THE COMBINED THERAPY IN CUSHING'S DISEASE

Pasireotide and Cabergoline

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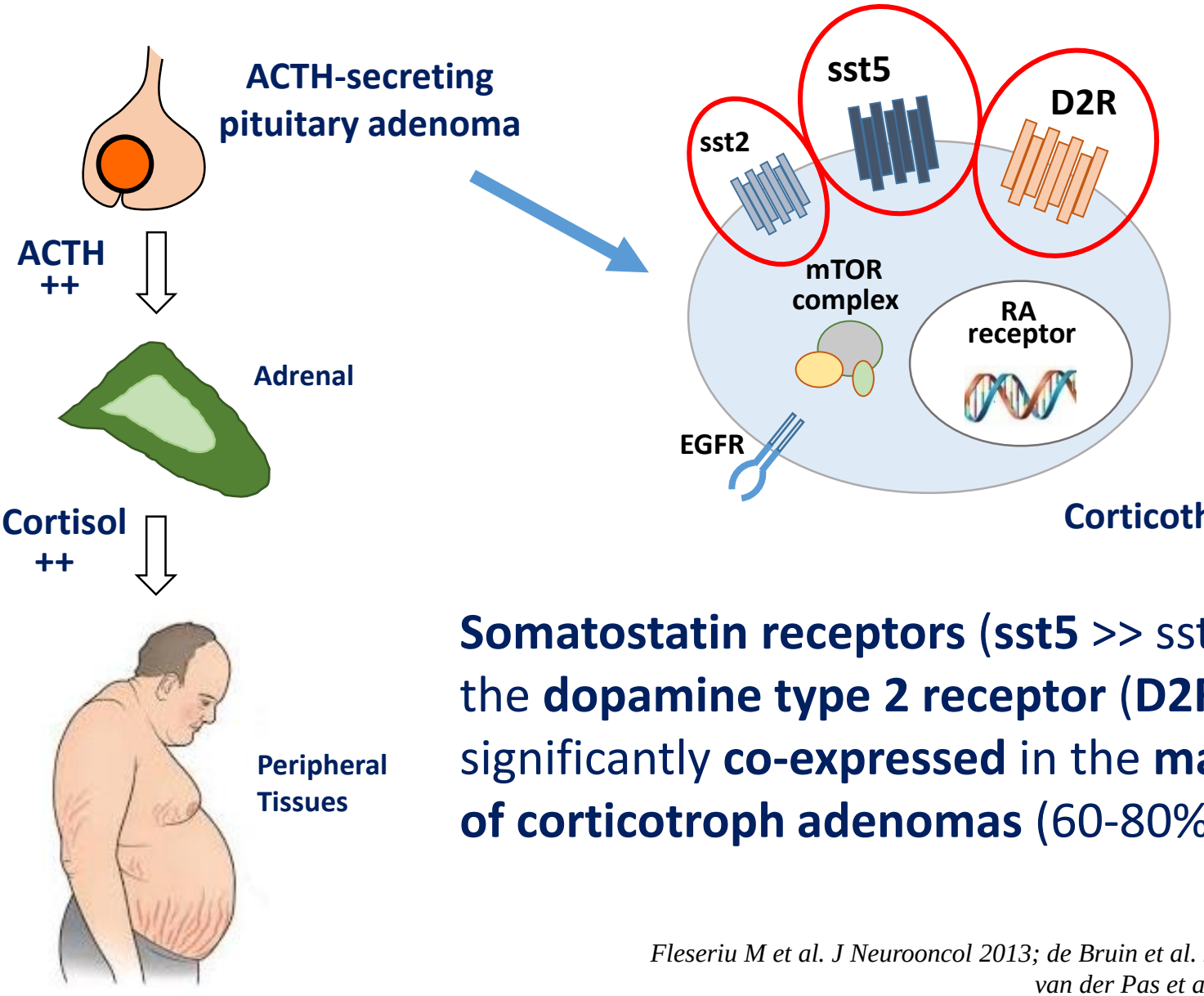
Pathophysiological Background

