Analoghi della Somatostatina

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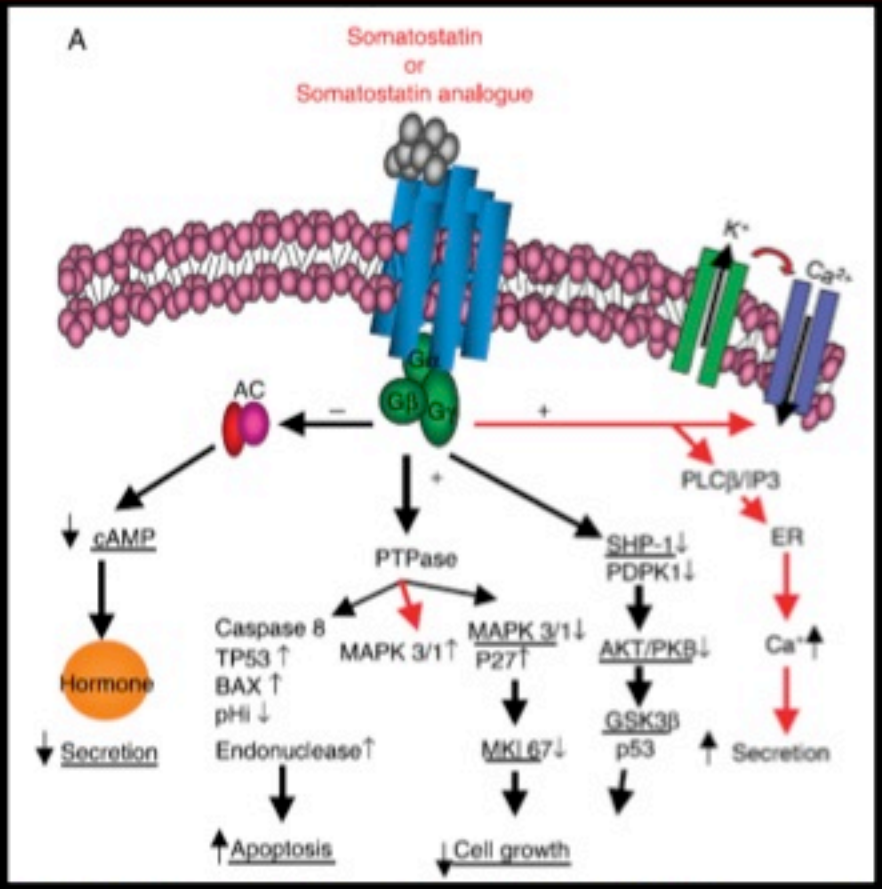
Somatostatina e Recettori Somatostatina (SSTRs)

Roma,
9-11 novembre 2012



Secrezione Ormonale

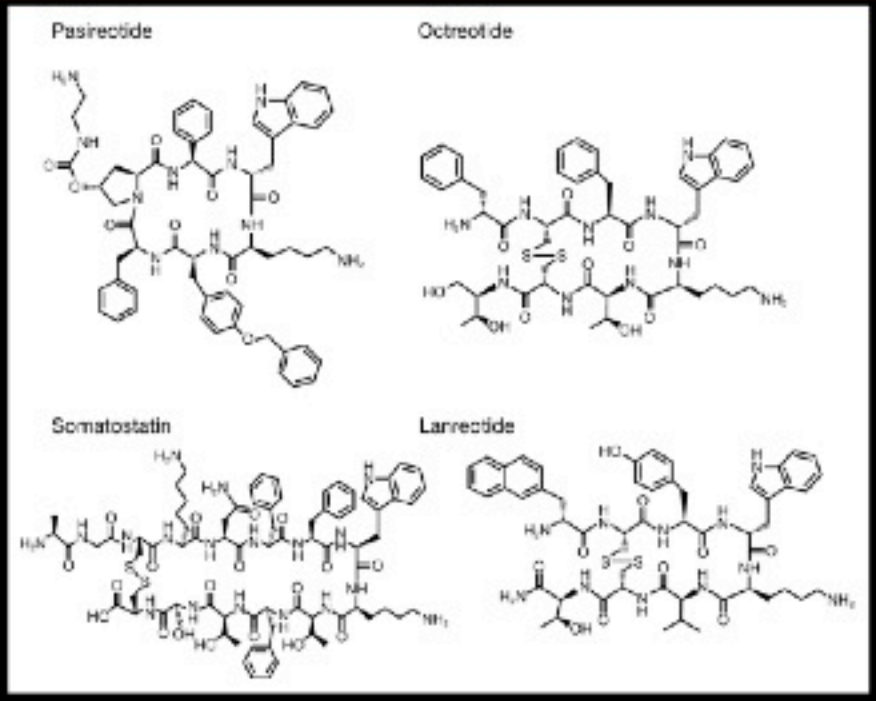
Crescita Cellulare

Table 1 Binding affinities of somatostatin (SRIF-14), pasireotide, octreotide, and lanreotide to the five human sst[1]

