Research Square

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Long-term metabolic and biochemical outcomes of pasireotide LAR in resistant acromegaly

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Abstract

Background

Pasireotide long-acting release (PAS-LAR) is a second-generation somatostatin receptor ligand approved for patients with acromegaly resistant/intolerant to first-generation analogues or combination medical therapy. Real-world evidence on its metabolic impact and tumour response remains limited.

Objective

To evaluate the long-term efficacy, metabolic safety, and tumour effects of PAS-LAR in a real-life cohort of acromegalic patients.

Methods

A retrospective study was carried out in a single tertiary endocrine centre in Romania. Thirty acromegalic patients previously treated with first-generation somatostatin receptor ligands (fg-SRLs) ± pegvisomant ± cabergoline were switched to PAS-LAR ± cabergoline. Data were collected at baseline, after 3- and 6-months of PAS-LAR treatment, and at the last available visit (median 36 months).

Results

Introduction

Acromegaly is a rare, chronic disease caused by excessive growth hormone (GH), usually from a pituitary tumour, leading to elevated insulin-like growth factor 1 (IGF-1) [1–3]. Inadequate control is associated with cardiovascular, metabolic and neoplastic comorbidities, shortened life expectancy and impaired quality of life [1, 4].

Treatment aims to normalize GH and IGF-1 levels, control tumour mass, and manage complications. Transsphenoidal (TS) surgery is first-line therapy, yet 40–60% of patients, require adjuvant medical therapy. First-generation somatostatin receptor ligands (fgSRLs), octreotide LAR and lanreotide Autogel,represent standard medical therapy, but many patients - particularly those with macroadenomas or high baseline hormonal level - show partial response or resistance. Alternatives include fgSRLs dose escalation, addition of cabergoline, or pegvisomant [3, 5–7].

Pasireotide long-acting release (PAS-LAR) is a second-generation multireceptor-targeted SRL with broader binding profile and a particular affinity for somatostatin receptor subtype 5 (SSTR5), frequently overexpressed in GH-secreting pituitary tumours [8, 9]. The pivotal Phase III PAOLA trial showed superior biochemical control versus high-dose octreotide LAR in inadequately controlled acromegaly [10], but

with higher incidence and severity of hyperglycaemia, a consequence of pasireotide's inhibitory effects on insulin and incretin secretion [11, 12].

This study reports our single-centre, real-world experience with PAS-LAR in Romanian patients resistant to previous multimodal therapy. The primary objective was to evaluate the long-term biochemical efficacy and tumour response of PAS-LAR. The secondary objective was to assess its impact on glucose metabolism and identify potential associations with glycemic deterioration. Understanding such factors may support individualized treatment selection.

Materials and methods

Study design and population

This retrospective observational study was conducted at the "C. I. Parhon" National Institute of Endocrinology, a national tertiary care referral centre in Bucharest, Romania. We reviewed medical record of all adult patients with confirmed acromegaly, who initiated treatment with PAS-LAR between June 2014 and December 2025.

Eligible patients had active disease (Romanian National Health Insurance House therapeutic protocol criteria), despite previous multimodal therapy (including surgery, radiotherapy, and/or medical treatment with fgSRLs, alone or in combination with cabergoline of pegvisomant). A minimum follow-up of 12 months after initiation of PAS-LAR was required. Patients with incomplete baseline and follow-up hormonal and metabolic data were excluded.

Ethical considerations

The study complied with the Declaration of Helsinki. All participants had previously provided written informed consent for anonymized data use.

Treatment protocol

According to the national therapeutic protocol, PAS-LAR is indicated as a second-line therapy: (a) after ≥ 3 months of maximum-dose fgSRL, without optimal control (defined as random GH > 1 ng/mL without ≥ 50% reduction from pre-treatment level); (b) in partial responders to maximum-dose fgSRLs, as an alternative to pegvisomant combination; or (c) in patients without optimal control with pegvisomant (monotherapy/combination), when second-generation SRLs have not been previously used. All patients met the criteria, having documented inadequate response to octreotide LAR/lanreotide Autogel), alone or combined with cabergoline and/or pegvisomant. Concomitant cabergoline was allowed.

PAS-LAR was administered as a deep intramuscularly injection every 28 days. Initial dose was 40 mg, increased to 60 mg after 3 months if GH and/or IGF-1 remained uncontrolled. Dose reduction (temporary

or permanently, in 20 mg increments) was permitted in case of adverse events.

Assessment and definitions

Clinical, biochemical, and radiological data were collected at baseline (before PAS-LAR) and 3 months, 6 months and the last follow-up (> 6 months). The long-term evaluation corresponded to the last available follow-up visit after at least 12 months of PAS-LAR treatment.

Hormonal profile

Random GH (ng/mL) and IGF-1 (ng/mL and x ULN). Therapeutic efficacy (and indication for medical treatment) was defined according to the Romanian National Health Insurance House therapeutic protocol

Optimal control - controlled symptoms, random GH < 1 ng/mL or GH during oral glucose tolerance test (OGTT) < 0.4 ng/mL, and age- and sex-adjusted normal IGF-1 (IGF-1 < 1.3xULN).

Partial response - controlled symptoms with > 50% reduction in GH and IGF-1, but random GH > 1 ng/mL/nadir GH in OGTT > 0.4 ng/mL and elevated IGF-1 (IGF-1 > 1.3xULN).

Therapeutic failure – persistent/progressive acromegaly symptoms, < 50% reduction in GH and/or IGF-1, and/or tumour progression.

