CME

Acromegaly Highlights: ENDO 2023

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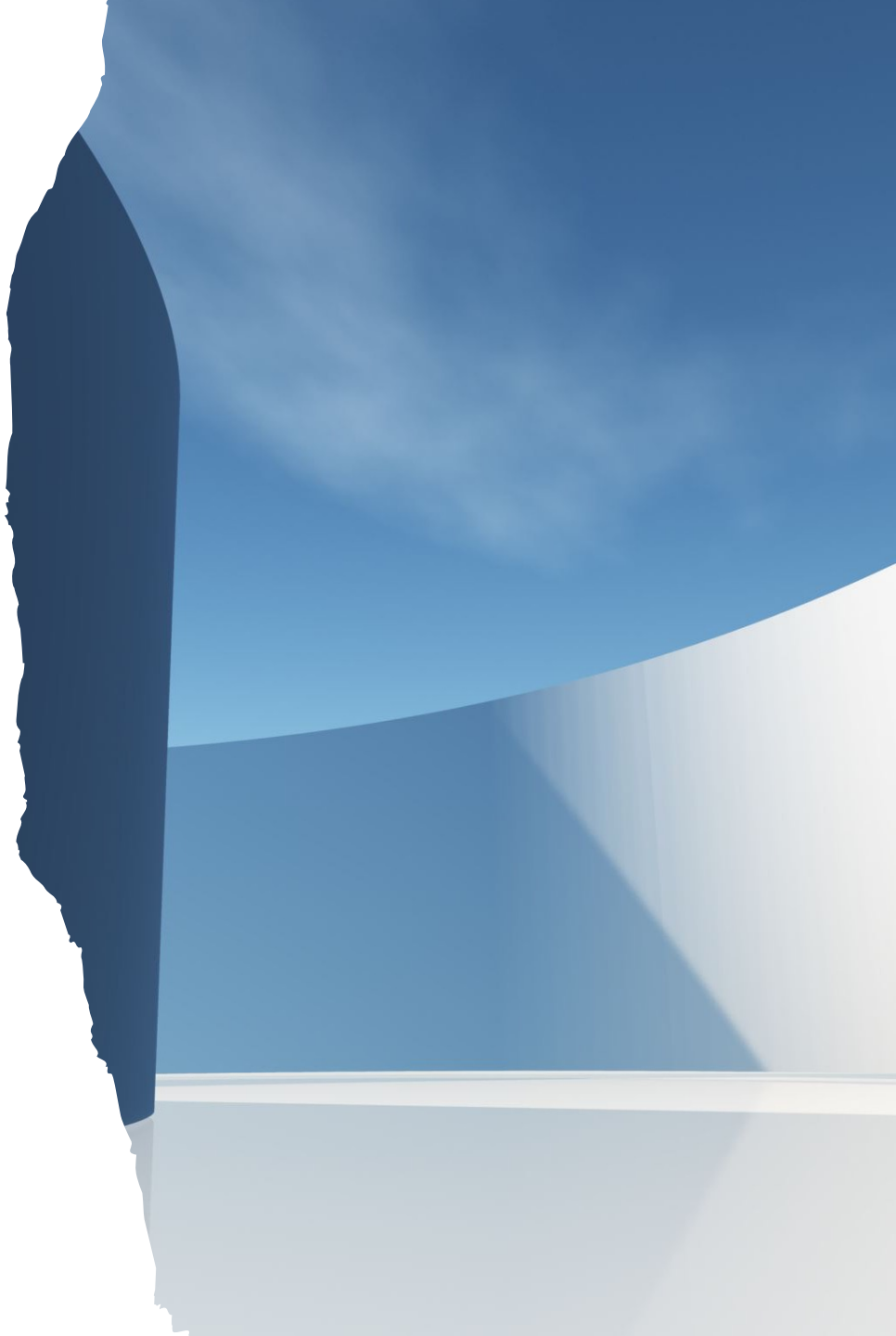


Disclosures

Contracted research

- Amryt Pharma
- CinCor Pharma
- Corcept Therapeutics
- Crinetics Pharmaceuticals
- Ionis Pharmaceuticals
- Ascendis Pharma
- Spruce Bioscience

Consulting

- Novo Nordisk
- Crinetics Pharmaceuticals
- Spruce Bioscience

Consulting and Speaking

- Amryt Pharma
- Recordati Rare Diseases

Other planners for this activity have nothing to disclose

What is Acromegaly?

