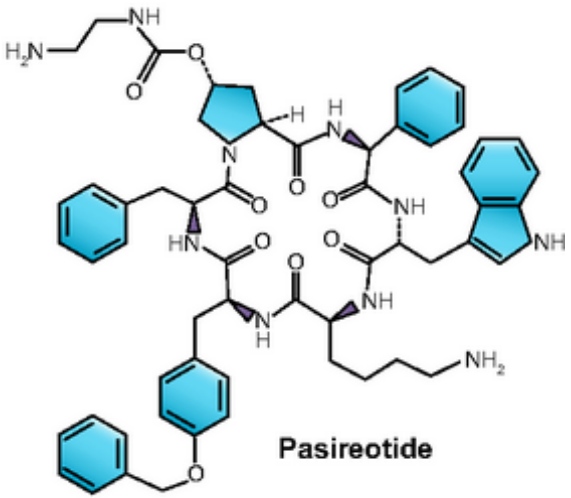
Pasireotide in acromegalia



Cuevas-Ramos D., Fleseriu M. 2016

Criticità:

Fattori predittivi di risposta

Efficacia nella real life

Profilo di sicurezza

Efficacia di Pasireotide Lar in pazienti resistenti alla terapia con analoghi della somatostatina di prima generazione: esperienza monocentrica

Chiloiro S[1], Bima C[1] , Visconti F.[1], Rossi L.[1], Giampietro A[1], Bianchi A[1], Lauretti L[2], Gessi M[3], Tartaglione T[4], Rindi G[3], Anile C [2], Pontecorvi A[1], De Marinis L[1].

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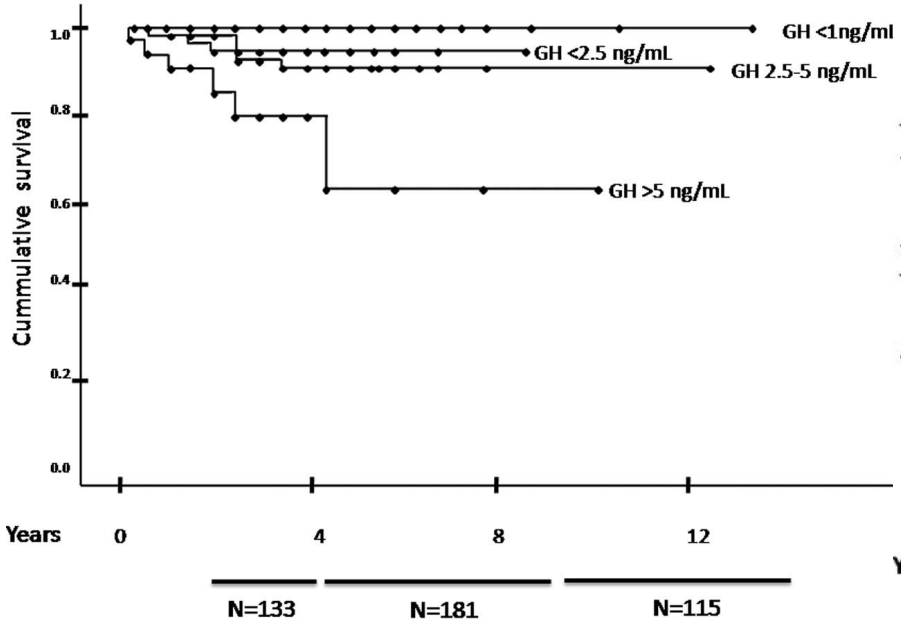
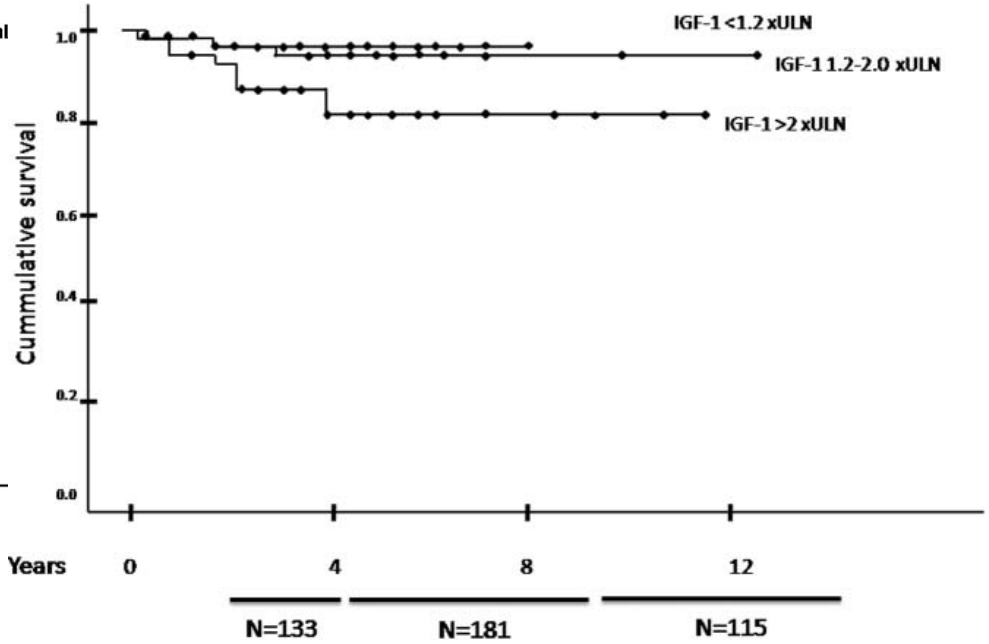
Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni NON ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario

