La terapia dell'ipersecrezione ormonale: l'acromegalia

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European Reference Network
for rare or low prevalence complex diseases

SPECIAL FEATURE
Clinical Practice Guideline

Acromegaly: An Endocrine Society Clinical Practice Guideline

Laurence Katznelson, Edward R. Laws, Jr, Shlomo Melmed, Mark E. Molitch, Mohammad Hassan Murad, Andrea Utz, and John A. H. Wass

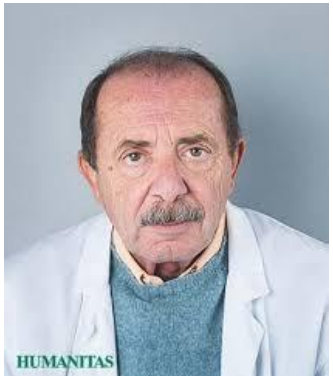
3.0 Goals of management

3.1 We suggest a biochemical target goal of an age-normalized serum IGF-1 value, which signifies control of acromegaly. (2|⊕⊕◯◯)

3.2 We suggest using a random GH < 1.0 μg/L as a therapeutic goal, as this correlates with control of acromegaly. (2|⊕◯◯◯)

3.3 We suggest maintaining the same GH and IGF-1 assay in the same patient throughout management. (2|⊕⊕◯◯)

mortalità e co-morbidità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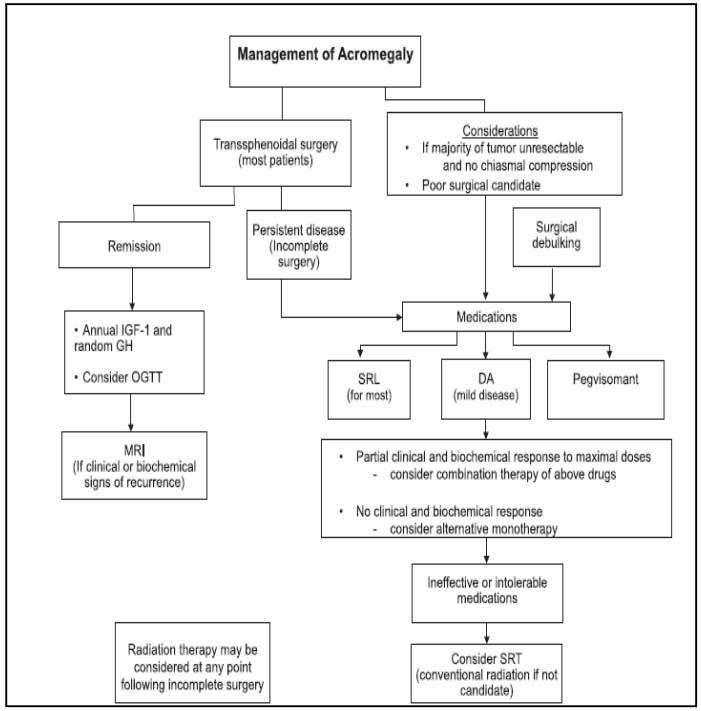


4.0 Surgery

Indications

4.1 We recommend transsphenoidal surgery as the primary therapy in most patients. (1|⊕⊕⊕◯)

4.2 We suggest that repeat surgery be considered in a patient with residual intrasellar disease following initial surgery. (2|⊕⊕◯◯)

- GH nadir <0.4 µg/l after OGTT using ultrasensitive assays
- Wait at least 12 weeks after surgery to assess IGF1 levels (delayed decline versus persistent postoperative GH)

2629 patients

Surgical Interventions and Medical Treatments in Treatment-Naïve Patients With Acromegaly: Systematic Review and Meta-Analysis

(*J Clin Endocrinol Metab* 99: 4003–4014, 2014)

Table 3. Meta-Analysis Results of GH-Defined Outcomes as Compared Between Surgical and Medical Interventions

Outcomes	Effect Size	95% CI	I^2, %	Heterogeneity *P* Value	*P* Value (Interaction)
Total remission[a]					
Medical Interventions	0.45	(0.32, 0.63)	86.3	.068	.02
Surgical Interventions	0.67	(0.59, 0.75)	82.0	.000	
Remission by cutoff criteria[a]					
Medical interventions	0.46	(0.33, 0.64)	87.8	.000	.05
Surgical interventions	0.65	(0.57, 0.75)	85.7	.000	
GH levels[b]					
Medical interventions	−24.02	(−31.00, −17.05)	92.1	.000	.78
Surgical interventions	−21.84	(−35.85, −7.83)	90.3	.000	
GH levels FUT ≤24 mo[b]					
Medical interventions	−24.27	(−31.16, −17.38)	90.2	.000	.97
Surgical interventions	−24.49	(−34.10, −14.88)	77.1	.004	
GH levels FUT ≥24 months[b]					
Medical interventions	−19.61	(−44.24, 5.02)	95.6	.000	.16
Surgical interventions	−38.58	(−59.69, −38.28)	70.4	.034	
Macroadenoma[c]	−24.92	(−34.09, −15.75)	54.7	.085	
GH levels macroadenoma[b]					
Medical interventions	−21.93	(−30.55, −13.31)	42.8	.174	.09
Surgical interventions	−37.54	(−53.83, −21.25)	0.0	.000	
GH levels tumor size[b]					
Microadenoma[c]	−5.85	(−10.75, −0.95)	48.5	.163	.003
Macroadenoma[c]	−24.92	(−34.09, −15.75)	54.7	.085	

Surgery is associated with
higher remission rate (at the longest follow up; 67 vs 45%)
higher remission rates in GH levels

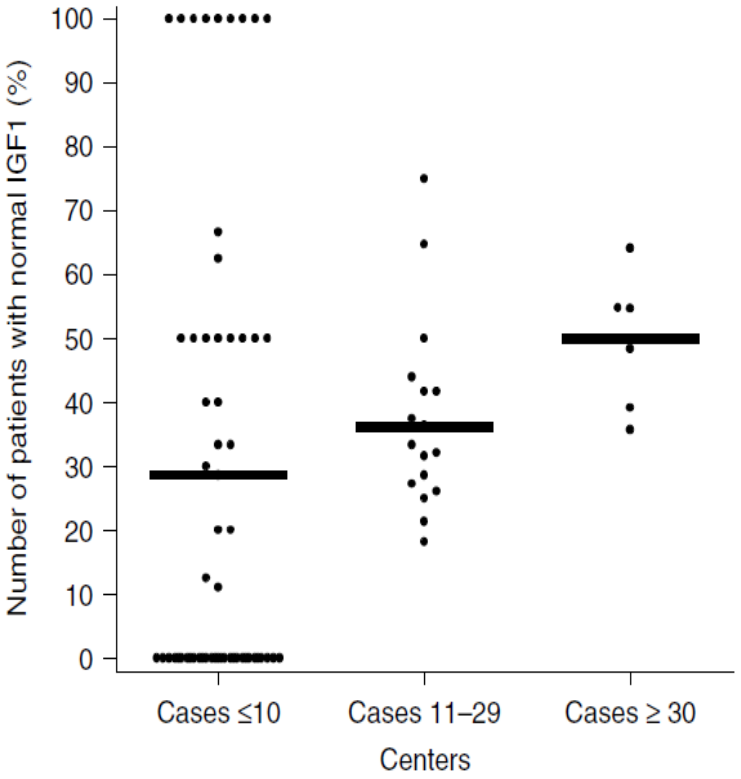
European Journal of Endocrinology (2013) **168** 39–47 ISSN 0804-4643

CLINICAL STUDY

Long-term outcome in patients with acromegaly: analysis of 1344 patients from the German Acromegaly Register

Number of surgical cases per center	Number of neurosurgical units	Total number of patients treated	Number of patients with normal IGF1 (%)
≤10	53	170	28.9
11–29	17	315	35.7
≥30	6	454	49.8

…più della metà dei pazienti è trattata da centri a basso volume…

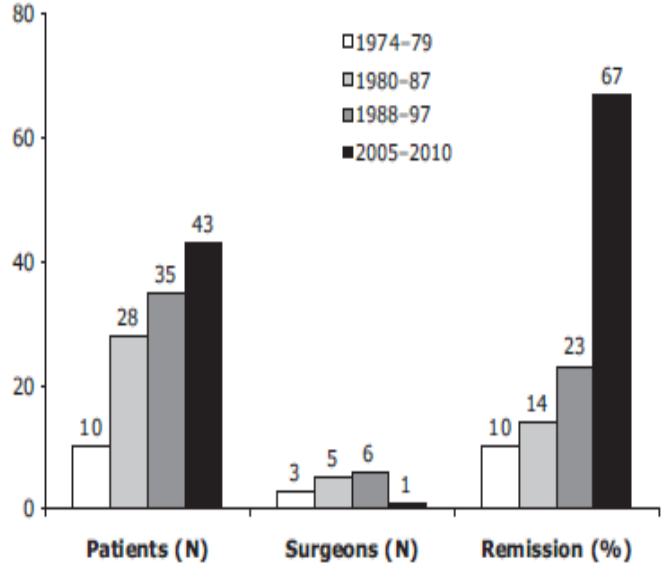


Clinical Endocrinology (2012) **76**, 399–406 doi: 10.1111/j.1365-2265.2011.04193.x

ORIGINAL ARTICLE

Acromegaly surgery in Manchester revisited – The impact of reducing surgeon numbers and the 2010 consensus guidelines for disease remission

Yi Yuen Wang*, Claire Higham†, Tara Kearney†, Julian R.E. Davis‡, Peter Trainer§ and Kanna K. Gnanalingham*



SPECIAL FEATURE

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Surgical debulking

4.5 In a patient with parasellar disease making total surgical resection unlikely, we suggest surgical debulking to improve subsequent response to medical therapy. (2|⊕⊕○○)

0021-972X/06/$15.00/0
Printed in U.S.A.

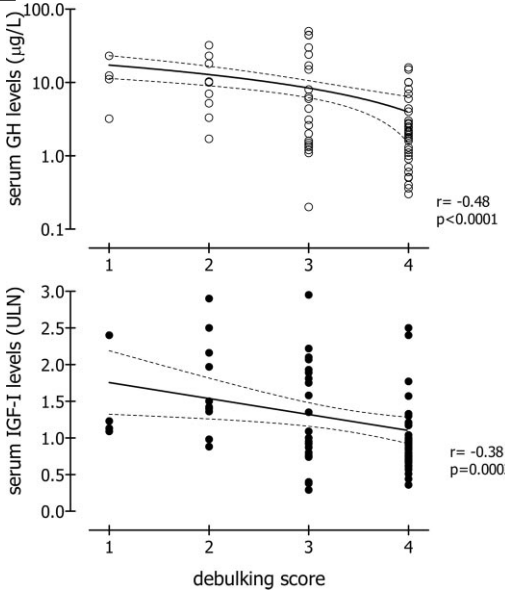
The Journal of Clinical Endocrinology & Metabolism 91(1):85–92

doi: 10.1210/jc.2005-1208

Partial Surgical Removal of Growth Hormone-Secreting Pituitary Tumors Enhances the Response to Somatostatin Analogs in Acromegaly

Annamaria Colao, Roberto Attanasio, Rosario Pivonello, Paolo Cappabianca, Luigi M. Cavallo, Giovanni Lasio, Alessandro Lodrini, Gaetano Lombardi, and Renato Cozzi

Pre-surgery: GH levels less than 2.5 in 14%;
IGF-I levels normalized in 10%
Postsurgical SSA treatment
lowered GH levels <2.5 in 56%
normalized IGF-I levels in 55%.

