First and second line treatments

European Reference Network
for rare or low prevalence complex diseases
Network
Endocrine Conditions
(Endo-ERN)
Member
AO di Padova — Italia

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Endo-ERN

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 ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

NOTHING TO DISCLOSE

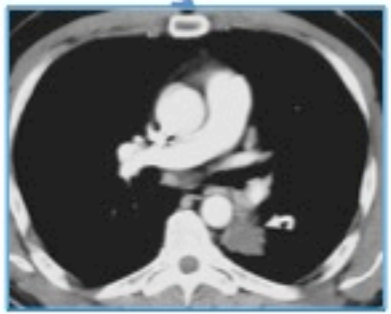
Cushing's Syndrome (CS)

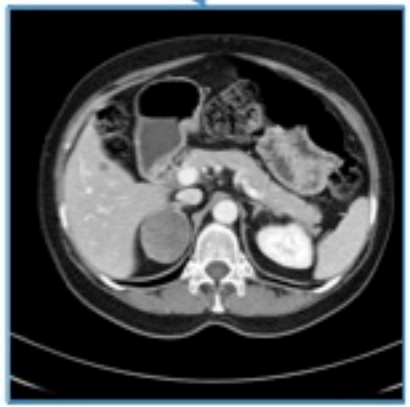
ACTH

dependent

independent

80%





pituitary

ectopic

10%

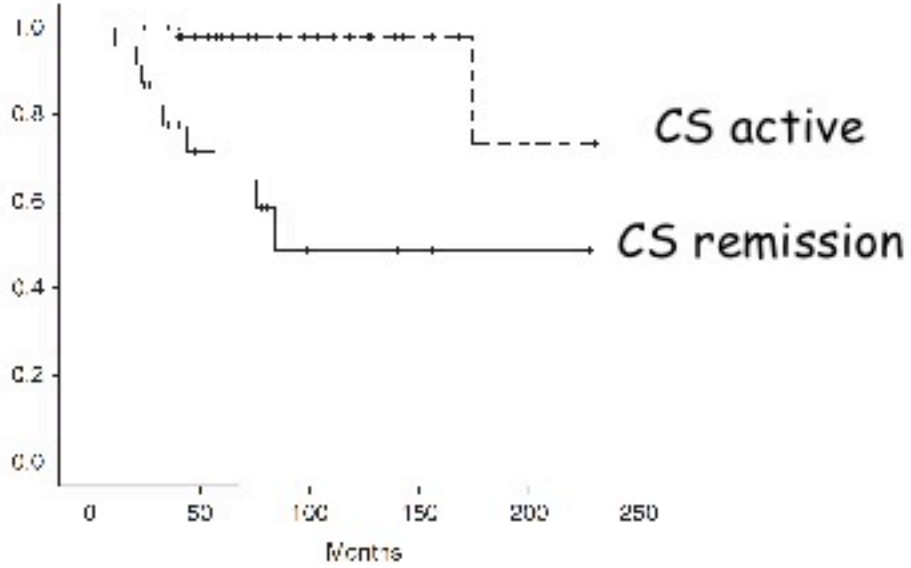
adrenal

10%

Mortality in active and remission CS

Surgical remission of Cushing's syndrome reduces cardiovascular risk

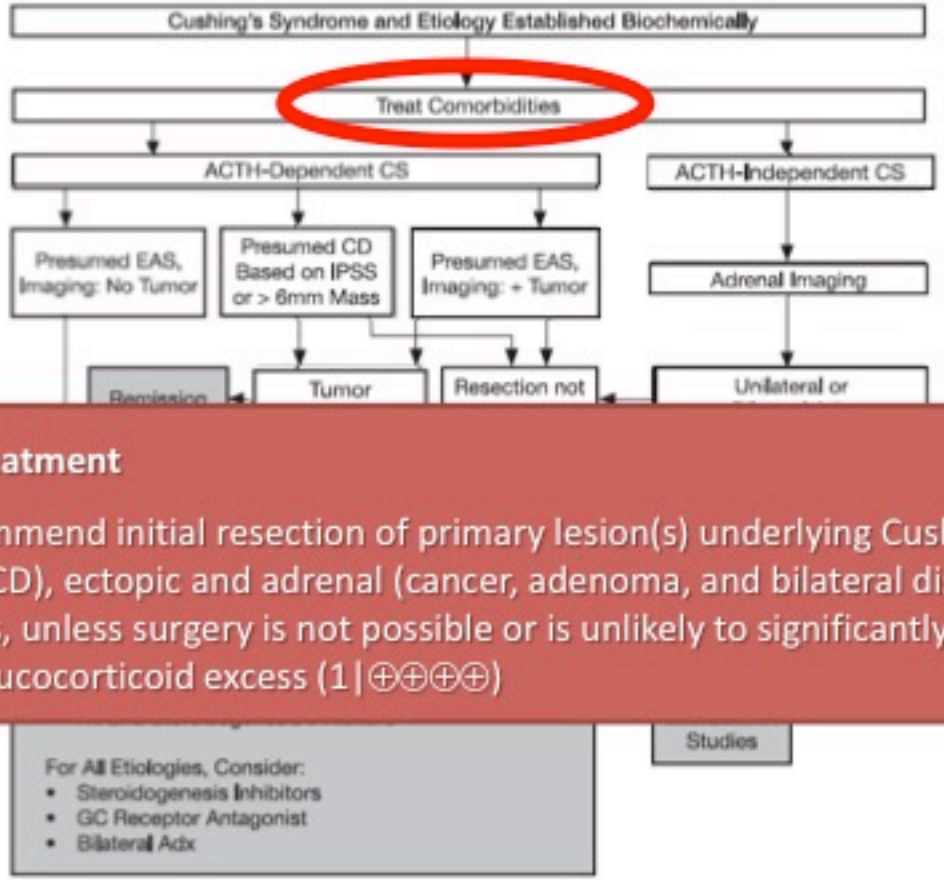
- 51 CS remission (5 years)
- 24 CS with active hypercortisolism
- 60 pituitry incidentaloma (controls)



