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Management of Pasireotide-Induced Hyperglycaemia with Proactive Monitoring and Early Intervention: Key Learnings from the Phase III, 24-Week PAOLA Study

MR Gadelha,[1] T Brue,[2] M Fleseriu,[3] I Shimon,[4] K Hermosillo Reséndiz,[5] A Kandra,[6] AM Pedroncelli,[6] A Colao[7]

[1]Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil; [2]Hôpital de la Timone, Aix-Marseille University, Centre National de la Recherche Scientifique, and Assistance Publique-Hôpitaux de Marseille, Marseille, France; [3]Northwest Pituitary Center, Oregon Health & Science University, Portland, Oregon, USA; [4]Rabin Medical Center, and Sackler School of Medicine, Tel-Aviv University, Petah-Tiqva, Israel; [5]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA; [6]Novartis Pharma AG, Basel, Switzerland; [7]Università Federico II di Napoli, Naples, Italy

INTRODUCTION

- Pasireotide is a multireceptor-targeted somatostatin analogue with affinity for four of the five somatostatin receptors.[1] Based on its high affinity for sst_2 and sst_5 receptors, pasireotide has proven to be an effective treatment for patients with acromegaly.[2,3]
- Sst_2 and sst_5 receptors also play important roles in blood glucose regulation[4]
  - Glucagon secretion is mainly mediated by sst_2
  - Insulin secretion is mediated by both sst_2 and sst_5.
- During a randomized, Phase III study (PAOLA) in patients with inadequately controlled acromegaly, pasireotide LAR provided superior efficacy over continued treatment with octreotide LAR or lanreotide Autogel[3]
  - Hyperglycaemia-related adverse events (AEs) were observed in 64% of patients receiving pasireotide LAR and 30% receiving octreotide LAR/lanreotide Autogel.
- This analysis from PAOLA explores the effect of the timing of antidiabetic medication (ADM) intervention on fasting plasma glucose (FPG) during pasireotide LAR treatment.

METHODS

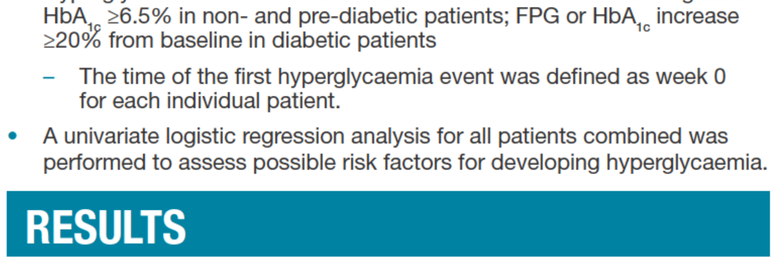
Patient Population

- Patients aged ≥18 years with inadequately controlled acromegaly.
- Mean growth hormone (GH) >2.5 µg/L and insulin-like growth factor 1 (IGF-1) >1.3 times the sex- and age-adjusted upper limit of normal.
- All received octreotide LAR 30 mg or lanreotide Autogel 120 mg monotherapy for ≥6 months before screening.

Study Design

- Prospective, multicentre, randomized, 24-week, parallel-group study (**Figure 1**).

Figure 1. Study Design



Analysis

- Patients randomized to pasireotide LAR 40/60 mg (pooled data) who received at least one dose of pasireotide and had a valid post-baseline safety assessment (safety population) were included in this analysis
  - FPG levels in these patients were measured monthly
  - Patients were categorized by baseline diabetic status (**Table 1**).