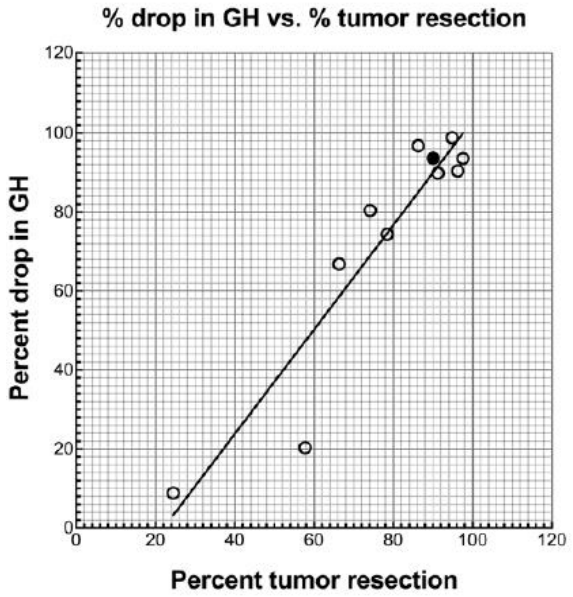


JNS

CLINICAL ARTICLE

Percent reduction of growth hormone levels correlates closely with percent resected tumor volume in acromegaly

Lucia Schwyzer, MD, Robert M. Starke, MD, John A. Jane Jr., MD, and Edward H. Oldfield, MD



Surg Endosc
DOI 10.1007/s00464-014-3815-0

REVIEW

Endoscopic endonasal transsphenoidal surgery of 1,166 pituitary adenomas

Fuyu Wang · Tao Zhou · Shaobo Wei · Xianghui Meng · Jiashu Zhang · Yuanzheng Hou · Guochen Sun

Table 5 Surgery complications in the 1,166 patients with pituitary adenomas

Type of complication	*n* (%) of patients
Transient diabetes insipidus	74 (6.35)
Permanent diabetes insipidus	8 (0.69)
Postoperative hemorrhage	8 (0.69)
CSF leak	7 (0.60)
Meningitis	12 (1.03)
Decreased visual acuity	5 (0.43)
Epistaxis	20 (1.72)
Anterior lobe insufficiency	15 (1.29)
SAH	1 (0.09)
Hyposmia	17 (1.46)
Coma	1 (0.09)
Total	168 (14.41)

J Neurosurg 108:525–532, 2008

Early results of surgery in patients with nonfunctioning pituitary adenoma and analysis of the risk of tumor recurrence

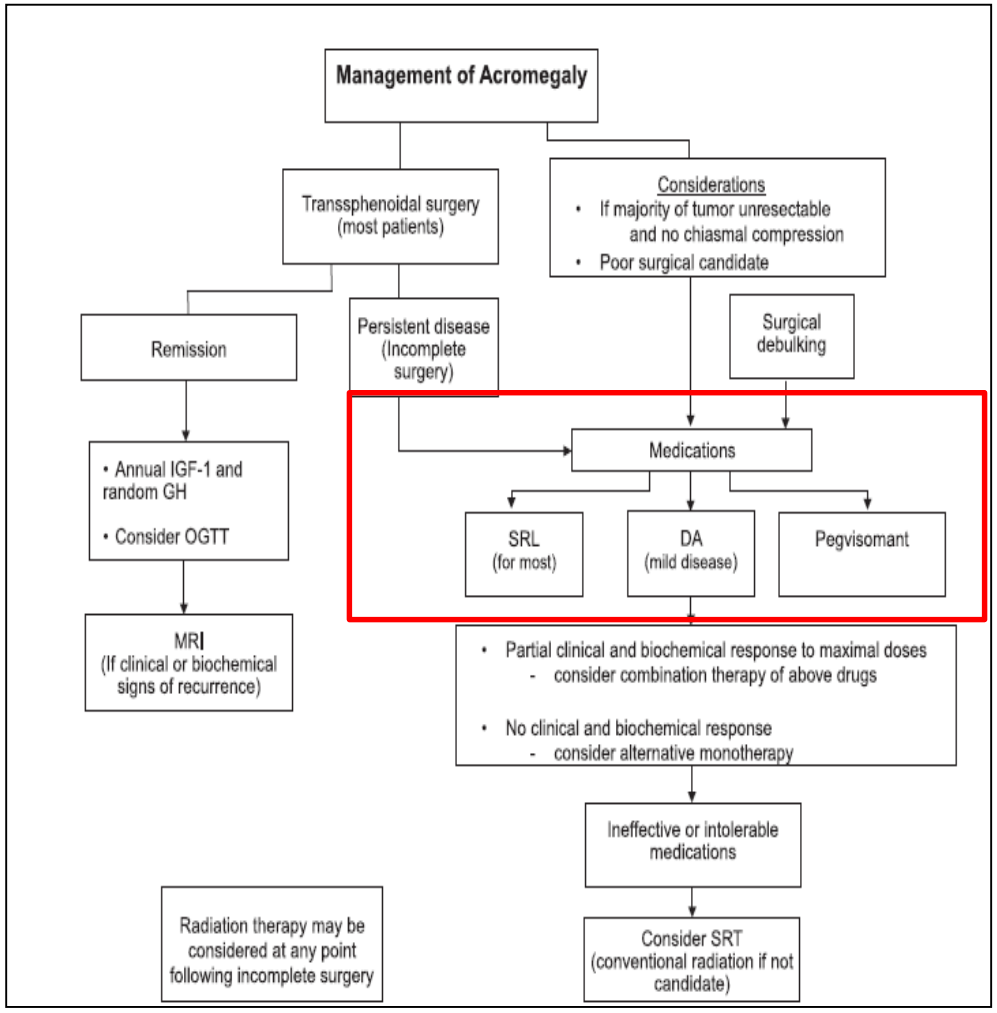
Marco Losa, M.D.,[1] Pietro Mortini, M.D.,[2] Raffaella Barzaghi, M.D.,[1] Paolo Ribotto, M.D.,[1] Maria Rosa Terreni, M.D.,[2] Stefania Bianchi Marzoli, M.D.,[3] Sandra Pieralli, M.D.,[4] and Massimo Giovanelli, M.D.[1]

[1]*The Pituitary Unit, Department of Neurosurgery,* [2]*Department of Anatomic Pathology,* [3]*Department of Ophthalmology,* [4]*Department of Neuroradiology, Istituto Scientifico San Raffaele, Università Vita-Salute, Milano; and* [5]*Department of Neurosurgery, University of Brescia, Italy*

	Post-intervento «new»	normalizzati
Ipogonadismo	**5,8%**	**32%**
Iposurrenalismo	**7,5%**	**41%**
Ipotiroidismo	**5,6%**	**35%**

Acromegaly: An Endocrine Society Clinical Practice Guideline

Laurence Katznelson, Edward R. Laws, Jr, Shlomo Melmed, Mark E. Molitch, Mohammad Hassan Murad, Andrea Utz, and John A. H. Wass



- First-generation SRL (octreotide LAR or lanreotide autogel)
- Cabergoline if IGF1 <2.5 times the upper limit of normal

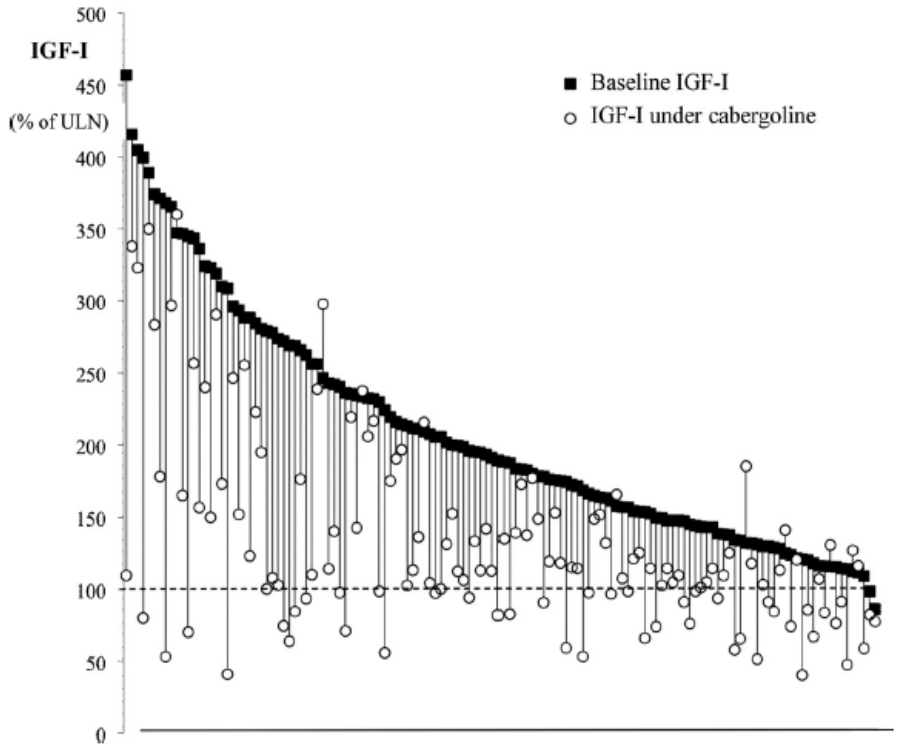
JCEM 2011

ORIGINAL ARTICLE

Endocrine Care

Place of Cabergoline in Acromegaly: A Meta-Analysis

Laure Sandret, Patrick Maison, and Philippe Chanson

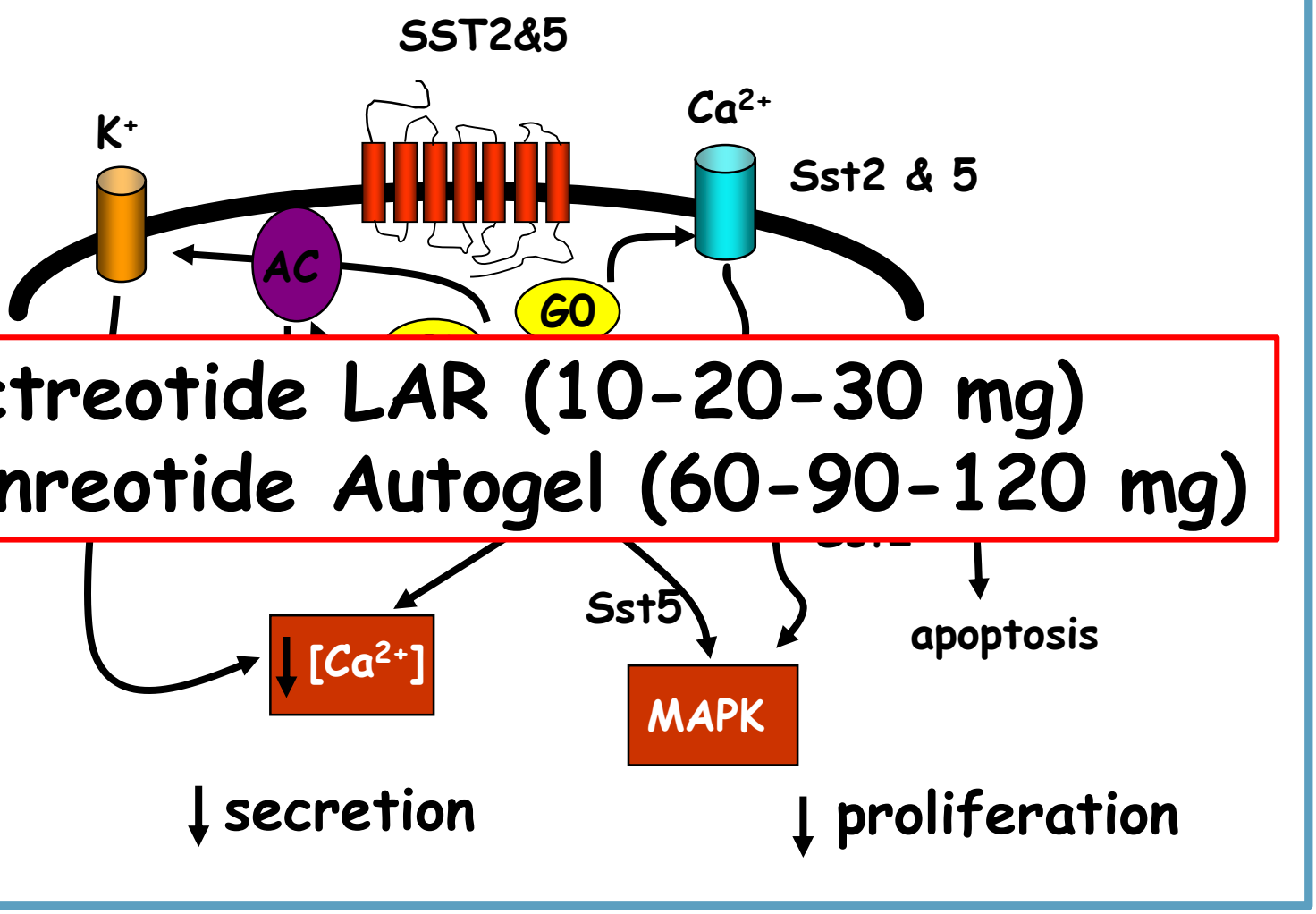


IGF-I normalization on cabergoline therapy was predicted in univariate analysis by the baseline IGF-I concentration

