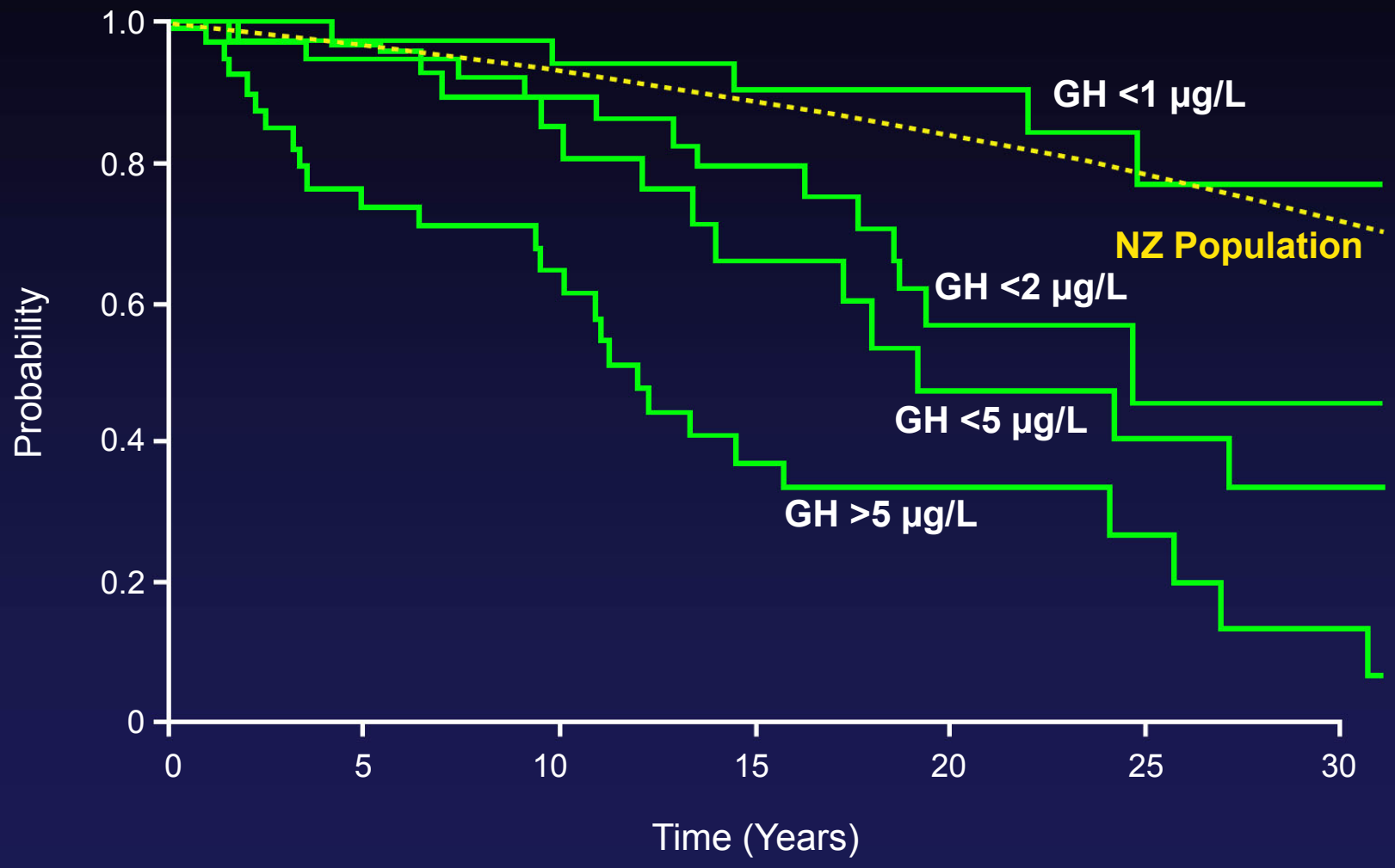
Update sulla terapia farmacologica dell'acromegalia

Agostino Paoletta

ULSS 15 "Alta Padovana" Cittadella (PD)