Compound	sst_1	sst_2	sst_3	sst_4	sst_5
Somatostatin (SRIF-14)	0.93 ± 0.12	0.15 ± 0.2	0.56 ± 0.17	1.50 ± 0.4	0.29 ± 0.04
Pasireotide	9.3 ± 0.1	1.0 ± 0.1	1.5 ± 0.3	>1000	0.16 ± 0.01
Octreotide	280 ± 80	0.38 ± 0.08	7.1 ± 1.4	>1000	6.3 ± 1.0
Lanreotide	180 ± 20	0.54 ± 0.08	14 ± 9	230 ± 40	17 ± 5

Analoghi della Somatostatina (SSAs)

Roma,
9-11 novembre 2012



Affinità Recettoriale

Farmacocinetica

SMS 1-14

T ½ 3 min

OCTREOTIDE

Octreotide sc: 50-500 mcg /8 ore

Octreotide LAR: 10-30 mg/28 giorni

LANREOTIDE

Lanreotide SR 30-60 mg/14-28 giorni

Lanreotide Autogel (ATG) 60-120 mg/ 21-42 giorni

PASIREOTIDE

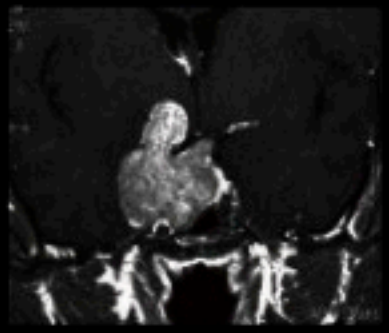
Pasireotide 200-900 mg/12 ore

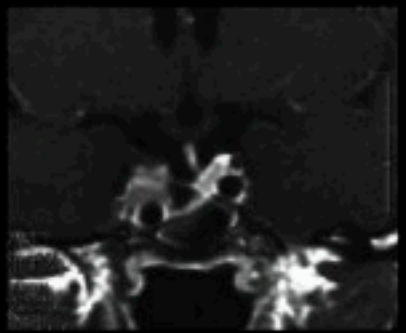
Efficacia clinica SSA

Roma,
9-11 novembre 2012

	Positive tumors/total tumors tested (%)				
	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
GH	21/36	87/100	23/47	2/40	84/104
	(53)	(87)	(51)	(5)	(81)
ACTH	14/22	15/22	3/21	7/21	38/51
	(63)	(79)	(37)	(33)	(75)
PRL	16/19	9/19	3/7	0/7	13/17
	(84)	(47)	(43)	(0)	(76)

GH (μg/L)		PRL (μg/L)	IGF-I (μg/L)	SSTR subtype[b]	
Basal	Under octreotide[c]			SSTR2	SSTR5
11 → 1 (91)		11	1171	371	555
22 → 4 (82)		17	885	366	744
109 → 26 (76)		12	881	153	129
141 → 36 (75)		2	1010	127	130
47 → 12 (75)		17	1008	93	75
5 → 3 (40)		18	63	ND	ND
26 → 15.8 (39)		19	1100	19	262
13 → 8.2 (37)		17	1187	20	4866
141 → 100 (29)		63	740	59	3745
195 → 151 (23)		30	849	2	210





Diversa espressione SSTRs negli adenomi

Diversa espressione SSTRs nello stesso tipo di adenoma

Diversa espressione SSTRs condiziona effetto anti-secretivo ed anti-proliferativo

Efficacia clinica SSA

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Polimorfismo SSTRs (SSTR2 e SSTR5)

European Journal of Endocrinology (2011) 165 517–525 ISSN 0804-4643

CLINICAL STUDY

Identification of somatostatin receptor type 5 gene polymorphisms associated with acromegaly

