THE COMBINED THERAPY IN CUSHING'S DISEASE

CABERGOLINE and KETOCONAZOLE

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CABERGOLINE AND KETOCONAZOLE, WHY TOGETHER?

- Complementary actions
- Increase effectiveness
- Using lower doses of each
- Reduce escape phenomen
- Oral administration
- Well tolerated ?

Both are used off-label

KETOCONAZOLE

Imidazole derivate used as antifungal agent

Cortisol lowering effect by inhibition of cytocrome P450

Extra adrenal effects

Therapeutic dose: 600-1200 mg/day

Avoid association with PPI

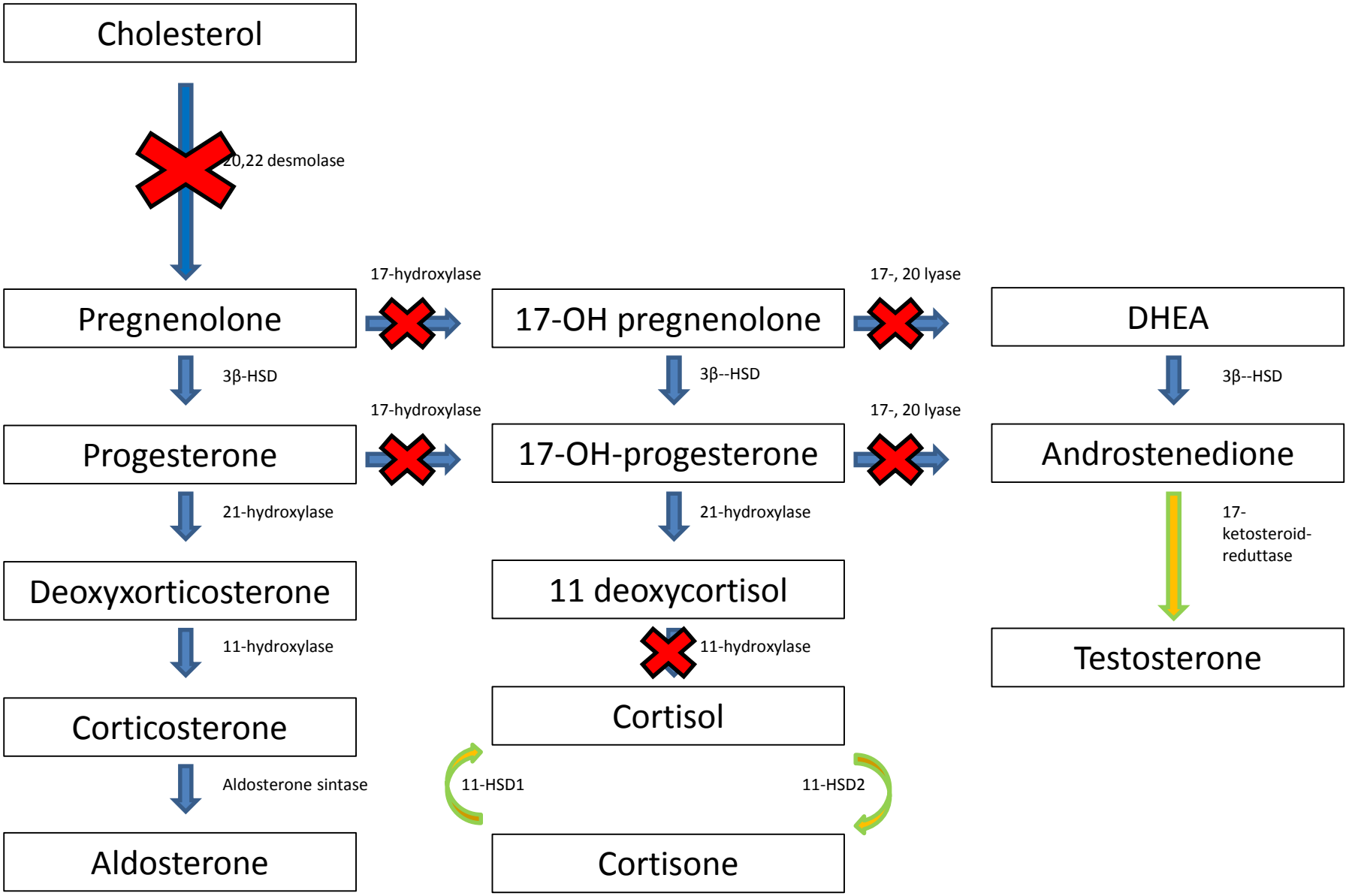
The most widely used cortisol lowering medication