Rare endocrine disorder caused by excess levels of growth hormone (GH).

In many cases, GH excess is caused by a benign tumor of the pituitary gland, which in turn causes overproduction of insulin-like growth factor 1 (IGF-1).

Common symptoms and Signs:

Symptoms and Signs

- Fatigue
- Excessive sweating
- Joint pain
- Soft tissue swelling, hands, feet, tongue
- Snoring
- Neuropathy: carpel tunnel syndrome
- Acrofog (forgetfulness)
- Headaches: tumor effect
- Visual disturbance: tumor effect
- Prominent forehead
- Protruding lower jaw
- Overbite
- Skin thickening

Current Therapies for Acromegaly

Targeting pituitary tumor and GH secretion

Dopamine agonist (off label)

Somatostatin analogue (SSA) or Somatostatin receptor ligand (SRL)

- 1st generation SSA
  - Octreotide injection
  - Lanreotide injection
  - Octreotide oral capsule
- 2nd generation SSA
  - Pasireotide injection

Targeting GH action

Pegvisomant

ENDO 2023

Endocrine Society Annual Meeting

Held June 15-18, 2023, in Chicago, Illinois

Abstracts published in online and in the Journal of the Endocrine Society

Clinical Trials

Paltusotine Therapy Long-Term Effects

- Paltusotine is an investigational oral, once-daily, non-peptide, SST2 agonist in development for the treatment of acromegaly and neuroendocrine tumors.
- Patients who completed ACROBAT Edge (IGF-1>1xULN) or Evolve (IGF-1<=1xULN) studies were eligible to enroll in Advance.
- Interim analysis results from pts with acromegaly treated with paltusotine for ≥2 years in ACROBAT Advance, an ongoing, 4-year, single-arm, open-label extension study.
- 43 pts enrolled in Advance (Edge, n=32; Evolve, n=11; 88% of eligible patients).
- Once-daily oral paltusotine treatment was well-tolerated, associated with stable IGF-I and symptom control relative to that achieved by iSRLs, and was preferred over injected therapy
- The most common TEAEs reported were headache (30.2%), arthralgia (25.6%), and fatigue (18.6%). No serious drug-related TEAEs were reported. Of 6 pts who discontinued the study, 1 (2.3%) was due to a TEAE (headache).
- Glycemic control was stable during paltusotine treatment.

	Baseline	Week 51/52	Week 77	Week 102
Median IGF-I	1.15 x ULN (n=43)	1.08 x ULN (n=37)	1.01 x ULN (n=27)	1.10 x ULN (n=10)
Median ASD Scores	8.57 (n=21)	--	8.0 (n=14)	--
Preferred by patients …	--		--	--
Paltusotine		32/36 (88.9%)		
Previous injections		2/36 (5.6%)		
No preference		2/36 (5.6%)		

ASD: Acromegaly Symptoms Diary

Gadelha MR et al. Oral, Once-Daily, Paltusotine (Non-Peptide Selective Somatostatin Receptor Subtype 2 Agonist) Therapy in Patients With Acromegaly Is Associated With Long-Term Biochemical and Symptom Control and Is Preferred Over Injectable Somatostatin-Receptor Ligands. Presented at ENDO 2023, Chicago, IL. June 15-18, 2023.

