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High Burden of Illness at Baseline in Patients with Uncontrolled Acromegaly Participating in the PAOLA Study

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INTRODUCTION

- Acromegaly is an endocrine disorder caused, in most cases, by a benign tumour of the pituitary gland[1] that secretes excess growth hormone (GH), with a concomitant increase in insulin-like growth factor 1 (IGF-1)
- Chronic hypersecretion of GH and IGF-1 results in multiple comorbidities, particularly cardiometabolic complications[2]
- First-generation somatostatin analogues have been shown to provide biochemical control in approximately half of patients with acromegaly[3]
- In the Phase III PAOLA study, pasireotide LAR, a next-generation somatostatin analogue, provided biochemical control in 15% (40 mg dose) and 20% (60 mg dose) of patients with acromegaly uncontrolled after treatment with first-generation somatostatin analogues, versus 0% who received continued treatment with octreotide LAR or lanreotide Autogel[4]
- This current analysis investigated overall baseline characteristics and response rates to pasireotide LAR according to baseline comorbidities in patients who participated in the PAOLA study

METHODS

Study Design

- PAOLA was a randomized, controlled, multicentre, Phase III study
- Male and female patients aged 18 years or older with uncontrolled acromegaly (GH >2.5 µg/L and IGF-1 >1.3 x upper limit of normal [ULN]) following ≥6 months of octreotide LAR 30 mg or lanreotide Autogel 120 mg monotherapy were randomized to receive pasireotide LAR 40 mg, 60 mg, or continued treatment with octreotide LAR 30 mg or lanreotide Autogel 120 mg
  - Dose decreases were permitted in each treatment group
- The primary endpoint was the proportion of patients with biochemical control (GH <2.5 µg/L and normal IGF-1) at 24 weeks

Classification of Comorbidities

- Patients participating in the PAOLA study were classified into five groups of comorbidities commonly associated with acromegaly: glucose related, endocrine related, lipid related, vascular disorders, and all other acromegaly-related disorders not included in these groups (**Table 1**)

Table 1. Baseline Conditions Comprising Group Comorbidity Classifications, Including Frequency at Baseline Ranked in Descending Order

Comorbidity	Pasireotide LAR 40 mg, n (%)	Pasireotide LAR 60 mg, n (%)	Active control, n (%)
Vascular disorders			
Hypertension	17 (26.2)	27 (41.5)	36 (52.9)
Glucose-related disorders			
Diabetes mellitus	18 (27.7)	11 (16.9)	16 (23.5)
Pre-diabetic	10 (15.4)	13 (20.0)	18 (26.5)
Impaired glucose tolerance	10 (15.4)	10 (15.4)	11 (16.2)
Type 2 diabetes mellitus	6 (9.2)	9 (13.8)	4 (5.9)
Impaired fasting glucose	2 (3.1)	1 (1.5)	3 (4.4)
Lipid-related disorders			
Dyslipidaemia	10 (15.4)	15 (23.1)	8 (11.8)
Hypercholesterolaemia	6 (9.2)	5 (7.7)	5 (7.4)
Endocrine-related disorders			
Goitre	9 (13.8)	14 (21.5)	23 (33.8)
Hypothyroidism	10 (15.4)	10 (15.4)	12 (17.6)
Adrenal insufficiency	8 (12.3)	6 (9.2)	10 (14.7)
Hypopituitarism	7 (10.8)	4 (6.2)	5 (7.4)
Hyperprolactinaemia	5 (7.7)	5 (7.7)	3 (4.4)
Hypogonadism	4 (6.2)	6 (9.2)	5 (7.4)
Diabetes insipidus	4 (6.2)	4 (6.2)	2 (2.9)
All other acromegaly-related disorders			
Depression	7 (10.8)	2 (3.1)	4 (5.9)
Headache	4 (6.2)	3 (4.6)	1 (1.5)
Osteoarthritis	4 (6.2)	3 (4.6)	6 (8.8)
Carpal tunnel syndrome	5 (7.7)	1 (1.5)	5 (7.4)
Insomnia	2 (3.1)	4 (6.2)	1 (1.5)
Arthralgia	2 (3.1)	3 (4.6)	2 (2.9)
Osteoporosis	3 (4.6)	2 (3.1)	4 (5.9)

Comorbidities listed as reported by the investigator

Analysis Sets

- Baseline characteristics were determined for the total population (N=198)
- Response rate reporting (proportion of patients with GH <2.5 µg/L and normalized IGF-1) for the comorbidity groups was based on patients who received pasireotide (N=130)
  - The pasireotide LAR 40 mg and 60 mg treatment groups were pooled for the purposes of the efficacy analysis

RESULTS

Patients

- 198 adults with uncontrolled acromegaly were enrolled
- Patients were randomized to pasireotide LAR 40 mg (n=65), 60 mg (n=65), or continued treatment with octreotide LAR 30 mg or lanreotide Autogel 120 mg (active control; n=68)
- Patient baseline characteristics were similar across the comorbidity groups (**Table 2**)
  - The majority of patients had type 2 diabetes mellitus at baseline