Since these are the definitions used in our National Helath Insurance House protocol, we could not use the criteria recommended by the most recent International Consensus Criteria on Acromegaly.

Glycemic profile: FPG (mg/dL), HbA1c (%), and diabetes/prediabetes according to American Diabetes Association (ADA) 2024 [13] criteria: normal (FPG < 100 mg/dL and HbA1c < 5.7%), prediabetes (FPG 100–125 mg/dL/HbA1c 5.7–6.4%), and diabetes mellitus (FPG ≥ 126 mg/dL/HbA1c ≥ 6.5%).

Lipid profile: total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides (mg/dl). Abnormal values: total cholesterol ≥ 200 mg/dL, TG ≥ 150 mg/dL), HDL-C < 40 mg/dL, LDL-C ≥ 130 mg/dL (based on ESC/EAS guidelines [14])

Anthropometry: body mass index (BMI, kg/m^2), categorized per World Health Organization criteria as: underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obesity class I (BMI 30.0–34.9 kg/m^2), obesity class II (BMI 35.0–39.9 kg/m^2), and obesity class III (BMI ≥ 40.0 kg/m^2).

Tumour evaluation

maximal tumour diameter on MRI at baseline and last visit. A ≥ 20% decrease defined significant shrinkage; ≥20% increase defined progression (comparison between last evaluation and the one at

initiation of PAS-LAR treatment).

The last follow up visit occurred at a median of 36.5 months (range 12–132 months).

Assays

Serum GH and IGF-1 were measured by chemiluminescent immunoassay (CLIA) technology, on Liaison XL analyser using reagents produced by Diasorin S.p.A. (Saluggia, Italy). FPG, total cholesterol, LDL-C, HDL-C, and Triglycerides were determined by enzymatic colorimetric methods on the Cobas automated chemistry analyser, with routine internal and external quality control procedures. HbA1c was measured by immunoturbidimetric assay (Roche Diagnostics) on the Cobas automated analyser, with routine internal and external quality control procedures.

Statistical analysis

Continuous variables were expressed as mean ± SD or median (IQR), according to data distribution assessed using the Shapiro–Wilk test. Normally distributed paired variables were compared using paired t-test, whereas non-normally distributed variables were analysed using Wilcoxon signed-rank test. Categorical variables were compared using Fisher's exact test. Correlations were assessed using Pearson's or Spearman's coefficients, as appropriate. A two-sided p-value < 0.05 was considered statistically significant.

Results

Patient characteristics

Thirty patients with resistant acromegaly were included (Table 1). Most were female (66.7%), with a mean age at diagnosis of 37.7 ± 12.8 years and a mean age at the start of PAS-LAR treatment of 44.4 ± 12.0 years. The mean duration of PAS-LAR treatment was 44.4 ± 31.2 months (median 36.5 months, IQR 17.2–60.5).

Table 1
Baseline demographic and clinical characteristics of the patients

Characteristic		Value (n = 30)
Sex	Female, n (%)	20 (66.7)
	Male, n (%)	10 (33.3)
Age (years)	At diagnosis, mean ± SD	37.7 ± 12.8
	At PAS-LAR start, mean ± SD	44.7 ± 11.9
Treatment duration (months)	Mean ± SD	44.4 ± 31.2
	Median (range)	36.5 (12–132)
Previous treatments	Neurosurgery, n (%)	29 (96.7)
	Radiotherapy, n (%)	13 (43.3)
Previous medical treatment	fg-SRLs alone	9 (30.0)
	fg-SRLs + CAB	8 (26.7)
	fg-SRLs + PEGV	5 (16.7)
	fg-SRLs + PEGV + CAB	8 (26.7)
Current medical treatment	PAS-LAR monotherapy	14 (46.7)
	PAS-LAR + CAB	16 (53.3)
Tumour at diagnosis	Macroadenoma, n (%)	30 (100)
	Max. diameter (mm), mean ± SD	27.8 ± 12.4

**N=number, PAS-LAR=pasireotide long acting, fg-SRLs=first generation somatostatin receptor ligands, CAB=cabergoline, PEGV=pegvsisomant, SD=standard deviation, max=maximum.*

All had multimodal therapy: 96.7% underwent neurosurgery and 43.3% radiotherapy. All had previously been treated with fgSRLs, alone or in combination with cabergoline ±pegvisomant. PAS-LAR was administered as monotherapy in 46.7% and combined with cabergoline in 53.3% (cabergoline was used prior to PAS -LAR in all these cases and continued throughout the follow-up). All patients had macroadenomas at diagnosis (mean maximum tumour diameter of 27.8 ± 12.6 mm). The immunohistochemical SSTR (somatostatin receptor) expression was available only in some cases, so we did not include this in the present study.

In our cohort, 13 patients (43.3%) had undergone radiotherapy before PAS-LAR. Mean age at irradiation was 37.1 ± 16.5 years. The interval between radiotherapy and PAS-LAR initiation was 8.5 ± 8.4 years (median of 6.0 years [IQR 3.0–12.0]). Biochemical response did not differ between irradiated and non-irradiated patients. At last follow-up, mean GH (2.21 ± 2.16 ng/mL vs 1.92 ± 1.47 ng/mL, p = 0.917) and

IGF-1 xULN (1.21 ± 0.60 xULN vs 1.22 ± 0.48 xULN, p = 0.817) were comparable. Time since irradiation did not significantly correlate with final IGF-1 (r = 0.049, p = 0.873) or percentage reduction (r = 0.015, p = 0.096). Mean IGF-1 reduction was similar (36.1 ± 29.0 in irradiated versus 35.7 ± 20.9 in non-irradiated, p = 0.972).

