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Treatment with Pasireotide LAR Normalizes Prolactin Levels in Patients with Acromegaly and Hyperprolactinemia: Randomized, Double-Blind, 12-Month, Phase III Study

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INTRODUCTION

- Acromegaly is a rare and serious disorder characterized by the chronic hypersecretion of growth hormone (GH) from a pituitary adenoma and subsequent hepatic overproduction of insulin-like growth factor 1 (IGF-1).
- Around 20–30% of patients with acromegaly also have hyperprolactinemia, which is associated with infertility, gonadal dysfunction, and reduced spinal bone mineral density.[1]
- Current medical therapy for patients with acromegaly and hyperprolactinemia typically involves the combination of a somatostatin analogue and a dopamine agonist to reduce GH/IGF-1 and prolactin levels, respectively.
- Pasireotide is a multireceptor-targeted somatostatin analogue with high affinity for four of the five somatostatin receptor subtypes (sst), including sst_2 and sst_5, which are the most prevalent sst on GH-secreting pituitary adenomas.[2]
- In a large, randomized, double-blind, Phase III trial in patients with acromegaly, pasireotide LAR was significantly superior to octreotide LAR at providing biochemical control (GH levels <2.5 µg/L *and* normal IGF-1 after 12 months of therapy; *P*=0.007)[3]
  - This poster reports the efficacy and safety of pasireotide LAR and octreotide LAR after 12 months of treatment in the subset of patients who had hyperprolactinemia at baseline.

METHODS

Study Design

- Medically naïve patients with active acromegaly (GH >5 µg/L or GH nadir ≥1 µg/L post-oral glucose tolerance test, and IGF-1 > upper limit of normal [ULN]) were eligible for enrollment into the 12-month study
  - Patients were either *de novo* with a visible pituitary adenoma on magnetic resonance imaging (MRI), or they could have undergone one or more previous pituitary surgeries.
- Patients were randomized 1:1 to pasireotide LAR 40 mg/28 days or octreotide LAR 20 mg/28 days
  - Dose titration to pasireotide LAR 60 mg or octreotide LAR 30 mg was permitted, but not mandatory, at month 3 or 7 based on biochemical response (mean GH ≥2.5 µg/L and/or IGF-1 >ULN). A dose decrease to pasireotide LAR 20 mg or octreotide LAR 10 mg was permitted in the event of tolerability issues, with the dose returned to pasireotide LAR 40 mg or octreotide LAR 20 mg once the problem had resolved.
- Patients with baseline prolactin levels above age- and sex-matched ULN were included in this analysis.

Assessments

- Mean prolactin, GH and IGF-1 levels were assessed at baseline and at months 3, 6, 9 and 12.
- The proportion of patients achieving GH <2.5 µg/L *and* normal IGF-1, GH <2.5 µg/L, normal IGF-1, and normal prolactin levels were assessed at month 12.
- Changes from baseline in tumor volume at month 12 were evaluated by gadolinium-enhanced pituitary MRI; a change of ≥20% was considered significant.
- Safety was assessed throughout the study and was primarily based on the monitoring of all adverse events (AEs).

Statistical Analysis

- This analysis included all the data collected during 12 months of treatment and the safety follow-up period.
- The last available concurrent prolactin, GH and IGF-1 values evaluated at the scheduled visit during the core study were used to compute the proportion of patients at month 12 achieving normal prolactin, GH <2.5 µg/L, normal IGF-1, and GH <2.5 µg/L *and* normal IGF-1.
- Patients without post-baseline prolactin, GH and IGF-1 values were considered to be non-normalized.

RESULTS

Patients

- Of the 358 patients who were randomized to pasireotide LAR (n=176) or octreotide LAR (n=182), 59 (16.5%) had hyperprolactinemia at baseline:
  - 29 and 30 patients in the pasireotide LAR and octreotide LAR treatment groups, respectively
  - Baseline characteristics were similar between treatment arms (**Table 1**).