8-Year Interim analysis – Pasireotide

- 8-year interim analysis evaluated the long-term safety of pasireotide treatment in pts with acromegaly, CD or other endocrine disorders.
- This ongoing, open-label, multicenter study allows continued treatment for pts who completed a previous pasireotide parent trial.
- The primary objective was to evaluate long-term safety, determined by frequency of adverse events (AEs)/serious adverse events (SAEs).
- Overall, 341 pts from 29 countries have entered the study from 14 parent studies; 228 pts had acromegaly.
- Hyperglycemia is an expected AE during pasireotide treatment, often occurring in the first 3 months of therapy. Incidence of new hyperglycemia-related AEs during rollover was low. No new safety signals were identified.
- These data support pasireotide as a well-tolerated long-term treatment and affirm that pts continue to receive long-term benefit, with a low discontinuation rate over 8 years.

Median exposure to all pasireotide formulations baseline to data cut-off: 45.3 months.

Median dose from rollover baseline:
45.4 mg/month with pasireotide LAR
1200 µg/day with pasireotide SC.

89/341 (26.1%) pts discontinued treatment; most common reason, consent withdrawal (n=21, 6.2%).

Most common AEs:
nasopharyngitis (acromegaly n=13, 5.7%),
hyperglycemia (acromegaly n=29, 12.7%),
back pain (acromegaly n=20, 8.8%),
headache (acromegaly n=21, 9.2%).
Overall, 18 (5.3%) pts discontinued treatment because of AEs.

SAEs were reported in 87 (25.5%) pts; the most common were cholelithiasis and COVID-19 (both n=9, 2.6%).

Gadelha M et al. An 8-Year Interim Report of the B2412 Study, an Open-Label, Multicenter Pasireotide Rollover Study for Patients Who Continued to Receive Benefit From Pasireotide at Completion of an Earlier Trial. Presented at ENDO 2023, Chicago, IL. June 15, 2023.

Risk Factors For Hyperglycemia with Pasireotide

- Hyperglycemia is a common adverse event with pasireotide.
- Samson et al looked at post-hoc analysis from a Phase IV study (B2219, NCT02060383) assessing predictors for hyperglycemia in patients receiving pasireotide.
- 190 patients with acromegaly and 59 with Cushing's disease were given pasireotide. At start of the study, none of the patients needed treatment for hyperglycemia or were managed with metformin alone.
- During the study, 88 and 15, respectively, did not require antihyperglycemic medication.
- Hyperglycemia and diabetes mellitus occurred in 21.1% and 14.2% of patients with acromegaly and 28.8% and 11.9% of patients with Cushing's disease, respectively.
- **Common characteristics of patients who did not develop hyperglycemia are listed in the table below.**