Irradiated patients had larger tumours at PAS-LAR initiation (20.0 ± 10.3 mm vs 14.5 ± 9.0 mm), without statistical significance (p = 0.128). Tumour response (decrease, stability or increase), was comparable (decrease in 30.8% of irradiated, 33.3% of non-irradiated).

Biochemical efficacy

At baseline, mean random GH was 4.53 ± 5.88 ng/mL, and mean IGF-I xULN (upper limit of normal, ULN) was 1.64 ± 0.79 xULN- see Fig. 1. Only 16.7% had an IGF-I xULN ≤ 1.0, being switched to PAS-LAR due to unsuppressed GH (OGTT)/increased random GH, per national protocol. PAS-LAR induced a significant and progressive reduction in GH and IGF-1 (Table 2). Median IGF-1 reduction was − 40%.

Table 2
Biochemical response to PAS-LAR treatment. Data are presented as mean ± SD or n (%)

Parameter	Baseline	3 months	6 months	Last visit	p value (vs baseline)
IGF-1 (x ULN)	1.64 0.79	1.21 ± 0.53	1.06 ± 0.53	0.99 ± 0.44	< 0.0001
Patients with IGF-1 < 1.3, n (%)	8 (26.7)	17 (56.7)	21 (70.0)	23 (76.7)	< 0.001
Patients with IGF-1 < 1, n (%)	5 (16.7)	11 (36.7)	16 (53.3)	18 (60.0)	-
GH (ng/mL)	4.53 ± 5.88	2.04 ± 1.77	1.69 ± 1.40	1.58 ± 1.43	< 0.001
Patients with GH < 1, n (%)	2 (8.0)	12 (40.0)	11 (36.7)	12 (40.0)	-

**PAS-LAR=pasireotide long acting, SD=standard deviation, n=number, IGF-1 = insulin-like growth factor 1, ULN=upper limit of normal, GH=growth hormone.*

Table 3: Patient stratification by median baseline IGF-1 xULN

Variable	High (≥ 1.4 xULN)	Low (< 1.4 xULN)	p value
Age at PAS-LAR start (years)	41.00 (36.0–52.0)	46.5 (40.0-57.5)	0.565
Baseline IGF-1 (xULN)	1.70 (1.50–2.60)	1.20 (1.00-1.30)	< 0.001
Baseline HbA1c (%)	5.80 (5.50–6.20)	5.65 (5.53–5.88)	0.563
Last IGF-1 (xULN)	1.20 (1.00-1.50)	0.70 (0.52–0.80)	< 0.001
Last HbA1c (%)	6.20 (6.10-7.00)	6.20 (6.00-6.70)	0.37
ΔHbA1c (last-baseline, %)	0.70 (0.30–1.10)	0.55 (0.32–1.10)	0.812
Biochemical control (IGF-1 ≤1.0 xULN)	5/16 (31.3%)	13/14 (92.9%)	0.002
Acceptable control (IGF-1 ≤1.3 xULN)	9/16 (56.3%)	14/14 (100%)	0.009

PAS-LAR-pasireotide long-acting, ULN-upper limit of normal, IGF-1-insulin-like growth factor 1, HbA1c-glycated hemoglobin.

Acceptable biochemical control (IGF-1 xULN < 1.3) increased from 26.7% at baseline to 56.7% at 3 months, 70.0% at 6 months and reached 76.7% at last follow-up (p < 0.001). Using the stricter cut-off (IGF-I xULN ≤ 1), control rates rose from 16.7% to 36.7%, 53.3%, and were 60.0% at the last follow-up. Mean random GH decreased significantly from 4.53 ± 5.88 to 1.58 ± 1.43 ng/mL (p < 0.001), while the proportion with random GH < 1.0 ng/mL increased from 8.0% to 40.0%.

Final IGF-1XULN levels were similar between PAS-LAR monotherapy (0.96 ± 0.48) and combination with cabergoline (1.01 ± 0.39, p = 0.487).

Stratification by pre-PAS-LAR-IGF-1 showed that lower baseline disease activity was associated with significantly higher rates of biochemical control at last follow-up, confirming pre-PAS-LAR IGF-1 as an indicator of treatment response (Table 3).

Glucose metabolism

PAS-LAR significantly worsened glycaemic parameters (Table 4, Fig. 2). Mean FPG increased by + 19.9 ± 28.4 mg/dL and mean HbA1c by + 0.67 ± 0.92%. At baseline, 26.7% had normal glycemia, 53.3% pre-diabetes, and 20.0% diabetes (ADA criteria). At last follow-up, only one patient remained normoglycemic; 50.0% had pre-diabetes and 46.7% diabetes. The prevalence of impaired fasting glucose (IFG, FPG 100–125 mg/dL) increased from 40.0% at to 50.0%, and FPG ≥ 126 mg/dL rose from 13.3% to 26.7%. Based on HbA1c, the prevalence of pre-diabetes rose from 36.7% to 53.3% and diabetes from 13.3% to 41.9%.