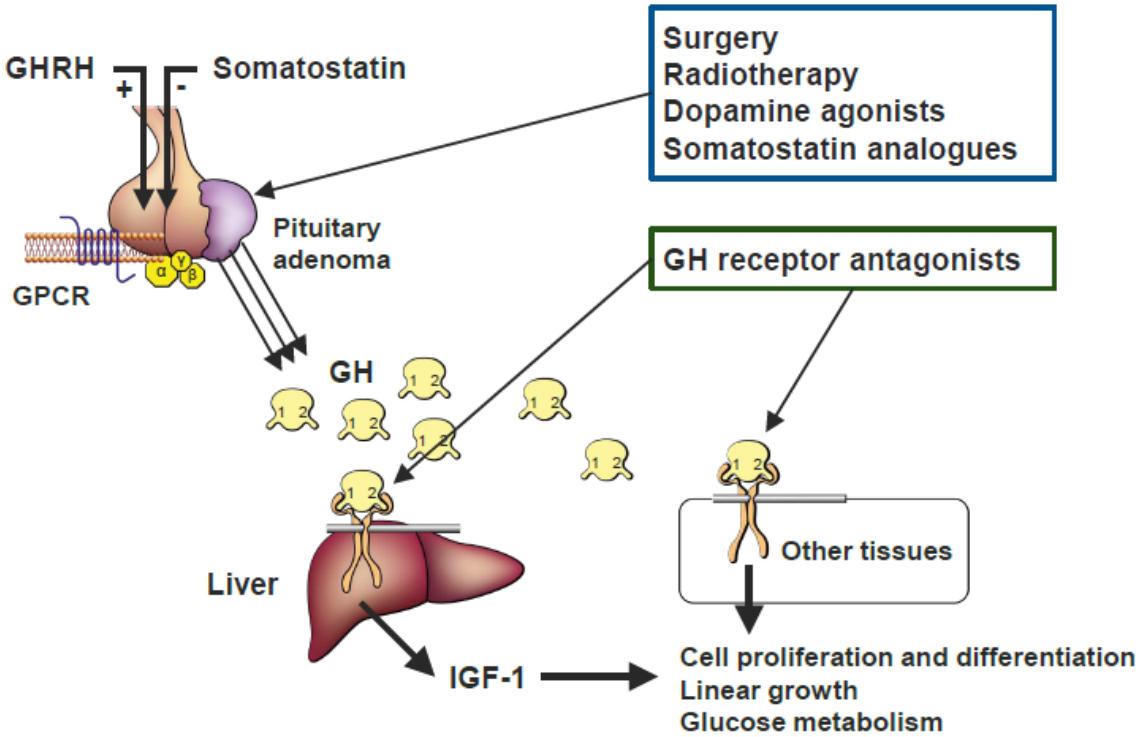
Survival and and acromegaly biochemical control