Darja Ciganska[1], Inga Bakere[2], Ivo Kapa[1], Raitis Peculis[1], Andra Valtere[4], Liene Nikitina-Zake[1], Ieva Lase[2], Helgi B Schiöth[5], Valdis Pirags[1,2,3,*] and Janis Klovins[1,5,*]

Mutation of Somatostatin Receptor Type 5 in an Acromegalic Patient Resistant to Somatostatin Analog Treatment

EMILIA BALLARÉ*, LUCA PERSANI*, ANDREA G. LANIA, MARCELLO FILOPANTI,

Varianti di SSTRs
SSTR5 - SSTR5TDM4/SSTR5TDM5

A Potential Inhibitory Role for the New Truncated Variant of Somatostatin Receptor 5, sst5TMD4, in Pituitary Adenomas Poorly Responsive to Somatostatin Analogs

Mario Durán-Prado,* Alexandru Saveanu,* Raul M. Luque,* Manuel D. Gahete, Francisco Gracia-Navarro, Philippe Jaquet, Henry Dufour, María M. Malagón, Michael D. Culler, Anne Barlier, and Justo P. Castaño

Diversa modulazione di risposta legata a
- GSα mutazioni
- espressione recettoriale globale
- PDE
- ZAC
- AIP …

Clinical Characteristics and Therapeutic Responses in Patients with Germ-Line *AIP* Mutations and Pituitary Adenomas: An International Collaborative Study

Adrian F. Daly,* Maria A. Tichomirowa,* Patrick Petrossians,* Elina Heliövaara,

JCEM 2010

Acromegalia

Selezione dei pazienti → studi clinici

→ predittività di risposta (risposta a breve termine)

Dose/intervallo di somministrazione

Formulazione farmaceutica del farmaco

Durata della terapia

1 - TERAPIA COMPLEMENTARE

- pazienti operati
- pazienti sottoposti a radioterapia

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2 - TERAPIA PRIMARIA

assenza di deficit neurologici

Secrezione ormonale

Riduzione di massa

(Shrinkage)

Primary Medical Therapy for Acromegaly: An Open, Prospective, Multicenter Study of the Effects of Subcutaneous and Intramuscular Slow-Release Octreotide on Growth Hormone, Insulin-Like Growth Factor-I, and Tumor Size

J. S. BEVAN, S. L. ATKIN, A. B. ATKINSON, P.-M. BOULOUX, F. HANNA, P. E. HARRIS, R. A. JAMES, M. MCCONNELL, G. A. ROBERTS, M. F. SCANLON, P. M. STEWART, E. TEASDALE, H. E. TURNER, J. A. H. WASS, AND J. M. WARDLAW

First-line octreotide-LAR therapy induces tumour shrinkage and controls hormone excess in patients with acromegaly: results from an open, prospective, multicentre trial

Annamaria Colao*, Rosario Pivonello*, Francesca Rosetot, Patrizia Tita†, Ernesto De Menis§, Antonina Barreca‖‖, Roberto Ferrari**, Franco Mahini**, Maura Arosio†† and Gaetano Lombardi*

Primary Treatment of Acromegaly with Octreotide LAR: A Long-Term (Up to Nine Years) Prospective Study of Its Efficacy in the Control of Disease Activity and Tumor Shrinkage

Renato Cozzi, Marcella Montini, Roberto Attanasio, Mascia Albizzi, Giovanni Lasio, Sandro Lodrini, Paola Dassie, Liana Cortesi, and Giorgio Pagani

Significant tumour shrinkage after 12 months of lanreotide Autogel-120 mg treatment given first-line in acromegaly

Annamaria Colao*, Renata S. Auriemma*, Alberto Rebora†, Mariano Galdiero*, Eugenia Resmini†, Francesco Minuto†, Gaetano Lombardi*, Rosario Pivonello* and Diego Feroneț

3 - TERAPIA PRIMA DELL'INTERVENTO (PRETREATMENT)

- miglioramento quadro clinico in attesa dell'intervento

- facilitazione intervento, riduzione problemi anestesiologici e complicanze intra/postoperatorie

- outcome dell'intervento

Preoperative Octreotide Treatment in Newly Diagnosed Acromegalic Patients with Macroadenomas Increases Cure Short-Term Postoperative Rates: A Prospective, Randomized Trial