IGF-1 (% of ULN)	IGF-1 normalization (% of patients)
150	53
150-199	29
200-249	25
>250	26

SRIF receptor subtype expression

	Positive tumors/total tumors tested (%)				
	SSTR1	*SSTR2*	*SSTR3*	*SSTR4*	*SSTR5*
GH	27/44	95/108	24/55	2/48	92/104
ACTH					
PRL					
NFA					
TSH					



TEM

Long-Acting Somatostatin Analog Therapy of Acromegaly: A Meta-Analysis

Pamela U. Freda, Laurence Katznelson, Aart Jan van der Lely, Carlos M. Reyes, Shouhao Zhao, and Daniel Rabinowitz

Department of Medicine (P.U.F., C.M.R.), Columbia University, College of Physicians and Surgeons, New York, New York 10032; Departments of Neurosurgery and Medicine (L.K.), Stanford University Medical Center, Stanford, California 94305; Department of Internal Medicine (A.J.v.d.L.), Erasmus Medical Center, The Netherlands; and Department of Statistics (S.Z., D.R.), Columbia University, New York, New York 10027

	% of subjects meeting efficacy criteria		Mean GH levels		Mean IGF-I levels	
	GH	IGF-I normalization	Pretherapy	On therapy	Pretherapy	On therapy
Octreotide LAR						
Unselected (n = 126)	54 ± 0.002[a]	63 ± 0.002[b]	15.8 ± 2.9	4.1 ± 0.8	601 ± 35	330 ± 75
Preselected (n = 486)	~~58 ± 0.003~~	~~68 ± 0.003~~	10.2 ± 2.3	2.3 ± 1.1	735 ± 48	313 ± 35
All subjects (n = 612)	57 ± 0.05[c]	67 ± 0.05[d]	12.6 ± 3.9	3.2 ± 1.53	644 ± 66	327 ± 30.5

IGF-I normalization occurred in a greater proportion of secondary octreotide LAR- *vs.* primary octreotide-treated subjects

Pasireotide LAR maintains inhibition of GH and IGF-1 in patients with acromegaly for up to 25 months: results from the blinded extension phase of a randomized, double-blind, multicenter, Phase III study

Michael Sheppard · Marcello D. Bronstein · Pamela Freda · Omar Serri · Laura De Marinis · Luciana Naves · Liudmila Rozhinskaya · Karina Hermosillo Reséndiz · Matthieu Ruffin · YinMiao Chen · Annamaria Colao

Biochemical control (GH<2.5+normal IGF-1) in:

48.6 % of patients in pasireotide LAR
45.7 % of patients in octreotide LAR

Table 2 Biochemical response rates

	Pasireotide LAR (n = 74)		Octreotide LAR (n = 46)	
	n/N (%)	95 % CI	n/N (%)	95 % CI
GH <2.5 µg/L *and* IGF-1 normalization				
Month 12	46/74 (62.2)	50.1, 73.2	24/46 (52.2)	36.9, 67.1
Month 19	34/74 (45.9)	34.3, 57.9	21/46 (45.7)	30.9, 61.0
Month 25	36/74 (48.6)	36.9, 60.6	21/46 (45.7)	30.9, 61.0
GH <2.5 µg/L *and* IGF-1 ≤1× ULN				
Month 12	53/74 (71.6)	59.9, 81.5	26/46 (56.5)	41.1, 71.1
Month 19	44/74 (59.5)	47.4, 70.7	23/46 (50.0)	34.9, 65.1
Month 25	45/74 (60.8)	48.8, 72.0	24/46 (52.2)	36.9, 67.1
GH <2.5 µg/L				
Month 12	58/74 (78.4)	67.3, 87.1	37/46 (80.4)	66.1, 90.6
Month 19	54/74 (73.0)	61.4, 82.6	33/46 (71.7)	56.5, 84.0
Month 25	52/74 (70.3)	58.5, 80.3	37/46 (80.4)	66.1, 90.6
IGF-1 normalization				
Month 12	55/74 (74.3)	62.8, 83.8	26/46 (56.5)	41.1, 71.1
Month 19	37/74 (50.0)	38.1, 61.9	24/46 (52.2)	36.9, 67.1
Month 25	38/74 (51.4)	39.4, 63.1	22/46 (47.8)	32.9, 63.1

Patients who discontinued treatment during the extension phase were considered to be non-responders at subsequent time points

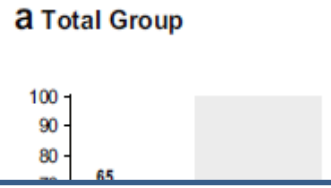
A multicenter, observational study of lanreotide depot/autogel (LAN) in patients with acromegaly in the United States: 2-year experience from the SODA registry Pituitary (2017) 20:605–618

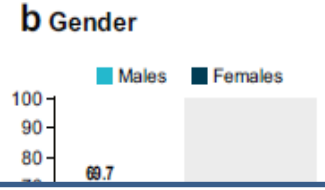
Roberto Salvatori[1] · Murray B. Gordon[2] · Whitney W. Woodmansee[3] · Adriana G. Ioachimescu[4] · Don W. Carver[5] · Beloo Mirakhur[6] · David Cox[6] · Mark E. Molitch[7]

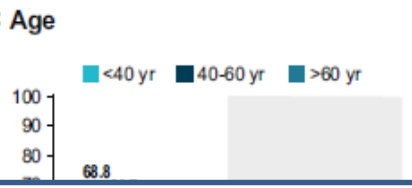
IGF-1 normalization + GH ≤2.5 µg/L in 65.0% (M12) and 54.8% (M24)

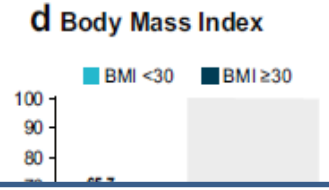
IGF-1 normalization + GH < 1.0 µg/L in 51.7% (M12) and 42.9% (M24)

A higher proportion of microadenoma patients had GH levels ≤2.5 and <1.0 µg/L at all time points compared with macroadenoma patients

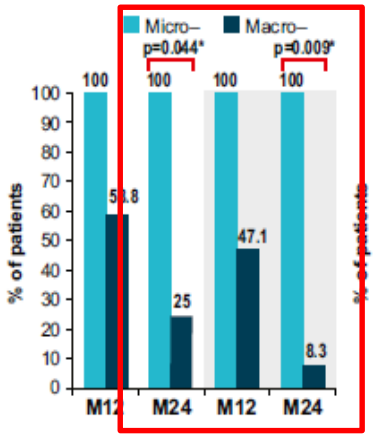


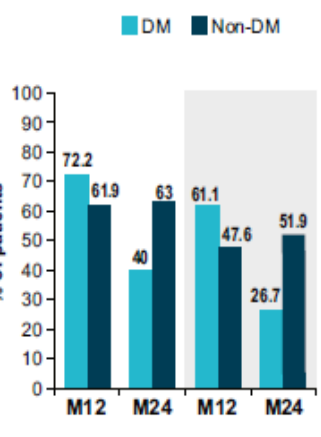


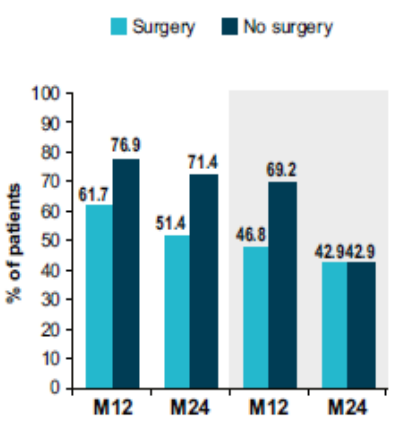


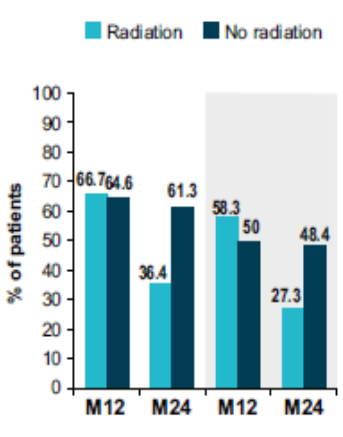


	% of subjects meeting efficacy criteria		Mean GH levels		Mean IGF-I levels	
	GH	IGF-I normalization	Pretherapy	On therapy	Pretherapy	On therapy
Lanreotide SR						
Unselected (n = 609)	48 ± 0.002	42 ± 0.002	15.1 ± 6.0	5.3 ± 2.4	689 ± 95	432 ± 97
Preselected (n = 305)	50 ± 0.005	56 ± 0.003	19.7 ± 4.0	3.5 ± 0.5	735 ± 48	321 ± 24
All subjects (n = 914)	48 ± 0.04	47 ± 0.03	16.9 ± 3.2	5.9 ± 1.3	741 ± 51	442 ± 30









Meta-Analysis on the Effects of Octreotide on Tumor Mass in Acromegaly

PLoS ONE

May 2012 | Volume 7 | Issue 5 | e36411

Andrea Giustina[1]*, Gherardo Mazziotti[1,2], Valter Torri[3], Maurizio Spinello[4], Irene Floriani[3], Shlomo Melmed[5]

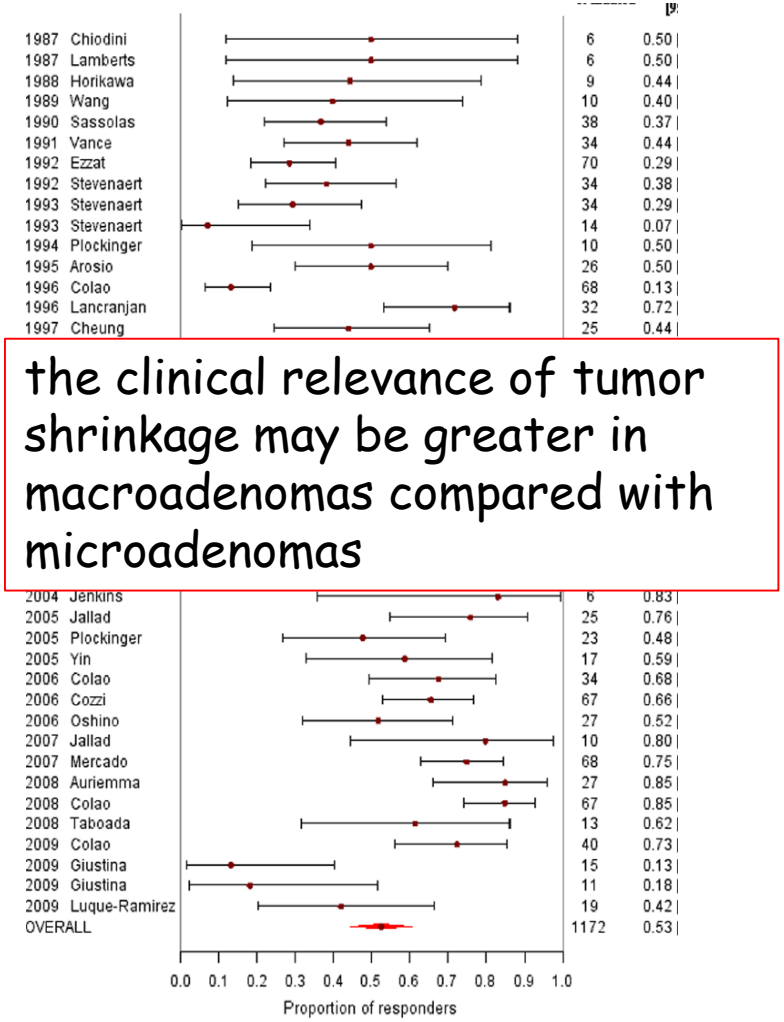
Pts with tumor shrinkage (%)

Octreotide sc	53
Octreotide LAR	66

Tumor shrinkage (%)

Octreotide sc	53
Octreotide LAR	66

the shrinkage effect of octreotide correlates with duration of therapy



the clinical relevance of tumor shrinkage may be greater in macroadenomas compared with microadenomas

Tumor Shrinkage With Lanreotide Autogel 120 mg as Primary Therapy in Acromegaly: Results of a Prospective Multicenter Clinical Trial

Philippe J. Caron, John S. Bevan, Stephan Petersenn, Daniel Flanagan, Antoine Tabarin, Gaëtan Prévost, Pascal Maisonobe, and Antoine Clermont, on behalf of the PRIMARYS Investigators