No prospective clinical trial available

Most studies involved a small n° of patients

In 2013 **warnings** from FDA and EMEA regarding the use of ketoconazole as an antifungal agent because of its potential severe **hepatotoxicity**

KETOCONAZOLE: MECHANISM OF ACTION



CLINICAL STUDY

Ketoconazole revisited: a preoperative or postoperative treatment in Cushing's disease

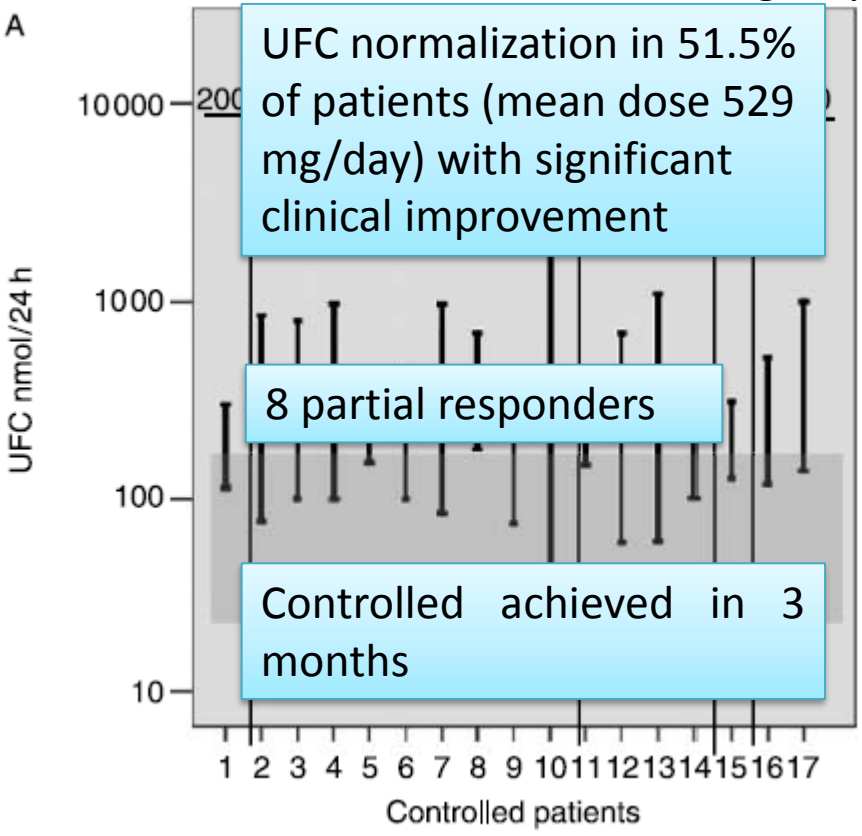
F Castinetti, I Morange, P Jaquet, B Conte-Devolx and T Brue