Sven M. Carlsen, Morten Lund-Johansen, Thomas Schreiner, Sylvi Aanderud, Øivind Johannesen, Johan Svartberg, John G. Cooper, John K. Hald, Stine L. Fougner, and Jens Bollerslev, on behalf of the Preoperative Octreotide Treatment of Acromegaly study group*

Risposta Biochimica

- OGTT

- GH < 2.5 ng/ml
- GH < 1.0 ng/ml
- IGF-I normale

- GH e IGF-I

GH/IGF-I Discordanze fino al 40% dei pazienti

- sistemi di dosaggio
- fattori interferenti (sesso e terapie concomitanti, nutrizione e malattie associate)
- effetto analoghi su secrezione epatica di IGF-I
- polimorfismi recettore del GH

Massa (shrinkage)

Giustina A Meta-Analysis on the effects of octreotide on tumor mass in acromegaly PLoS One. 2012

Octreotide – Lanreotide

Almeno riduzione del 20%

50-70% dei pazienti

Fattori determinanti
- formulazione farmaceutica
- risposta biochimica
- durata trattamento
- micro/macroadenomi
- primary therapy

Acromegalia

Resistenza agli analoghi

DEFINIZIONE

Criteri di - biochemical resistence
- tumor resistence

Durata della terapia (12 mesi)

Dose ottimale

Cosa fare ?

4 DEBULKING

TABLE 8. Definition of response to 12-month treatment of SA at therapeutic dosages in acromegaly

Full response	Control of GH and IGF-I levels and >20% tumor shrinkage in patients treated first-line Control of GH and IGF-I levels and >20% tumor shrinkage or stabilization of tumor remnant in patients treated second-line or in those with no tumor on magnetic resonance imaging at baseline
Partial response	Significant decrease (>50%) of GH and/or IGF-I levels with no achievement of control and/or >20% tumor shrinkage in patients treated first-line or second-line
Poor response or resistance	Nonsignificant decrease of GH and IGF-I levels with no achievement of control and no tumor shrinkage in patients treated first-line or increase in tumor size in any patient

Colao End Rev 2011

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 Lanzi, Alessandro Lodrini, Gaetano Lombardi, and Renato Cozzi

Karavitaki N, Turner HE, Adams CB, Cudlip S, Byrne JV, Fazal-Sanderson V, Rowlers S, Trainer PJ, Wass JA 2008 Surgical debulking of pituitary macroadenomas causing acromegaly improves control by lanreotide. Clin Endocrinol (Oxf) 68:970–975

Acromegalia

Roma,
9-11 novembre 2012

5 TERAPIA COMBINATA

DOPAMINERGICI *Sandret JCEM 2011*

Cabergoline mean dose (mg/wk)	Duration of treatment (months)	Under somatostatin analog and cabergoline: IGF-I (ng/ml), mean (SD)	IGF-I (% of ULN), mean (SD)	% change in IGF-I	% of patients with normal IGF-I	GH (ng/ml), mean (SD)	% of patients with GH < 2.5 ng/ml
3.5	3	340 (83)	100 (22)	25.7	50	6.1 (5.3)	40
2.6	7	457 (289)	130 (67)	28.7	42	4.6 (2.6)	21
1.1	14.2	423 (175)	155 (23)	27.3	50	1.58 0.4)	25
1.8	55.4	281 (133)	120 (91)	45.3	60	1.7 (1)	70
2.4	6.3	334 (170)	125 (64)	55.4	56	2.8 (4.1)	71

GH ANTAGONISTA

Combined treatment for acromegaly with long-acting somatostatin analogs and pegvisomant: long-term safety for up to 4.5 years (median 2.2 years) of follow-up in 86 patients