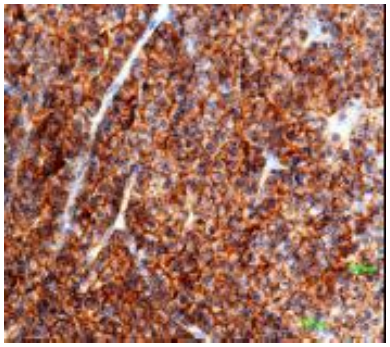


Somatostatin receptors (**sst5** >> sst2) and the **dopamine type 2 receptor** (**D2R**) are significantly **co-expressed** in the **majority of corticotroph adenomas** (60-80%)

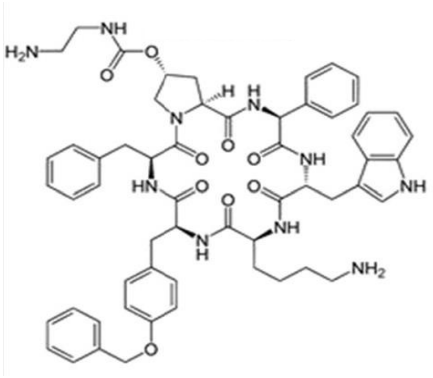
Fleseriu M et al. J Neurooncol 2013; de Bruin et al. JCEM 2009; van der Pas et al JCEM 2013

Pathophysiological Background

sst5



Pasireotide



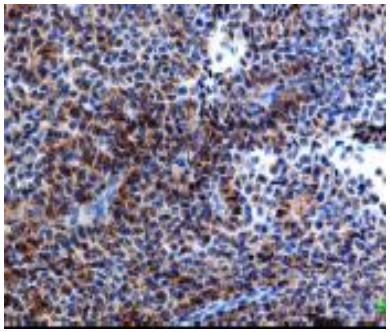
Somatostatin receptors' panligand

Sst5 > sst2 > sst3 > sst1

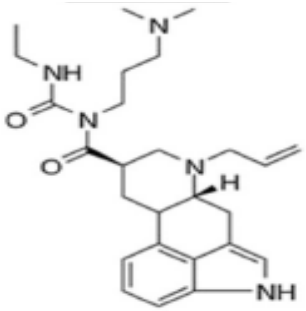
Binding affinity in the (sub)nanomolar range

Receptor cross-talk/hetero-dimerization → **possible enhanced pharmacological effects**

D2R



Cabergoline



Dopamine agonist
(D2R selective binding affinity)

63-69 hrs plasma half-life, good safety profile

IC_{50} for D2R about **10-fold higher** compared **to Bromocriptine**

Pivonello et al. EJE 2007; Kidd et al. Cancer 2008; van der Pas et al. JCEM 2013; Rocheville et al. Science 2000

Cabergoline and Cushing's Disease

Pivonello 2009[28]	Prospective, single centre	20	CD unsuccessfully treated with surgery	1 mg/week, monthly increment of 1 mg to a maximum of 7 mg/week	24-h UFC at or below the ULN [normal range: 97–372 nmol/l (35–135 ng/ml)]	3 months (predefined) 12 months (predefined) 24 months (predefined)	35% 50% 40%
Godbout 2010[26]	Retrospective, multicentre	30	CD unsuccessfully treated with surgery (n = 27) and primary treatment with cabergoline (n = 3)	0·5–1 mg/week titrated to maximum 6 mg/week	UFC normalization (reference range not given)	3–6 months 12–60 months	37% 30%
Lila 2010[27]	Prospective, single centre	18	CD unsuccessfully treated with surgery	1 mg/week, monthly increment of 1 mg to maximum dose of 5 mg/week	Midnight serum cortisol <138 nmol/l (50 ng/ml) or low-dose dexamethasone suppression serum cortisol <50 nmol/l (18 ng/ml)	5 months (predefined) 12 months (predefined)	28% 22%
Vilar 2010[29]	Prospective, single centre	12	CD unsuccessfully treated with surgery	2–3 mg/week	24-h UFC within the normal range [28–248 nmol/l (10–90 ng/ml)]	6 months (predefined)	25%

Few clinical studies (3/4 prospective) in patients mainly treated **after uncessfull surgery**, with **variable dose titration** and **follow-up (3-60 months)**