Mortality in Acromegaly



Holdaway IM,JCEM; 2004, 89:667

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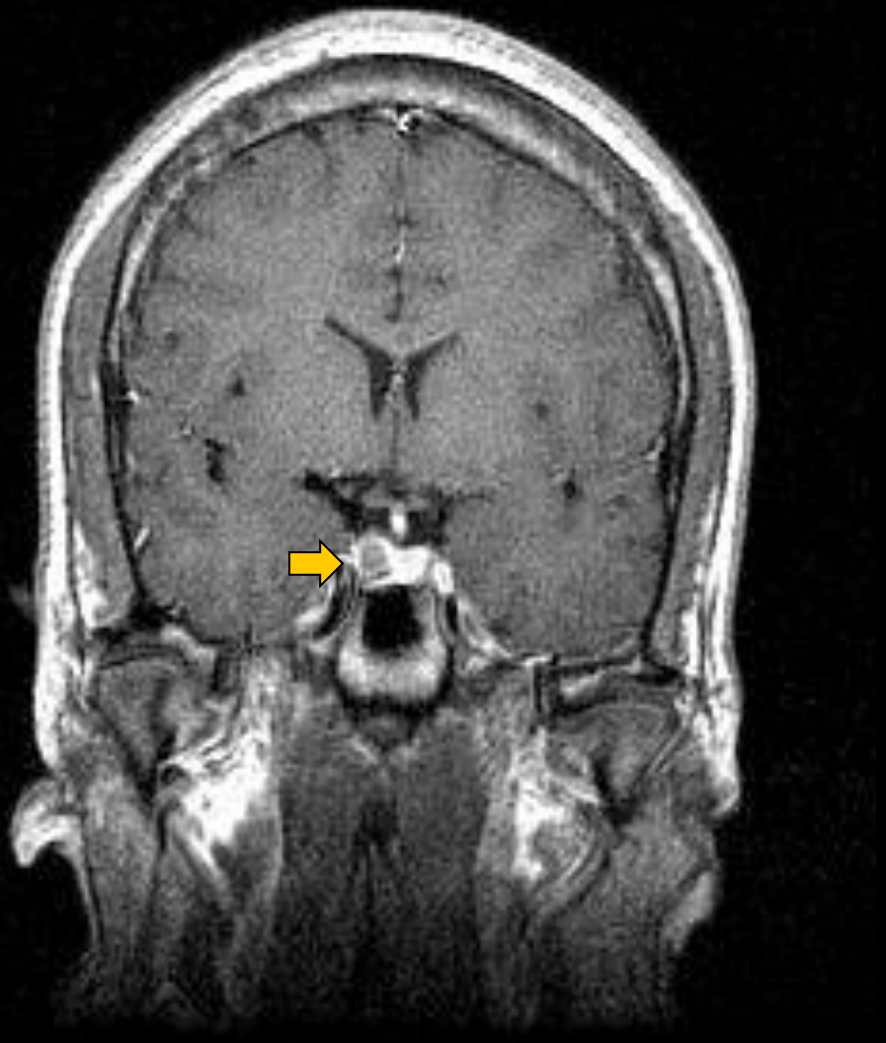
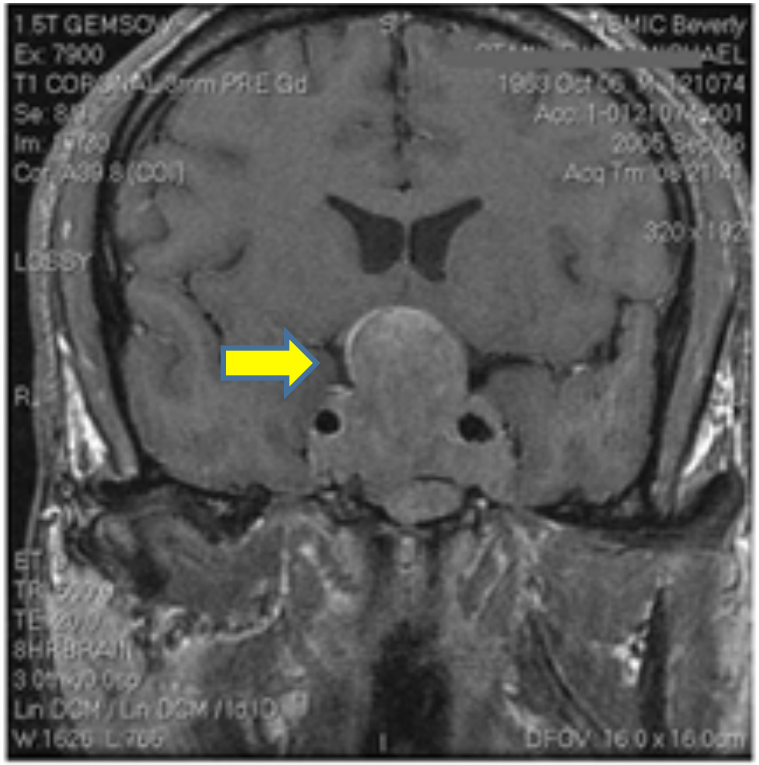
Bari,
7-10 novembre 2013