SJCMM Neggers, WW de Herder, JAMJL Janssen, RA Feelders and AJ van der Lely

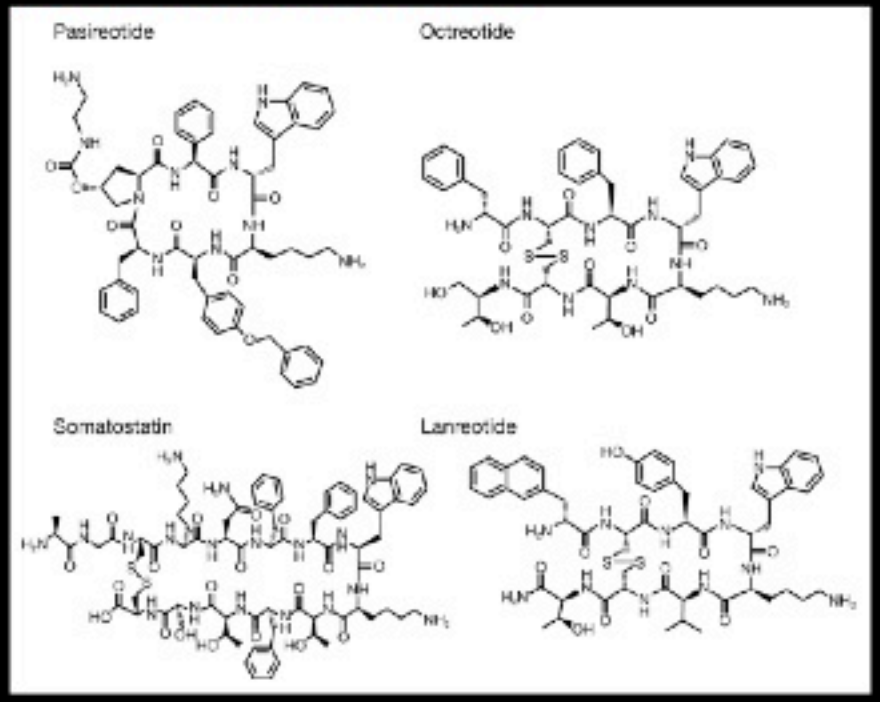
Coadministration of lanreotide Autogel and pegvisomant normalizes IGF1 levels and is well tolerated in patients with acromegaly partially controlled by somatostatin analogs alone

Aart-Jan van der Lely, Ignacio Bernabeu, Jan Gup, Philippe Caron, Annamaria Colao, Josef Marek, Sebastian Neggers and Pascal Birman

- Massa
- Controllo biochimico malattia
- Controllo quadro clinico
  (Metabolismo glucidico; Qualità di vita)
- Compliance
- Costi

Acromegalia

6- PASIREOTIDE



Studi in vitro

Exapeptide ciclico

Maggior emivita (7-11 ore) e durata d'azione

Multi Ligand
(Ligando Universale)

Recycling diverso

Ruolo di SSTR 5: affinità 40 volte maggiore

Studio in acuto *(Van der Hoeck JCEM 2004)*

12 pazienti
Octreotide 100 mcg sc vs Pasireotide 100, 250 mcg sc.

Acromegalia

Roma,
9-11 novembre 2012

6- PASIREOTIDE

Studio Fase II

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

JCEM 2010

Octreotide 100 mcg tid → Pasireotide 200, 400, 600 bid

Normalizzazione **GH/IGF-I**

9% octreotide, 19% pasireotide (28 gg), 27% pasireotide (74 gg)

Tumor **shrinkage**

> 20% nel 39%

Effetti collaterali: gastrointestinali, diabete

Cushing's disease

Roma,
9-11 novembre 2012

Octreotide

Pasireotide

SSTR5

The Effects of SOM230 on Cell Proliferation and Adrenocorticotropin Secretion in Human Corticotroph Pituitary Adenomas

Dalia L. Batista, Xun Zhang, Roger Gejman, Peter J. Ansell, Yunli Zhou, Sarah A. Johnson, Brooke Swearingen, E. Tessa Hedley-Whyte, Constantine A. Stratakis, and Anne Klibanski

JCEM 2006

Treatment of Pituitary-Dependent Cushing's Disease with the Multireceptor Ligand Somatostatin Analog Pasireotide (SOM230): A Multicenter, Phase II Trial

M. Boscaro, W. H. Ludlam, B. Atkinson, J. E. Glusman, S. Petersenn, M. Reincke, P. Snyder, A. Tabarin, B. M. K. Biller, J. Findling, S. Melmed, C. H. Darby, K. Hu, Y. Wang, P. U. Freda, A. B. Grossman, L. A. Frohman, and J. Bertherat

JCEM 2009


THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A 12-Month Phase 3 Study of Pasireotide in Cushing's Disease