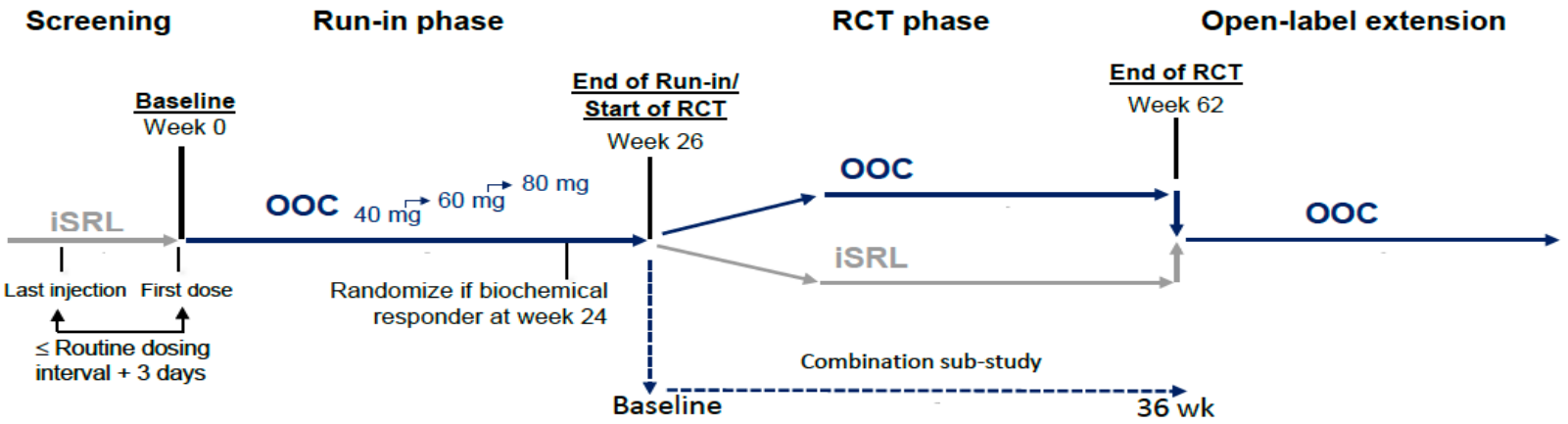
Baseline measures	Acromegaly (N=190)	Cushing's disease (N=59)
Age of <40 years	62.5%	86.7%
Glycated hemoglobin (HbA_{1c}) < 6.5%	98.9%	100%
Fasting plasma glucose (FPG) <100 mg/dL	76.1%	100%

- **Risk factors associated with pasireotide-induced hyperglycemia in acromegaly include:**
  - Age, baseline A1c, baseline prediabetes or diabetes

Samson SL et al. A Post Hoc Analysis of the Phase IV B2219 Study to Determine Predictive Factors for Hyperglycemia During Treatment With Pasireotide. Presented at ENDO 2023, Chicago, IL. June 15, 2023.

Predictors of Response to Oral Octreotide Capsules

- Global MPOWERED trial showed that oral octreotide capsules (OOC) were noninferior to injectable somatostatin receptor ligands (iSRLs) in maintenance of biochemical response in those previously responding to both OOC and iSRLs.
- Objective: identify patient/disease characteristics to predict likelihood of OOC responsiveness.
- Included patients aged 18-75 years, acromegaly diagnosis at screening, and ≥6 months iSRL treatment. All patients received OOC during the 26-week run-in phase.
- Responders at week 24 were randomized to receive OOC or iSRLs during the subsequent RCT phase (IGF-1<1.3x ULN and GH < 2.5 ng/ml)



Response at the end of run-in:

Fleseriu M et al. *Lancet Diabetes Endocrinol.* 2022 Feb;10(2):102-111

Predictors of Response to Oral Octreotide Capsules

- Relationship of baseline characteristics with OOC response during the run-in phase measured by comparing group randomized to the RCT phase (n=92) to the group not randomized (n=54, non-responders + responders not randomized).

- Baseline IGF-I level on iSRLs, but not other acromegaly baseline characteristics, was the sole predictor of subsequent OOC response.

	Randomized (n=92)	Non-randomized (mean; n=54)	Adjusted p-value of response
IGF-I level prior to OOC initiation (mean)	0.8 x ULN	1.0 x ULN	$p < .0001$
GH level (mean)	0.78 ng/mL	1.06 ng/mL	$P = .11$
Symptoms of GH excess			$P = 1.0$
Prior iSRL dose	Low dose: 19 Middle: 33 High: 40	Low: 11 Middle: 22 High: 21	$P = 1.0$

Response at the end of run-in:
- IGF-1<1.3x ULN
- GH 2.5 ng/ml

Fleseriu M et al. Predictors of Response to Oral Octreotide Capsules in Patients With Acromegaly in a Large Prospective International Trial. Presented at ENDO 2023, Chicago, IL. June 15, 2023.