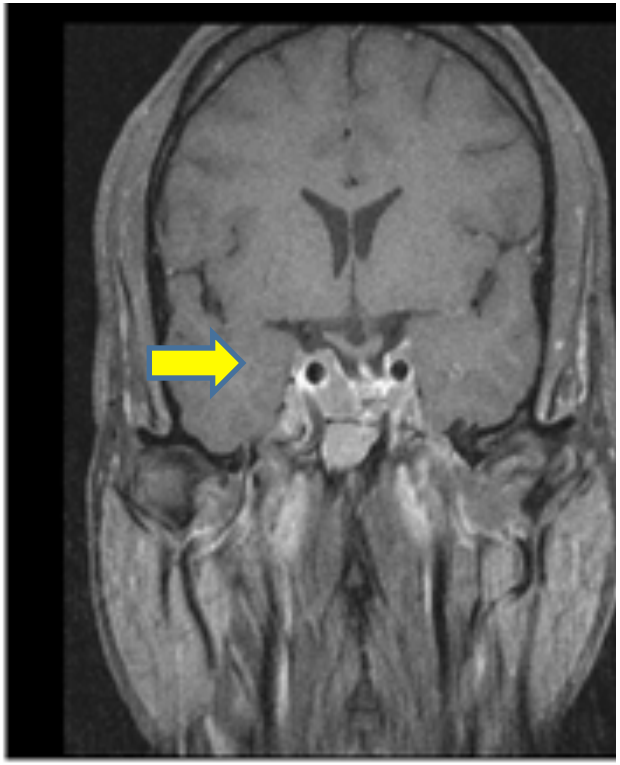
Perchè la terapia farmacologica ?



Surgery



Preoperative



Postoperative

Radiation therapy in Acromegaly

1128 patients

935 patients

Risk of cerebrovascular events/stroke (21% at 20 years) and secondary brain tumors (2% at 20 years)

88%–97%

Normalization of GH and IGF-1 in 50%–60% at 10 years.