Table 4
Glycemia parameters and classification according to ADA guideline [13]

Parameter	Baseline	3 months	6 months	Last visit	p value
FPG (mg/dL), mean ± SD	100.5 ± 17.7	120.9 ± 35.1	121.9 ± 34.5	120.4 ± 30.1	0.0008
Normal (< 100), n (%)	14 (46.7)	5 (16.7)	5 (16.7)	7 (23.3)	-
IFG (100–125), n (%)	12 (40.0)	18 (60.0)	16 (53.3)	15 (50.0)	-
Diabetes (≥ 126), n (%)	4 (13.3)	7 (23.3)	9 (30.0)	8 (26.7)	-
HbA1c (%), mean ± SD	5.90 ± 0.84	6.41 ± 0.87	6.54 ± 0.92	6.57 ± 0.85	0.0001
Normal (< 5.7%), n (%)	15 (50.0)	3 (10.0)	2 (6.7)	2 (6.7)	-
Pre-diabetes (5.7–6.4%), n (%)	11 (36.7)	19 (63.3)	16 (53.3)	16 (53.3)	-
Diabetes (≥ 6.5%), n (%)	4 (13.3)	8 (26.7)	12 (40.0)	12 (40.0)	-
Overall glycemic status					
Normal, n (%)	8 (26.7)	1 (3.3)	0 (0.0)	1 (3.3)	-
Pre-diabetes, n (%)	16 (53.3)	17 (56.7)	14 (46.7)	15 (50.0)	-
Diabetes, n (%)	6 (20.0)	12 (40.0)	16 (53.3)	14 (46.7)	-

**ADA=American Diabetes Association, IFG=impaired fasting glucose, FPG=fasting plasma glucose, n=number.*

Among the 24 patients without diabetes at baseline, 8 (33.3%) developed new-onset diabetes. All 8 patients with normal baseline glycemia deteriorated: 5 progressed to pre-diabetes and 3 to diabetes. Of

16 patients with baseline pre-diabetes, 5 (31.3%) progressed to diabetes, 10 remained pre-diabetic, and only 1 reverted to normoglycemia.

Among the 14 patients with diabetes al last follow-up, mean HbA1c was 7.2 ± 0.9%; 42.9% (6/14) had HbA1c ≥ 7.0%. Most were managed with oral agents, mainly metformin. Two patients (6.7%) required insulin due to severe hyperglycemia, leading to PAS-LAR discontinuation. Overall, mean HbA1c increased from 5.90 ± 0.84% to 6.57 ± 0.85% ($p < 0.001$). Median HbA1c at last follow-up was 6.20% (IQR 6.03–6.88%), remaining < 7% in most patients under appropriate antidiabetic therapy (with Metformin, DPP-4 inhibitors, GLP-1 receptor agonists).

Correlations between patient characteristics and glucose metabolism after PAS-LAR therapy

To explore the metabolic variability, baseline disease burden was assessed using IGF-1 at diagnosis. Diagnostic IGF-I xULN values significantly correlated with change in FPG (rho = 0.559, p = 0.002), and HbA1c (rho = 0.551, p = 0.002). Stratification by median IGF-1 (3.4 xULN) showed greater HbA1c increase in the high IGF-1 group (ΔHbA1c 1.10% [0.55–1.35] vs 0.40% [-0.05-0.80], p = 0.010), despite similar final HbA1c values. Pre-PAS-LAR IGF-I x ULN also significantly correlated with FPG (rho = 0.461, p = 0.009).

Patients were stratified by the median baseline IGF-1 (1.4 xULN) into high (≥ 1.4 xULN, n = 16) and low (< 1.4 xULN, n = 14) groups (Table 3). At the last follow up, the low IGF-1 group had superior biochemical outcomes: IGF-1 ≤ 1.0 xULN in 92.9% vs 31.3% (p = 0.002) and IGF-1 < 1.3 xULN in 100% vs 56.3% (p = 0.009). Median IGF-1 was 0.70 xULN (0.52–0.80) in the low group vs 1.20 xULN (1.00-1.50), respectively (p < 0.001). Baseline and final HbA1c were similar between these groups (5.85% vs 5.80%, p = 0.563; 6.20% vs 6.20%, p = 0.370), as was the median HbA1c change (0.55 vs 0.70%, p = 0.812).

Age at PAS-LAR initiation correlated positively with HbA1c change (rho = 0.371, p = 0.040), indicating greater increases in older patients. Lower baseline FPG was associated with larger FPG rise during treatment (rho=-0.355, p = 0.050).

No sex differences were observed. At last follow-up, median FPG was 113 mg/dL (109.0-133.0) in females vs 107.5 mg/dL (100.0-115.1) in males (p = 0.190), and median HbA1c 6.3% (6.1–6.9) vs 6.1% (5.9–6.8) (p = 0.361). Diabetes prevalence was similar (50.0% vs 40.0%, OR = 1.50, p = 0.704).

Patients who developed diabetes tended to be older (median 41.0 years vs 31.5 years), without statistical significance (p = 0.072). A trend toward higher baseline IGF-I xULN values was observed in patients who developed diabetes (median 1.6 vs 1.3 xULN, p = 0.071). Baseline HbA1c, FPG and pre-PAS-LAR BMI were similar between groups (p = 0.152, p = 0.374, and p = 0.192, respectively).

Previous medical therapies did not significantly impact glucose metabolism. At last follow-up, HbA1c was similar in PAS-LAR monotherapy vs PAS-LAR plus cabergoline (6.3% vs 6.1%, p = 0.068). HbA1c change was also comparable (median + 0.6 vs + 0.7, p = 0.812).

Lipid metabolism

PAS-LAR did not significantly affect lipid profile ($p > 0.05$), which remained stable during follow-up (Table 5, Fig. 3A-D). Hypercholesterolemia (≥ 200 mg/dL) remained 36.7% at baseline and last visit. Hypertriglyceridemia (≥ 150 mg/dL) decreased from 36.7% to 30.0%. Low HDL-C (< 40 mg/dL) declined from 13.3% to 3.3%, while high LDL-C (≥ 130 mg/dl) was similar (23.3% vs 20.0%, $p = 0.805$).