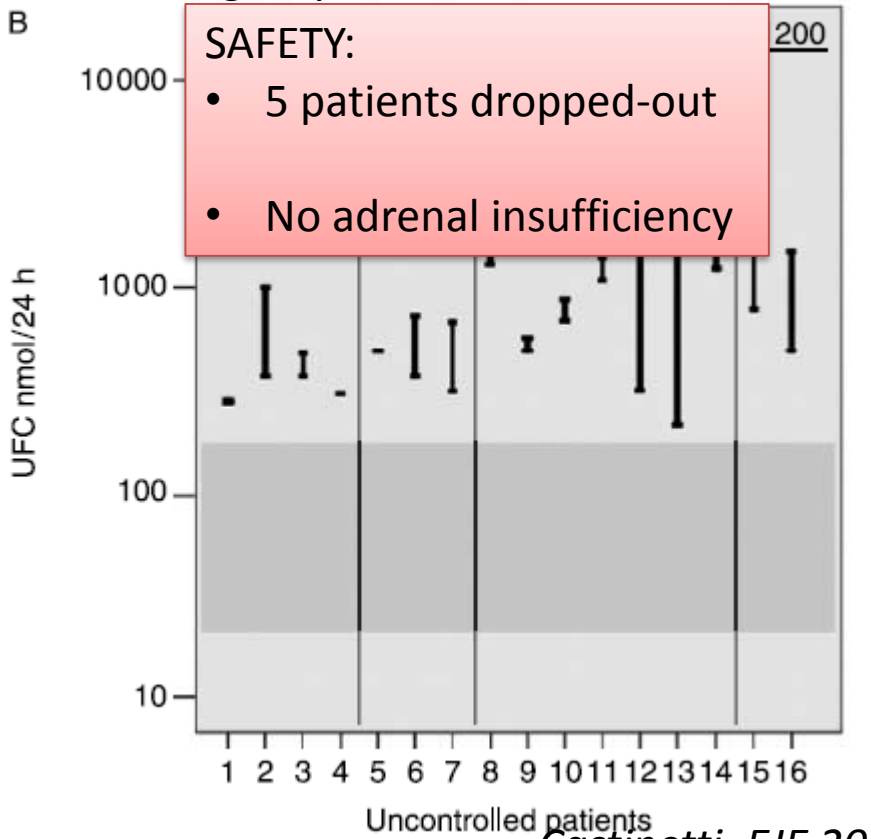
Department of Endocrinology, Diabetes, Metabolic Diseases and Nutrition, Hôpital de la Timone, Centre Hospitalier Universitaire de Marseille and Faculté de Médecine, Université de la Méditerranée, 264 rue St Pierre, Cedex 5, 13385 Marseille, France

38 patients (17 with persistent disease)

Mean follow-up: 22.6 months (6-72 months)

Ketoconazole started 200-400 mg/day up to 1200 mg/day





Castinetti, EJE 2008

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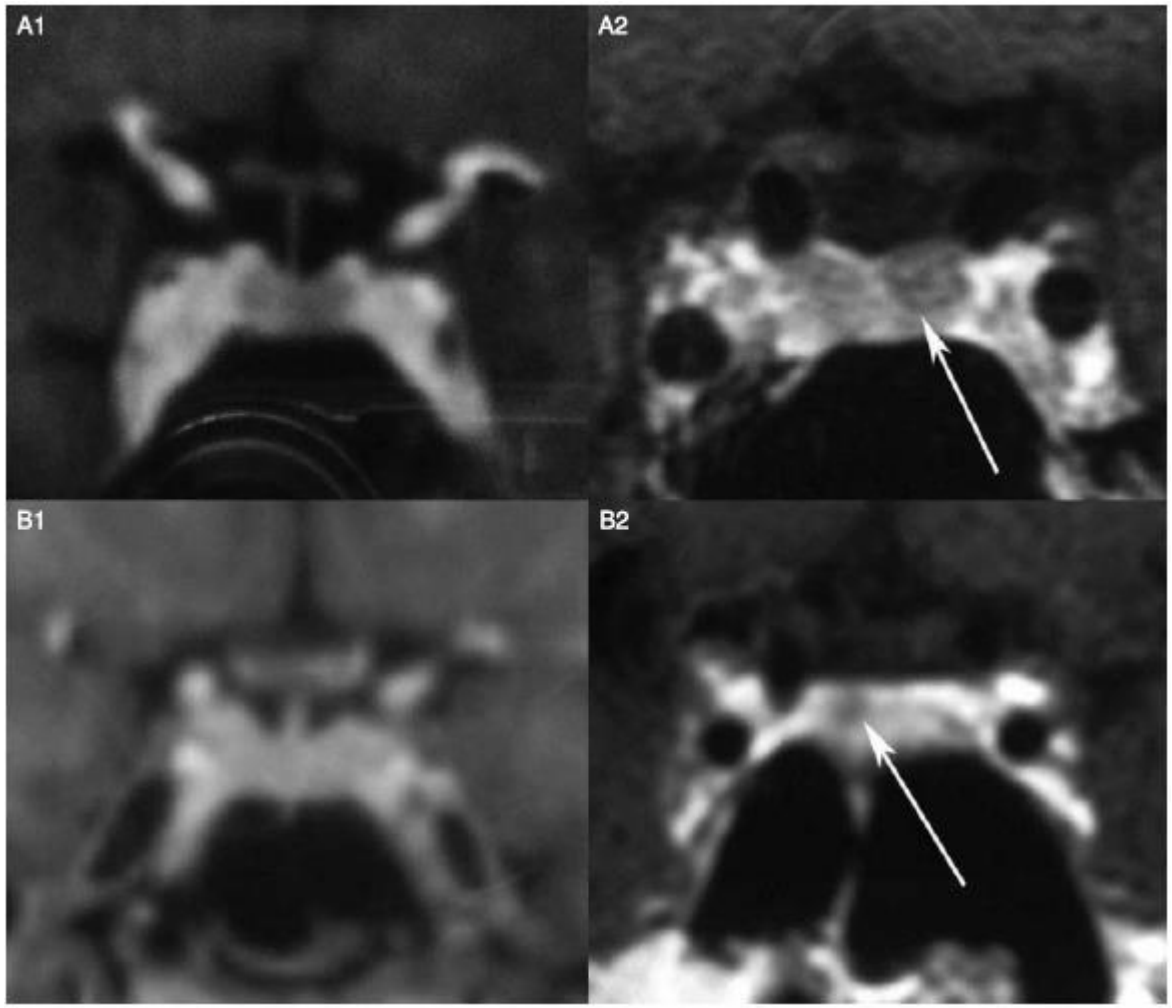