Terzolo M, EJE 2014

Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline

Lynnette K. Nieman, Beverly M. K. Biller, James W. Findling, M. Hassan Murad, John Newell-Price, Martin O. Savage, and Antoine Tabarin



First line treatment

- ✓ We recommend initial resection of primary lesion(s) underlying Cushing's disease (CD), ectopic and adrenal (cancer, adenoma, and bilateral disease) etiologies, unless surgery is not possible or is unlikely to significantly reduce glucocorticoid excess (1|⊕⊕⊕⊕)

JCEM, 2015

Goals of CS treatment

The main goals of therapy in CS are

1 normalization of cortisol levels

2 reversal of clinical picture

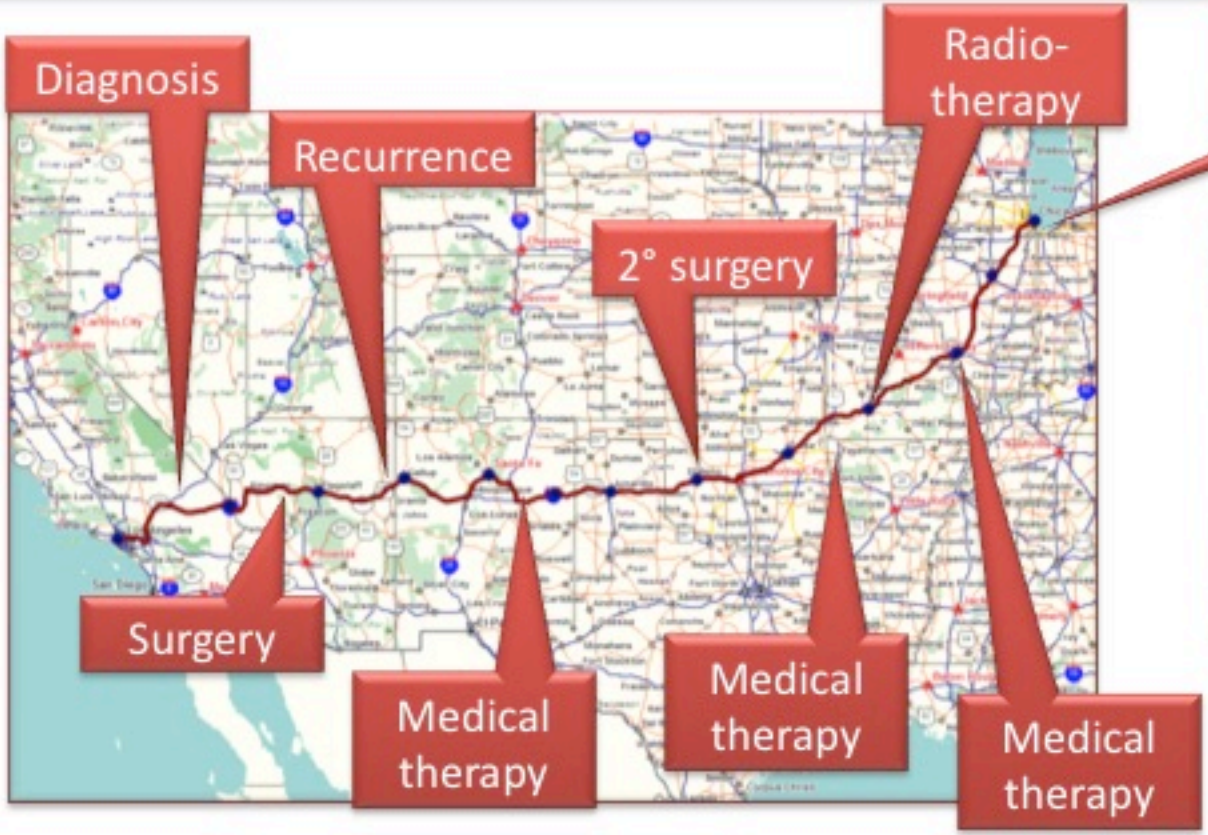
3 prevention or recovery of the concomitant comorbidities and clinical complications

4 long-term disease control (without disease recurrence)