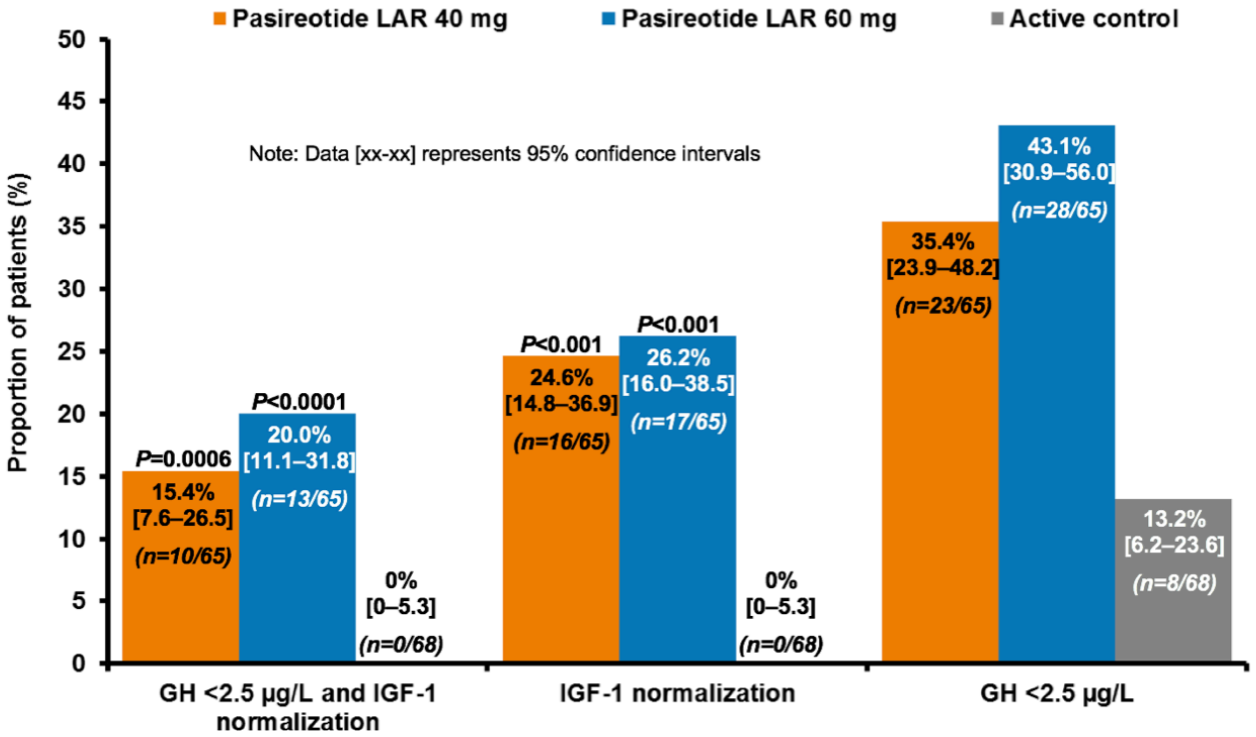
Mercado et al.J Clin Endocrinol Metab. 2014Dec;99(12):4438-46

Therapeutic Options



Fleseriu M et al. Discov Med 2014; 17: 329-338

Efficacy of Pasireotide Lar in PAOLA



15.4% and 20.0% of Pasireotide LAR 40 mg and 60 mg patients achieved biochemical control at 24 weeks, compared with no patients in the active control group

Gadelha MR et al. Lancet Diabetes Endocrinol. 2014;2(11):875-84.

Aim

- ✓ to analyze to clinical and morphological features of acromegaly patients resistant to first generation SSA and treated with Pasireotide Lar;
- ✓ to identify the outcome of Pasireotide Lar therapy;
- ✓ to identify prognostic markers of treatment responsiveness

Material and methods

A mono-centric, longitudinal study was designed

Inclusion Criteria	Exclusion Criteria
1. Resistance to first generation SSAs 2. Duration of Pasireotide Lar therapy of at least 6 months	1. Previous radiotherapy

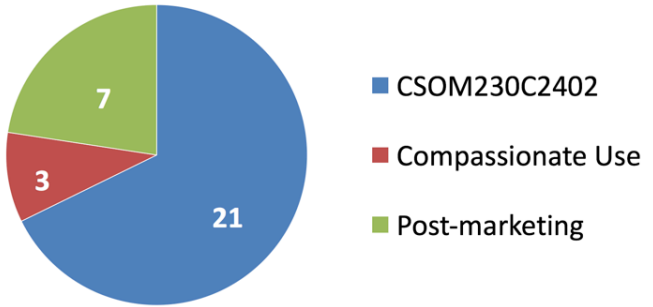
Resistance to first-generation SSA treatment: definition
1. Partial response: significant decrease (50%) of GH and/or IGF-I levels with no achievement of control and/or 20% tumor shrinkage in patients treated first-line or second-line 2. Poor response or resistance: Non significant decrease of GH and 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 *A. Colao et al, Endocrine Reviews 2011*

Results

31 patients met the inclusion criteria.