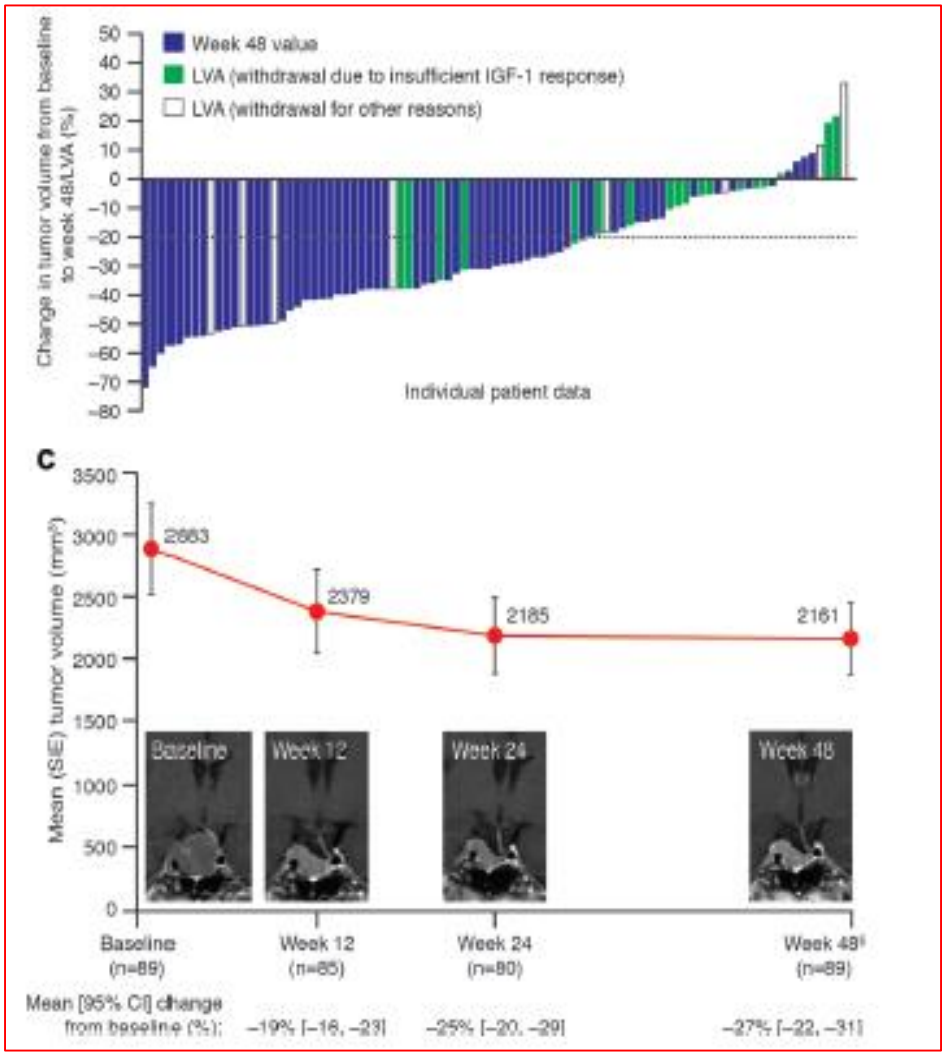
J Clin Endocrinol Metab, April 2014, 99(4):1282–1290

significant reduction if > 20%

Primary treatment with lanreotide Autogel 120 mg every 28 days provides tumor volume reduction in 62.9% of patients at 1 year.

These reductions were evident in 54.1% of patients by the first postbaseline visit at 3 months

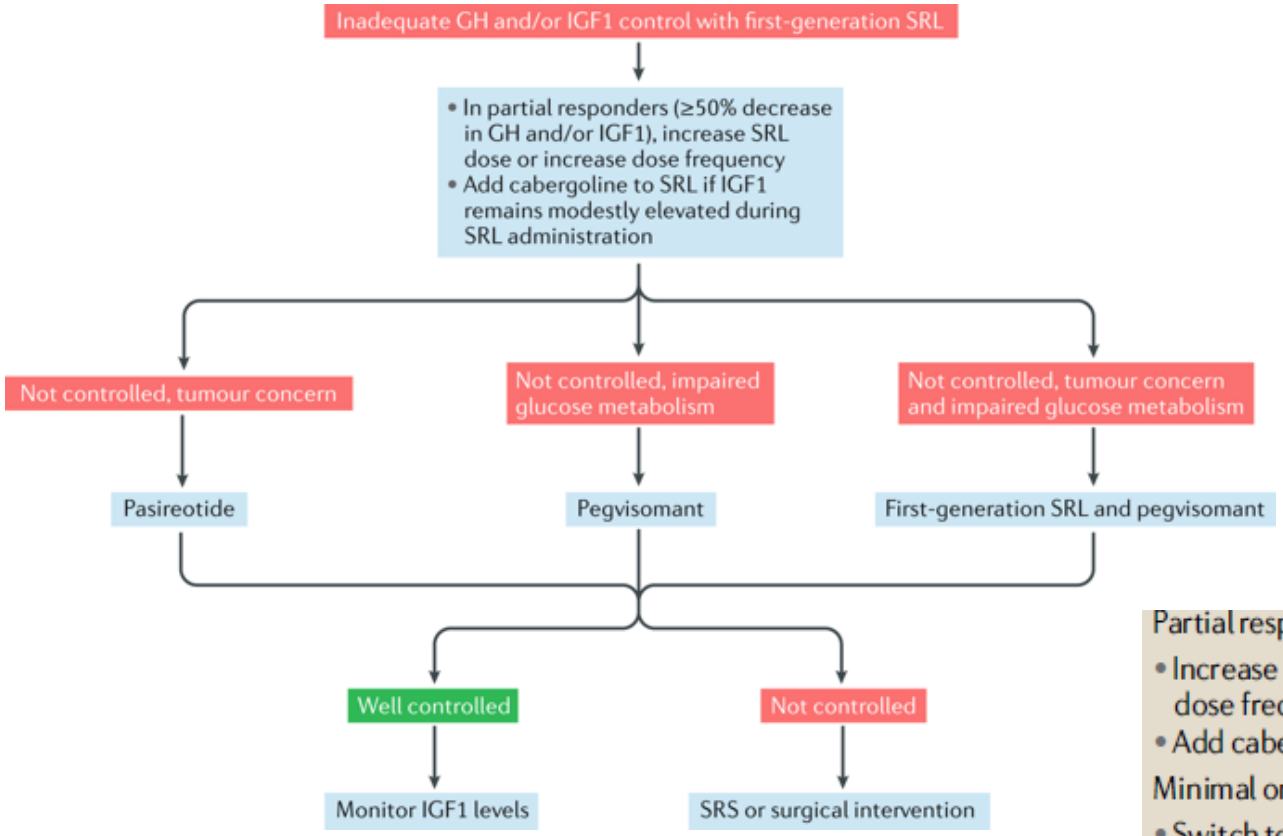
Response at 3 months can predict long-term response



A Consensus Statement on acromegaly therapeutic outcomes

HUMANITAS UNIVERSITY

Shlomo Melmed et al. *Nature Reviews Endocrinology* **14**, 552–561 (2018)



Partial response:

- Increase first-generation SRL dose and/or increase dose frequency of lanreotide autogel
- Add cabergoline to SRL if IGF1 is moderately elevated

Minimal or no response and tumour concern:

- Switch to pasireotide LAR

Minimal or no response and impaired glucose metabolism:

- Switch to pegvisomant

Minimal or no response, tumour concern and impaired glucose metabolism:

- Add pegvisomant to first-generation SRL

European Journal of Endocrinology (2009) **161** 331–338 ISSN 0804-4643

CLINICAL STUDY

High-dose intramuscular octreotide in patients with acromegaly inadequately controlled on conventional somatostatin analogue therapy: a randomised controlled trial

Andrea Giustina[1], Stefania Bonadonna[1], Giovanna Bugari[2], Annamaria Colao[3], Renato Cozzi[4], Salvatore Cannavo[5], Laura de Marinis[6], Ettore degli Uberti[7], Fausto Bogazzi[8], Gherardo Mazziotti[1], Francesco Minuto[9], Marcella Montini[10] and Ezio Ghigo[11]

Conclusion: High-dose octreotide treatment is safe and effective (normalisation of IGF1 levels) in a subset of patients with active acromegaly inadequately controlled with long-term SSA. Individualised octreotide doses up to 60 mg/28 days may improve outcomes of SSA therapy.

High-Dose and High-Frequency Lanreotide Autogel in Acromegaly: A Randomized, Multicenter Study

Andrea Giustina,[1] Gherardo Mazziotti,[2] Salvatore Cannavò,[3] Roberto Castello,[4] Giorgio Arnaldi,[5] Giovanna Bugari,[6] Renato Cozzi,[7] Diego Ferone,[8] Anna Maria Formenti,[1] Enza Gatti,[9] Silvia Grottoli,[10] Pietro Maffei,[11] Filippo Maffezzoni,[1] Marcella Montini,[12] Massimo Terzolo,[13] and Ezio Ghigo[10]

Conclusion: HF and HD LAN-ATG regimens are effective in normalizing IGF-I values in about one-third of patients with active acromegaly inadequately controlled by long-term conventional SRLs therapy. (***J Clin Endocrinol Metab*** **102: 2454–2464, 2017)**

Cabergolina (terapia combinata)

77 pazienti

Normalizzazione IGF-I: 52% dei pz

Risposta correlata a:

•livelli basali di IGF-I (0.74; *P*0.001)

Nessuna correlazione con il dosaggio di cabergolina , la durata del trattamento e i livelli basali di PRL

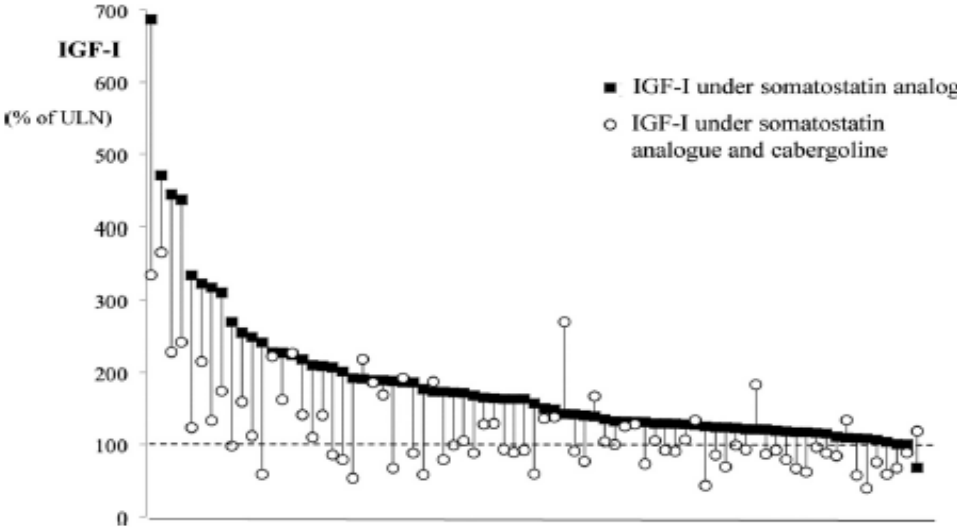


FIG. 2. Individual IGF-I levels, expressed as a percentage of the age-adjusted ULN ran during treatment with somatostatin analogs alone (*black squares*) and after cabergolin adjunction (*open circles*) in patients with acromegaly.