THESE ARE IDEAL GOALS, DIFFICULT TO ACHIEVE IN CLINICAL PRATICE

➔ FREQUENTLY CS PATIENTS REQUIRE A MULTIMODAL TREATMENT APPROACH

Duration of hypercortisolism in CD



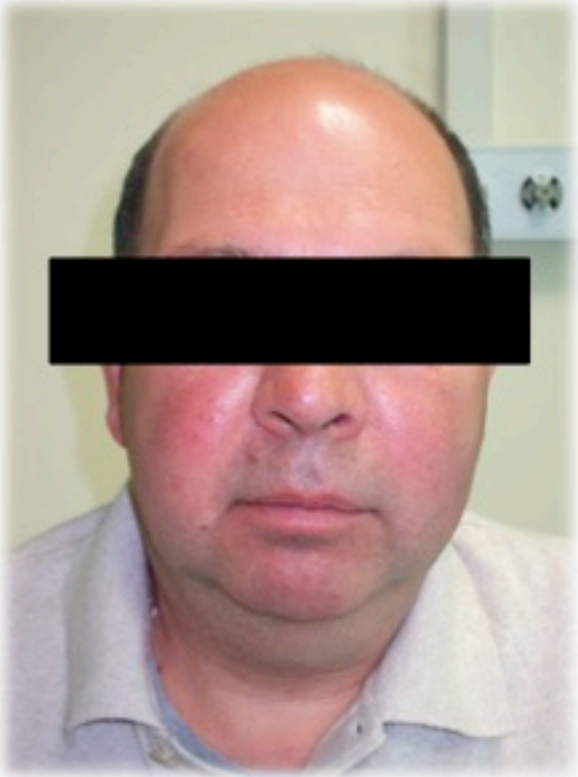
Stefano, 54 yrs

-Florid clinical phenotype
-Spontaneous ribs fractures
-Arterial Hypertension
-Mood lability

ACTH-dependent hypercortisolism
CRH test➔ ACTH +160%
HDDST➔ serum cortisol -85%
Negative pituitary MRI

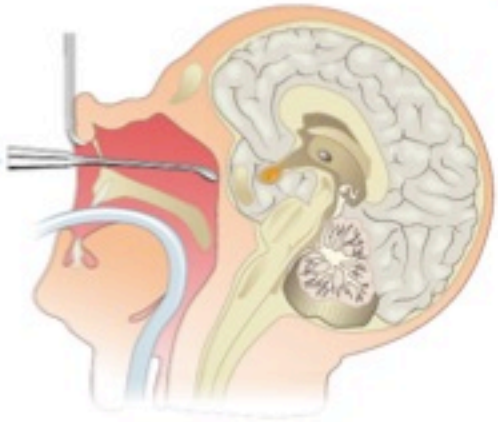
Cushing's Disease confirmed by BIPSS

THERAPY?



Factors that influence the outcome of surgery for CD

- Male gender
- Macroadenoma with diameter >2 cm
- Tumor with suprasellar extension
- Tumor with cavernous sinus invasion
- No tumor identification at presurgical imaging evaluation
- No tumor identification at surgical intervention
- No tumor identification at postsurgical pathological examination
- Surgeon inexperience



28 studies (2000-2010)
Remission 51 - 97%,
Recurrence 5 -27%

TABLE 8. Remission and failure in control and sample patient

Parameter	Literature Controls	Study Sample
Total no. of patients	4,470	14
Total studies	42	1
Patients in remission	3,192	12
Patient-mos in remission	194,955	414
Patients in treatment failure	1,247	2
Patient-mos in failure	33,538	42

average cure rate 72% for 4470 CD pts from 38 studies

Pivonello et al, Endocrine Reviews 2015

Erfe, JNS 2017

Medical Treatment in Cushing's Disease

In patients not suitable for surgery

When

Prior

- In preparation for surgery (especially in patients with diabetes, hypertension and marked coagulopathy)
- Prior to adrenalectomy

After

- After unsuccessful pituitary surgery
- In recurrence after pituitary surgery
- After radiotherapy

Bertagna, JCEM 2013 Nieman, JCEM 2015

Cushing's Disease: Which drug ?

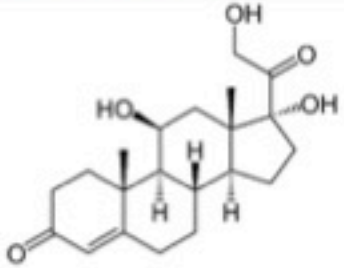
Pituitary

- Pasireotide
- Cabergoline
- Temozolamide
- Rosiglitazone
- Retinoic acid

Adrenal

- Ketoconazole
- Metyrapone
- Mitotane
- Osilodrostat
- Levo-Ket
- Etomidate

Glucocorticoid receptor



- Mifepristone

STEFANO ♂

Ketoconazole 400 mg / daily waiting for neurosurgery

↓

2 weeks after: **AST 680 UI/L, ALT 870 UI/L, GGT 340 UI/L**
→ **KET discontinuation**
6 weeks to normalize liver function