Response rate: 25 - 50%

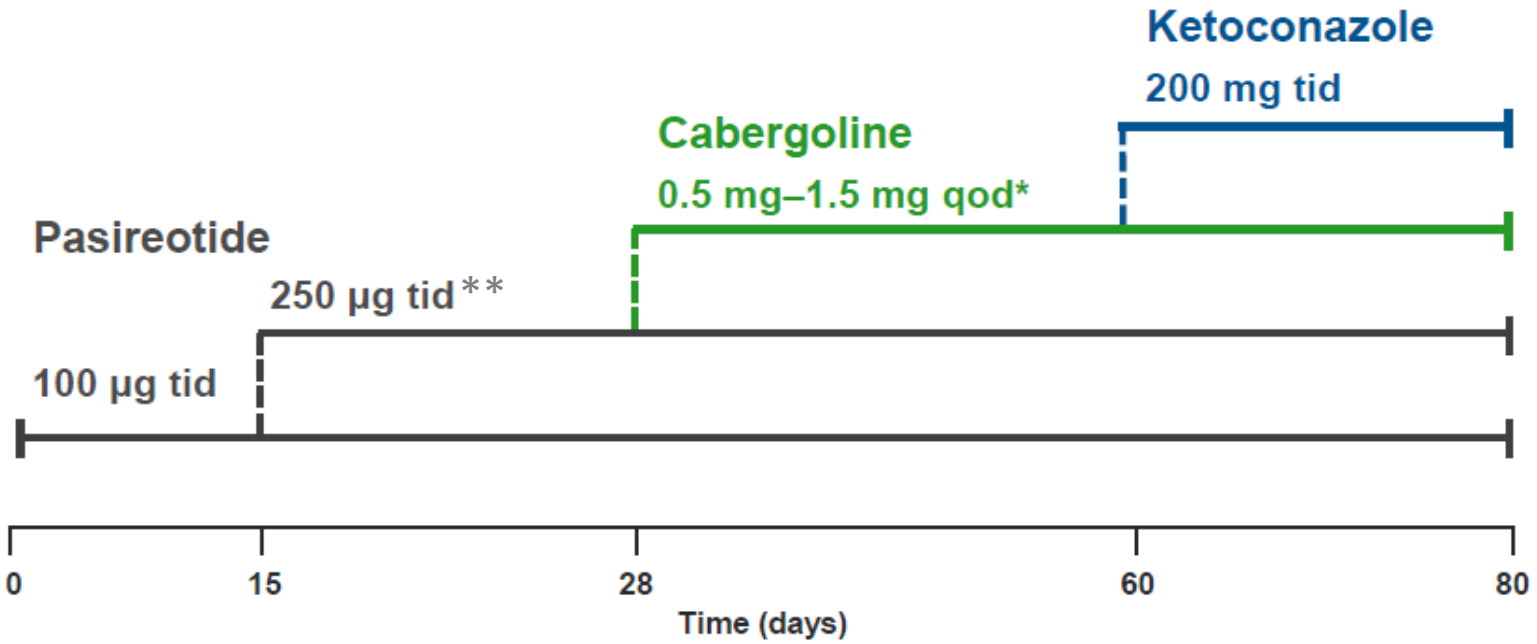
Gadelha et al. Clin Endocrinol 2014

Pasireotide and Cabergoline

Pasireotide Alone or with Cabergoline and Ketoconazole in Cushing's Disease

Richard A. Feelders, M.D., Ph.D.

Prospective, open-label, multicentre study to assess the efficacy of **pasireotide alone** and following **sequential addition of cabergoline (and ketoconazole)** in 17 patients with uncontrolled CD



***Cabergoline** was initiated at a dose of 0.5 mg qod and increased to 1 mg qod and 1.5 mg qod after **5** and **10 days**, respectively (**max dose 4.5 - 6 mg/week**)

