INTRODUCTION

The therapeutic goal in acromegaly is to reduce morbidity and mortality by removing tumor mass and restoring growth hormone (GH) and insulin-like growth factors (IGF-1) levels to within normal range.

Somatostatin analogs (SSAs) are the conventional medical therapy in patients with acromegaly in whom surgery is not effective, as well as in those who have a minimize chance of surgical cure (because of extra-axial extension of the tumor) or are not candidates for surgery.

Pasireotide is a multiplex-targeted SSA with a broader somatostatin receptor profile than currently available SSAs that was developed with the goal of improving biochemical control rates in patients with acromegaly.

In a large, randomized, double-blind, Phase III trial in medically naïve patients with acromegaly, pasireotide long-acting release (LAR) was significantly superior (P=0.007) to octreotide LAR providing biochemical control at month 12.

An extension phase allowed patients who did not have biochemical control (GH <2.5 µg/L and IGF-1 level within normal limits) to switch to the other treatment, and those who were controlled or receiving clinical benefit from study drug to continue receiving their randomized therapy beyond month 13.

Efficacy results for up to 12 months after crossover last visit at which efficacy parameters were evaluated and reported here. Safety results include data up to 13 months after crossover.

Study Design

Medically naïve de novo post-pituitary surgery or de novo with visible pituitary adenoma on magnetic resonance imaging who refused pituitary surgery who was contraindicated patients with active acromegaly (GH ≥5 µg/L and/or GH nadir ≥1 µg/L, post-on oral-glucose tolerance test, and IGF-1 1.2 SD above normal limits [ULN]) were eligible for enrollment into the 12-month core study. Patients were randomized to pasireotide LAR 40 mg/28 days or octreotide LAR 30 mg/28 days, with dose titration to pasireotide LAR 60 mg/28 days or octreotide LAR 30 mg/28 days permitted, but not mandatory, at month 3 or 7. Dose decreases were permitted for tolerability (Figure 1).

A protocol amendment implemented shortly after the trial had begun established a double-blind extension phase whereby patients could either remain on their randomized therapy or crossover to the other treatment.

Prior to the protocol amendment, patients who were inadequately controlled with octreotide LAR could switch to pasireotide LAR at month 12, but not vice versa.

Following this amendment, patients with GH ≥2.5 µg/L and/or IGF-1 >ULN (age and sex-matched) could switch to the other treatment – either pasireotide LAR 20 mg/28 days or octreotide LAR 20 mg/28 days at the end of the core study (month 13).

After crossover, dose escalation to pasireotide LAR 60 mg or octreotide LAR 30 mg was permitted, but not mandatory, at month 17 or 20 (GH ≥2.5 µg/L and/or IGF-1 >ULN). Dose decreases were permitted for tolerability (Figure 1).

RESULTS

Patients

141 (80.1%) patients receiving pasireotide LAR and 156 (85.7%) patients receiving octreotide LAR completed the 12-month core study.

Of the 239 patients who entered the extension, 119 patients crossed over to other therapy – either pasireotide LAR or octreotide LAR, 81 patients were crossed over to pasireotide LAR, 28 patients to octreotide LAR. Median duration of treatment after crossover was 420 days in the median pasireotide LAR treatment arm and 364 days in the octreotide LAR treatment arm.

31 patients received pasireotide LAR and 13 octreotide LAR patients discontinued within 13 months after crossover.

Efficacy

Of the 81 patients inadequately controlled with octreotide LAR who switched to pasireotide LAR, 14 (17.3%) had biochemical control 12 months after crossover (Table 1).

Of the 38 patients inadequately controlled with pasireotide LAR who switched to octreotide LAR, none had biochemical control 12 months after crossover (Table 1).

METHODS

Study Design

Medically naïve (either post-pituitary surgery or for whom pituitary surgery was contraindicated) patients with acromegaly (GH de novo) and/or pituitary adenoma on magnetic resonance imaging who refused pituitary surgery at month 12.

Study drug related AE(s)

Discontinued due to AE(s)

Deaths

 Leading to Discontinuation of Drug Study by Treatment

CONCLUSIONS

Pasireotide LAR holds promise as a treatment option for patients with acromegaly inadequately controlled with octreotide LAR. The safety profile seen with pasireotide LAR after crossover was consistent with the safety profile in the core phase. As observed during the core phase, the safety profile of pasireotide LAR was comparable to octreotide LAR with a higher incidence and degree of hyperglycemia in the pasireotide LAR treatment arm. Hyperglycemia associated with pasireotide LAR appeared to be reversible upon discontinuation of pasireotide LAR.

Further randomized studies are warranted to confirm the efficacy of pasireotide LAR in patients inadequately controlled with octreotide LAR. Further research is warranted to understand this patient population ongoing (PAOLA; Z00203C2402).

REFERENCES