Table 2. Baseline Demographics by Comorbidity Group for the Total Population

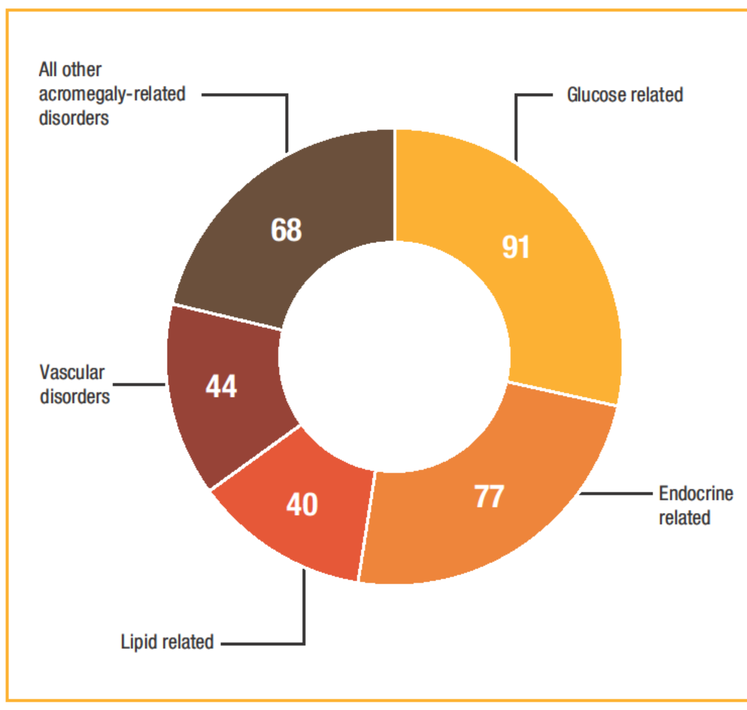
	Glucose-related disorders	Endocrine-related disorders	Lipid-related disorders	Vascular disorders	All other acromegaly-related disorders
n	145	127	56	80	111
Mean age, years (SD)	47.1 (13.97)	45.8 (13.65)	52.3 (13.56)	51.9 (12.19)	48.6 (12.55)
Gender, n (%) Male Female	 59 (40.7) 86 (59.3)	 56 (44.1) 71 (55.9)	 56 (44.1) 39 (69.6)	 35 (43.8) 45 (56.3)	 41 (36.9) 70 (63.1)
Mean weight, kg (SD)	85.4 (18.9)	86.6 (19.9)	85.6 (19.3)	89.9 (20.1)	85.8 (20.9)
Mean BMI, kg/m^2 (SD)	29.9 (6.0)	29.8 (5.9)	31.1 (5.7)	31.5 (6.2)	29.9 (6.2)
Baseline diabetic status, n (%) Diabetic Pre-diabetic NGT Missing	 104 (71.7) 41 (28.3) 0 (0.0) 0 (0.0)	 94 (74.0) 20 (15.7) 13 (10.2) 0 (0.0)	 46 (82.1) 7 (12.5) 3 (5.4) 0 (0.0)	 64 (80.0) 14 (17.5) 1 (1.3) 1 (1.3)	 81 (73.0) 21 (18.9) 9 (8.1) 0 (0.0)
Mean baseline GH, µg/L (SD)	12.7 (23.8)	12.4 (22.9)	9.0 (15.8)	10.3 (13.9)	10.6 (20.7)
Mean baseline IGF-1, x ULN (SD)	2.9 (1.1)	2.7 (1.1)	3.0 (1.1)	3.1 (1.1)	2.9 (1.1)

BMI, body mass index; NGT, normal glucose tolerance; SD, standard deviation

Comorbidities at Baseline

- Glucose-related and endocrine-related comorbidities were most common in the overall patient population (**Table 2**) and in patients who achieved biochemical control with pasireotide LAR treatment (**Figure 1**)
- Most patients had multiple comorbidities: 49% of patients had comorbidities belonging to three or more of the comorbidity groups

Figure 1. Number of Individual Identified Comorbidities (Shown According to Group Category) in Patients Who Received Pasireotide LAR Treatment and Achieved Biochemical Control (GH <2.5 µg/L and Normal IGF-1)



Efficacy

- Response rates to pasireotide LAR were similar across the comorbidity groups, ranging from 14.3% to 19.1% at week 12, and from 15.4% to 20.6% at week 24 (**Figure 2**)
- Reductions in median GH and IGF-1 values with pasireotide LAR treatment at week 24 were similar across all of the comorbidity groups (**Figure 3**)

Figure 2. Proportion of Patients Who Received Pasireotide LAR Treatment and Achieved Biochemical Control (GH <2.5 µg/L and Normal IGF-1) at Weeks 12 and 24 According to Comorbidity Group