No tumor growth

Appearance of pituitary adenoma in 5/15

Ketoconazole in Cushing's Disease: Is It Worth a Try?

Frederic Castinetti, Laurence Guignat, Pauline Giraud, Marie Muller, Peter Kamenicky, Delphine Drui, Philippe Caron, Fiorina Luca, Bruno Donadille, Marie Christine Vantyghem, Helene Bihan, Brigitte Delemer, Gerald Raverot, Emmanuelle Motte, Melanie Philippon, Isabelle Morange, Bernard Conte-Devolx, Laurent Quinquis, Monique Martinie, Delphine Vezzosi, Maelle Le Bras, Camille Baudry, Sophie Christin-Maitre, Bernard Goichot, Philippe Chanson, Jacques Young, Olivier Chabre, Antoine Tabarin, Jerome Bertherat, and Thierry Brue

200 patients

40 as a presurgical treatment

Antisecretory efficacy (n=39)
- 19 Controlled (48.7%)
- 14 Partially controlled (35.6%)
- 6 Uncontrolled (15.4%)

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

32 as a primary treatment (CI or refusal to surgery)

Antisecretory efficacy (n=32)
- 16 Controlled (50%)
- 9 Partially controlled (28.1%)
- 7 Uncontrolled (21.8%)

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

128 as a secondary treatment
- Unsuccesful surgery (n=93)
- Following radiotherapy (n=35)

Antisecretory efficacy (n=126)
- 62 Controlled (49.2%)
- 28 Partially controlled (22.2%)
- 36 Uncontrolled (28.5%)

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

Tolerance data in 190 patients

Escape in 15% of patients

Predictors of response: female gender

Castinetti, EJE 2008

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Table 2. Reasons for Ketoconazole Withdrawal[a]

Reasons for ketoconazole withdrawal (118/160 patients)	n (%)
Lack of efficacy	43 (26.8)
Patients with initial UFC control and secondary failure of the drug	11 (6.9)
Adverse effects (see Table 3)	[illegible]
Decision to perform another treatment despite ketoconazole efficacy	22 (13.7)
Bilateral adrenalectomy	7 (4.4)
Transsphenoidal surgery	15 (9.3)
Visualization of adenoma on MRI (considered normal before ketoconazole)	8 (5)
Radiotherapy efficacy	8 (5)
Patient's decision	3 (1.8)
Pregnancy	1 (0.6)

[a] At their last visit, 42 patients were still on treatment. Forty patients with ketoconazole as a presurgical treatment are not included in this table.