Table 5
Mean values of lipid profile parameters through PAS-LAR treatment

Parameter	Baseline	3 months	6 months	Last visit	p value
Total C (mg/dL)	192.0 ± 49.9	189.4 ± 40.6	183.0 ± 47.2	185.3 ± 44.9	0.395
HDL-C (mg/dL)	55.1 ± 17.9	58.0 ± 15.9	57.1 ± 16.4	56.5 ± 12.0	0.528
LDL-C (mg/dL)	110.1 ± 43.6	106.2 ± 37.5	103.2 ± 44.6	103.0 ± 42.7	0.321
TG (mg/dL)	134.6 ± 80.1	131.7 ± 91.3	108.4 ± 46.9	121.0 ± 55.1	0.206

**PAS-LAR=pasireotide long-acting release; C=cholesterol, TG=triglycerides*

Body mass index

At baseline, the mean BMI was 28.6 ± 5.0 kg/m^2, with most patients classified as overweight (56.7%). At the last follow up, a modest but statistically significant decrease in BMI was observed (27.8 ± 4.7, $p = 0.050$). The distribution of patients across BMI categories remained relatively stable (Table 6, Fig. 3E).

Table 6
Body mass index distribution at baseline and last follow-up visit

BMI category	Pre PAS-LAR, n (%)	Last visit, n (%)
Underweight	1 (3.3)	1 (3.3)
Normal weight	3 (10.0)	4 (13.3)
Overweight	17 (56.7)	16 (53.3)
Obesity class I	4 (13.3)	6 (20.0)
Obesity class II	4 (13.3)	3 (10.0)
Obesity class III	1 (3.3)	0 (0.0)
Mean ± SD (kg/m^2)	28.6 ± 5.0	27.8 ± 4.7

BMI=body mass index; PAS-LAR= pasireotide long-acting release; SD=standard deviation. P = 0.050

Tumour response

All 30 patients had evaluable pituitary MRI at baseline and at least one follow-up. Mean maximal tumour diameter decreased from 16.89 ± 9.96 mm to 15.16 ± 9.67 mm, not statistically significant (p = 0.127), with a mean reduction of 5%. Tumour shrinkage occurred in 10 patients (33.3%), including ≥ 20% reduction in 5 (16.7%). Tumour size was stable in 17 (56.7%) and increased in 3 (10.0%).

We assessed the association between tumour response and biochemical control. Of 5 patients with significant tumour shrinkage, only one achieved IGF-1 control. Among those with stable or increased tumour size, 48.0% achieved biochemical control (p = 0.368). Percentage tumour change did not correlate with final IGF-1 level (r = 0.148, p = 0.436). When stratifying patients according to tumour dynamics, all with tumour progression (n = 3) had persistently elevated IGF-1 and no biochemical control, suggesting treatment resistance. In contrast, about half of patients with stable tumour size (n = 17) achieved control. Although limited by small sample size, progressive and stable tumours appear to represent distinct clinical subgroups.

Adverse events and tolerability

PAS-LAR was generally well tolerated. The most frequently reported adverse events were glycemic disturbances. Mild gastrointestinal symptoms (grade 1–2), mainly transient diarrhoea and nausea, were common and self-limiting. No new cases of cholelithiasis requiring intervention or clinically significant QTc prolongation were detected. Two patients (6.5%) discontinued treatment due to severe, insulin-requiring hyperglycemia, after 12 and 18 months, respectively.

Discussion

Our real-world data confirm that PAS-LAR is highly effective for achieving biochemical control in pre-treated/resistant acromegaly. However, this efficacy comes at a significant metabolic burden, with frequent worsening of glucose metabolism and a considerable rate of new-onset diabetes. This dual effect highlights the main challenge of PAS-LAR therapy: balancing its potent antisecretory and antitumoral efficacy with the need for proactive and rigorous glycemic management.

Biochemical efficacy is robust, with 53.3% achieving control at 6 months, increasing to 60.0% at the last follow-up. These are consistent with the ~ 40% rate reported in the PAOLA trial among fgSRLs-resistant patients [15]. Using a less stringent threshold (IGF-1 < 1.3xULN), control was achieved in 76.7% of patients at last follow-up, slightly higher than reported by Urbani et al (67%) [16]. This greater effectiveness may reflect more flexible dose titration and follow-up in routine practice, as well as slightly different cut-off for normal IGF-1 used (< 1.3xULN versus <1xULN in the study of Urbani et al). The potential confounding effect of cabergoline is likely limited, as it had been initiated prior to PAS-LAR and was maintained at stable doses throughout follow-up. Due to the relatively small sample size, subgroup analysis comparing PAS-LAR monotherapy and combination therapy was not performed.

IGF-1 and GH reflect different aspects regarding biochemical response: IGF-1 relates to clinical severity and comorbidities, whereas GH relates to tumour output, size and recurrence [17]. In our study, both IGF-

1 xULN (from 1.64 to 0.99) and random GH (from 4.53 to 1.58 ng/mL) decreased in parallel, indicating broad therapeutic impact. The proportion achieving random GH < 1.0 ng/mL increased from 8.0% to 40.0%, suggesting effective suppression of tumour hormonal activity.