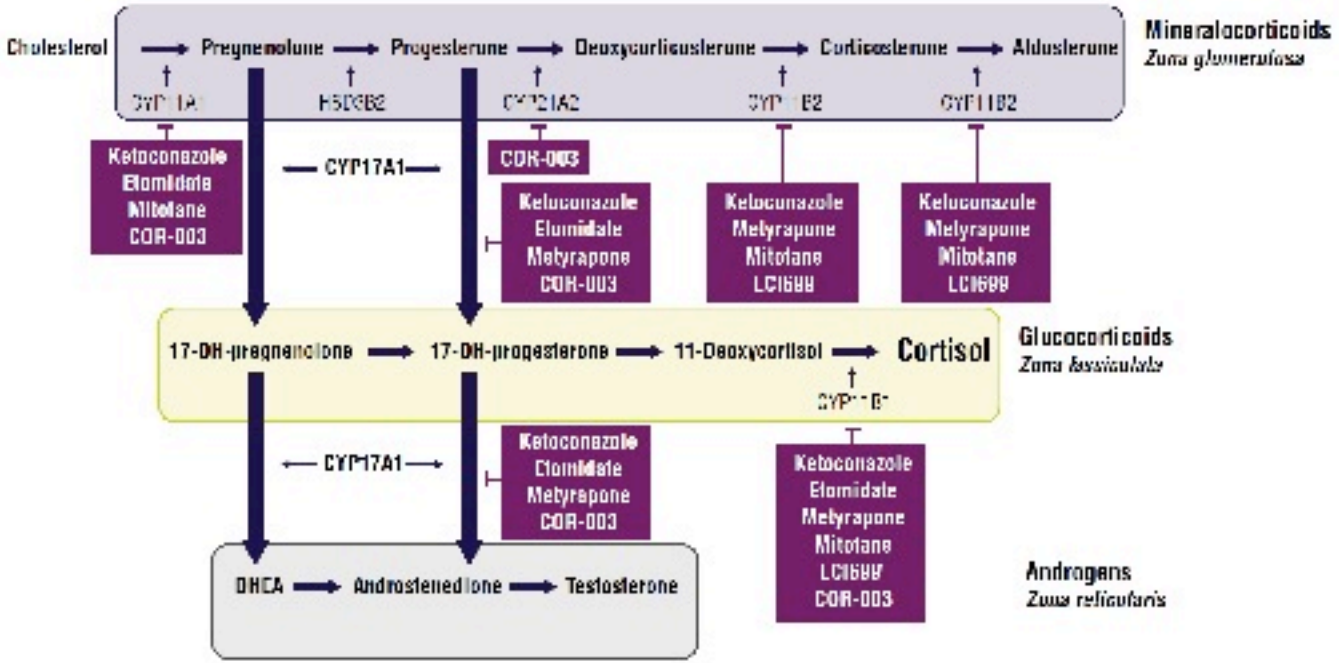
↓

Surgery with TNSF microscopic approach
Pathological examination: **Negative for ACTH staining**

→ **persistence of hypercortisolism**

Updates on the role of adrenal steroidogenesis inhibitors in Cushing's syndrome: a focus on novel therapies

Maria Fleseriu[1] · Frederic Castinetti[2]



M Fleseriu, Pituitary 2016

Ketoconazole (KET)

- approved in Europe for treatment of CS (adult & adolescence > 12 yr)
- potent inhibitor of P450 enzymes involved in the adrenal/gonadal steroidogenesis (➔ negative impact also on testicular function)
- effect on ACTH-secreting tumour?

Pharmacologic pofile:

- Racemic mixture of 2S,4R and 2R,4S enantiomers with different inhibitory potency
- orally 200-1200 mg/d
- rapid action, short half-life (3,3 h): twice/thrice daily dosing
- caution to acid-lowering drugs ➔reduced absorbiment

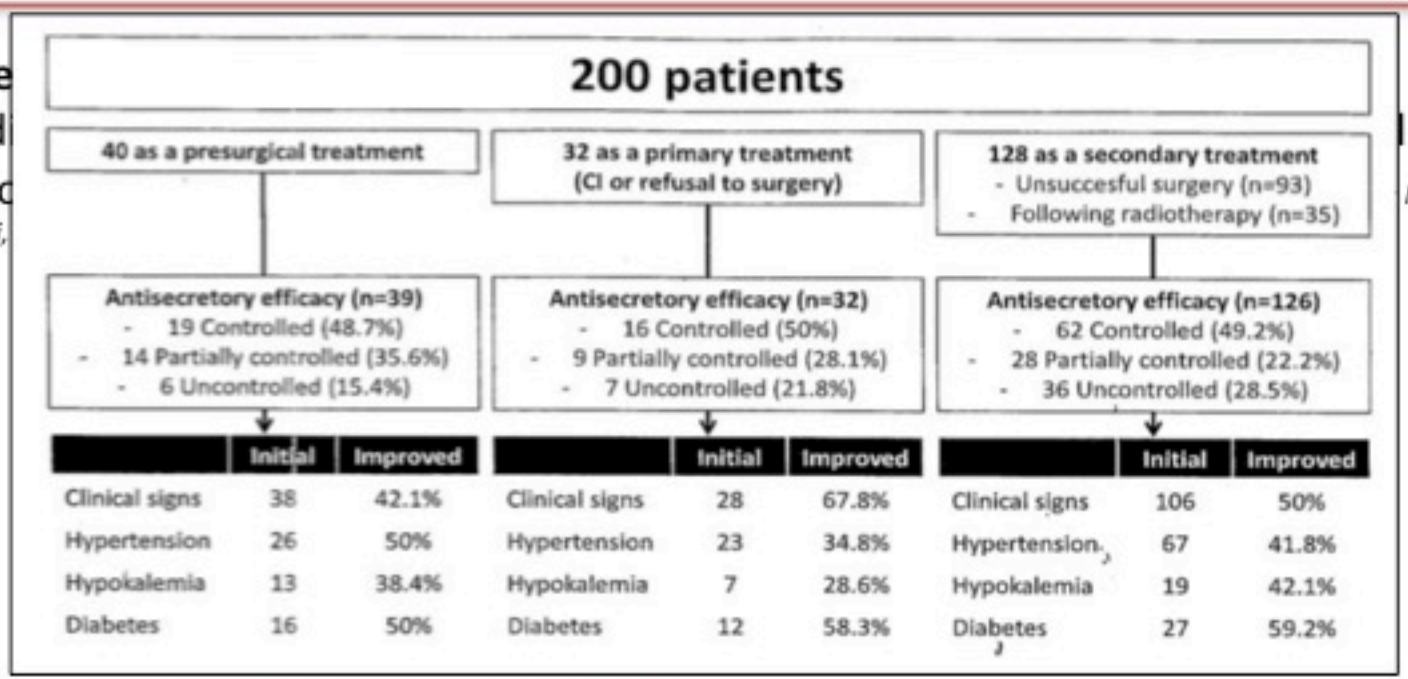
FresKO study

Studie

5 studi lled

cortisc *Moncet, 2007;*

Castinetti,



	Initial	Improved
Clinical signs	38	42.1%
Hypertension	26	50%
Hypokalemia	13	38.4%
Diabetes	16	50%

