24 had no clinically significant effect on liver function tests, which included aspartate aminotransferase, alanine aminotransferase, total bilirubin, γ-glutamyltransferase, alkaline phosphatase, and albumin.

This PK/PD analysis found an approximately dose-proportional relationship for pasireotide LAR dose-exposure over the 40- to 60-mg range that was evaluated. Efficacy end points of GH and IGF-1 suppression had a positive relationship with pasireotide exposure, with greater response rates at the higher dose of 60 mg.

Biochemical Control of Acromegaly Continued in PAOLA Trial Extension

Written by Kathy Boltz, PhD

Monica R. Gadelha, MD, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, presented a preliminary analysis of the phase 3 PAOLA study [NCT01137682] that showed that biochemical control continued through extension week 28. The intent within this extension phase was to assess pasireotide long-acting release (LAR) in patients with acromegaly over an extended period of time.

Dr Gadelha and colleagues examined data through extension week 28 of the extension phase of the 24-week, randomized, phase 3 PAOLA study, which enrolled patients with inadequately controlled acromegaly [Gadelha MR et al. *Lancet Diabetes Endocrinol*. 2014]. The 24-week, phase 3 study had found that biochemical control, defined as growth hormone < 2.5 μg/L and normalized insulinlike growth factor 1 (IGF-1), was achieved by significantly more patients who received pasireotide LAR 40 mg (15%; n = 10/65; $P = .0006$) or 60 mg (20%; n = 13/65; $P < .0001$) than those who received octreotide LAR or lanreotide Autogel (0%; n = 0/68). The most common adverse events in the phase 3 trial were hyperglycemia, diabetes, and diarrhea. Serious adverse events were reported in 6 patients receiving pasireotide 40 mg, 2 receiving pasireotide 60 mg, and 3 in the active control group.

The patients who were in the control group continued to receive the same doses in the extension phase from week 24 through a 4-week bridging phase. Next, patients from the control group who were not biochemically controlled received open-label pasireotide LAR 40 mg, and their dose was increased to 60 mg if their disease became uncontrolled. These were the crossover group.

The patients who were not in the control group remained on pasireotide LAR at 40 or 60 mg during the 4-week bridging phase. If they had not achieved biochemical control, they received open-label pasireotide LAR 60 mg beginning at extension week 4. These patients, the treatment groups, received a total of 52 weeks of treatment with pasireotide LAR for this analysis.

At extension week 28, biochemical control was achieved by 18% of the patients in the pasireotide LAR 40-mg group (n = 9/49; 95% CI, 9 to 32) and by 33% in the pasireotide LAR 60-mg group (n = 15/45; 95% CI, 20 to 49). Among the crossover group, 20% achieved biochemical control (n = 10/50; 95% CI, 10 to 34).

All 3 groups had a drop in IGF-1 levels during the extension time. At week 28, normal IGF-1 was obtained in 33% of the patients receiving pasireotide LAR 40 mg, in 38% receiving pasireotide LAR 60 mg, and in 24% of the crossover group. Growth hormone levels of < 2.5 μg/L were achieved by 39% of the patients receiving pasireotide LAR 40 mg, 47% of those receiving pasireotide LAR 60 mg, and 42% of the crossover group.

The safety profile was very similar to that of the core study. This longer-term treatment identified no new treatment-emergent safety signals.

Pasireotide may be a viable, long-term treatment option for patients with acromegaly that is inadequately controlled with first-generation somatostatin analogues.

Early Initiation of Low-Dose Levothyroxine After Radioactive Iodine Appears Safe

Written by Kathy Boltz, PhD

Spyridoula Maraka, MD, Mayo Clinic, Rochester, Minnesota, USA, reported on results from an interim safety analysis, which found that initiating low-dose levothyroxine at 4 weeks after patients received radioactive iodine (RAI) for Graves' disease (GD) appears safe and shows no increased incidence of hyperthyroidism.