****Pasireotide** max dose **750 ug/daily**

Feelders et al. NEJM 2010

Pasireotide Alone or with Cabergoline and Ketoconazole in Cushing's Disease

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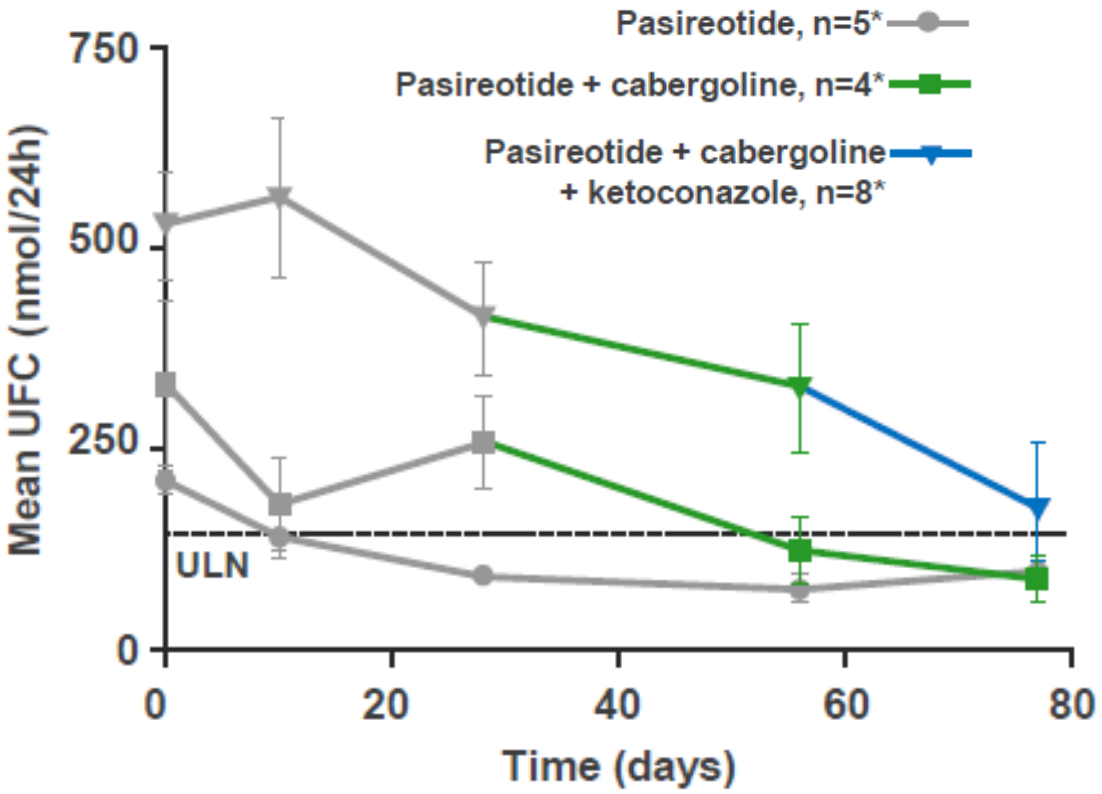


UFC normalization
(primary end point)

Pasireotide : 5/17 (29%)

Pasireotide + Cabergoline : 9/17 (29% **+ 24%**)

54%

Pasireotide + Cabergoline + Ketoconazole : 15/17 (54% **+ 34%**)

88%

Clinical features (e.g. blood pressure, waist circumference, weight) of CD **also improved**

Glycated hemoglobin level raised from 5.8 ± 0.2% (basal) to 6.7±0.3% (study end), less compared to the Pasireotide Phase III Study (7.2 - 7.4%)

Feelders et al. NEJM 2010

Pasireotide and Cabergoline

- Glucose homeostasis -

Pasireotide Phase III Study: "The most frequently reported grade 3 or 4 adverse events were hyperglycemia and diabetes mellitus, occurring in 13% and 7% of patients, respectively"

Colao et al. NEJM 2012

Disruption of the Dopamine D2 Receptor Impairs Insulin Secretion and Causes Glucose Intolerance

Garcia-Tornadù et al. Endocrinology 2010

Randomized Pilot Study of Cabergoline, a Dopamine Receptor Agonist: Effects on Body Weight and Glucose Tolerance in Obese Adults