Tumour shrinkage occurred in 33.3% of patients, lower than the 44% and 63% reported by Urbani et al and Gadelha et al, respectively [16, 18]. These may reflect cohort characteristics, particularly the high proportion previously irradiated (43.3%), potentially limiting further tumour volume reduction. Tumour behaviour is influenced by both neoplastic cells and microenvironment [19]. Beyond GH suppression, PAS-LAR may exert anti-proliferative effects through modulation of tumour-stromal interactions via somatostatin receptor 1 (SST1) promoting a less fibrotic, immunosuppressive and pro-mitotic tumour microenvironment [20], These mechanisms may contribute to long-term tumour stability even without major shrinkage.

A key finding was the dissociation between anti-proliferative and anti-secretory effects of PAS-LAR, which do not always parallel each other [21]. Tumour shrinkage did not correlate with biochemical control, suggesting partially distinct SSTR-mediated pathways [22]. Tumour growth control and hormone suppression may vary according to individual SSTR expression profile and downstream signalling integrity.

Approximately 43.3% of patients had prior radiotherapy, with a mean interval of 8.5 years before PAS-LAR initiation. As radiotherapy effects on hormonal and tumour control are often delayed [23–25], these patients were likely within a phase of potential maximal benefit from irradiation. Prior radiotherapy did not significantly influence biochemical or tumour response, suggesting largely independent therapeutic effects.

PAS-LAR significantly impacted glucose metabolism, with two-fold increased diabetes prevalence and 33.3% of initially non-diabetic patients developing the condition during treatment. This aligns with pivotal trials and large scale-meta-analyses [10, 26, 27], including reports of a nearly four-fold increased diabetes risk [27]. Although glycemic deterioration was frequent, most cases were manageable with standard antidiabetic therapy, mainly metformin-based regimens. These data emphasize that hyperglycemia is a common but predictable adverse effect requiring proactive monitoring and timely therapeutic intervention throughout treatment. Two patients (6.7%) discontinued PAS-LAR due to insulin-requiring hyperglycemia, a lower rate than reported (10–14%) [16, 18].

An important finding was the identification of factors influencing glycemic deterioration. Higher IGF-1 at diagnosis significantly correlated with greater worsening of glucose parameters, suggesting that patients with more active disease may be particularly vulnerable to PAS-LAR-induced hyperglycemia. Chronic GH/IGF-1 excess promotes insulin resistance. PAS-LAR suppresses GH/IGF-1 while also inhibiting insulin secretion via SSTR5 in pancreatic β-cells. This dual effect may amplify glucose dysregulation in patients with higher baseline disease activity and pre-existing insulin resistance.

The association between higher IGF-I x ULN at diagnosis and greater glycemic deterioration adds to the growing evidence regarding factors that influence PAS-LAR-induced hyperglycemia. Chiloiro et al [28] identified baseline GH, rather than IGF-1, as predictive ($p = 0.04$), whereas IGF-1 was not associated ($p = 0.943$). In contrast, we found a strong correlation with baseline IGF-1, but not with GH. Both studies support the concept that higher baseline disease activity increases metabolic vulnerability. Combination of PAS-LAR with pegvisomant may attenuate, but does not completely prevent PAS-LAR induced hyperglycemia [28–31].

Baseline glycemic status (pre-PAS-LAR FPG and HbA1c) did not significantly predict diabetes at last follow-up. Although unexpected, this aligns with PAOLA and other clinical practice data showing that PAS-LAR-induced hyperglycemia may occur even with initially normal glucose metabolism [10, 16, 26, 27]. In our cohort, 33.3% of non-diabetic patients developed diabetes, and all patients with normal baseline deteriorated. These findings suggest that PAS-LAR-associated hyperglycemia may occur across different metabolic phenotypes and requires proactive monitoring irrespective of baseline metabolic status [16, 27, 32].

Unlike Corica et al [32], we found no significant association between sex and glycemic outcomes. While they reported female sex as a strong factor influencing diabetes during PAS-LAR therapy (OR = 66, $p = 0.007$), diabetes prevalence in our cohort was similar in females and males. Differences in sample size, population characteristics, or female predominance in our group (66.7 vs 62%) may partly explain this discrepancy.

Previous therapies did not significantly influence glucose metabolism during PAS-LAR, nor did concomitant cabergoline. In all patients receiving combination treatment, cabergoline had been initiated prior to PAS-LAR and maintained at stable doses during follow-up, indicating that the diabetogenic effect of PAS-LAR is independent of previous/concomitant treatments. These data are consistent with other studies reporting no worse metabolic outcomes in patients previously on combination regimens [32], and no treatment-related predictors of long-term PAS-LAR response [18]. Pooled analyses from Phase 3 studies identified baseline glycemic status and older age – not prior therapies – as main risk factors for PAS-LAR-associated hyperglycemia [12]. In addition, cabergoline may exert neutral or even favourable metabolic effects, particularly regarding weight/BMI, supporting its safe combination with PAS-LAR [33].

Despite the overall trend towards glycemic deterioration, a subset of patients maintained normal fasting plasma glucose at the last follow-up. Identifying markers of this apparent metabolic resilience – genetic factors, preserved β-cell function, or other characteristics – represents an important area for future research and may support individualized therapy [21, 34].

In contrast to its glycemic effects, PAS-LAR did not significantly alter lipid parameters. Total cholesterol, LDL-C, HDL-C, and triglycerides remained stable, consistent with a recent large meta-analysis of 896 patients [27]. Although that study reported a modest but statistically significant HDL-C increase, we observed only a non-significant upward trend, likely reflecting smaller sample size. Overall, PAS-LAR appears metabolically neutral regarding lipid profile and does not promote an atherogenic phenotype.

This may represent an important consideration in long-term cardiovascular risk management, particularly in patients with persistent metabolic comorbidities related to acromegaly.