Most patients with GD are treated with RAI and reevaluated 2 to 3 months later; the majority are hypothyroid by that time, and some have related troublesome symptoms and possible development or worsening of Graves' orbitopathy.

This randomized double-blind controlled trial [NCT01950260] was designed to determine whether early treatment with levothyroxine after RAI therapy for GD would prevent overt hypothyroidism. This interim analysis for safety was performed after the first 17 patients were enrolled, with 11 patients receiving levothyroxine, 25 μg QD, and 6 receiving placebo in a single tablet at 4 weeks after RAI therapy. At 6 weeks after RAI therapy, the levothyroxine dose was increased to 50 μg QD and the placebo to 2 tablets per day. At 8 weeks after RAI therapy, the

Table 1. Results After 8 Weeks

Variables	Drug (n = 11)	Placebo (n = 6)	OR Estimate	95% CI for OR
TSH (8 wk)			0.98	0.94 to 1.03
No.	10	6		
Median (Q1, Q3)	9.8 (0.0, 49.0)	11.9 (0.0, 20.3)		
Free thyroxine (8 wk)			1.30	0.44 to 3.88
No.	10	6		
Median (Q1, Q3)	0.7 (0.5, 1.2)	0.6 (0.4, 2.3)		
Hyperthyroid, No. (%)			2.25	0.23 to 22.14
No	9 (81.8)	4 (66.7)		
Yes	2 (18.2)	2 (33.3)		
Hypothyroid, No. (%)			1.67	0.21 to 13.22
No	5 (45.5)	2 (33.3)		
Yes	6 (54.5)	4 (66.7)		
TSQ (8 wk)			0.83	0.59 to 1.17
No.	7	5		
Median (Q1, Q3)	12 (12.0, 22.0)	12 (11.0, 13.0)		
HRQOL (8 wk)			0.87	0.69 to 1.09
No.	7	4		
Median (Q1, Q3)	46 (39.0, 67.0)	36 (31.5, 42.5)		

HRQOL, health-related quality of life; TSH, thyroid-stimulating hormone; TSQ, thyroid symptom questionnaire.
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treating physician evaluated the patients and treated them as clinically indicated for reaching euthyroidism.

Exclusion criteria included a clinical manifestation of Graves' orbitopathy, recent history of arrhythmias or any history of ventricular arrhythmias, preexistent cardiomyopathy, malnutrition, or psychiatric history. Researchers also considered the likelihood of whether patients would return for follow-up visits.

The enrolled patients were a median of 52.7 years of age in the levothyroxine arm and 55.3 years in the placebo arm. The levothyroxine arm was 72.7% women, and the placebo arm was 66.7% women. Median thyroid size was 30 g in both arms. Median free thyroxine was 2.7 ng/dL in the levothyroxine arm and 1.9 ng/dL in the placebo arm.

Patient history was taken at weeks 0, 8, and 24. Physical examinations and goiter size measurements occurred at weeks 0 and 8. Quality-of-life questionnaires were used at weeks 4, 6, 8, and 24.

Only 1 adverse event was reported: a patient in the levothyroxine arm had heart palpitations that led to the decision to discontinue the study drug. This patient had a history of chronic atrial fibrillation and discontinued beta-blocker therapy during the study.

At 8 weeks, overt hypothyroidism occurred in 54.5% of patients who received levothyroxine and in 66.7% of patients who received the placebo (Table 1). The rate of hyperthyroidism was lower in the levothyroxine group (18.2%) than in the placebo group (33.3%).

The thyroid symptom questionnaire scores were similar between the levothyroxine and placebo groups. The health-related quality-of-life questionnaire found that the levothyroxine group was more symptomatic than the placebo group (median score, 46 vs 36).

Initiating low-dose levothyroxine at 4 weeks after RAI appears safe and does not increase the risk of hyperthyroidism. The data, though statistically insignificant, suggest that this strategy might prevent overt hypothyroidism. The research team plans to continue the trial to completion without modifying the protocol.