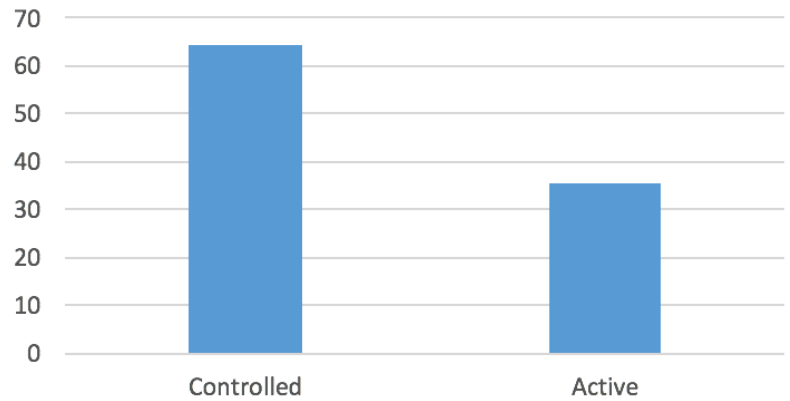
Gender F num. (%) M num. (%)	 20 (64.5%) 11 (35.5%)
Mean age at acromegaly diagnosis, yrs. (SD)	38 (10)
Mean GH at acromegaly diagnosis ng/mL (SD)	34.6 (18)
Mean IGF-I x ULN at acromegaly diagnosis (SD)	3.3 (0.9)
Cavernous sinus invasion n (%)	31 (100%)
Infiltration of Third Ventricle n (%)	4 (12.9%)
Radical neurosurgery n (%)	0 / 31
Ki67 Li % (SD)	2.5 (1.5)
Mean age at Pasireotide treatment start, yrs. (SD)	43 (10)
Man GH at Pasireotide treatment start ng/mL (SD)	7.2 (3.8)
Mean IGF-I x ULN at Pasireotide treatment start (SD)	2.4 (1)

- ✓ All patients had undergone partial pituitary neurosurgery
- ✓ All patients failed to reached the acromegaly biochemical control with first generation SSAs, being resistant to first generation SSAs



Results

- ✓ 20 of 31 patients (64.5%) reached the biochemical control of acromegaly
- ✓ In a single case, at neuro-radiological follow-up, volumetric reduction of residual pituitary adenoma occurred.

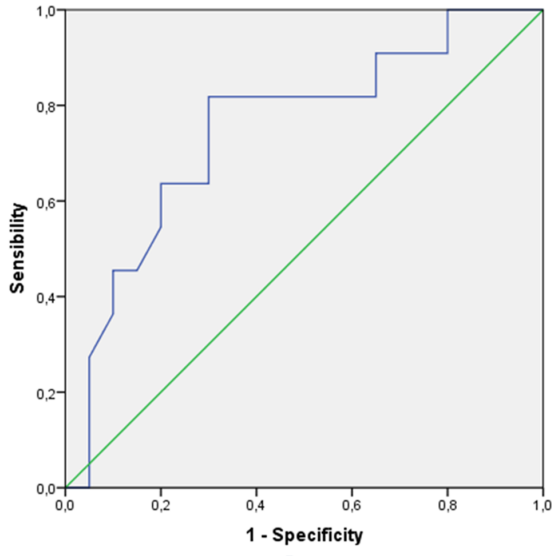


Results

	Responsive pts	Not Responsive pts	p-value
Gender **F, n (%)** **M, n (%)**	 9 (69.2%) 11 (61.1%)	 4 (30.8%) 7 (38.9%)	 0.6
Mean age at acromegaly diagnosis, yrs (SD)	39.5 (9)	37.4 (12)	0.3
Mean GH at acromegaly diagnosis, ng/mL (SD)	34.5 (22)	34.8 (11)	0.9
Mean IGF-I x ULN at acromegaly diagnosis (SD)	2.9 (0.9)	3.9 (0.4)	**0.04**
Age at Pasireotide treatment start, yrs (SD)	44.4 (8)	41.4 (14.5)	0.4
Mean GH at Pasireotide treatment start, ng/mL (SD)	7 (4.8)	7.8 (1.3)	0.3
Mean IGF-I x ULN at Pasireotide treatment start (SD)	2.2 (0.9)	2.9 (1.1)	0.09