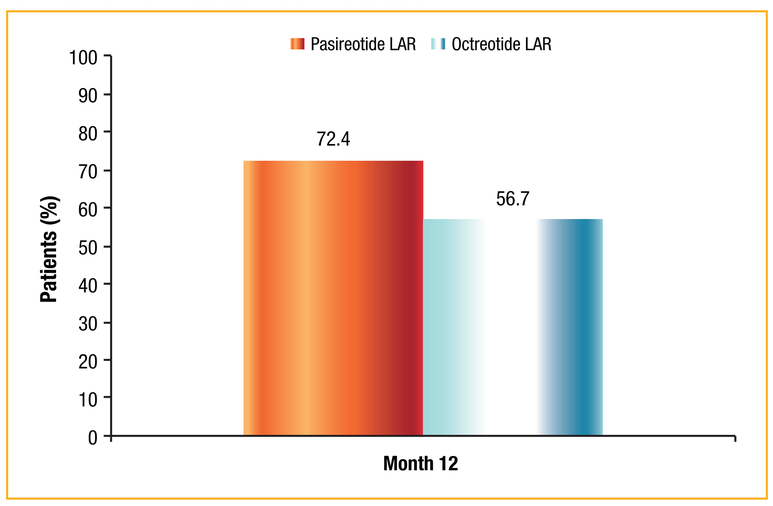
Table 1. Patient Demographics and Characteristics at Baseline

Demographic variable	Pasireotide LAR N=29	Octreotide LAR N=30
Median age, years	45.0	43.5
Male:female	16:13	15:15
Race, n (%)		
Caucasian	17 (58.6)	13 (43.3)
Asian	8 (27.6)	9 (30.0)
Native American	2 (6.9)	1 (3.3)
Black	0 (0.0)	2 (6.7)
Other	2 (6.9)	5 (16.7)
Median time since diagnosis, months	6.1	4.2
Previous surgery, n (%)	6 (20.7)	8 (26.7)
Median time since surgery, months	7.3	7.1
Mean GH level, µg/L	42.3	33.6
Mean standardized IGF-1, xULN	3.3	3.1
Mean prolactin level, µg/L	83.5	55.9

Efficacy of Treatment on Mean Prolactin, GH and IGF-1 Levels

- Following 12 months of treatment in patients with baseline hyperprolactinemia, 21/29 (72.4%; 95% CI 52.8, 87.3) patients in the pasireotide LAR arm and 17/30 (56.7%; 95% CI 37.4, 74.5) in the octreotide LAR arm had normal prolactin levels (**Figure 1**).

Figure 1. Proportion of Patients with Normalized Prolactin Levels at Month 12, for Patients with Prolactin >ULN at Baseline



