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

as playing a key role in reproductive regulation, specifically as a modulator of gonadotropin-releasing hormone secretion [Topaloglu AK et al. *Nat Genet*. 2009]. The aim of this study [NCT01872078], presented by Jyothis T. George, PhD, University of Oxford, Oxford, United Kingdom, was to assess the effect of the NKB receptor antagonist, AZD4901, on LH secretion and testosterone levels in women with PCOS.

A total of 67 women with PCOS were randomized to receive AZD4901 20, 40, or 80 mg/day, or placebo for 28 days. All of the patients had a clinical diagnosis of PCOS with polycystic ovarian morphology, free testosterone (>0.85 upper limit of normal), and oligomenorrhea. The patients had intensive LH and testosterone sampling at baseline (day –1), day 7, and day 28. The primary end point was the change in 8-hour LH area under the curve (AUC) between baseline and day 7. The secondary end points were the change in total testosterone levels from baseline to days 7 and 28 and in LH pulse frequency at days 7 and 28.

The LH AUC was 67.4 ± 1.6 IU/L*h at baseline and 36 ± 2.3 IU/L*h at day 7 in the AZD4901 80-mg group compared with 61.1 ± 1.9 IU/L*h at baseline and 69.8 ± 1.7 IU/L*h at day 7 in the placebo group (a 52% reduction relative to placebo, adjusted for baseline; 95% CI, 30% to 67%; $P = .0003$). LH pulse frequency was 5.8 ± 2.1 pulses/8 hours at baseline and 3.7 ± 2.1 pulses/8 hours at day 7 in the AZD4901 80-mg group compared with 7.2 ± 2.3 pulses/8 hours at baseline and 6.8 ± 2.6 pulses/8 hours at day 7 in the placebo group, an adjusted mean change of –3.55 pulses/8 hours vs placebo ($P < .0001$).

Total testosterone levels were 2.2 ± 1.3 nmol/L at baseline and 1.6 ± 1.5 nmol/L at day 7 in the AZD4901 80-mg group compared with 1.5 ± 1.7 nmol/L at baseline and 1.6 ± 1.9 nmol/L at day 7 in the placebo group (a 29% adjusted reduction relative to placebo; 95% CI, 14% to 41%; $P = .0006$). At day 28, testosterone was reduced by 17% in the AZD4901 80-mg group.

A post hoc analysis in the anovulatory patients, defined as patients with serum P≥6 ng/mL throughout the study, showed that LH AUC was reduced in the ADZ4901 80-mg group by 46% at day 7 ($P = .0004$) and by 35% at day 28 ($P = .0203$); LH pulse frequency was –3.9 pulses/8 hours at day 7 ($P < .0001$) and –1.89 pulses/8 hours at day 28 ($P = .0205$); and testosterone was reduced by 27% at day 7 ($P = .0005$) and by 20% at day 28 ($P = .0111$) compared with placebo.

After 7 days of treatment with AZD4901 80 mg, women with PCOS had significant reductions in LH, LH pulse frequency, and total testosterone. These effects persisted for 28 days in nonovulating women. AZD4901 was safe and well tolerated. Longer-duration studies are needed to further evaluate its therapeutic potential, including metabolic responses.

Improvements in Diabetes Control Similar in Patients Who Undergo LAGB or Intensive Management

Written by Jill Shuman

Because of advances in both the surgical and nonsurgical treatment of obesity in adults with type 2 diabetes mellitus (T2DM), there is increasing controversy regarding the best treatment algorithm for patients who are obese with T2DM.

The SLIMM-T2D study [NCT01073020] was a 1-year pragmatic randomized trial within a single hospital setting. The trial was designed to compare clinical outcomes between patients who are obese with T2DM who underwent laparoscopic adjustable gastric band surgery (LAGB) or Roux-en-Y gastric bypass (RYGB) and those who participated in Why WAIT, a nonsurgical intensive diabetes and weight loss intervention. Why WAIT incorporated intensive diet, exercise, education, and drug modification using a multidisciplinary approach that included a dietitian, a psychologist, a diabetes educator, an exercise physiologist, and a physician who prescribed medications considered weight neutral. Patients in the Why WAIT intervention received 2 hours of instruction per week and individualized exercise training for the first 12 weeks, with monthly one-on-one support visits for the remainder of the 1-year follow-up.

The primary end point was the number of patients with fasting blood sugar < 126 mg/dL and HbA_{1c} < 6.5% at 1 year. Secondary end points included measurement of metabolic and cardiovascular risk factors.

Data from the RYGB arm of the trial were previously published [Halperin F et al. *JAMA Surg*. 2014] and showed that, compared with medical management, RYGB produced sustained and statistically significant improvements in HbA_{1c} and fasting glucose ($P = .03$), as

Table 1. Baseline Patient Characteristics

Mean age, y	51 ± 10
Mean weight, kg	109 ± 15
Body mass index, kg/m^2	36.5 ± 3.7
Duration of type 2 diabetes mellitus, y	9 ± 5
HbA_{1c}, %	8.2 ± 1.2
Percentage on insulin	40