Retrospective Studies

Treatment Patterns in Acromegaly Treatment

- De-identified data were extracted from MarketScan®, a US health insurance claims database.
- Eligible patients: those receiving monotherapy or combination therapy for ≥90 days without treatment gaps; ≥2 claims associated with acromegaly; data ≥3 months before and ≥6 months after diagnosis/first treatment claim; and ≥18 years old at diagnosis.
- Outcomes: demographic characteristics; treatment frequency by LOT and changes between LOTs; treatment persistence for first LOT monotherapies; and treatment up-/down titration.

	iSRLs (n=430)	DAs (n=304)	GHRAs (n=93)	Total (N=882)
LOTs 1 2 3	-	-	-	 524 (59.4%) 204 (23.1%) 154 (17.5%)
LOT 1	OCT: 133 (27.7%) LAN: 91 (21.1%)	304 (34.5%)	93 (10.5%)	-
Monotherapy Initiated	-	-	-	764 (94.6%)
Monotherapy Median persistence	20.0 months	14.4 months	24.8 months	-
≥ Dose increase	291 (67.6%)	-	-	-
≥ Dose reduction	193 (45.0%)	-	-	-

- Approximately 1/3 of patients initiated treatment with dopamine agonists, with the shortest treatment persistence. OCT and LAN monotherapies were also commonly used as first LOT and had longer persistence. Recommendations for individualized therapy should consider medication persistence and real-world treatment patterns.

LOT: line of treatment

Fleseriu M et al. Treatment Patterns in Acromegaly: Analysis of Real-World US Insurance Claims from the MarketScan® Database. Presented at ENDO 2023, Chicago, IL. June 15, 2023.

Does Time to Remission Predicts Survival in Acromegaly?

- The UK Acromegaly Register looked at data to assess time to first remission, defined as the difference between the date of diagnosis and date of the GH ≤2 μg/L (following surgery and/or medical therapy).

- 3750 patients in registry. 2472 (65%) achieved remission.

- The mean time to remission with somatostatin analogs (SSA) therapy was 4.5 yrs.
- The mean time to remission with dopamine agonist (DA) therapy was 7.3 years (*P*< .001 compared to SSA therapy).

- The mean survival in those who achieved remission was 25.5 years.
- The mean survival in those who did not achieve remission was 21.9 years (*P*< .001 compared to achieving remission).

- In patients who achieved remission within one year; 15% mortality rate (median follow up of 23.9 years).
- In patients who achieved remission after one year; 23% mortality rate.

- Conclusion: After adjustment for age at diagnosis, baseline GH, gender, shorter time to remission is associated with improved survival.

Deshmukh H et al. Time to first remission, medical therapy and survival in Acromegaly: UK Acromegaly register (UKAR) study Presented at ENDO 2023, Chicago, IL. June 15, 2023.

Pre-op treatment

Neoadjuvant Therapy Before Surgery

- Ten patients given neoadjuvant pretreatment with somatostatin analogs prior to pituitary surgery.
- Retrospective study compared radiographic and long-term biochemical outcomes and compared to historical control patients who underwent resection only.

	Neoadjuvant therapy prior to surgery	Historical controls (surgery only)
Volume of total tumor	30% reduction	
Volume of tumor in cavernous sinus	48% reduction	
Biochemical remission	60%	50%
Gross total resection - Knosp grade 3 - Knosp grade 4	70% 100% 29%	50% 100% 14%

- Conclusion: In this series of acromegalic patients with macroadenomas invading the cavernous sinus, neoadjuvant somatostatin analog therapy was associated with a trend toward increased rates of gross total resection and biochemical remission.

Rapoport B et al. Somatostatin Analog Neoadjuvant Treatment Before Endoscopic Surgery For Growth-Hormone Producing Pituitary Adenomas Invading The Cavernous Sinus: Case Series, Systematic Literature Review and Meta-Analysis. Presented at ENDO 2023, Chicago, IL. June 15, 2023.