	Initial	Improved
Clinical signs	28	67.8%
Hypertension	23	34.8%
Hypokalemia	7	28.6%
Diabetes	12	58.3%

	Initial	Improved
Clinical signs	106	50%
Hypertension	67	41.8%
Hypokalemia	19	42.1%
Diabetes	27	59.2%

- 75% decrease of UFC at least 50%
- 49% with normalization of UFC levels at last follow-up
- variable response on the basis of UFC levels, < in males
- stop treatment in 20 % pts because intolerance (GI symptoms, fatigue)
- ↑ liver enzymes (<5 x ULN) in 13% pts, severe (>5 x ULN) in 2.5%

Castinetti, 2014

Ketoconazole (KET)

Conclusions

- Indications from uncontrolled retrospective studies may overestimate its efficacy
- It can be a good temporary option or an alternative as chronic treatment for selected pts with CS, preferable in women rather in men
- It is necessary to control liver enzymes before its use or after any dose change

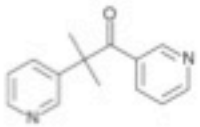
Disadvantages:

- Escape phenomenon in up to 23% of pts with initial response
- Multiple daily doses
- Drug interactions (oral anticoagulants, statin, mifepristone, cyclosporine and tacrolimus)

! Prolongation of QTc at ECG → careful with PASIREOTIDE combination

Metyrapone (MET)

Inhibits 11beta-hydroxylase (and other steroidogenesis steps) blocking the final step of cortisol production



Pharmac

- oral u rom 500-6000 mg/d
- rapid ife (1,9 h)➔multiple daily dosing 3-6 times

Reports in 5 retrospective studies *(Jeffcoat 1977; Thoren 1985; Verhelst, 1991; Valassi, 2012; van der Bosch 2014)* including 120 pts, until the UK retrospective multicenter study *(Daniel, 2015)* in 195 Pts ➔normalization of cortisol in 71%, esca

- AE: hyperandrog

  hypokalemia

MET block 11-hydroxylase → increase of steroid precursors → cross-reaction with cortisol → USE OF LC-MS/MS !!!!!!!!!

Pituitary-directed Drugs

Past/Failed promises

Neuromodulator Drugs
(Cyproheptadine, ketanserin, valproic acid)
PPAR-gamma agonist

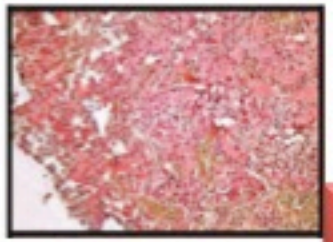
Future?

Retinoic Acid agonist
(Bexarotene)
EGFR inhibitor (Lapatinib)

Present

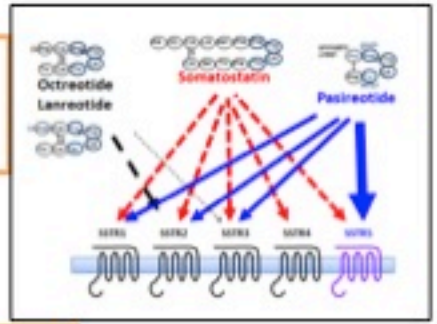
Dopamine agonists

New Sst analogs



D2 receptor expression in 83% of corticotroph pituitary tumors

Cabergoline



Pasireotide

STEFANO ♂

Cabergoline up to 3.5 mg/week for 5 mo, well tolerated,
NO EFFECT ON CORTISOL SECRETION

↓

Pasireotide LAR up to 40 mg/month (enrolled into clinical trial) with diabetes mellitus development **(HbA1c →9.5%),** insulin treatment, no normalization of UFC: discontinuation of the drug
The patient refused pituitary radiotherapy or bilateral adrenalectomy

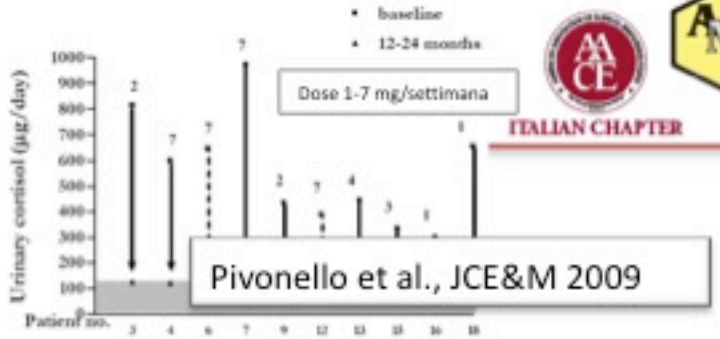
↓

LOST in FOLLOW- UP

Cabergoline

The Medical Treatment of Cushing's Disease: Effectiveness of Chronic Treatment with the Dopamine Agonist Cabergoline in Patients Unsuccessfully Treated by Surgery

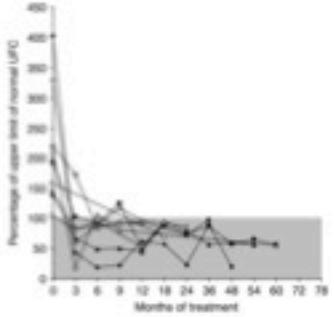
3 months: 75% (15/20)
12-24 months: 40% (8/20)