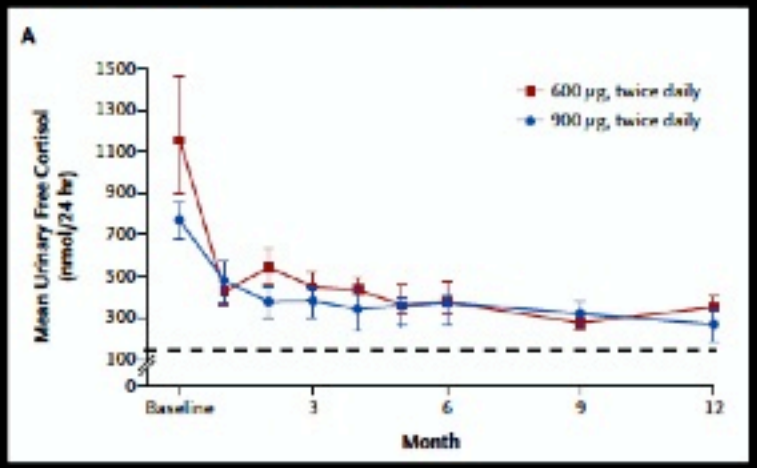
Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D., John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D., Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc., Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D., for the Pasireotide B2305 Study Group

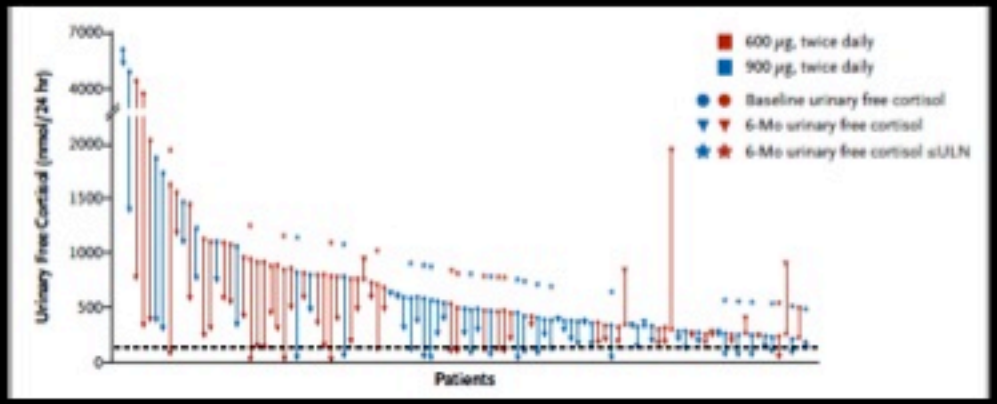
NEJM 2012

Cushing's disease

Roma,
9-11 novembre 2012

Biochimica

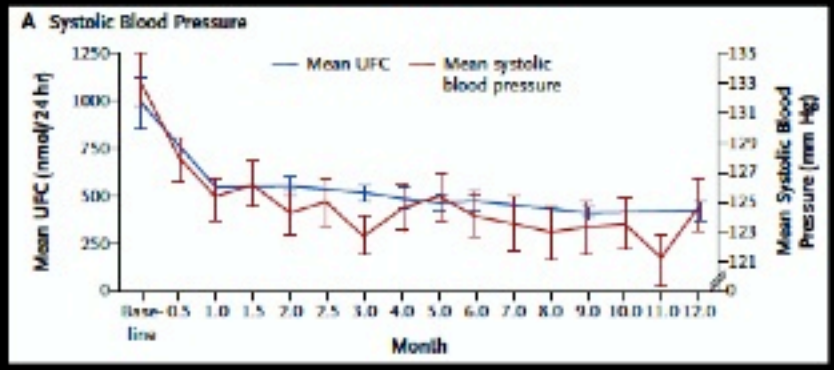




normalizzazione UFC

6 mesi 16-29 % - 12 mesi 13-25%

Clinica



Adverse events

Peggioramento glicemico 73%

Hb glicosilata 5.8 → 7.2%

Acromegalia

Roma,
9-11 novembre 2012

EFFETTI COLLATERALI

Locali
Addominali
Alopecia

Aritmie: bradicardia, QT

Calcolosi colecistica
- asintomatica
- complicata

Metabolismo glucidico
- ipoglicemia
- insulino resistenza
- funzione beta cellulare

Effects of Somatostatin Analogs on Glucose Homeostasis: A Metaanalysis of Acromegaly Studies

Gherardo Mazziotti, Irene Floriani, Stefania Bonadonna, Valter Torri, Philippe Chanson, and Andrea Giustina

JCEM 2009

Non funzionanti

TSH-omi