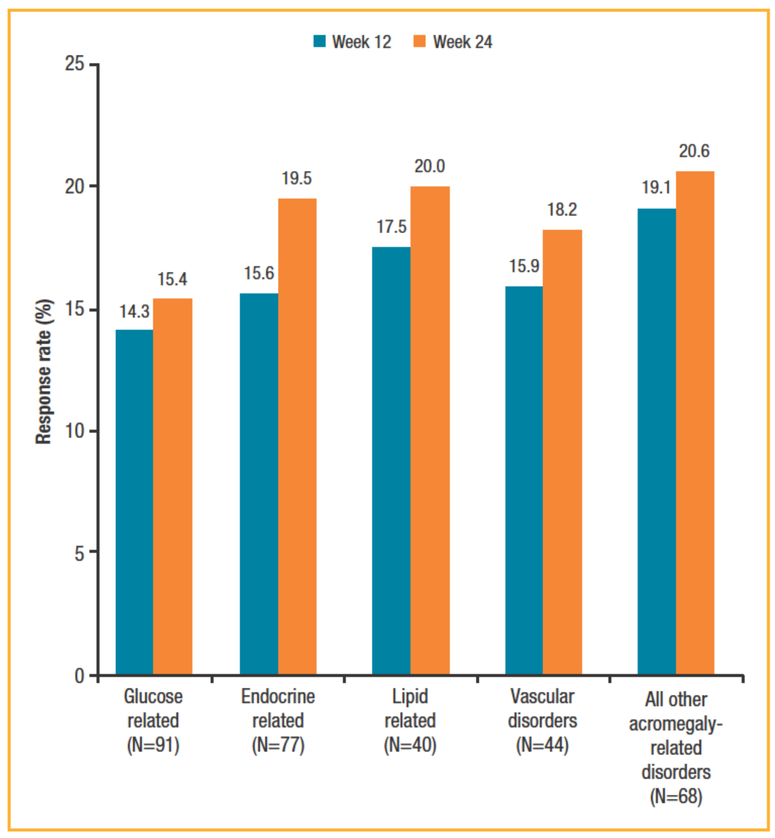
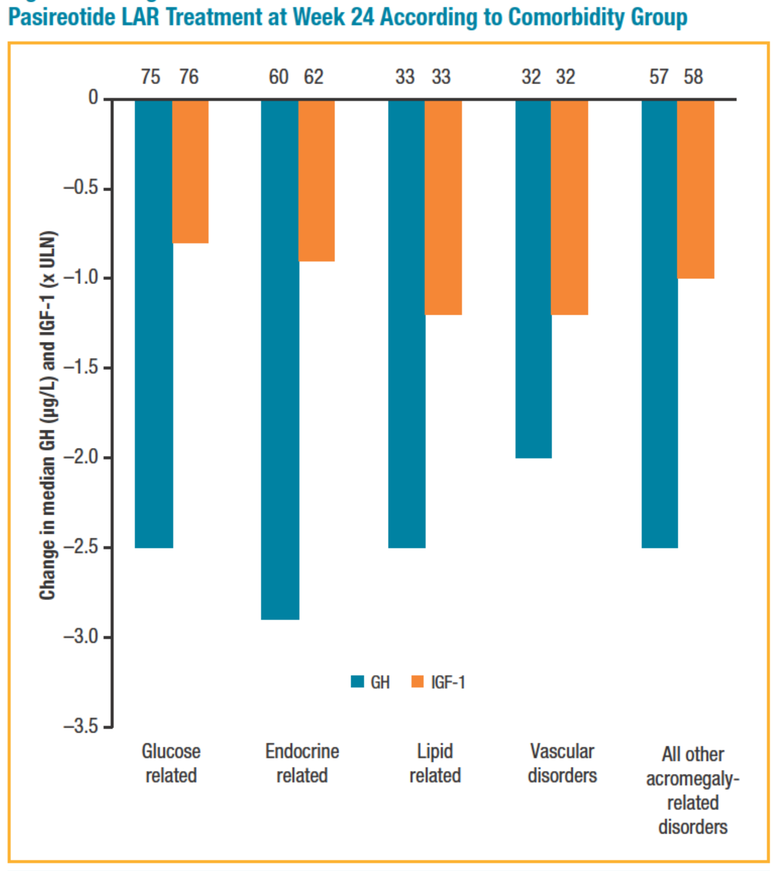


Figure 3. Change from Baseline in Median GH and IGF-1 Values with Pasireotide LAR Treatment at Week 24 According to Comorbidity Group



Number of patients with observations at both baseline and week 24 shown above each bar

CONCLUSIONS

- Most patients with uncontrolled acromegaly who participated in the PAOLA study had multiple comorbidities
- The efficacy of pasireotide LAR treatment was similar regardless of baseline comorbidity
- Patients with uncontrolled acromegaly have a high burden of illness that requires treatment intervention

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