Sandret & Chanson, JCEM 2011

Pasireotide

Partial response:

- Increase first-generation SRL dose and/or increase dose frequency of lanreotide autogel
- Add cabergoline to SRL if IGF1 is moderately elevated

Minimal or no response and tumour concern:

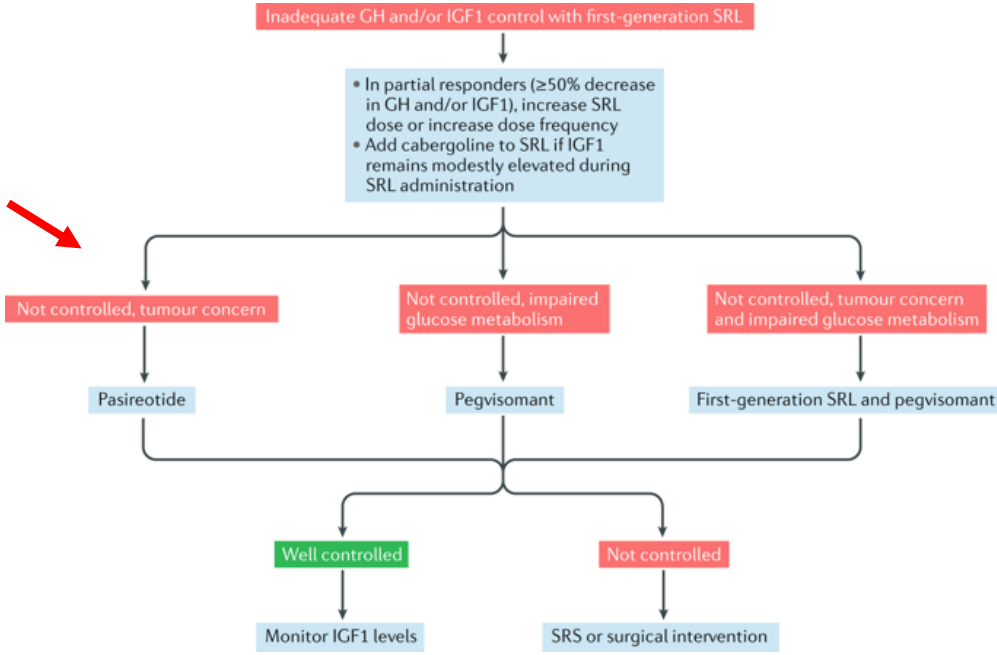
- Switch to pasireotide LAR

Minimal or no response and impaired glucose metabolism:

- Switch to pegvisomant

Minimal or no response, tumour concern and impaired glucose metabolism:

- Add pegvisomant to first-generation SRL



SRL	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Octreotide	280	0.38	7.1	>1,000	6.3
Lanreotide	180	0.54	14	230	17
Pasireotide	9.3	1.0	1.5	100	0.16

Data are mean IC_{50} values expressed as nmol/l. Adapted from Bruns et al. [18].

ORIGINAL ARTICLE

Endocrine Care

Pasireotide (SOM230) Demonstrates Efficacy and Safety in Patients with Acromegaly: A Randomized, Multicenter, Phase II Trial

S. Petersenn, J. Schopohl, A. Barkan, P. Mohideen, A. Colao, R. Abs, A. Buchelt, Y.-Y. Ho, K. Hu, A. J. Farrall, S. Melmed, B. M. K. Biller, and the Pasireotide Acromegaly Study Group

biochemical control in 27% of patients

ORIGINAL ARTICLE

Endocrine Care

Pasireotide Versus Octreotide in Acromegaly: A Head-to-Head Superiority Study

A. Colao, M. D. Bronstein, P. Freda, F. Gu, C.-C. Shen, M. Gadelha, M. Fleseriu, A. J. van der Lely, A. J. Farrall, K. Hermosillo Reséndiz, M. Ruffin, Y. Chen, and M. Sheppard*, on behalf of the Pasireotide C2305 Study Group

biochemical control in 31.3% of patients

Hyperglycemia related AEs in up to 60%

Pituitary (2015) 18:385–394
DOI 10.1007/s11102-014-0585-6

CrossMark

Pasireotide LAR maintains inhibition of GH and IGF-1 in patients with acromegaly for up to 25 months: results from the blinded extension phase of a randomized, double-blind, multicenter, Phase III study

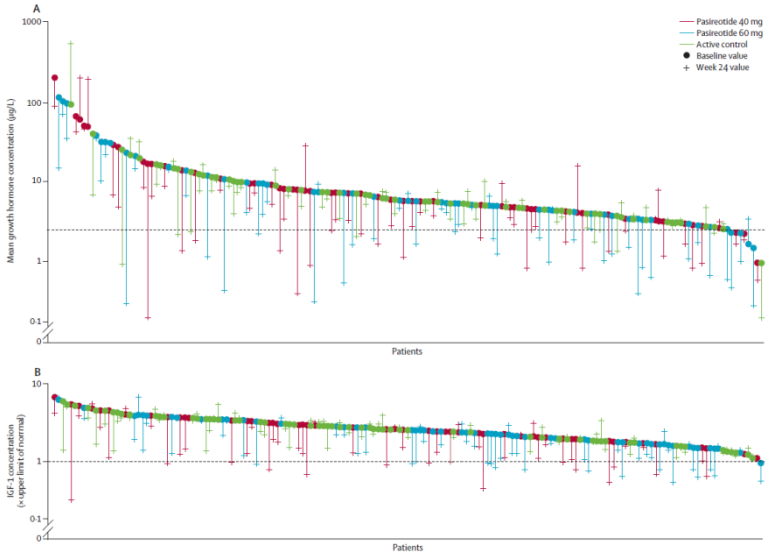
Michael Sheppard · Marcello D. Bronstein · Pamela Freda · Omar Serri · Laura De Marinis · Luciana Naves · Liudmila Rozhinskaya · Karina Hermosillo Reséndiz · Matthieu Ruffin · YinMiao Chen · Annamaria Colao

biochemical control in 48.6% of patients

Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial

*Mônica R Gadelha, Marcello D Bronstein, Thierry Brue, Mihail Coculescu, Maria Fleseriu, Mirtha Guitelman, Vyacheslav Pronin, Gérald Raverot, Ilan Shimon, Kayo Kodama Lievre, Juergen Fleck, Mounir Aout, Alberto M Pedroncelli, Annamaria Colao, on behalf of the Pasireotide C2402 Study Group**

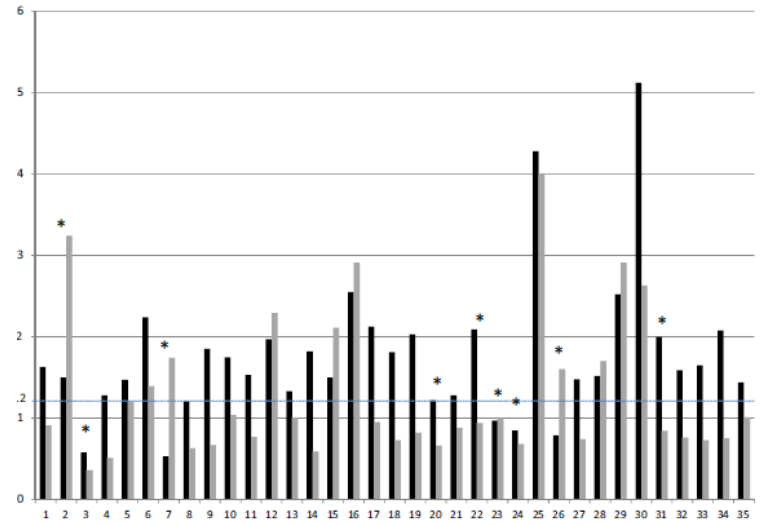
Biochemical control (2 h mean GH <2.5 µg/L and normalised IGF-1 at 24 weeks) 15% patients in the pasireotide-LAR 40 mg group and 20% patients in the pasireotide-LAR 60 mg group



Efficacy and safety of long-acting pasireotide in patients with somatostatin-resistant acromegaly: a multicenter study

Ilan Shimon[1] · Zaina Adnan[2] · Alexander Gorshtein[1] · Lior Baraf[3] · Nariman Saba Khazen[4] · Michal Gershinsky[4] · Yulia Pauker[4] · Ali Abid[2] · Mark J Niven[5] · Carmela Shechner[6] · Yona Greenman[7]

IGF-1 normalized in 19 patients, IGF-1 between 1-1.2 × ULN was reached in five, and in additional two patients IGF-1 was significantly suppressed

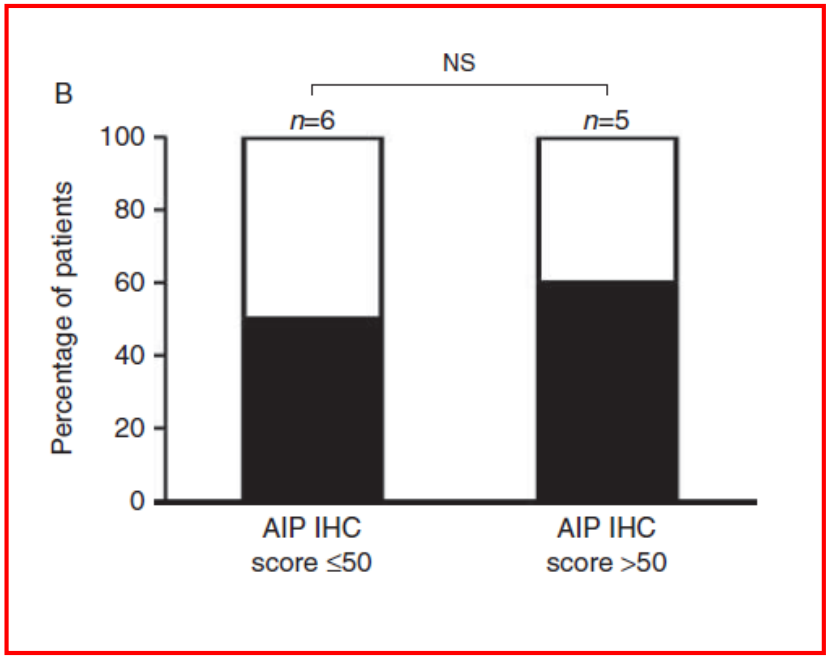


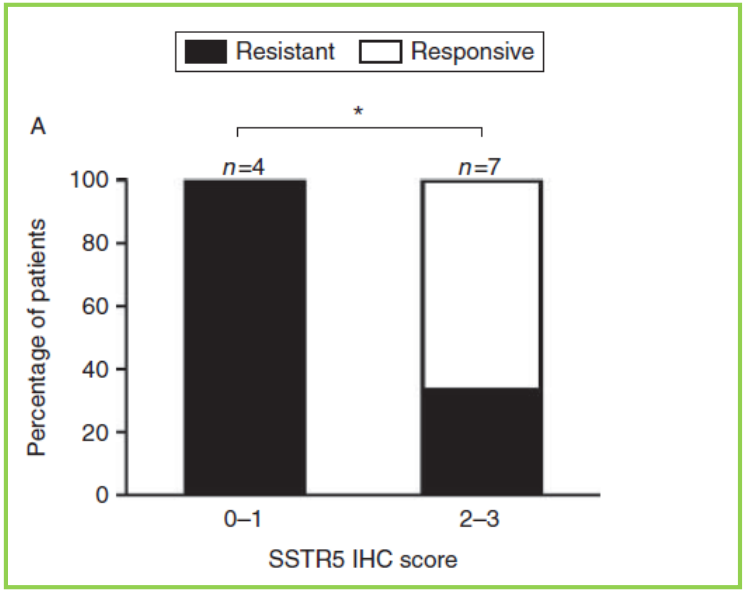
deterioration of glucose control in 63% of patients, requiring initiation or intensification of antidiabetic treatment

Factors predicting pasireotide responsiveness in somatotroph pituitary adenomas resistant to first-generation somatostatin analogues: an immunohistochemical study

Donato Iacovazzo[1,3], Eivind Carlsen[2], Francesca Lugli[3], Sabrina Chiloiro[3], Serena Piacentini[3], Antonio Bianchi[3], Antonella Giampietro[3], Marilda Mormando[3], Andrew J Clear[4], Francesco Doglietto[5], Carmelo Anile[6], Giulio Maira[7], Libero Lauriola[8], Guido Rindi[8], Federico Roncaroli[9], Alfredo Pontecorvi[3], Márta Korbonits[1,*] and Laura De Marinis[3,*]

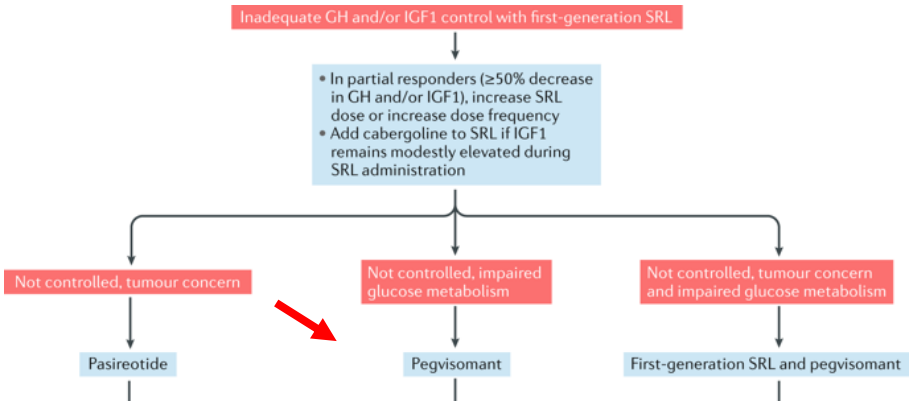
European Journal of Endocrinology (2016) **174**, 241–250





Sparsely granulated adenomas responded better to pasireotide compared to densely granulated ones

Pegvisomant



Partial response:

- Increase first-generation SRL dose and/or increase dose frequency of lanreotide autogel
- Add cabergoline to SRL if IGF1 is moderately elevated

Minimal or no response and tumour concern:

Of the patients treated for 12 months or more, 87 of 90 (97%) achieved a normal serum IGF-1 concentration.