Biomarker for GH action

Serum Soluble Alpha Klotho

- Serum concentrations of soluble alpha klotho (sαKL) is elevated in acromegaly patients and decrease with disease control (JCEM 2021; 106: e2887-9).
- Interpretation of data limited since there is no reference data (i.e., from healthy individuals).
- sαKL was measured in 890 healthy Caucasian subjects to obtain reference data points. Also measured IGF-I and IGFBP3 as comparators. Subjects with on-functioning pituitary adenoma (NFPA) and prolactinoma also included.

	sαKL (interquartile range, IQR)
Total (n=890)	672 (543-846) pg/mL
Males (n=436)	651 (537-815) pg/mL
Females (n=454)	687 (546-881) pg/mL (*P* = .01)
NFPA (n=18; 50% female)	Similar to controls
Prolactinoma (n=66; 60% female)	902 (754-1228) pg/mL (*P*<.001)

IQR: range for the middle 50% of the data

- Other observations
  - Age: IGF and IGFBP 3 varied per decade. sαKL differed only between younger adults (<40 yrs) vs older adults (> 70 yrs)
  - Oral estrogen use reduced sαKL
  - sαKL correlated to IGF-1 but not IGFBP-3
  - sαKL concentrations showed weaker negative correlation to age and BMI as compared to IGF-1.

Schweizer et al. Reference interval for serum soluble alpha klotho, a sensitive biomarker of growth hormone (GH) excess. Presented at ENDO 2023, Chicago, IL. June 15, 2023.

Disease Monitoring

Acro-TIME score

- Aim of this investigation: develop a score that includes clinical, pathological, and immune markers to identify first generation somatostatin ligands (fg-SRLs) resistant acromegaly patients that require second line of treatment.
- 43 acromegaly patients included based on following criteria:
  (1) first line of treatment with surgery
  (2) post-surgical fg-SRLs therapy
  (3) availability of tumor samples for experiments
- 18 clinical, pathological and immune features analyzed as possible predictors of fg-SRLs response.
- Score assigned to each covariate proportional to its beta coefficient. The score values ranged from 18.5 to 24 in cases responsive to fg-SRLS and from -5.5 to 21.5 in fg-SRLs resistant cases.
- A score <19 was chosen as cut-point to identify fg-SRLs resistance (*P*< .001). A score <19 was associated to fg-SRLs resistance in 84.6% of cases (*P*< .001).
- This new score integrates clinical, pathological, immunological data and may predict fg-SRLs resistance and the need of second line therapies.

Fg-SRLs resistance associated with…	Beta coefficients (lower means more resistance)
Age at acromegaly diagnosis <37 years (P=.04)	3.7
Cavernous sinus invasion (p<0.001)	-3
Ki-67>1.5% (P=.04)	-0.2
Score 0-1 of SSTR2A of 2-3	20
Ratio CD68+/CD8+ cells<5.7/HPF (P =.03)	-0.9
Persistence of post-surgery residual tumor (P=.004)	-0.9

SSTR2A volante score: a scoring system for SSTR2A expression

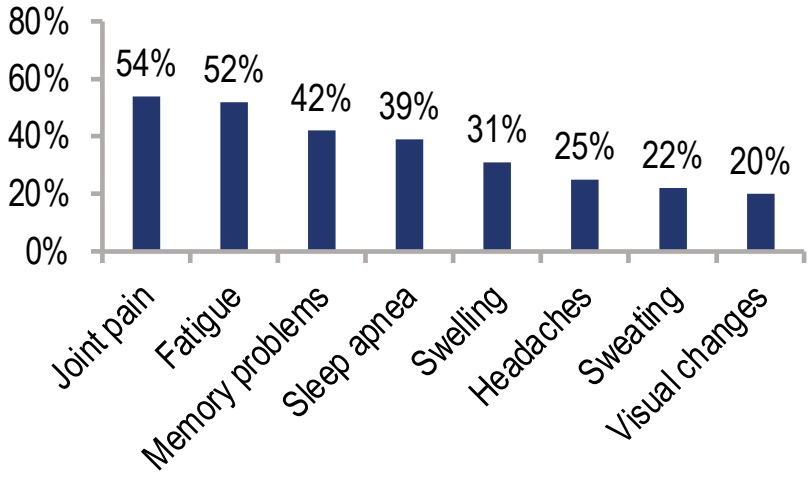
Chiloiro S et al. The acro-TIME score: a new clinical, pathological and immune integrative approach to early identify acromegaly patients resistant to treatment with first generation somatostatin ligands. Presented at ENDO 2023, Chicago, IL. June 15, 2023.