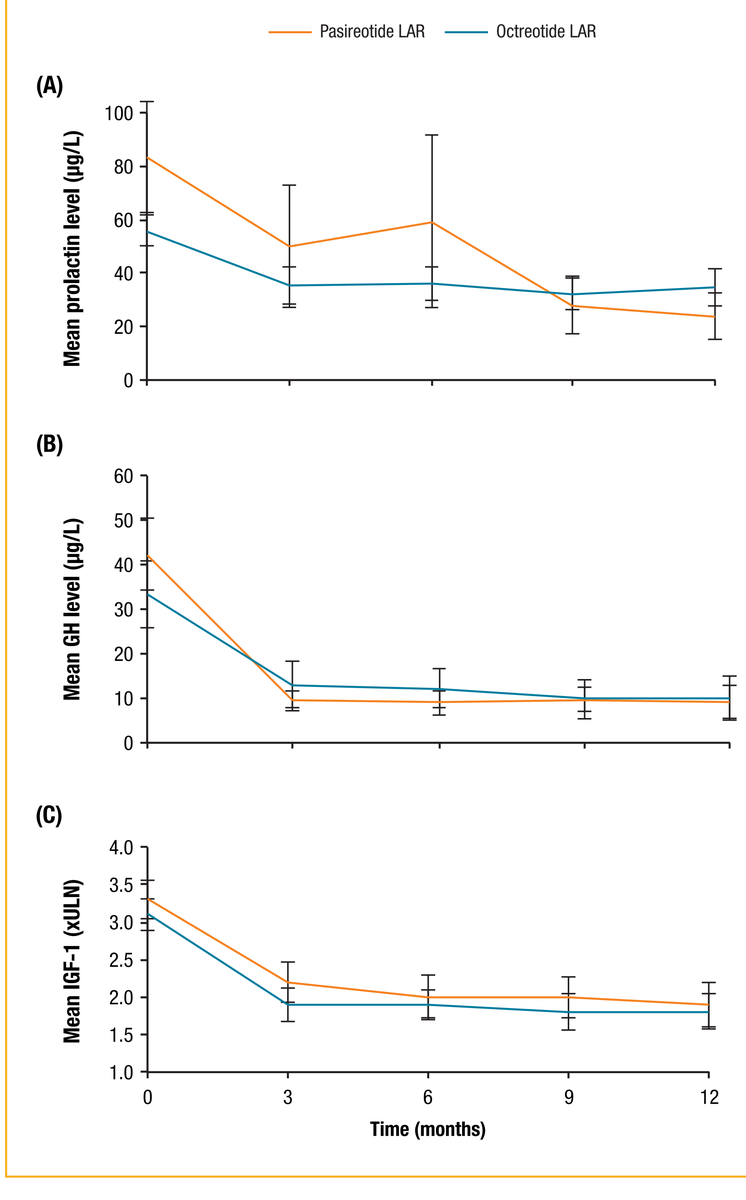
- GH levels <2.5 µg/L at month 12 were observed in 34.5% of patients (n=10) who received pasireotide LAR and 43.3% of patients (n=13) who received octreotide LAR; the equivalent proportions of patients with normal IGF-1 levels were 24.1% (n=7) and 26.7% (n=8), respectively (**Table 2**).
- Following 12 months of treatment, 10.3% (n=3) and 16.7% (n=5) of patients had normal IGF-1 *and* GH <2.5 µg/L in the pasireotide LAR and octreotide LAR treatment arms, respectively (**Table 2**).

Table 2. GH and IGF-1 Response at Month 12 for Patients with Prolactin >ULN at Baseline

Response at month 12	Pasireotide LAR, n (%) [95% CI] N=29	Octreotide LAR, n (%) [95% CI] N=30
GH <2.5 µg/L	10 (34.5) [17.9, 54.3]	13 (43.3) [25.5, 62.6]
Normal IGF-1	7 (24.1) [10.3, 43.5]	8 (26.7) [12.3, 45.9]
GH <2.5 µg/L *and* normal IGF-1	3 (10.3) [2.2, 27.4]	5 (16.7) [5.6, 34.7]

- At month 12, mean prolactin levels had decreased by 65.7% in the pasireotide LAR arm and by 39.8% in the octreotide LAR arm (**Figure 2A**).
- Mean GH (75.7% and 69.1%) and IGF-1 (45.0% and 40.1%) levels also decreased in both the pasireotide LAR and octreotide LAR arms, respectively (**Figures 2B and 2C**).

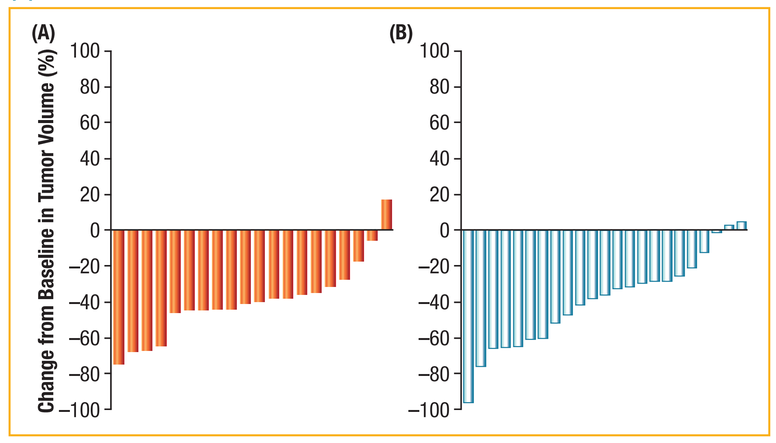
Figure 2. Mean (±SE) (A) Prolactin, (B) GH and (C) IGF-1 Levels over Time for Patients with Prolactin >ULN at Baseline