The rate of hypopituitarism 60% at 10 years

Biochemical control 30%–60% at 5 years

The rate of hypopituitarism 20%–40% over 5 years

Minniti G et al. *2011*

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Efficacia clinica

Effects of octreotide LAR in acromegaly

First author, year (Ref.)	n	Maximal duration (months)	Dose (mg/q 28 d)	GH levels ≤2.5 μg/liter, n (%)	Normal IGF-I for age, n (%)	Tumor reduction >20% of baseline, n (%)
Davies, 1998 (113)	12	12	20–40	6 (50)	7 (60)	2 (17)
Lancranjan, 1999 (114)	149	12	10–30	104 (70)	98 (66)	Not shown
Cozzi, 2003 (115)	110	48	10–30	79 (72)	82 (75)	38/83 (46)
Ayuk, 2004 (116)[a]	91	12	10–30	61 (67)	48 (72)	Not shown
Jallad, 2005 (117)	57	24	10–30	32 (56)	20 (36)	19/25 (76)
Cozzi, 2006 (118)	67	108	10–30	46 (69)	47 (70)	55 (82)
Mercado, 2007 (119)	68	12	10–30	30 (44)	23 (34)	51 (75)
Valentim, 2008 (120)	276	24	20–30	157 (57)	185 (67)	243 (88)
Oki, 2009 (121)	30	24	10–40	11 (37)	16 (53)	Not shown
Colao, 2009 (122)[b]	40	12	20–30	16 (40)	16 (40)	29 (73)
Ghigo, 2009 (123)	56	12	20–40	Not shown	19 (34)	5 (9)
Total	956		10–40	542/900 (60)	561/956 (59)	442/627 (70)

Effects of lanreotide ATG in acromegaly

First author, year (Ref.)	No. of patients	Treatment		Treatment outcome, n (%)		
		Maximal duration (months	Dose (mg/q 28 d)	GH levels ≤2.5 μg/liter	Normal IGF-I for age	Tumor reduction >20% of baseline
Attanasio, 2008 (128)	26	12	60–120	11 (42)	14 (54)	16/22 (73)
Chanson, 2008 (129)	62	12	60–120	53 (85)	24 (38)	Not shown
Colao, 2009 (130)	26	12	60–120	14 (54)	14 (54)	20/26 (77)
Melmed, 2010 (131)	99	12	60–120	53 (54)	58 (59)	Not shown
Lombardi, 2009 (132)	51	12	120	32 (63)	19 (37)	Not shown
Total	264		60–120	163 (62)	129 (49)	36/48 (75)

Endocrine Reviews, April 2011,

A role of primary medical therapy

- In patients with adenoma who have a minimal chance of surgical cure (invasive , large , high GH levels)
- In patients with poor clinical conditions
- In patients who prefer medical treatment

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Risultati - II

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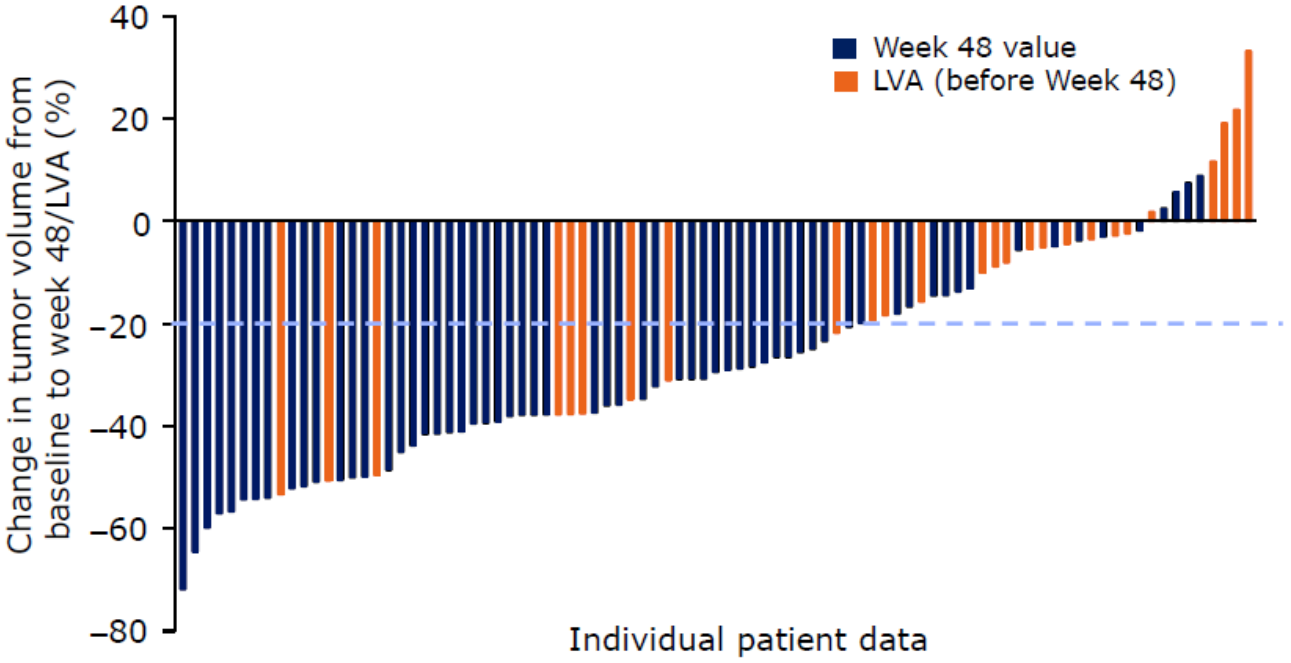
Individual tumor volume reductions