Table 1. Categorization by Baseline Diabetic Status

Category	Definition
Non-diabetic	FPG <100 mg/dL *and* HbA_{1c} <5.7% *and* 2-h post-OGTT glucose <140 mg/dL
Pre-diabetic	FPG 100–<126 mg/dL *or* HbA_{1c} 5.7–<6.5% *or* 2-h post-OGTT glucose 140–<200 mg/dL
Diabetic	Current/prior ADM use *or* FPG ≥126 mg/dL *or* HbA_{1c} ≥6.5% *or* 2-h post-OGTT glucose ≥200 mg/dL

HbA_{1c}, glycated haemoglobin; OGTT, oral glucose tolerance test

- Hyperglycaemia was defined as first occurrence of: FPG ≥126 mg/dL or HbA_{1c} ≥6.5% in non- and pre-diabetic patients; FPG or HbA_{1c} increase ≥20% from baseline in diabetic patients
  - The time of the first hyperglycaemia event was defined as week 0 for each individual patient.
- A univariate logistic regression analysis for all patients combined was performed to assess possible risk factors for developing hyperglycaemia.

RESULTS

Patient Population

- Of the 125 patients included (safety population), 19 were non-diabetic, 24 were pre-diabetic and 82 were diabetic
  - Of these, five non-diabetic (26.3%), nine pre-diabetic (37.5%) and 68 diabetic (82.9%) patients experienced hyperglycaemia.

Initiation of Antidiabetic Medication in Diabetic Patients

- ADM was initiated or adjusted in 36 of 68 diabetic patients who had a hyperglycaemia event
  - This occurred after 0–<15 days in seven patients, 15–<30 days in eight patients and ≥30 days in 21 patients
  - ADM was not initiated/adjusted in 32 diabetic patients.
- The mean time from study baseline to first hyperglycaemia event was similar irrespective of when ADM was initiated/adjusted (29–36 days) and longer for patients who did not receive an antidiabetic intervention (79 days) [**Table 2**].

Table 2. Mean Time from Study Baseline to First Hyperglycaemia Event in the 68 Patients with Diabetes Mellitus at Baseline

Time to antidiabetic intervention from hyperglycaemia event	Mean time from study baseline to hyperglycaemia event (days)
0–<15 days, n=7	29.4 ± 0.8
15–<30 days, n=8	35.9 ± 14.0
≥30 days, n=21	35.9 ± 15.9
No intervention, n=32	78.8 ± 52.9

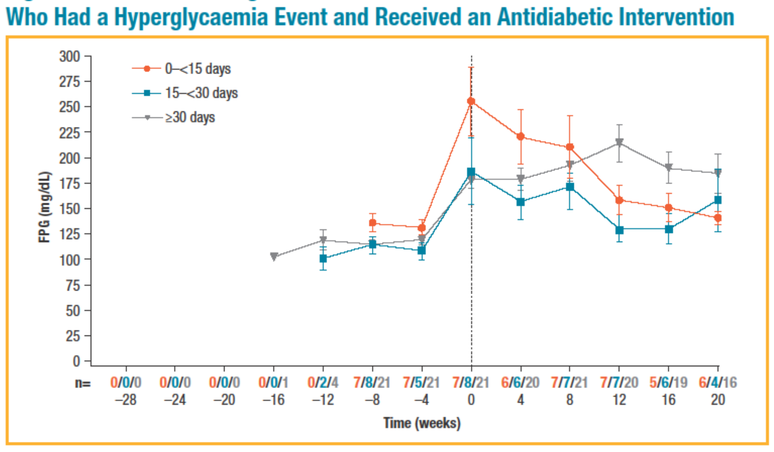
Note: Data are mean ± standard deviation (SD)

- 60 diabetic patients (88.2%) completed the study
  - Six patients discontinued because of an AE (0–<15 and 15–<30 days, n=1 for each; ≥30 days and no ADM, n=2 for each)
  - Two patients discontinued as a result of consent withdrawal (15–<30 days and no ADM, n=1 for each).

Changes in Fasting Plasma Glucose in Diabetic Patients Who Had a Hyperglycaemia Event

- At the time of each patient's first hyperglycaemia event (designated week 0), mean FPG was higher in patients who received ADM within 15 days than in those receiving ADM after 15–<30 and ≥30 days (**Figure 2**).
- The largest decrease in FPG from week 0 to last available assessment was seen in patients who received ADM within 15 days of the hyperglycaemia event (**Figure 2; Table 3**).
- Smaller changes in FPG were observed when ADM was initiated after 15–<30 and ≥30 days (**Figure 2; Table 3**).