Pivonello et al., JCE&M 2009

Cabergoline monotherapy in the long-term treatment of Cushing's disease

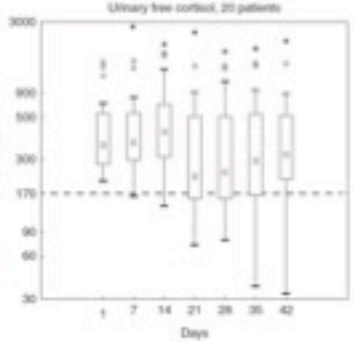
Goudbout A et al., EJE 2010



3-6 months: 36% (11/30)
12-60 months: 30% (9/20)

Limited value of cabergoline in Cushing's disease: a prospective study of a 6-week treatment in 20 patients

Burman P et al., EJE 2016



Reduction UFC >50% in 5/20 patients (25%), increase UFC 3/20 (15%)

Pasireotide in Cushing's disease: rationale

- **Pasireotide**
  - Somatostatin analogue targeting multiple somatostatin receptor subtypes[1]
  - Highest affinity for sst_5, the most prevalent somatostatin receptor subtype on ACTH-secreting pituitary adenomas[2]
  - Inhibits ACTH production in corticotroph adenomas in vitro[3]
  - **Phase 2, 15-day study** demonstrated promising clinical efficacy: [4]

76% (22/29) pts achieved reduced UFC levels

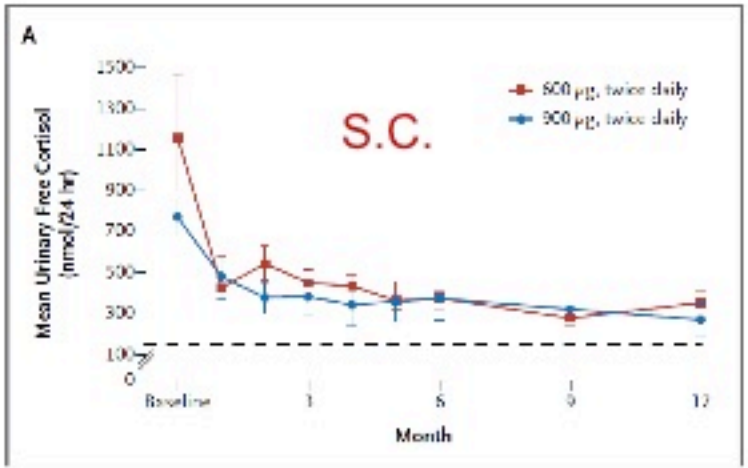
17% (5/29) pts achieved normalized UFC levels

mean UFC level decreased from baseline by 44.5% (p = 0.021)

1. *Bruns C et al. Eur J Endocrinol 2002;146:707–716*
2. *Hofland LJ et al. Endocr Rev 2003;24:28–47*
3. *Hofland LJ et al. Eur J Endocrinol 2005;152:645–654*
4. *Boscaro M et al. J Clin Endocrinol Metab 2009;94:115–122*

Pasireotide in CD

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



PAS 600 ug

PAS 900 ug

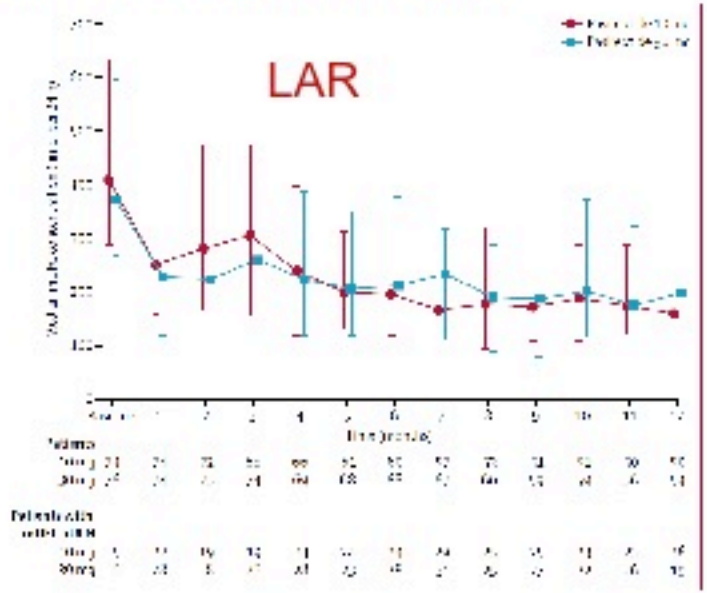
At month 6°UFC <ULN

15% in 600-µg group

26% in 900-µg group

Colao, NEJM, 2012

Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial



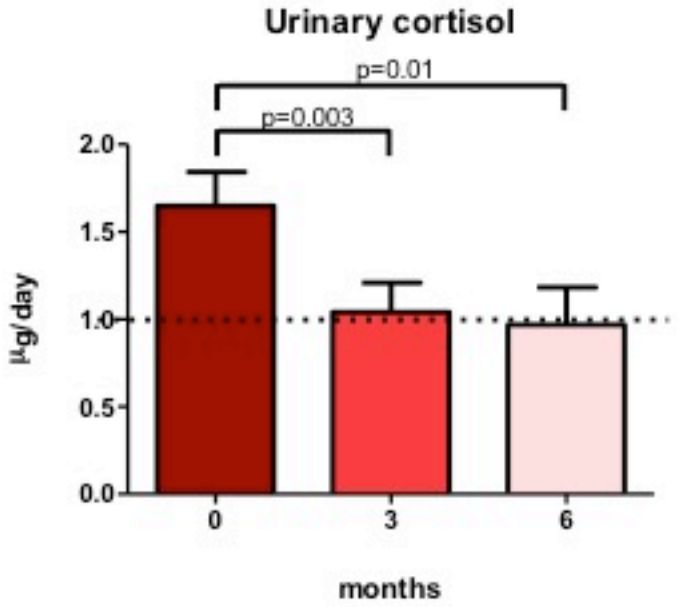
PAS 10 mg

PAS 30 mg

At month 7°
UFC <ULN
in about 40% of pts

Lacroix, Lancet Diab Endo, 2017

Real life: PAS in 27 CD (3 drop out) for 6 mo at a median dose of 600 ucg twice /d