Serum insulin and glucose concentrations were significantly decreased ($p<0{\cdot}05$)

Van der Lely et al. 2001 Lancet

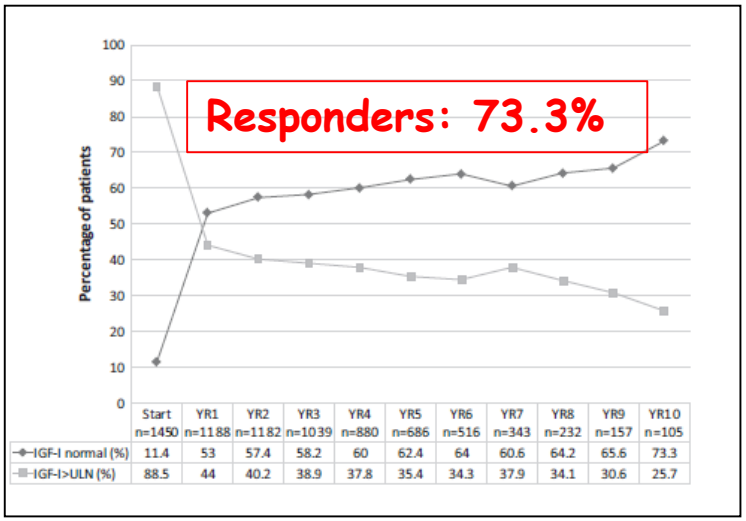
IGF-1 normalization

The French ACROSTUDY	**63%**	*Ann Endocrinol 2015 Dec;76(6):664-70*
The Spanish ACROSTUDY	**67%**	*Pituitary. 2016 Apr;19(2):127-37*
The German ACROSTUDY	**58%**	*Eur J Endocrinol. 2009 Nov;161 Suppl 1:S3-S10*
Thr Italian ACROSTUDY	**70%**	*Endocrine. 2015 Feb;48(1):334-41*

Long-term treatment with pegvisomant: observations from 2090 acromegaly patients in ACROSTUDY

European Journal of Endocrinology (2018) **179**, 419–427

Michael Buchfelder[1], Aart-Jan van der Lely[2], Beverly M K Biller[3], Susan M Webb[4], Thierry Brue[5], Christian J Strasburger[6], Ezio Ghigo[7], Cecilia Camacho-Hubner[8], Kaijie Pan[9], Joanne Lavenberg[9], Peter Jönsson[10] and Juliana H Hey-Hadavi[8]



	Start n=1450	YR1 n=1188	YR2 n=1182	YR3 n=1039	YR4 n=880	YR5 n=686	YR6 n=516	YR7 n=343	YR8 n=232	YR9 n=157	YR10 n=105
IGF-I normal (%)	11.4	53	57.4	58.2	60	62.4	64	60.6	64.2	65.6	73.3
IGF-I>ULN (%)	88.5	44	40.2	38.9	37.8	35.4	34.3	37.9	34.1	30.6	25.7

AEs considered treatment related were experienced by 16.1% of patients:

- lipohypertrophy (*n* = 31),
- liver test elevations (*n* = 30),
- gastro-intestinal disorders (*n* = 26),
- asthenia (*n* = 9),
- headache (*n* = 7),
- lipodystrophy (*n* = 5)

	Increased	Decreased	Unchanged
Tumor size	6.8%	16.8%	16.8%

…Among patients who had an increase as per local reading, the central reading confirmed an increase in 24% of cases

While most patients (55.5%) received the medication as monotherapy at the start of PEGV treatment, over time that percentage decreased and combination therapy was increasingly employed …

J Endocrinol Invest (2018) 41:575–581
https://doi.org/10.1007/s40618-017-0773-0

ORIGINAL ARTICLE

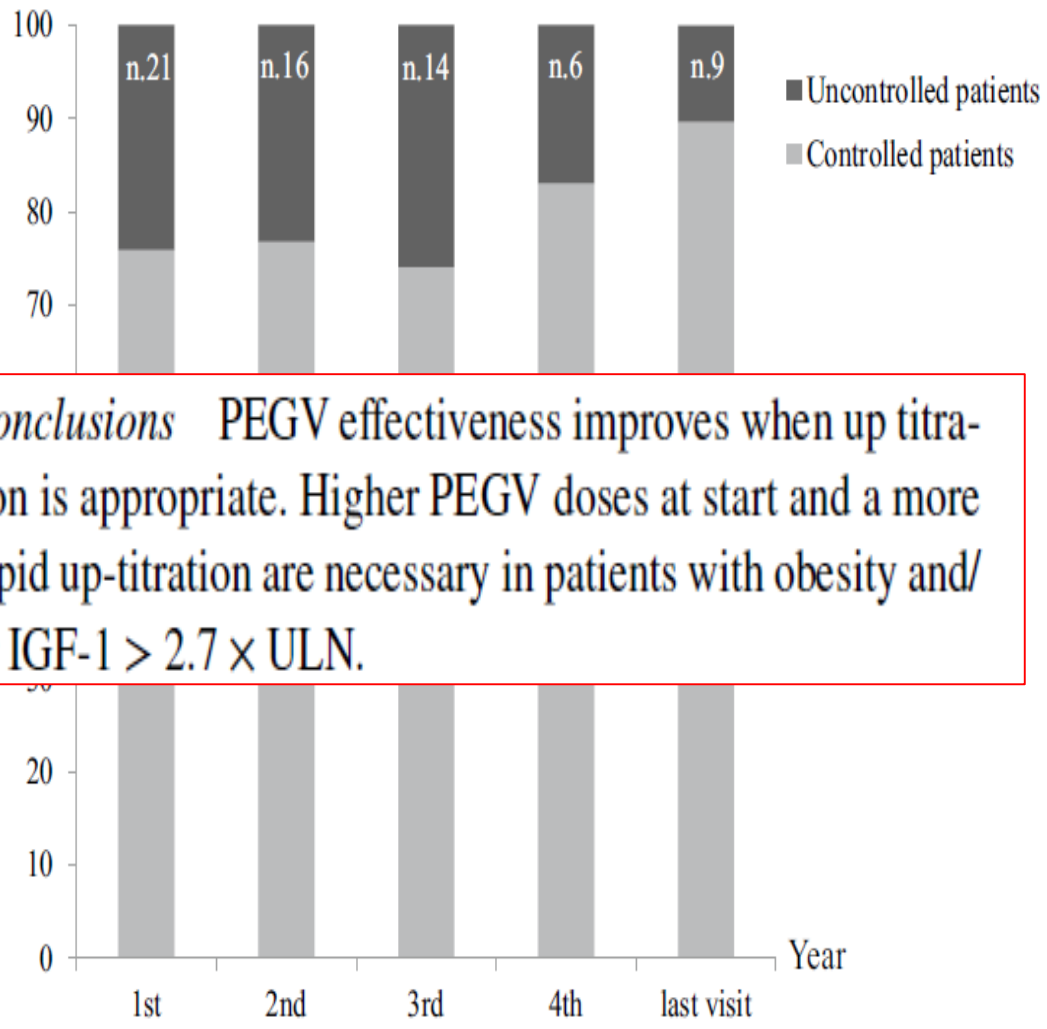
How to improve effectiveness of pegvisomant treatment in acromegalic patients

M. Ragonese[1] · S. Grottoli[2] · P. Maffei[3] · A. Alibrandi[4] · M. R. Ambrosio[5] · G. Arnaldi[6] · A. Bianchi[7] · S. Puglisi[1] · M. C. Zatelli[5] · L. De Marinis[7] · E. Ghigo[2] · A. Giustina[8] · F. Maffezzoni[8] · C. Martini[3] · L. Trementino[6] · S. Cannavo[1]

Disease control was associated with lower baseline GH, IGF-1 and IGF-1 xULN

PEGV resistance was associated with higher BMI

Diabetic patients needed higher doses of PEGV than non-diabetic ones



Conclusions PEGV effectiveness improves when up titration is appropriate. Higher PEGV doses at start and a more rapid up-titration are necessary in patients with obesity and/or IGF-1 > 2.7 x ULN.

Terapia combinata

Partial response:

- Increase first-generation SRL dose and/or increase dose frequency of lanreotide autogel
- Add cabergoline to SRL if IGF1 is moderately elevated

Minimal or no response and tumour concern:

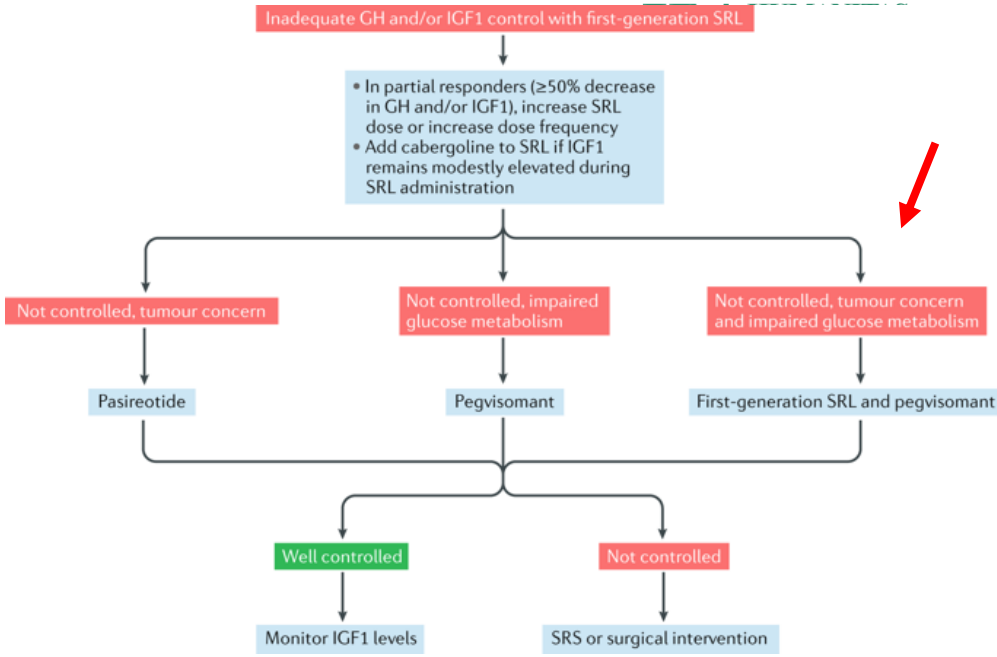
- Switch to pasireotide LAR

Minimal or no response and impaired glucose metabolism:

- Switch to pegvisomant

Minimal or no response, tumour concern and impaired glucose metabolism:

- Add pegvisomant to first-generation SRL



4.5 Interazioni con altri medicinali ed altre forme d'interazione

Non sono stati effettuati studi d'interazione. Si deve valutare se proseguire il trattamento con gli analoghi della somatostatina. L'uso di questo medicinale in combinazione ad altri medicinali per il trattamento dell'acromegalia non è stato studiato in modo approfondito.