Figure 2. Mean FPG during Pasireotide Treatment in the 36 Diabetic Patients Who Had a Hyperglycaemia Event and Received an Antidiabetic Intervention



Note: Data are mean ± SD for those patients who had evaluable measurements at the specific time point. The dotted vertical line at week 0 indicates the time of the first hyperglycaemia event for each individual patient. Time points to the left of that line indicate weeks prior to first hyperglycaemia event

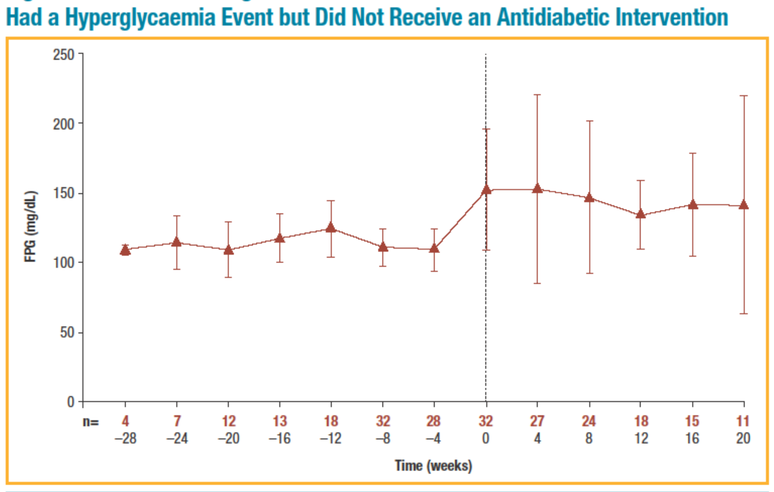
Table 3. Change in FPG from Week 0 to Last Available Assessment in Diabetic Patients Who Had a Hyperglycaemia Event (LOCF Analysis)

	0–<15 days (n=7)	15–<30 days (n=8)	≥30 days (n=21)	No ADM (n=32)
Week 0, mg/dL	255.9 ± 89.8	186.9 ± 92.2	178.7 ± 38.0	152.4 ± 44.0
Absolute change, mg/dL	–108.3 ± 88.1	–35.0 ± 87.1	12.3 ± 76.2	–3.0 ± 63.1
Percentage change, %	–35.4 ± 23.9	–9.6 ± 36.6	8.3 ± 39.9	–1.0 ± 34.4

Note: Data are mean ± SD. LOCF, last observation carried forward

- In diabetic patients who did not receive ADM, no substantial changes in mean FPG were observed (152.4 ± 44.0 mg/dL at week 0 to 149.4 ± 65.7 mg/dL at last available assessment) [**Figure 3; Table 3**].

Figure 3. Mean FPG during Pasireotide Treatment in the 32 Diabetic Patients Who Had a Hyperglycaemia Event but Did Not Receive an Antidiabetic Intervention