Data are from ITT population (n=89). LVA, last post-baseline value available

The Endocrine Society Meeting – San Francisco – June 2013

"PRIMARYS"

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- Lanreotide autogel as first line therapy in newly diagnosed acromegaly patients with a macroadenoma.

- Investigators observed clinically relevant tumor volume reductions, in a majority of patients:

  > 20% in 63% of pz.

- Data from secondary biomarker endpoints of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels were further supportive of these findings:

  GH < 2.5 ug/L in 78% of pz.

  IGF-I normalized in 50% of pz.

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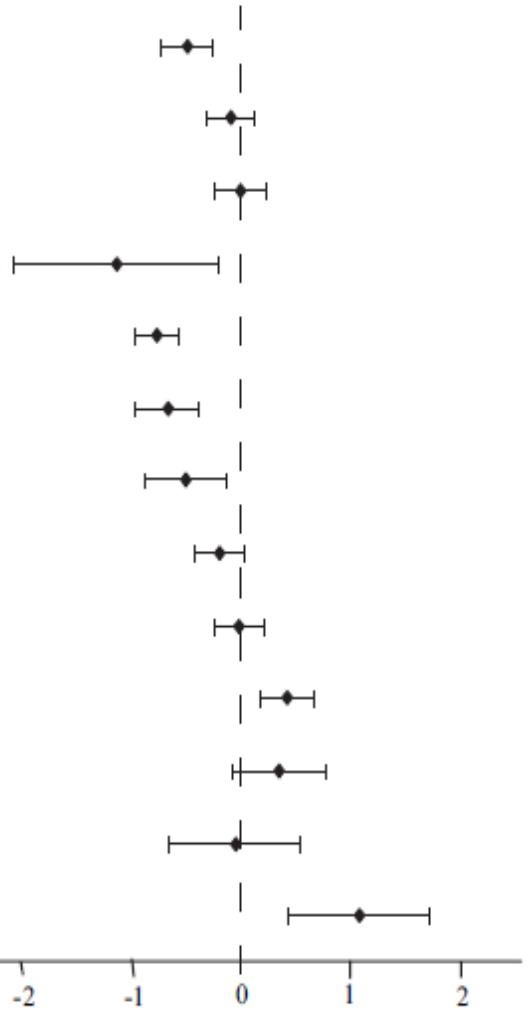
Are comorbidities improved with long-term controlled disease?

TABLE 2. Results of metaanalysis of somatostatin analogs treatment on the heart in acromegaly

Factors	Number of trials	Number of Patients	Q test	Weighted mean (SD) change (before - after)	Global Effect Size (95% CI)
HR	16	199	<0.001	-5.8 (2.1) beats/min	
SBP	16	199	<0.01	-2.5 (2.9) mmHg	
DBP	15	180	<0.05	-1.7 (1.9) mmHg	
LVM	7	51	<0.01	-50.3 (13.3) g	
LVMi	14	143	ns	-22.3 (6.7) g/m^2	
IVS	10	110	<0.05	-0.3 (0.2) mm	
LVPW	9	91	<0.01	-0.8 (0.4) mm	
LVEDD	8	71	ns	-1.5 (2.2) mm	
LVESD	8	75	ns	0.4 (2.0) mm	
E/A	5	61	ns	0.2 (0.1)	
EF	15	188	<0.001	3.3 (1.7) %	
FS	6	56	<0.01	-0.7 (2.0) %	
Ex Dur	7	75	<0.01	1.6 (0.4) min	