Results

IGF-I value 3.3 time higher than the upper limit of normality (ULN) can predict the unresponsiveness/resistance to Pasireotide Lar therapy



AUC (95%CI)	0.75 (0.56-0.93)
p-value	0.02
OR (95%CI)	10.5 (1.7-63.9)

Results

Compound	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
RECEPTOR SUBTYPE AFFINITY (IC50, nM)					
Somatostatin-14	2.26	0.23	1.43	1.77	0.88
Somatostatin-28	1.85	0.31	1.3	ND	0.4
Octreotide	1140	0.56	34	7030	7
Lanreotide	2330	0.75	107	2100	5.2
Pasireotide	9.3	1	1.5	>100	0.16

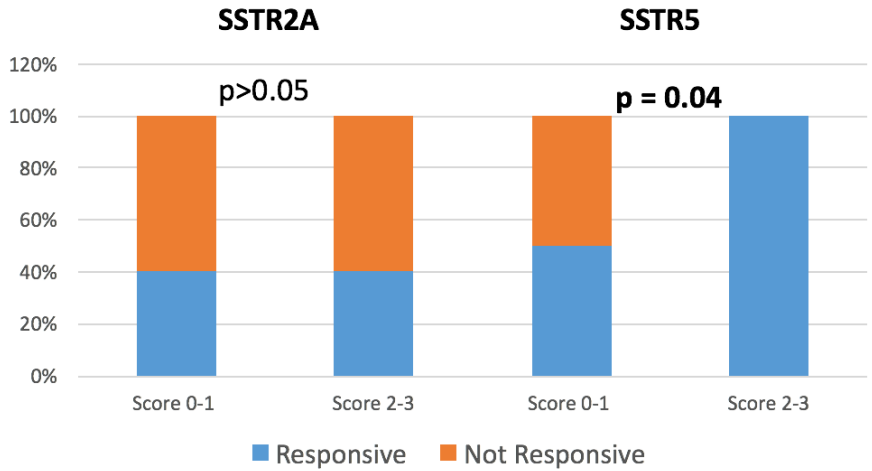
Gadelha M, Lancet Endocrinology, 2: 875-884, 2014

Score 0: no immunoreactivity;

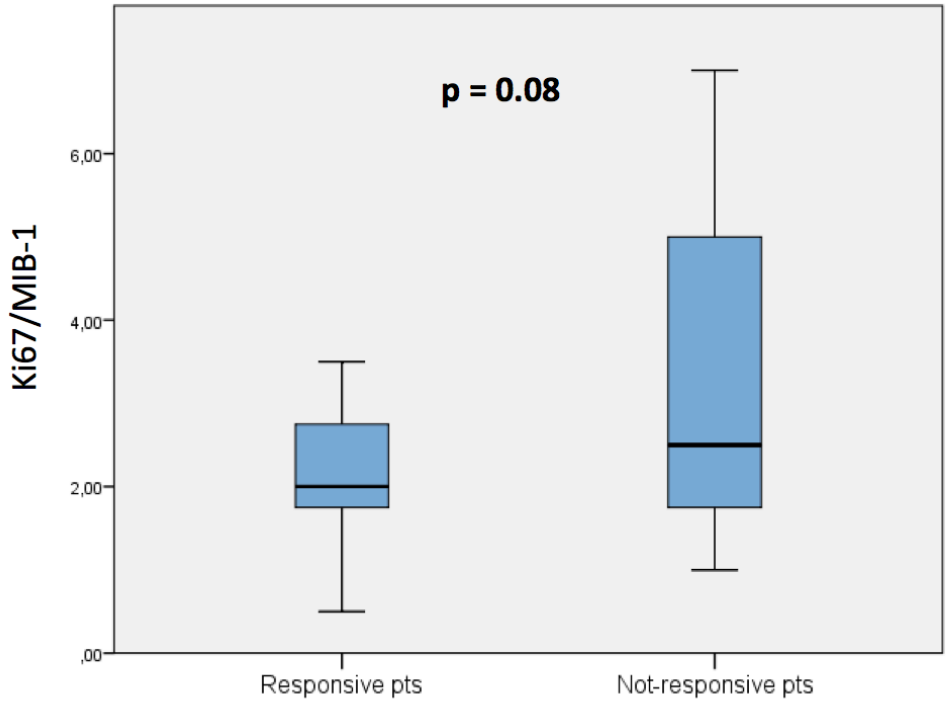
Score 1: cytoplasmic immunoreactivity;