Gibson et al. Diabetes Obes Metab. 2012

Effect of Cabergoline on Metabolism in Prolactinomas

Auriemma et al. Neuroendocrinology 2013

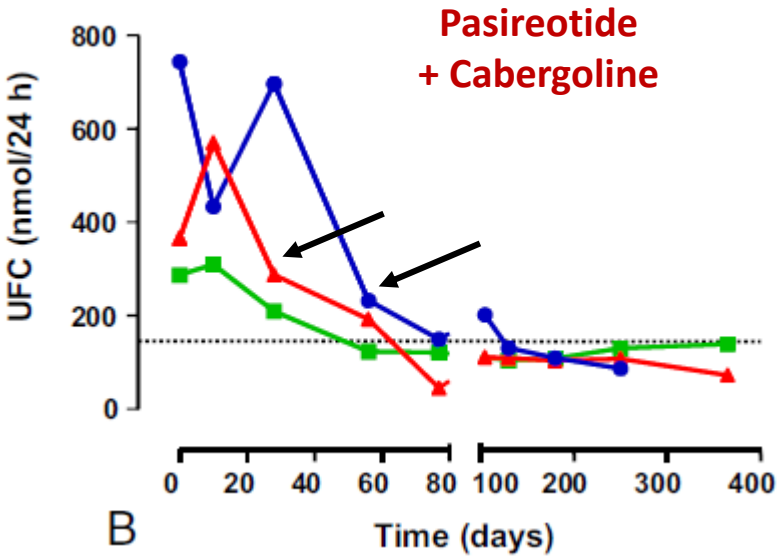
Cushing's Disease?

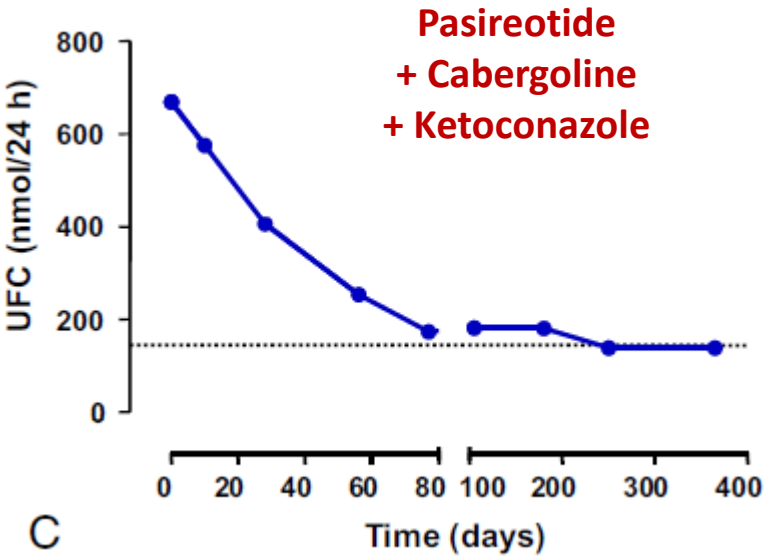
"**Fasting serum glucose** and **insulin levels**, as well as **HOMA-IR, significantly decreased**; the prevalence of diabetes mellitus and impairment of glucose tolerance changed from 25 and 37.5% at baseline to 10 and 20% after 24 month treatment, respectively".

Pivonello et al. JCEM 2009

Pasireotide and Cabergoline

Biochemical responses were maintained for more than 1 years with medical combination therapy (extension study)





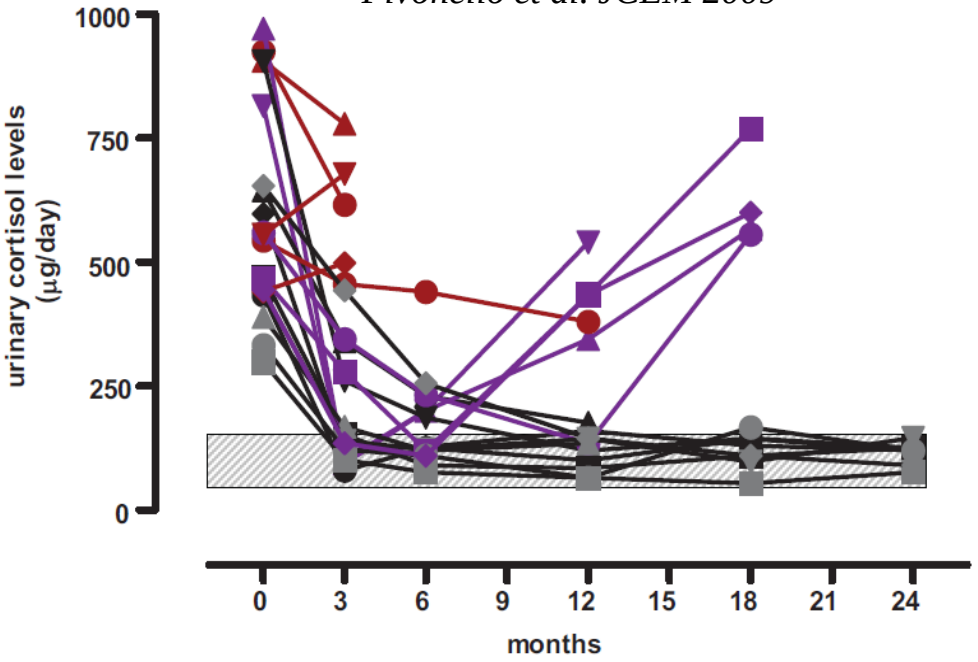
In the two patients represented by the **blue** and **red curve** (**black arrows**), ketoconazole was withdrawn after the regular study period of 80 days, and **combined therapy with Pasireotide and Cabergoline** succeeded **to maintain normal UFC levels up to 400 days**