Patient Reported Outcomes

Macro Registry

- MACRO registry: prospective, observational cohort study of patients with active acromegaly on medical therapy or eligible for medical therapy.
- Patients and physicians completed questionnaires at enrollment and then every 3 months for up to 3 years.
- Parameter assessed: Demographic, disease activity, treatment information (rating of symptoms, biochemical control), patient-reported outcomes (PROS)
- Well-controlled symptoms as reported by patients were associated with significantly higher (better) AcroQOL scores across all scales and 5 of the 6 Acro-TSQ domains ($P < .001$ except injection site interference) and less impairment on 3 of 4 WPAI scales ($P < .001$ except absenteeism).

Symptoms in Biochemically Controlled Patients at Baseline



In the biochemically controlled patient group, 107/147 (73%) patients and 106/147 (72%) physicians reported symptoms as ‘well controlled’.

Acro-QOL: Acromegaly Quality of Life Questionnaire
Acro-TSQ: Acromegaly Treatment Satisfaction Questionnaire
WPAI: Work Productivity and Activity Impairment Questionnaire

Geer EB et al. Matched Physician- And Patient-reported Responses Of Acromegaly Symptom Control: Comparisons From The Macro Registry. Presented at ENDO 2023, Chicago, IL. June 17, 2023.

Macro Registry

Concordance between patient-reported and physician-reported ratings of symptom control at baseline					
Patient rating, n (%)	**Physician rating, n (%)**				**Significance**
	Unsure	Not controlled	Partially controlled	Well controlled	
Unsure	0	1 (0.5)	10 (5)	6 (3)	Kappa = 0.231 $P < .001$
Not controlled	2 (1)	2 (1)	6 (3)	1 (0.5)	
Partially controlled	3 (1.5)	5 (2.5)	20 (10.1)	21 (10.6)	
Well controlled	1 (0.5)	1 (0.5)	26 (13.1)	94 (47.2)	

Memory problems, fatigue, and joint pain were the most frequently reported symptoms at baseline by biochemically controlled patients that were not reported by their matched physician (33%, 25% and 18% of patients, respectively).

Geer EB et al. Matched Physician- And Patient-reported Responses Of Acromegaly Symptom Control: Comparisons From The Macro Registry. Presented at ENDO 2023, Chicago, IL. June 17, 2023.

Clinical Pearls

- Once-daily oral paltusotine treatment was well-tolerated, associated with stable IGF-I and symptom control relative to that achieved by injectable SRLs, and was preferred over injected therapy.
- Pasireotide is a well-tolerated long-term treatment, with a low discontinuation rate over 8 years. Risk factors for hyperglycemia include age, baseline A1c, baseline prediabetes or diabetes.
- Baseline IGF-I levels with injectable SRLs was the sole predictor of subsequent oral octreotide capsules (OOC) response.
- Patients who achieve remission quicker have a slighter better survival rate.
- Soluble alpha klotho may prove to be a valuable biomarker for activity of GH action and acromegaly.
- Acro-TIME score integrates clinical, pathological, immunological data and may predict first generation SRLs resistance and the need of second line therapies.
- Adequate symptom control and physician-patient agreement on the extent of symptom control continues to be underrecognized and constitutes an unmet need in acromegaly patients.