{131}I-refractory DTC were randomly assigned 2:1 to receive lenvatinib or placebo until disease progression [Schlumberger M et al. *N Engl J Med.* 2015]. The primary end point was PFS, and the secondary end points were overall response rate, overall survival, and safety. Patients who were assigned to placebo were able to switch to open-label lenvatinib after disease progression. All patients received concomitant thyroid hormone suppression, primarily via levothyroxine.

In this exploratory analysis, patients in the lenvatinib arm experienced higher TSH levels by cycle 1 that peaked by cycle 2 and steadily declined after cycle 4. In contrast, patients in the placebo arm did not experience consistent changes in TSH levels. In the lenvatinib arm, 28.4% of patients experienced worst postbaseline TSH levels > 5.5 mIU/L compared with 6.2% of patients in the placebo arm.