Mean BMI decreased modestly, but significantly during follow-up (p = 0.050), despite PAS-LAR-related hyperglycemia. Few studies have evaluated weight changes, but our findings align with the modest BMI reduction observed by Gadelha et al. [18]. Absence of clinically relevant weight gain is an important finding, suggesting that PAS-LAR-associated metabolic disturbances do not necessarily translate into worsening anthropometric profile. Together with stable lipid profile, particularly triglycerides, this supports a heterogeneous rather than uniformly adverse metabolic effect of PAS-LAR.

Limitations

This study has limitations. Its retrospective design introduces potential information bias and incomplete data. Being single-centre, external validity may be limited. The relatively small sample size (n = 30), although acceptable for a rare disease, reduces statistical power, particularly for subgroup analyses. Additionally, insulin resistance indices were not systematically assessed.

Conclusion

In this cohort of pre-treated patients with acromegaly, PAS-LAR demonstrated sustained biochemical efficacy, achieving strict disease control in 60% of cases. This benefit was accompanied by a substantial but generally manageable metabolic burden, predominantly affecting glucose metabolism. Higher baseline IGF-1 levels were associated with greater HbA1c increase during follow-up, suggesting that patients with more active disease require closer metabolic surveillance and earlier antidiabetic intervention during PAS-LAR therapy.

Despite the emergence of newer therapeutic options, PAS-LAR remains an important second-line treatment for resistant acromegaly due to its proven efficacy and broad clinical availability.

Declarations

Conflict of Interest

The authors declare that they have no financial or non-financial conflicts of interest related to this study.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the “C. I. Parhon” National Institute of Endocrinology, Bucharest, Romania.

Consent to participate

All participants had previously provided written informed consent for the use of their anonymized clinical data for research purposes.

Consent to publish

Consent to publish has been received from all participants.

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Author Contribution

Author contributionsIFB, CCC and CP contributed to the study conception. Material preparation, data collection and analysis were performed by IFB and CC. The first draft of the manuscript was written by IFB. CC and CP commented on previous versions of the manuscript. All authors read, reviewed and approved the final manuscript.

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Figures

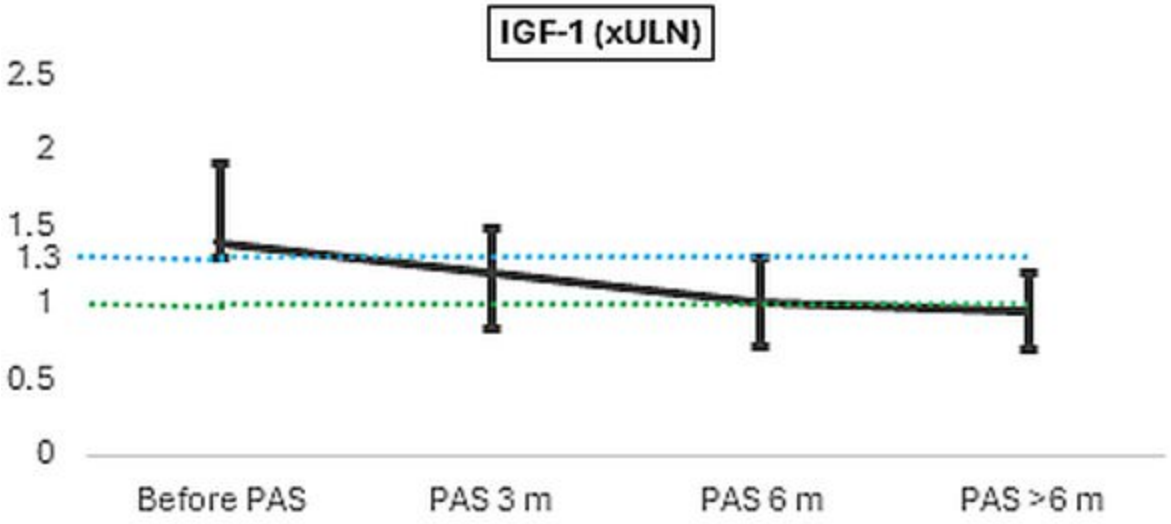


Figure 1

Biochemical response (IGF-1 xULN) after switching to PAS-LAR therapy. Median IGF-1 xULN values before and during PAS-LAR in the cohort. The green dotted line shows the IGF-1 cut-off of ≤1 xULN, while the blue dotted line shown the less stringent cut-off of ≤1.3 xULN for biochemical control *PAS-LAR=pasireotide long-acting, IGF-1-insulin-like growth factor 1 (sex- and age-adjusted values), ULN-upper limit of normal, m-months*