Interestingly, **no escape from response was observed** during the core study or extension **for those patients receiving medical combination therapy**

Feelders et al. JCEM 2010

Cabergoline and Cushing's Disease
- Escape from Response-

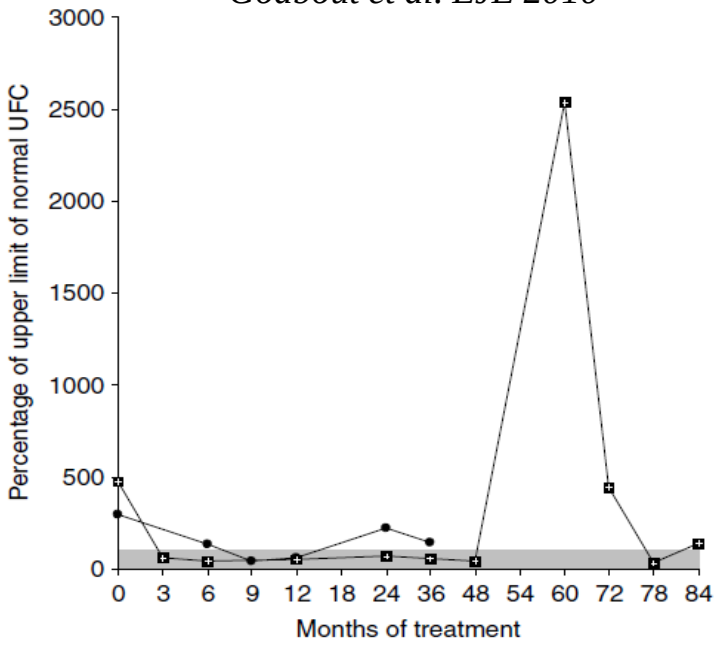
Pivonello et al. JCEM 2009



5/20 (25%) patients - 2 full responders and 3 partial responders - experienced **treatment escape** after **12–18 month treatment**

Interestingly, **in most cases** the authors observed an **early escape** after **reaching normal** (or close to normal) **UFC levels**

Godbout et al. EJE 2010



Escape in **5/30 (17%) patients**

Authors observed escape to treatment after **2 and 5 years** in 2 full responders patients