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Terapia con SSA ad alte dosi

"L'aumento della dose di SSA migliora il controllo biochimico della malattia"

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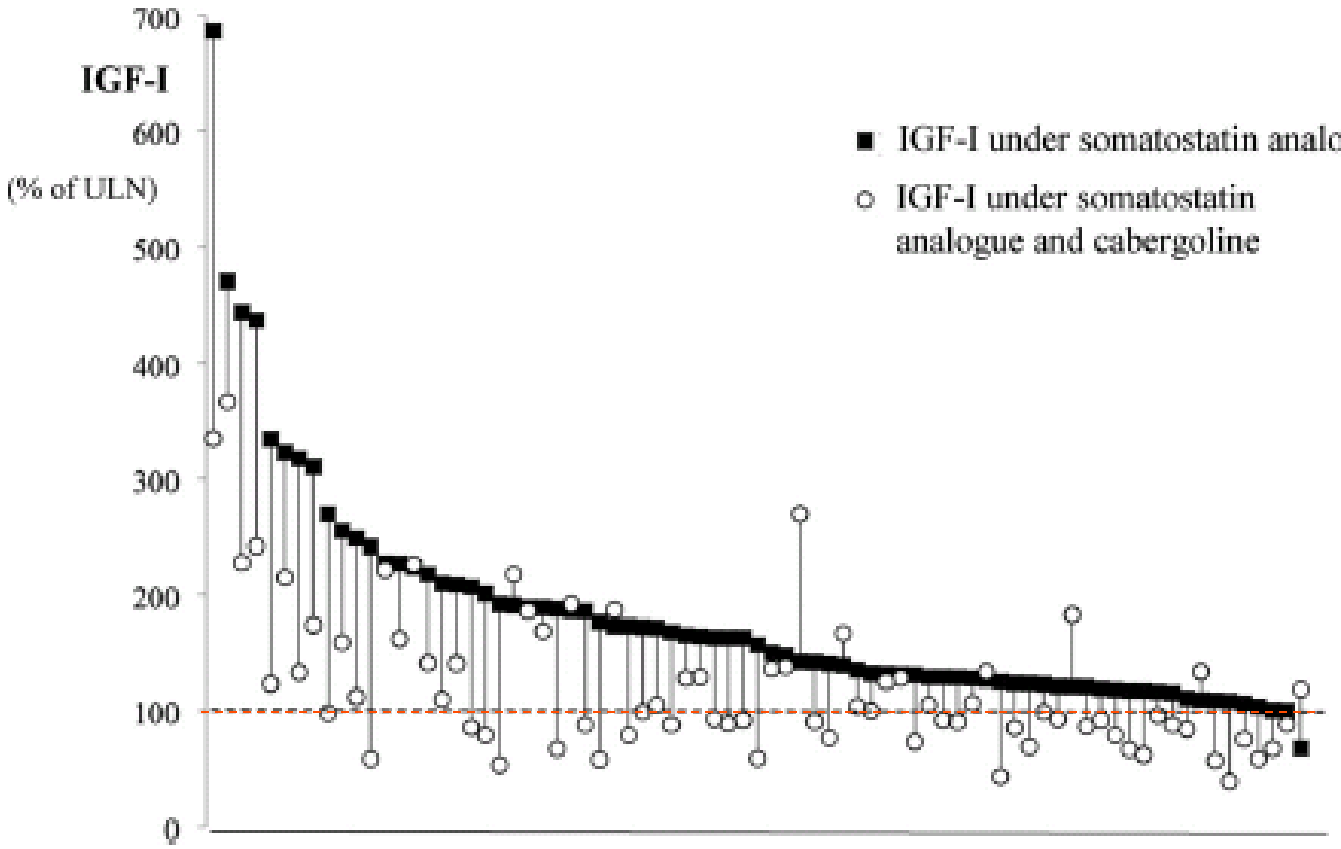
LA TERAPIA COMBINATA