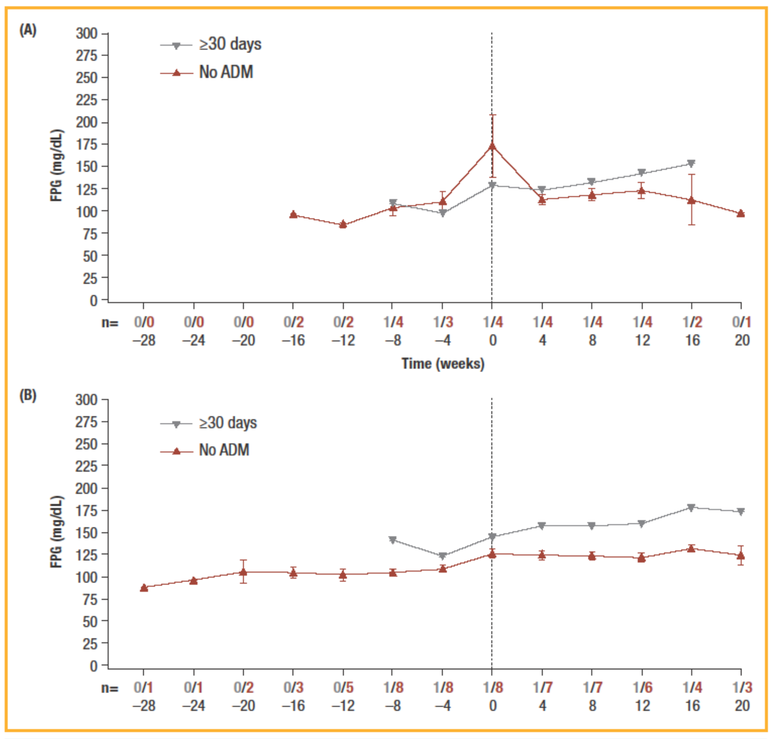


Note: Data are mean ± SD for those patients who had evaluable measurements at the specific time point. The dotted vertical line at week 0 indicates the time of the first hyperglycaemia event for each individual patient. Time points to the left of that line indicate weeks prior to first hyperglycaemia event

Changes in Fasting Plasma Glucose in Non- and Pre-diabetic Patients

- ADM was initiated in one of five non-diabetic patients and one of nine pre-diabetic patients who experienced hyperglycaemia; ADM was initiated ≥30 days after the first hyperglycaemia event in both patients.
- FPG increased slightly from week 0 to last available assessment in the non-diabetic and pre-diabetic patients who received ADM.
- Mean FPG levels decreased from 173.0 ± 70.9 mg/dL at week 0 to 123.0 ± 18.6 mg/dL at the last available assessment in non-diabetic patients who did not receive ADM (**Figure 4A**).
- No substantial change in mean FPG was observed from week 0 to the last available assessment in the pre-diabetic patients who did not receive ADM (**Figure 4B**).

Figure 4. Mean FPG during Pasireotide Treatment in (A) the Five Non-diabetic and (B) the Nine Pre-diabetic Patients Who Had a Hyperglycaemia Event



Note: For patients who did not receive antidiabetic treatment (n=4/5 non-diabetic patients; n=8/9 pre-diabetic patients), data are mean ± SD according to evaluable measurements at the specific time point. The dotted vertical line at week 0 indicates the time of the first hyperglycaemia event for each individual patient. Time points to the left of that line indicate weeks prior to first hyperglycaemia event.

Logistic Regression Analysis

- Logistic regression analysis showed that a number of parameters significantly predicted the development of hyperglycaemia during pasireotide treatment (**Table 4**).

Table 4. Risk Factors for Developing Hyperglycaemia

Risk factor	Odds ratio (two-sided CI)	*P* value
BMI ≥25 kg/m²	2.33 (1.28, 4.26)	0.006
Unit increase in baseline HbA_{1c}	4.30 (2.14, 8.64)	<0.0005
Diabetes at baseline	4.80 (1.66, 13.91)	0.004
History of dyslipidaemia	3.59 (1.83, 7.05)	<0.0005

BMI, body mass index; CI, confidence interval

CONCLUSIONS

- **In patients receiving pasireotide who experience hyperglycaemia, early intervention with ADM can improve hyperglycaemia control**
  - **Intervention within 2 weeks led to a rapid decrease in mean FPG from >250 mg/dL at the time of the first hyperglycaemia event.**
- **The enhanced efficacy of pasireotide is based on its high affinity for sst_2 and sst_5 receptors, which also play important roles in blood glucose regulation. Hyperglycaemia is therefore not an unexpected side effect of treatment.**
- **Logistic regression analysis identified a number of risk factors that may predict the development of hyperglycaemia during pasireotide treatment. Patients on pasireotide treatment should be closely monitored for changes in glucose homeostasis.**
- **These data suggest that pasireotide-induced hyperglycaemia can be managed with proactive monitoring and early intervention.**

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