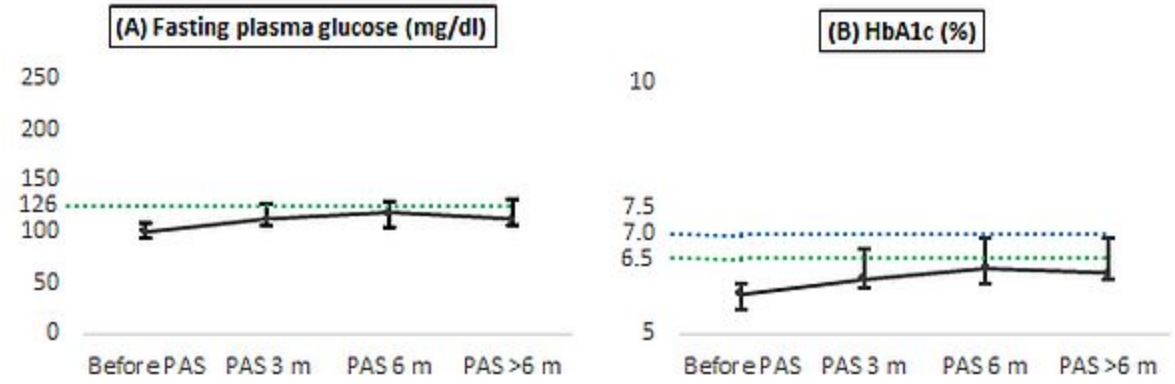


Figure 2

Changes in fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) values after switching patients to pasireotide LAR therapy Median FPG (A) and HbA1c (B) before and during PAS-LAR Therapy in the entire cohort**.** The green dotted line indicates: (A) the diagnostic FPG value for diabetes mellitus (≥ 126 mg/dL); (B) the diagnostic HbA1c value for diabetes mellitus (≥6.5%); the blue dotted line indicates the HbA1c value (≤7%) defined as acceptable for diabetic patients. *PAS-LAR-pasireotide long-acting, FPG-fasting plasma glucose; HbA1c-glycated hemoglobin, m-months*

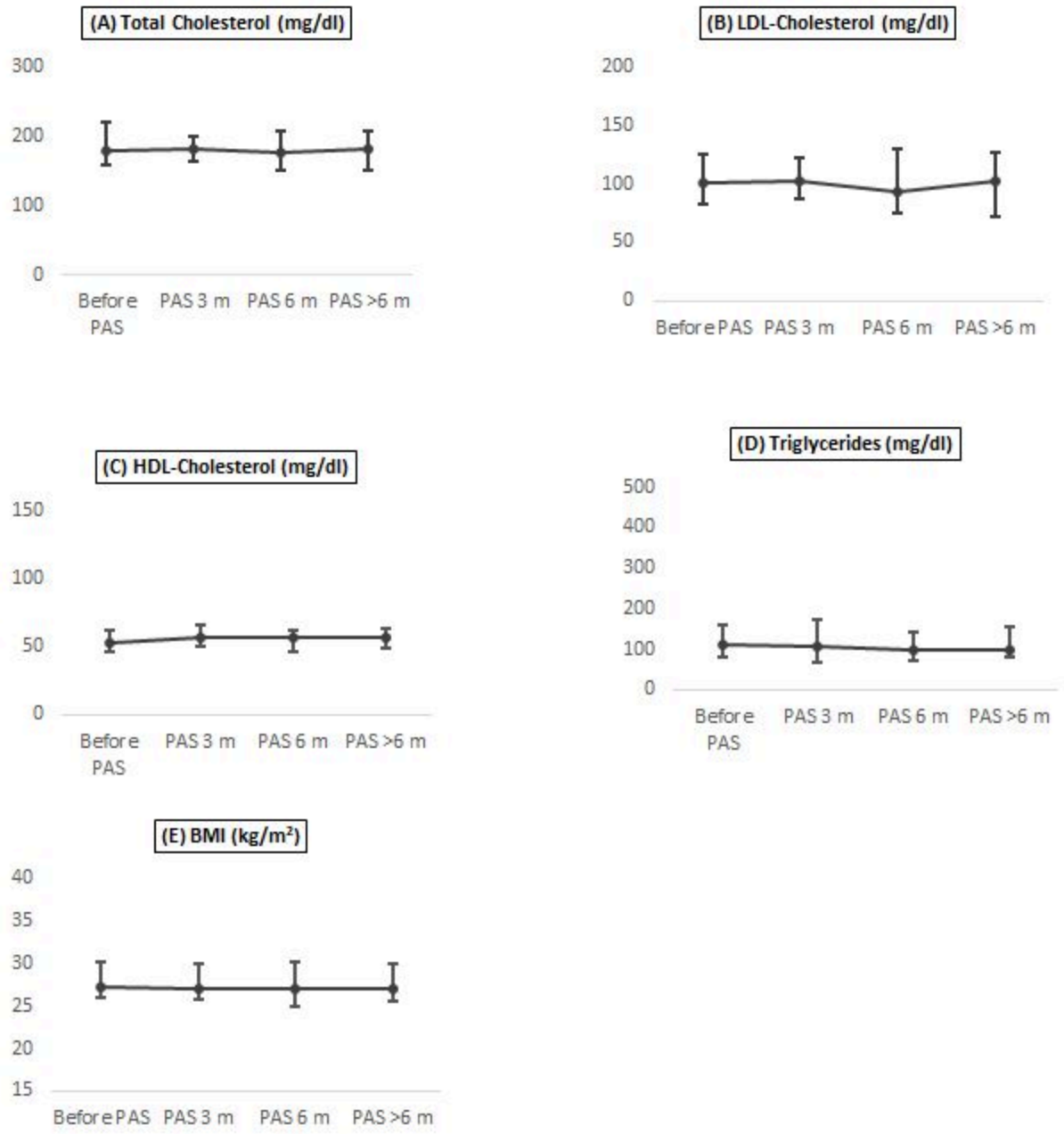


Figure 3

Changes in the lipid metabolism (total cholesterol, HDL-C, LDL-C, Triglycerides) and BMI after switching to PAS-LAR therapy Median values of total cholesterol (A), LDL-C (B), HDL-C (C), Triglycerides (D) and BMI before and during PAS-LAR therapy in the entire cohort. *HDL-high density lipoprotein; LDL-low density lipoprotein; BMI-body mass index; PAS-LAR=pasireotide long-acting, m-months*