ANALOGHI DELLA SOMATOSTATINA + DOPAMINO-AGONISTI

ANALOGHI DELLA SOMATOSTATINA + PEGVISOMANT

SSA and Cabergoline treatment in acromegalic patients



52%
achieved normal IGF-I levels

45%
GH<2.5ug/l

Sandret L et al. JCEM 2011;96:1327-1335

The Journal of Clinical Endocrinology & Metabolism 92(12):4598–4601

doi: 10.1210/jc.2007-1234

Long-Term Efficacy and Safety of Combined Treatment of Somatostatin Analogs and Pegvisomant in Acromegaly

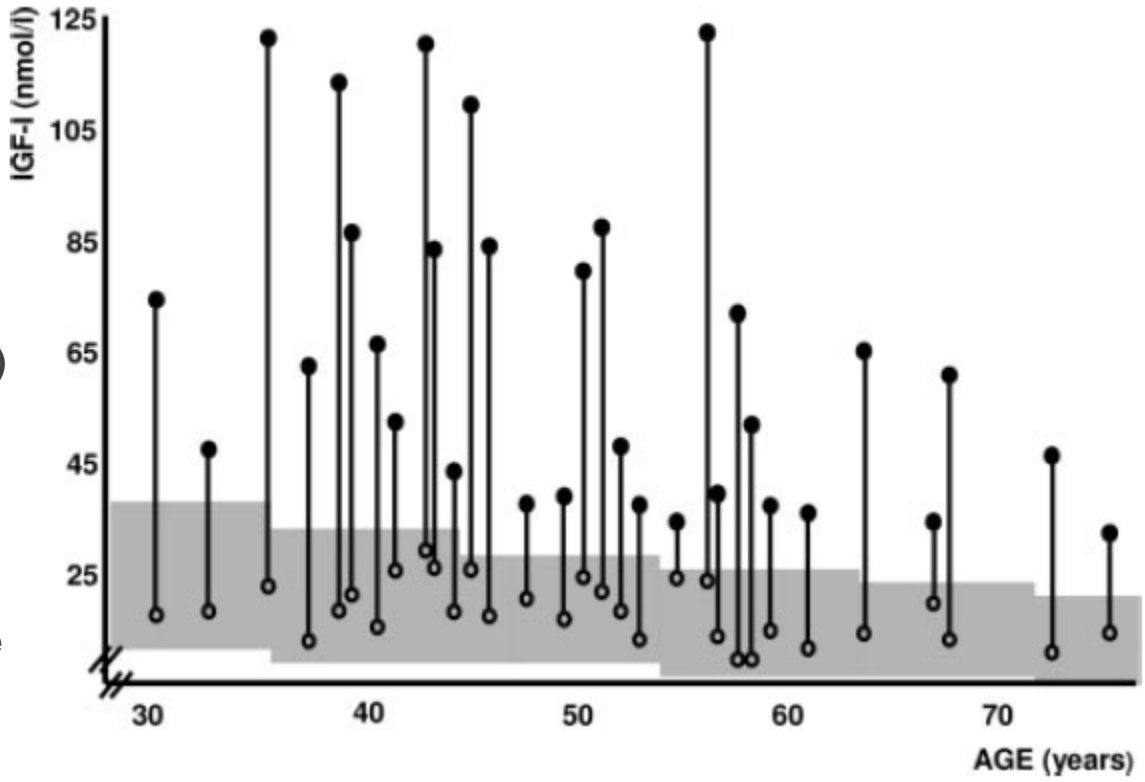
Sebastian J. C. M. M. Neggers, Maarten O. van Aken, Joop A. M. J. L. Janssen, Richard A. Feelders, Wouter W. de Herder, and Aart-Jan van der Lely

Casi n= 32

Octreotide LAR 30 mg/mese (n= 10)

Lanreotide Autogel 120 mg/mese (n= 22)

Pegvisomant 40-160 mg/settimana
(dose media 60 mg/settimana)
somministrazione mono o bisettimanale