JCEM ONLINE
Hot Topics in Translational Endocrinology—Endocrine Care

Growth Hormone Receptor Variants and Response to Pegvisomant in Monotherapy or in Combination with Somatostatin Analogs in Acromegalic Patients: A Multicenter Study

M. Filopanti, L. Olgiati, G. Mantovani, S. Corbetta, M. Arosio, V. Gasco, L. De Marinis, C. Martini, F. Bogazzi, S. Cannavò, A. Colao, D. Ferone, G. Arnaldi, F. Pigliaru, A. Peri, G. Angeletti, M. L. Jaffrain-Rea, A. G. Lania, and A. Spada*

TABLE 1. Basal clinical and biochemical differences between 127 acromegalic patients carrying flGHR or d3GH allele

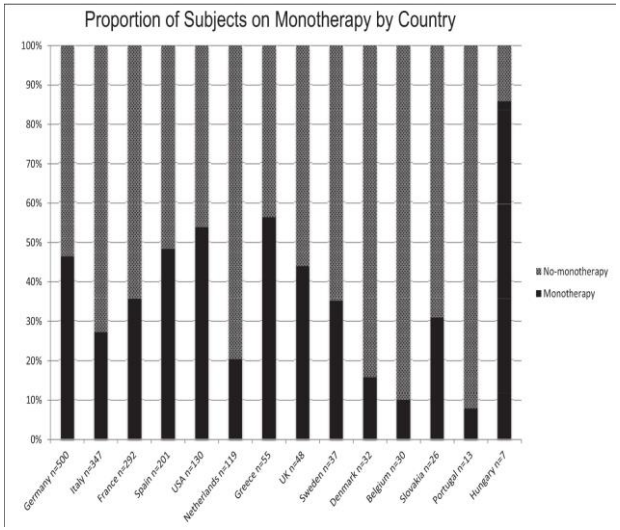
			d3 carriers		
	All patients	fl/flGHR	d3GHR (fl/d3 + d3/d3)	fl/d3GHR	d3/d3GHR
n	127	68	59	41	18
Age at diagnosis (yr)	42.2 ± 13.2	41.3 ± 12.4	43.1 ± 14.1	44.2 ± 13.8	40.7 ± 14.7
Male ratio (%)	57	62	46	44	72
Weight (kg)	83 ± 20	79 ± 17	80 ± 22	78 ± 20	88 ± 21
Height (cm)	170 ± 11	171 ± 11	169 ± 11	169 ± 11	170 ± 11
Dimension (% macroadenomas)	76	65	87	85	89
Extrasellar extent (%)	72	71	73	70	71
GH at diagnosis (μg/liter)	25.9 (13.7–58.3)	28.0 (12.1–50.0)	24.2 (13.9–67.9)	24.2 (12.2–50.0)	19.5 (7.1–73.0)
IGF-I SDS at diagnosis	9.0 ± 4.8	9.0 ± 4.4	8.5 ± 4.2	8.7 ± 4.5	7.7 ± 3.0
Pre-PEG-V GH (μg/liter)	13.3 (5.8–30.4)	11.5 (7.0–30.3)	15.5 (5.0–31.7)	12.2 (6.0–25.7)	12.0 (6.9–30.1)
Pre-PEG-V IGF-I SDS	7.7 ± 4.9	7.1 ± 4.5	8.4 ± 5.4	7.9 ± 5.0	5.6 ± 3.9
Treatment					
Previous surgery (%)	75	80	69	71	67
Radiotherapy (%)	10	13	7	7	5
PEG-V monotherapy (%)	50	48	54	49	67

Fourteen patients have been previously reported (20).

[a] fl/flGHR *vs.* d3GHR (fl/d3 + d3/d3). Bonferroni correction, $P < 0.004$.

LONG-TERM TREATMENT WITH PEGVISOMANT AS MONOTHERAPY IN PATIENTS WITH ACROMEGALY: EXPERIENCE FROM ACROSTUDY

Pamela U. Freda, MD[1]; Murray B. Gordon, MD, FACE[2]; Nicky Kelepouris, MD[3]; Peter Jonsson, MSc[4]; Maria Koltowska-Haggstrom, MD, PhD[5]; A. J. van der Lely MD, PhD[6]



Endocrine (2015) 48:334–341
DOI 10.1007/s12020-014-0393-9

ORIGINAL ARTICLE

ACROSTUDY: the Italian experience

S. Grottoli · P. Maffei · F. Bogazzi · S. Cannavò · A. Colao · E. Ghigo · R. Gomez · E. Graziano · M. Monterubbianesi · P. Jonsson · L. De Marinis

When pegvisomant started:

41.9 % pegvisomant monotherapy

50.4 % SSA + Pegvisomant

5 % SSA + Pegvisomant + cabergoline

2.6 % Pegvisomant + cabergoline

Terapia combinata SMS-PEG: possibili vantaggi

HUMANITAS UNIVERSITY

Riduzione del dosaggio settimanale di PEG

Ulteriore controllo del metabolismo glicemico

Miglior controllo della crescita tumorale

Table 1 | Efficacy and/or safety of SSA–PEG-V combination treatment in patients with acromegaly

Study	Number of participants	Study duration	Treatment protocol	Safety	Efficacy
Feenstra *et al.* (2005)[4] Neggers *et al.* (2007),[6] (2008)[12] and (2009)[5]	87	Mean 29.2 months (range 1.2–57.4 months)	SSA every 28 days and PEG-V twice a week	Confirmed	Confirmed
Jørgensen *et al.* (2005)[10]	11	3 months	SSA every 28 days and PEG-V daily	Confirmed	Confirmed
Biering *et al.* (2006)[9]	2	NA	SSA every 28 days and PEG-V daily	Confirmed	NA
Harris *et al.* (2007)[11]	24	40 weeks	SSA every 28 days and PEG-V daily	Confirmed	NA

Abbreviations: NA, not available; SSA, somatostatin analog; PEG-V, pegvisomant.

Neggers et al. 2010 Nat Rev Endocrinology

Long-term treatment of somatostatin analog-refractory growth hormone-secreting pituitary tumors with pegvisomant alone or combined with long-acting somatostatin analogs: a retrospective analysis of clinical practice and outcomes

Antonio Bianchi[1*], Ferdinando Valentini[2], Raffaella Iuorio[3], Maurizio Poggi[4], Roberto Baldelli[5], Marina Passeri[6], Antonella Giampietro[1], Linda Tartaglione[1], Sabrina Chiloiro[1], Marialuisa Appetecchia[5], Patrizia Gargiulo[3], Andrea Fabbri[6], Vincenzo Toscano[4], Alfredo Pontecorvi[1] and Laura De Marinis[1]

Journal of Experimental & Clinical Cancer Research 2013, **32**:40

Table 2 Logistic regression analysis: variables determining the decision to prescribe PEGV with or without SSA therapy (dependent variable)

COVARIATES	OR (95% CI)	P
GH at baseline (μg/L)	1.015 (0.983-1.043)	1.047
IGF-I SDS at baseline	1.003 (0.999-1.007)	0.097
Δ IGF I [a] SDS	1.446 (1.153-1.814)	0.001
Detectable adenoma at baseline [b]	13.757 (2.547-74.307)	0.002

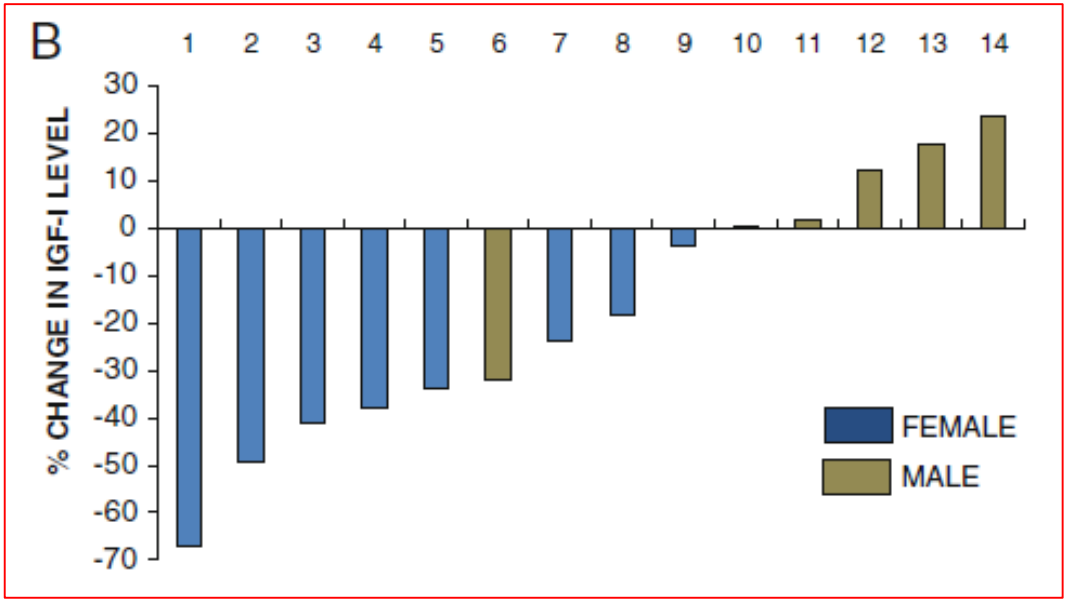
Group PEG+SSA showed:

- higher IGF-I and GH levels
- higher rates residual tumor tissue at baseline
- more substantial responses to SSA monotherapy
- worse outcomes (IGF-I normalization rates, final IGF-I levels)

Pegvisomant and cabergoline combination therapy in acromegaly

I. Bernabeu · C. Alvarez-Escolá · A. E. Paniagua · T. Lucas · I. Pavón · J. M. Cabezas-Agrícola · F. F. Casanueva · M. Marazuela

Pituitary (2013) 16:101–108



IGF-I levels returned to normal in 4 patients (28%) at the end of the study.
In addition, some decline in IGF-I levels was observed in a further 5 patients.

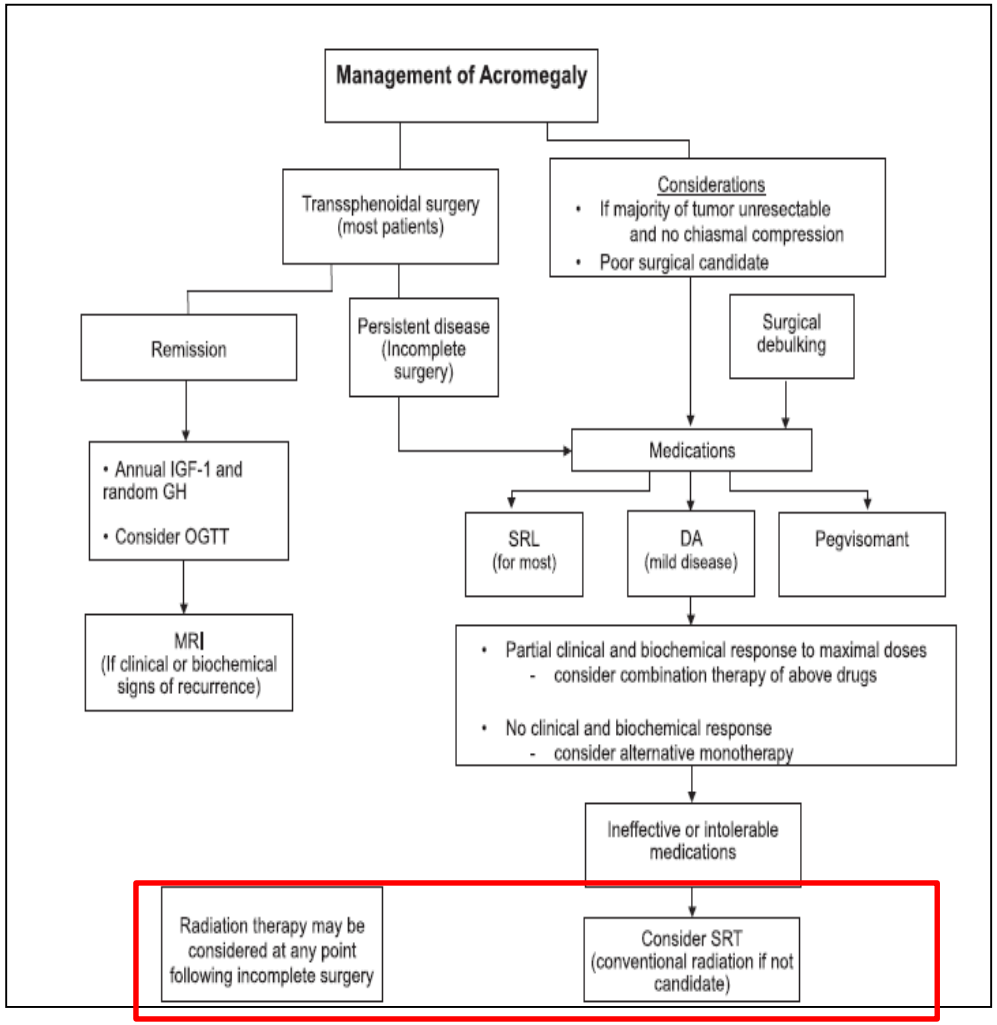
Better response to combination therapy related to:

