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.

Worst postbaseline TSH levels were not associated with dose modification of lenvatinib, study drug withdrawal, treatment exposure, or lenvatinib-related adverse events. However, lenvatinib-related thyrotoxicosis and exacerbation of hypothyroidism occurred primarily in patients who had worst postbaseline TSH levels >5.0 mIU/L. In addition, QTc prolongation occurred more frequently in patients who had worst postbaseline TSH levels of >5.0 mIU/L (12.5%) compared with patients who had worst postbaseline TSH levels of >0.5 to 5.0 mIU/L (6.4%) or ≤0.5 mIU/L (4%). PFS, overall survival, and overall response rate were not significantly different among the worst postbaseline TSH level categories.

Dr Sherman indicated that the data from this exploratory analysis of the SELECT trial suggest that there is no association between worst postbaseline TSH levels on overall lenvatinib safety or efficacy, as well as lenvatinib exposure. In addition, although increased TSH levels occurred frequently, it was not known if the rise was a result of lenvatinib or modification of TSH-suppression therapy because of patient intolerance to TSH suppression. Dr Sherman stated that a longitudinal analysis of TSH levels may be warranted and could provide further information than this single–time point analysis.

Liraglutide, Roflumilast Improve Body Weight in Obese Women With PCOS

Written by Emma Hitt Nichols, PhD

Treatment of obese women with polycystic ovarian syndrome (PCOS) with liraglutide or roflumilast, but not metformin, resulted in a significant decrease in body weight and improvement in metabolic and endocrine parameters. Mojca Jensterle, MD, University Medical Center Ljubljana, Ljubljana, Slovenia, presented data from the PDE-4 Inhibitor Roflumilast and GLP-1 Agonist Liraglutide in Polycystic Ovary Syndrome trial [NCT02187250].

Women with PCOS struggle with weight loss, and weight reduction through lifestyle changes and pharmacotherapy such as metformin may improve cutaneous manifestations and menstrual cycle regularity and fertility and reduce cardiovascular disease factors. Potential alternatives to metformin include glucagon-like peptide-1 (GLP-1) receptor agonists [Kahal H et al. *Clin Endocrinol (Oxf).* 2014; Elkind-Hirsch K et al. *J Clin Endocrinol Metab.* 2008] or PDE4 inhibitors, which increase GLP-1 plasma levels through completely different pathways involved in PDE4 regulation of signaling cascades linked to GLP-1 release [Vollert S et al. *Diabetologia.* 2012; Wouters EF et al. *J Clin Endocrinol Metab.* 2012; Calverley PMA et al. *Lancet.* 2009].

The purpose of this study was to determine if treatment of obese women with PCOS with liraglutide or roflumilast improved body weight compared with metformin. In this prospective, open-label, phase 4 trial, 45 obese women with PCOS were randomly assigned to receive metformin, liraglutide, or roflumilast for 12 weeks. At baseline, mean body mass index was 38.6±6.0 kg/m^2, and mean age was 30.7±7.9 years. Women were eligible if they had no significant cardiovascular, kidney, or hepatic disease; had no history of neuropsychiatric events; and did not use a medication known to affect reproductive or metabolic functions. The primary outcome of the study was changes in anthropometric measures of obesity.

Compared with baseline, patients who received liraglutide and roflumilast experienced a significant decrease in body weight of 3.1 kg (±3.5 kg; $P=.006$) and 2.1 kg (±2.0 kg; $P=.002$), respectively, whereas patients who received metformin did not experience a significant body weight loss (−0.1±1.9 kg). In the liraglutide arm, but not the metformin or roflumilast arms, there was a significant decrease in visceral adipose tissue area from baseline (160.3±67.9 cm^2 to 140.7±60.8 cm^2; $P=.015$).

Significant improvement was detected in some metabolic and endocrine parameters among patients who received liraglutide and roflumilast. There was a significant decrease in mean serum glucose levels before and after a 120-minute oral glucose tolerance test in the liraglutide arm ($P\leq.05$ for both), but not the metformin or roflumilast arms. In the roflumilast arm, total testosterone levels and free androgen index significantly decreased from baseline ($P=.05$ and $P=.016$, respectively).

In conclusion, Dr Jensterle stated that the results from this study suggest that treatment of obese women with PCOS with liraglutide was superior to metformin and roflumilast in the reduction of body weight and improvement in body composition, with roflumilast superior to metformin. However, treatment with roflumilast, but not metformin or liraglutide, reduced testosterone levels.

LH and Testosterone Significantly Reduced With NKB Receptor Antagonist in PCOS

Written by Toni Rizzo

Polycystic ovary syndrome (PCOS) affects 5% to 10% of women of reproductive age. PCOS is characterized by accelerated luteinizing hormone (LH) pulse frequency and elevated serum testosterone concentrations, menstrual irregularity, and polycystic ovaries. Currently, there is no approved treatment for PCOS. Recently, hypothalamic neurokinin B (NKB) has been characterized