Score 2: membranous staining in less than 50% of cells or incomplete membranous staining;

Score 3: circumferential membranous staining in more than 50% of tumour cells

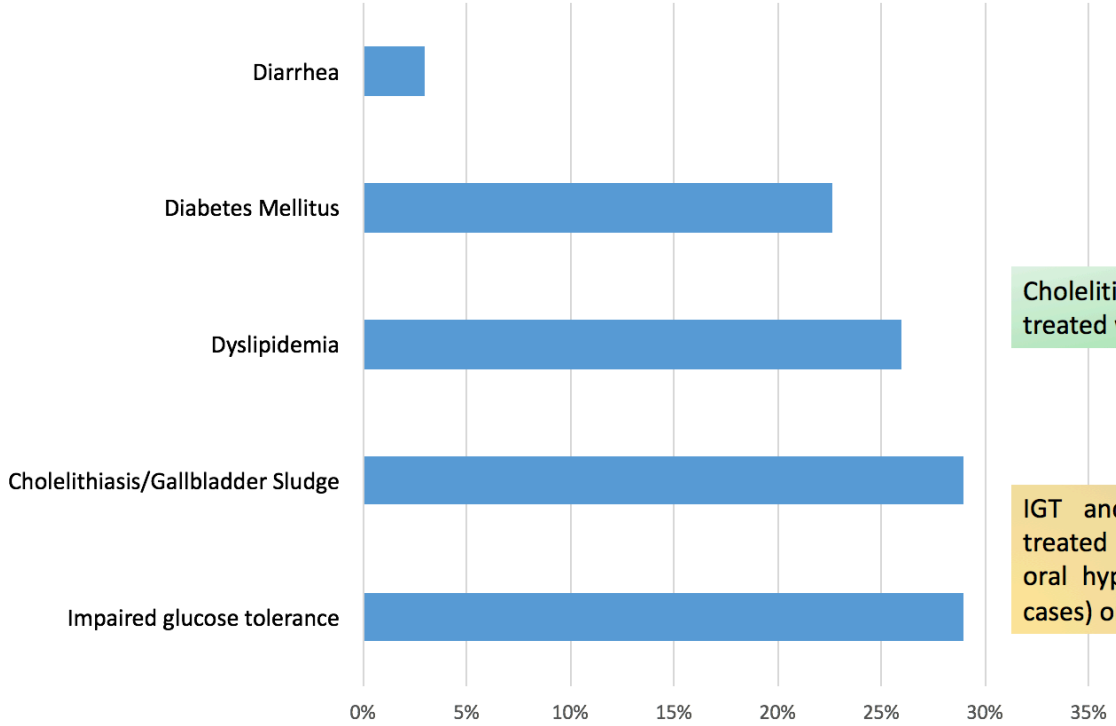


Results



- ✓ Mean Ki67/MIB-1 Li was 2.5%
- ✓ None case had a KI67/MIB-1 lower than 1.5%

Results



Cholelitiasis/gallbladder sludge was treated with ursodeoycholic acid

IGT and diabetes mellitus were treated with hypo-caloric diet and oral hypoglycemic agents (42% of cases) or insulin (9% of cases).

Pasireotide Lar was never withdrawn for the occurrence of adverse events

In conclusion…

- ✓ Pasireotide Lar allow the biochemical control of acromegaly in a high percentage of first generation SSA resistant patients of our mono-centric series;
- ✓ The main determinant of Pasireotide Lar resistance were IGF-I value higher than 3.3 ULN, the low expression of SSTR5.

Grazie!

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