- lower baseline IGF-I
- female gender
- lower body weight
- higher PRL levels

All patients whose IGF-I levels returned to normal had previously been irradiated

Acromegaly: An Endocrine Society Clinical Practice Guideline

Laurence Katznelson, Edward R. Laws, Jr, Shlomo Melmed, Mark E. Molitch, Mohammad Hassan Murad, Andrea Utz, and John A. H. Wass



Therapy if biochemical control is not achieved after second-line therapy

- Stereotactic radiosurgery or surgical intervention (or reintervention)

Stereotactic Radiosurgery for Acromegaly: An International Multicenter Retrospective Cohort Study

Dale Ding, MD ✉, Gautam U Mehta, MD, Mohana Rao Patibandla, MBBS, Cheng-Chia Lee, MD, Roman Liscak, MD, Hideyuki Kano, MD, PhD, Fu-Yuan Pai, BA, Mikulas Kosak, MD, Nathaniel D Sisterson, BA, Roberto Martinez-Alvarez, MD, PhD, ...
Show more

The actuarial rates of initial and durable endocrine remission at 10 yr were 69% and 59%, respectively

Mean time to durable remission after SRS 38 mo

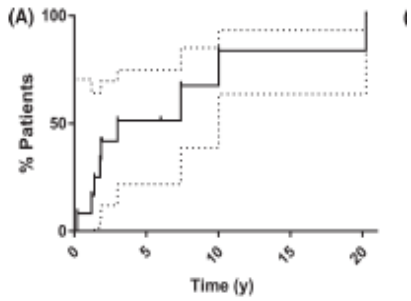
Cessation of IGF-1 lowering medication prior to SRS was the only independent predictor of durable remission

development of ≥1 new endocrinopathy in 26%

ORIGINAL ARTICLE

Radiosurgery as primary management for acromegaly

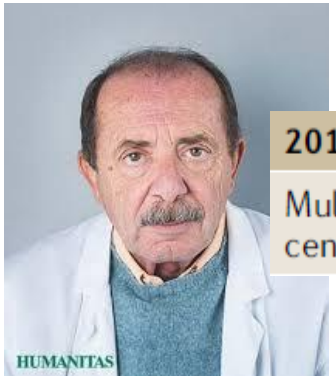
Hugh P. Sims-Williams[1] | Kaveesha Rajapaksa[1] | Saurabh Sinha[1] | Matthias Radatz[1,2] | Lee Walton[2] | John Yianni[1,2] | John Newell-Price[3,4]



Time for 50% to achieve control
on medication: 3 years
off medications: 7.4 years

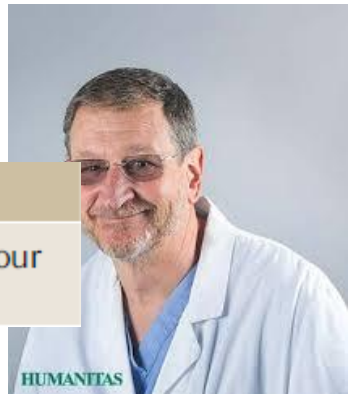
At 20 years of follow-up, control was seen in all on acromegaly-specific medication (n = 12) and 75% of those off medication

53% of patients developed new hypopituitarism at a median follow-up of 146 months
The development of first onset of hypopituitarism occurred as late as 20 years after treatment



2018 consensus recommendation

Multidisciplinary team approach at a pituitary tumour centre of excellence, where possible



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ICH Endocrinologia e Andrologia Medica

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Nazarena Betella
Walter Vena
Flaminia Carrone
Emilia Biamonti
Sara Piccini

Giulia Tarantola
Livin Nurcin

ENETS
European Reference Network
for rare or low prevalence complex diseases
HUMANITAS RESEARCH HOSPITAL
HU HUMANITAS UNIVERSITY

Format: Abstract

J Clin Endocrinol Metab. 2018 Oct 19. doi: 10.1210/jc.2018-01524. [Epub ahead of print]

Pasireotide responsiveness in acromegaly is mainly driven by somat expression.

Muhammad A[1], Coopmans EC[1], Gatto F[2], Franck SE[1], Janssen JAMJL[1], van der Lely AJ[1], Hofland LJ[1], Neggers

Author information

Abstract

BACKGROUND: The response to first-generation somatostatin receptor ligands (SRLs) treatment in somatostatin receptor subtype 2 (SSTR2). However, pasireotide shows the highest binding affinity f acromegaly SSTR5 expression is better at predicting the response to pasireotide LAR (PAS-LAR) tr

AIM: To investigate in active acromegaly patients whether response to SRL treatment correlates to SSTR2 and SSTR5 expression are correlated to response to PAS-LAR treatment.

METHODS: We included 52 patients from a cohort that initially received SRL treatment, followed by treatment, and finally PAS-LAR treatment. The long-term response to PAS-LAR was evaluated usin patients, somatotroph adenoma tissue samples were available to evaluate SSTR2 and SSTR5 expr immunoreactivity score (IRS).

RESULTS: The percentage IGF-I (x ULN) reduction which was observed after SRL treatment correla follow-up ($r = 0.40$, $P = 0.003$, $n = 52$). After exclusion of SRL pretreated patients, SSTR2 IRS was p 0.58, $P = 0.039$, $n = 9$), while SSTR5 IRS showed no relation ($r = 0.35$, $P = 0.36$, $n = 9$).

CONCLUSIONS: In a cohort of patients partially responsive to SRLs, the IGF-I lowering effects of PA effect of SRLs treatment and seemed to be mainly driven by SSTR2 expression instead of SSTR5.

J Endocrinol Invest (2015) 38:1099–1109
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ORIGINAL ARTICLE

Does pegvisomant treatment expertise improve control of resistant acromegaly? The Italian ACROSTUDY experience

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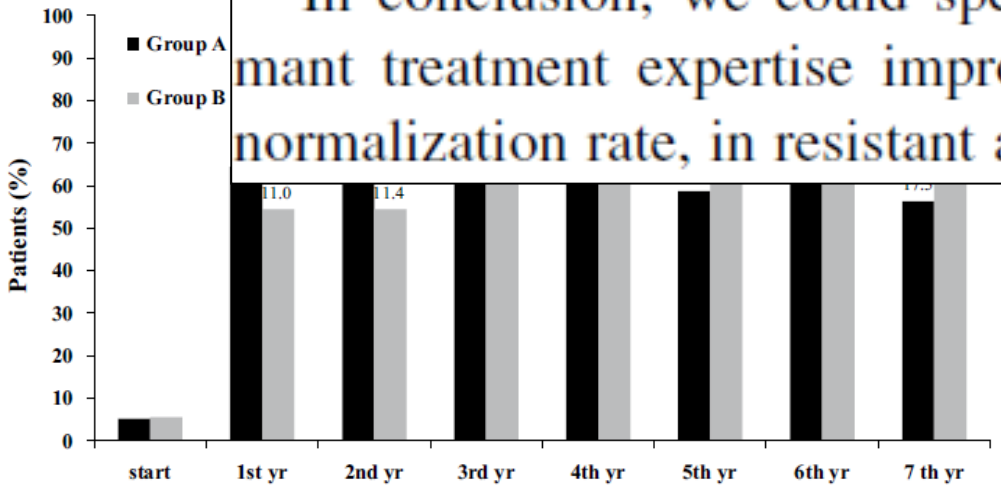
Group A: patients from centers treating more than 15 pts
Group B: patients from centers treating less than 15 pts

Table 1 Characteristics of patients enrolled in group A and B

	Group A	Group B	*p*
No. of cases	204	137	–
Gender (M/F)	97/107	74/63	ns
Weight (mean ± SD)	82.5 ± 16.4 kg	79.0 ± 16.2 kg	ns
BMI (mean ± SD)	28.9 ± 6.0	27.2 ± 3.6	<0.01
Age at diagnosis (mean ± SD)	42.0 ± 13.2 years	42.7 ± 14.4 years	ns
Age at pegvisomant start (mean ± SD)	48.9 ± 14.1 years	52.6 ± 14.1 years	<0.02
Disease duration before starting pegvisomant (mean ± SD)	6.9 ± 6.9 years	9.8 ± 9.0 years	<0.0001

In conclusion, we could speculate that better pegvisomant treatment expertise improves safety, but not IGF-1 normalization rate, in resistant acromegaly patients.



…sibly

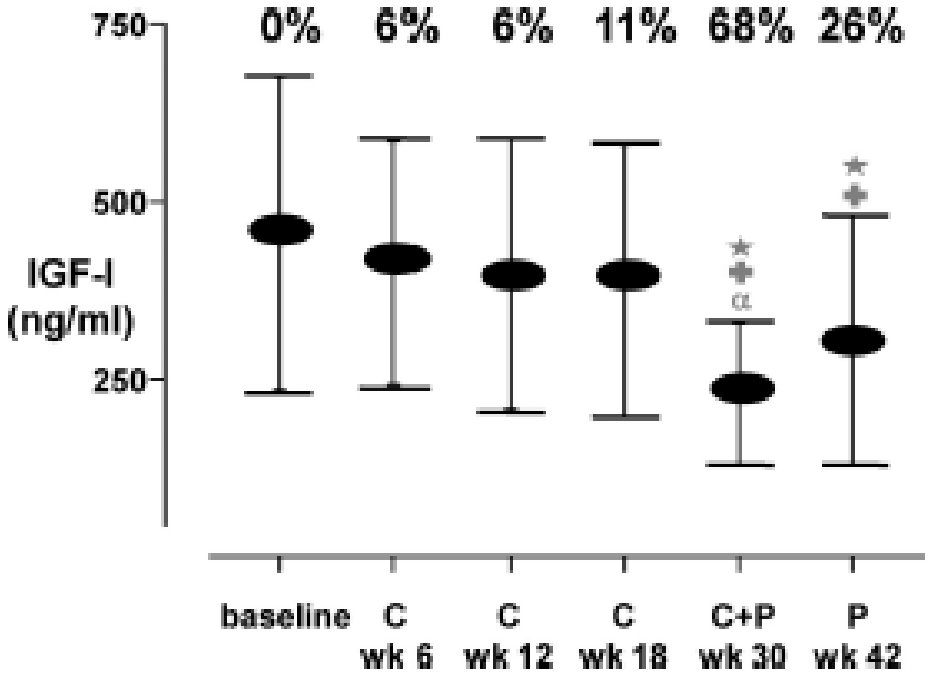
- the occurrence of a more aggressive disease in many patients of group A
- dose titration

	Group A	Group B	*p*
Number of patients evaluable for AE	204	137	
Patients with AE	46 (22.5 %)	52 (38 %)	<0.005
Patients in whom drug was withdrawn due to serious AE	11 (5.4 %)	8 (5.8 %)	NS
Number of AE	82	117	<0.0001

Effective Combination Treatment with Cabergoline and Low-Dose Pegvisomant in Active Acromegaly: A Prospective Clinical Trial

J Clin Endocrinol Metab, April 2012, 97(4):1187–1193

C. E. Higham, A. B. Atkinson, S. Aylwin, M. Bidlingmaier, W. M. Drake, A. Lewis, N. M. Martin, V. Moyes, J. Newell-Price, and P. J. Trainer



Pituitary centers of excellence

BOX 1. General characteristics of a PTCOE are:

- Provide the best care for patients with pituitary tumors and related pathologies
- Independent of health authorities, administra organizations
- Widely recognized by endocrinologists and
- Aimed to the advancement of pituitary scien
- Providing adequate patient education and co
- Recognized by external national and/or inter neurosurgical medical societies
- Act as training center for residents in the trea pathologies

BOX 2. Mission of the PTCOE

1. Provide the best standard of care to patients with pituitary tumors and disorders
2. Organize multidisciplinary clinical management
3. Liaision between experienced neurosurgeons and expert neuroendocrinologists
4. Work with the supporting specialties
5. Train fellows in the management of pituitary tumors and related disorders
6. Provide courses, publications and lectures for primary care physicians and other specialists
7. Capture and track clinical data
8. Provide up to date and comprehensive patient information
9. Present results and outcomes to scientific bodies and administrators
10. Support endocrine units located outside the PTCOE
11. Advise health administrators and authorities on specific problems
12. Advance the science and scholarship of pituitary tumors
13. Include tumor data on National or Regional registries

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