⇩

selection and growth of **corticotroph cells not expressing high levels of D2R**

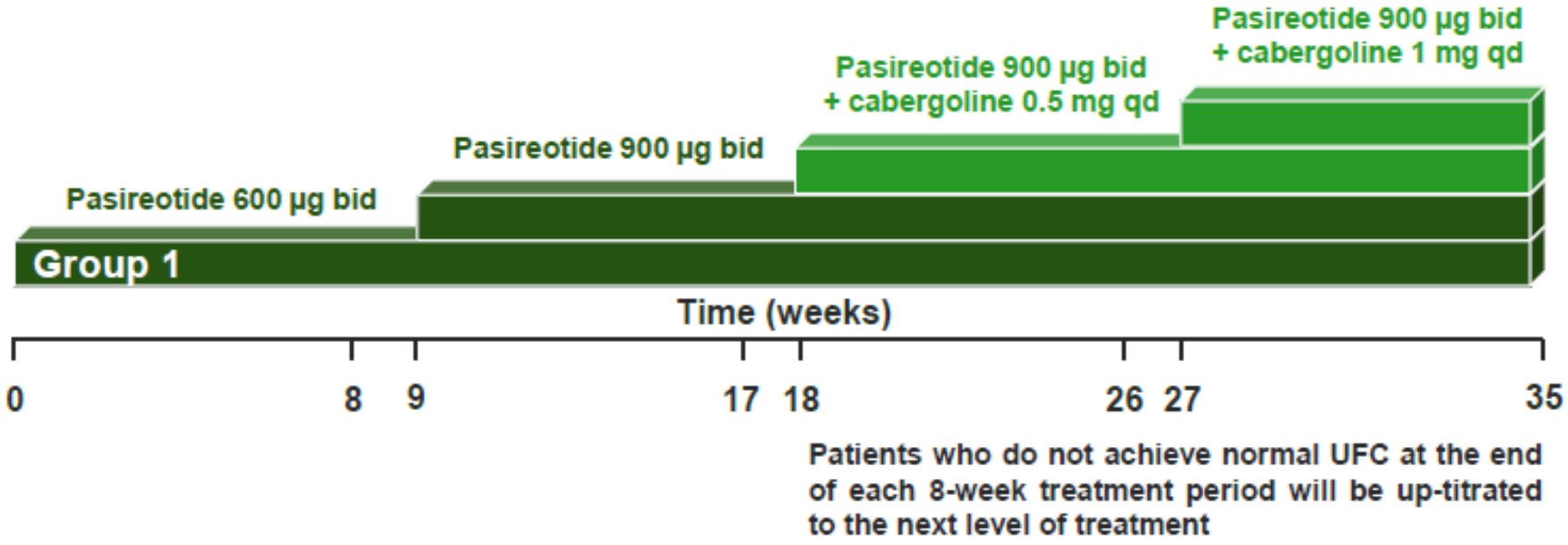
Pasireotide and Cabergoline

Study of the **Efficacy and Safety** of **Pasireotide s.c. +/- Cabergoline in Patients With Cushing's Disease** (MACS2125)

Interventional Phase II Study

Group 1: patients who are not treated with pasireotide at screening

Group 2: patients who are currently treated with maximal tolerated doses of pasireotide monotherapy for at least 8 weeks, but still with elevated UFC.



bid, twice daily; qd, once daily; mUFC, mean UFC

ClinicalTrials.gov

Study of the **Efficacy and Safety** of **Pasireotide s.c. +/- Cabergoline in Patients With Cushing's Disease** (MACS2125)

ClinicalTrials.gov

Primary Outcome Measures:

Proportion of patients who attain **normalization of UFC**

- week 35 for Group 1
- week 17 for Group 2

The study will also assess **drug safety**, **changes in QoL** and changes on **clinical signs and symptoms**

Inclusion of patients with **recurrent**, **persistent** and **newly diagnosed CD**

(De novo CD can be included only **if they are not considered candidates for pituitary surgery)**

Washout periods before screening assessments are performed:

- Inhibitors of steroidogenesis (**ketoconazole, metyrapone**): **1 week**
- Progesterone receptor antagonist (**mifepristone**): **4 weeks**
- **Bromocriptine, cabergoline** and PPARγ agonists: **4 weeks**
- Octreotide LAR, Lanreotide SR and autogel: 14 weeks; Octreotide s.c.: 1 week
- Pasireotide LAR: 12 weeks; **Pasireotide s.c**.: **4 weeks** ;

Special safety assessments: blood glucose, insulin, HbA1c, GH and IGF-1, thyroid and liver function tests, gallbladder examinations and ECGs

CONCLUSIONS

1. The widely described **co-expression of SSTRs** (in particular **sst5**) **and D2R** on corticotroph adenoma cell membrane represent a **strong molecular rationale for the combination therapy with Pasireotide and Cabergoline in Cushing's Disease**

2. **Sst5 and D2R co-stimulation** may result in a **synergistic effect of the two drugs**, due to the demonstrated receptor **cross-talk on cell membrane**

3. Differently from what observed during monotherapy (in particular for Cabergoline), **combination treatment with Pasireotide and Cabergoline results in a sustained patients' response**, with **no escape showed** up to more than 1 year follow-up

4. **Addition of Cabergoline to Pasireotide** may result in **beneficial effects** on patients' **glucose homeostasis**

5. Both **Pasireotide and Cabergoline seem to be more effective** in patients with **mild to moderate UFC levels**.
   In patients with severe hypercortisolism, starting treatment with steroidogenesis inhibitors or glucocorticoid-receptor antagonist (later on withdrawn) could be a feaseable strategy to overcome this possible limitation

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GRAZIE PER L'ATTENZIONE