UFC <ULN in 65% of pts

Pivonello, submitted

Pasireotide profile

- ✓On-label treatment for CD when surgery failed or is not indicated
- ✓Rapid action
- ✓On the evidence of large prospective multicenters studies of pts moderate to very severe disease cortisol control after long-term treatment was up to 25%
- ✓A preliminary real-world evidence prospective study seems to suggest an efficacy in disease control of 65% in very mild to moderate disease
- ✓Positive impact on either clinical picture or tumor mass
- ✓Safety was similar to that of other Sst analogues, except for the degree of hyperglycemia requiring additional medical intervention
- ✓Most frequently reported AEs were gastrointestinal and possible cholelitiasis
- ✓Up to 70% pts with Pas s.c. and Lar had at least one hyperglycemia-related AE

STEFANO ♂

After 10 months

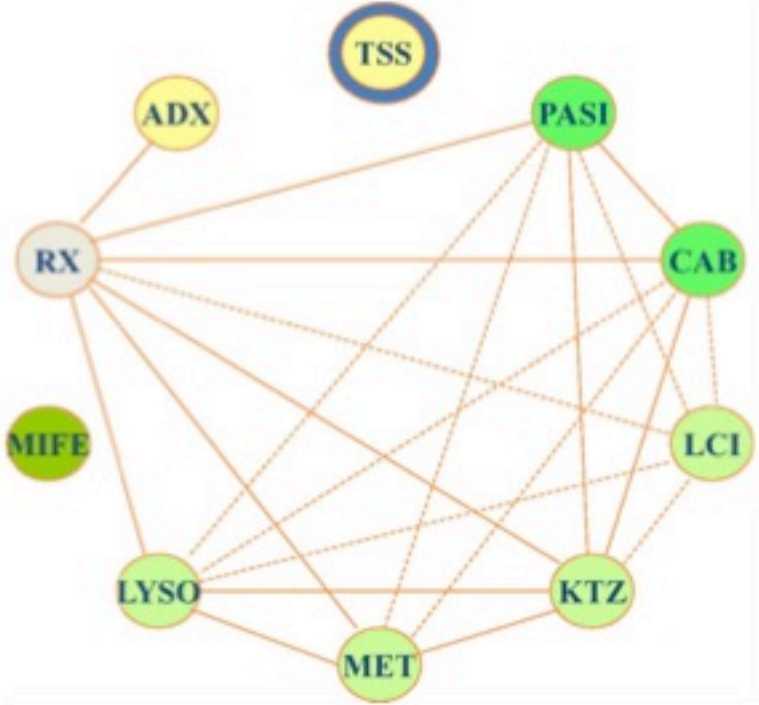
↓

UFC 678-890-756 nmol /24h (< 160 nmol/24h)
Start METyrapone 750 mg (at first in a clinical trial)
then *on label* treatment for 15 mo

↓

control of hypercortisolism, no more moon face, reduction of body weight (-6 kg), HbA1c (-1.4%), waist (-4cm), reduced antihyepertensive drugs