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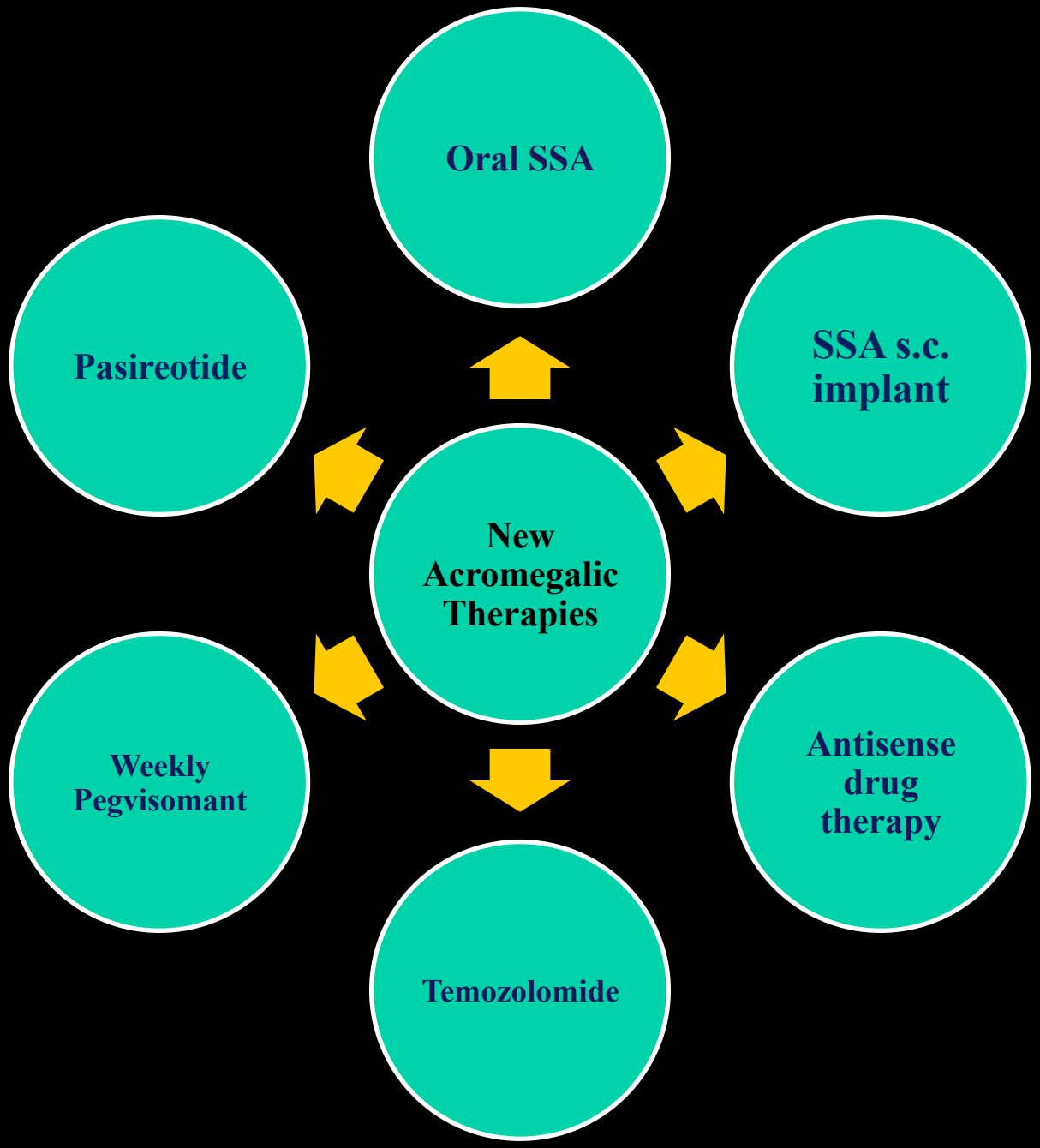
What about of the future?


Oral SSA
SSA s.c. implant
Antisense drug therapy
Temozolomide
Weekly Pegvisomant
Pasireotide
New Acromegalic Therapies

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Agostino Paoletta

ULSS 15 "Alta Padovana" Cittadella (PD)