Evaluation of Tumor Response

- At month 12, tumor volume had decreased from baseline by a mean of 39.7% (median 40.6%; interquartile range 33.2%, 45.5%) in the pasireotide LAR treatment group and 39.5% (median 36.3%; interquartile range 25.5%, 60.8%) in the octreotide LAR treatment group.
- Any reduction or no change in tumor volume from baseline to month 12 was reported in 95.0% (n=19/20) and 91.3% (n=21/23) of patients in the pasireotide LAR and octreotide LAR treatment arms, respectively (**Figure 3**).
- Significant (≥20%) reductions in tumor volume were reported in 85.0% (n=17/20) and 82.6% (n=19/23) of patients receiving pasireotide LAR and octreotide LAR treatment, respectively.

Figure 3. Percentage Change in Tumor Volume from Baseline at Month 12 for Patients with Prolactin >ULN at Baseline, Treated with (A) Pasireotide LAR and (B) Octreotide LAR



Safety and Tolerability

- The most common AEs, regardless of relationship to study drug, for those patients with hyperprolactinemia at baseline are shown in **Table 3**
  - Most AEs were mild or moderate in nature.
- The safety profile of pasireotide LAR was similar to that of octreotide LAR, except for the degree of hyperglycemia
  - 48.3% of patients (n=14) who received pasireotide LAR reported hyperglycemia-related AEs, compared with 13.3% of patients (n=4) who received octreotide LAR
  - Grade 3 or 4 hyperglycemia-related AEs were experienced by 20.7% of patients (n=6) who received pasireotide LAR, compared with no patients who received octreotide LAR.

Table 3. Frequent AEs (Occurring in ≥15% of Patients in Either Treatment Arm), Regardless of Relationship to Study Drug, for Patients with Prolactin >ULN at Baseline

Adverse event, n (%)	Pasireotide LAR N=29	Octreotide LAR N=30
Diabetes mellitus	8 (27.6)	2 (6.7)
Diarrhea	7 (24.1)	15 (50.0)
Cholelithiasis	7 (24.1)	11 (36.7)
Headache	7 (24.1)	7 (23.3)
Increased creatine phosphokinase	6 (20.7)	3 (10.0)
Back pain	5 (17.2)	3 (10.0)
Abdominal distention	5 (17.2)	2 (6.7)
Hyperglycemia	5 (17.2)	2 (6.7)
Abdominal pain	3 (10.3)	7 (23.3)
Alopecia	2 (6.9)	7 (23.3)
Nausea	2 (6.9)	5 (16.7)

CONCLUSIONS

- **In this subset of patients with acromegaly and hyperprolactinemia, pasireotide LAR and octreotide LAR normalized prolactin levels in 72.4% and 56.7% of patients, respectively. Of note, a decrease in prolactin levels is not commonly reported with somatostatin analogue therapy.**
- **Mean GH and IGF-1 levels were also suppressed during treatment with pasireotide LAR and octreotide LAR.**
- **Most patients had a decrease in tumor volume, which may be particularly important in patients with hyperprolactinemia caused by compression of the pituitary stalk.**
- **Pasireotide LAR and octreotide LAR were generally well tolerated; the safety profile of pasireotide LAR was similar to that of octreotide LAR, except for the degree of hyperglycemia.**
- **Pasireotide LAR and octreotide LAR may be effective treatments for patients with a GH- and prolactin-secreting pituitary adenoma.**

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