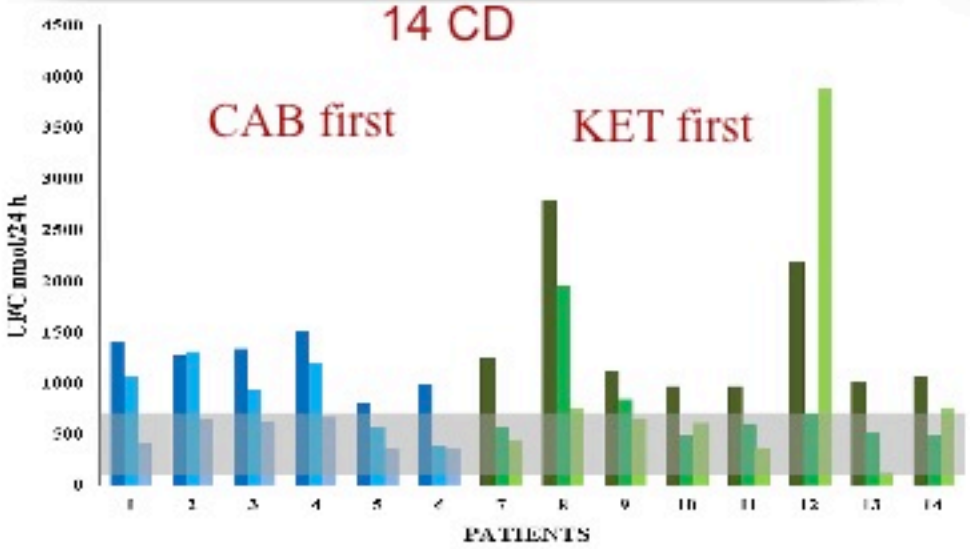
CS treatment: the Cushingame



Bertagna X, JCEM 2013

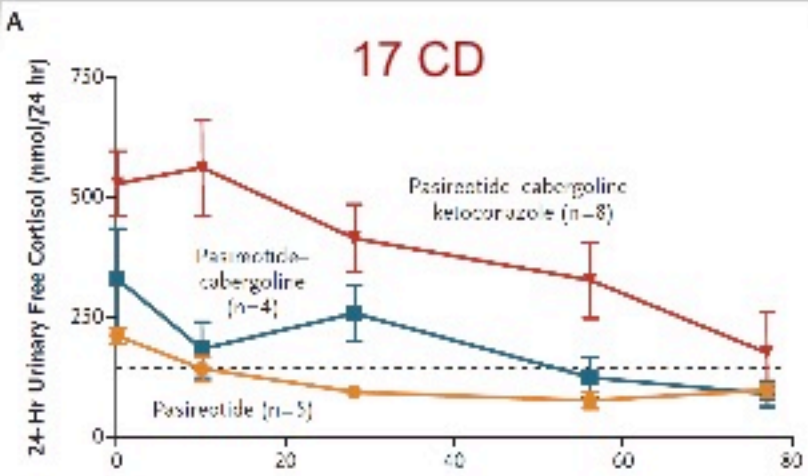
Combination therapy/1

Combination therapy for Cushing's disease: effectiveness of two schedules of treatment. Should we start with cabergoline or ketoconazole?



Barbot, Pitutiary 2014

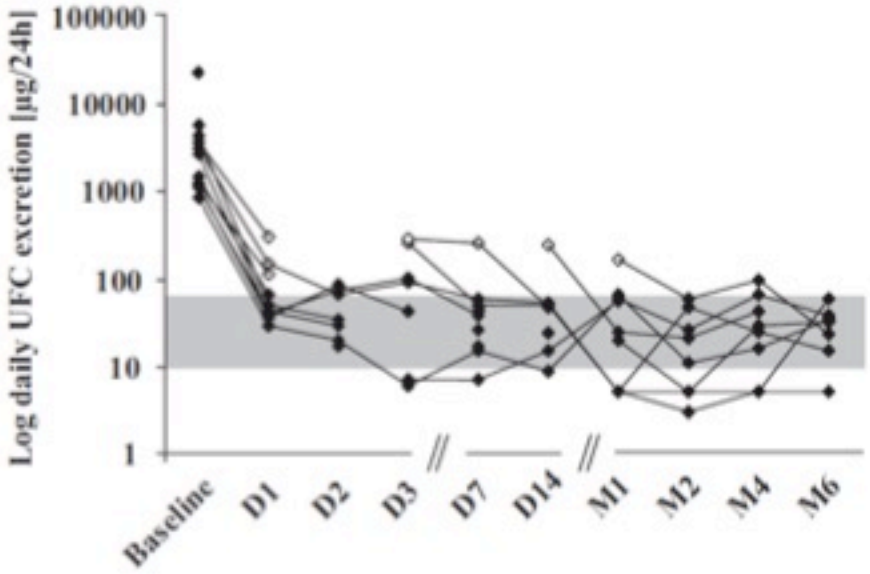
Pasireotide Alone or with Cabergoline and Ketoconazole in Cushing's Disease



PAS 100ug x3➔ PAS 250 ug x3
PAS 250ug x3 + CAB 0.5 mg 3 day/wk
PAS 250ug x3 + CAB 1 mg 3 day/wk
PAS 250ug x3 + CAB 1.5 mg 3 day/wk
PAS 250ug x3 + CAB 1.5 mg 3 day/wk + KET 200mg X3

Feelders, NEJM 2010

Combination therapy/2



High dose:

- Mitotane: 3-5 g/24h
- Metyrapone: 3-4.5 g/24h
- Ketoconazole: 400-1200 mg/24h

The gray area indicates the normal range of UFC excretion.
D, days after start of therapy; M, months; □, UFC excretion determined without hydrocortisone withdrawal; ■, UFC excretion determined during hydrocortisone withdrawal

Kamenicky, JCEM 2011

Cushing's Syndrome treatment: A Clinical Challenge

Several therapeutic options

Different patients

How to choose the second-line tailored treatment for each patient when the surgery fails?

Treatment choice

➔ ***Fast control of hypercortisolism:***

- *Metyrapone, Ketoconazole*
- *Pasireotide s.c.*
- *Etomidate e.v. (not available in Italy)*
- *Pas+Cab+ketoconazole*
- *Ketoconazole+Metyrapone+Mitotane*

➔ ***gender and age issues:***

- *Ketoconazole not in ♂*
- *Metyrapone and Mitotane not in fertile ♀*

➔ ***adverse events : QTc with Ket, Pas, liver function with Ket***

➔ ***previous DM patients*** *:careful pasireotide!*

➔ ***available drugs***

➔ ***Cushingame***


Steroidogenesis inhibitors:
LCI699
COR-003 (levoketoconazole)
Phase III
acetyl coa transferase:
ATR-101 (adrenal cancer)
Phase I
Melanocortin receptor
MCR-2 antagonist:
GPS1573 e GPS1574
In vitro
New drugs in CS
Retinoic acid agonist:
BEXAROTENE
HSP-90 inhibitors:
SILIBININ
Phase II
New SSA:
DG-3173
Phase I
EGFR inhibitors:
GEFITINIB
In vitro
Chimeric compound: DR + SSTR
Cyclin dependent kinase inhibitors:
R-ROSCOVITINE
Studio di fase II

Any question?

Roma, 9-12 novembre 2017

Padova Pituitary-Adrenal Team

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