Table 3. Adverse Effects Induced by Ketoconazole[a]

	Frequency	Mean Dose (mg/d)	Min–Max
Liver enzyme increase	30 (15.8%)	772.4 ± 305.7	400–1200
Gastrointestinal complaints	25 (13.1%)	625 ± 258.3	400–1200
Adrenal insufficiency	10 (5.4%)	700 ± 256	400–1200
Pruritus	7 (3.7%)	700 ± 385.6	400–1200
Intense fatigue	2 (1.25%)	700	600–800
Hair loss	2 (1.25%)	700	600–800
Leg edema	2 (1.25%)	800	800–800
Muscle pain	2 (1.25%)	700	200–1200
Dyspnea	1 (0.6%)	400	400
Hypertriglyceridemia	1 (0.6%)	800	800
Leukoneutropenia	1 (0.6%)	600	600
Dizziness	1 (0.6%)	1200	1200
Increased creatinine level	1 (0.6%)	600	600

[a] For these results, n = 190.

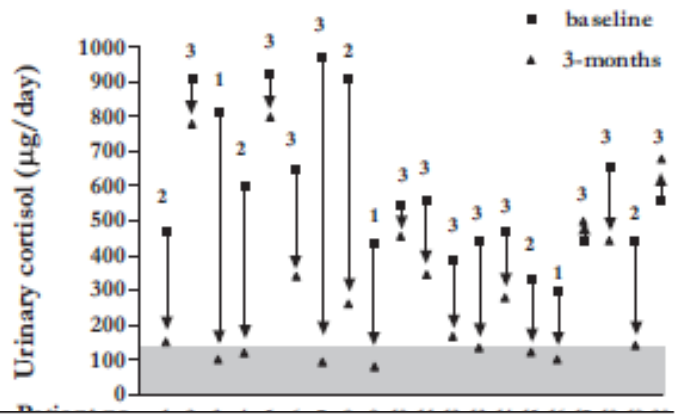
Castinetti, EJE 2008

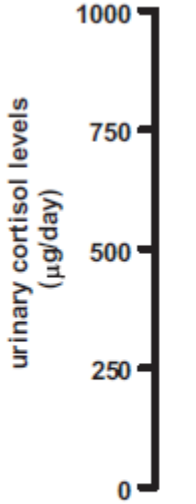
CABERGOLINE

- Ergot derivate with potent agonist action on D2R
- Longer half-life and higher affinity for D2R than bromocriptine
- Approved for treatment of hyperprolactinemia
- D2R expressed in 80% of ACTH pituitary adenomas
- Initial response in 75% of cases; effective in 30-40% of patients in the long term
- Escape in 25% of cases
- Potential positive effects on blood pressure and glucydic metabolism
- Feasible option during pregnancy

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

20 patients
Responders: 75% (8/20 full and 7/20 partial)





Parameter	Responsive patients (n = 15) Baseline	Responsive patients (n = 15) 3-month treatment	*P* value	Resistant patients (n = 5) Baseline	Resistant patients (n = 5) 3-month treatment	*P* value
Body mass index (kg/m^2)	27.5 ± 0.8	28.0 ± 0.8	0.115	27.7 ± 1.3	28.4 ± 1.3	0.066
Waist to hip ratio	1.10 ± 0.04	1.08 ± 0.04	0.001	1.05 ± 0.06	1.07 ± 0.06	0.221
Systolic blood pressure (mm Hg)	146.0 ± 3.6	135.7 ± 2.9	0.001	149.0 ± 5.8	138.0 ± 3.7	0.041
Diastolic blood pressure (mm Hg)	94.0 ± 2.4	87.3 ± 2.2	0.002	95.0 ± 4.2	88.0 ± 3.7	0.038
Heart rate (beats/min)	69.5 ± 1.8	74.1 ± 2.3	0.014	63.2 ± 1.3	65.0 ± 0.5	0.109
Fasting serum glucose (mg/dl)	129.3 ± 5.6	121.8 ± 4.0	0.004	124.2 ± 7.7	116.2 ± 3.1	0.136
Fasting serum insulin (µU/ml)	11.0 ± 1.2	10.1 ± 1.2	0.001	14.4 ± 1.2	13.7 ± 1.1	0.104
HOMA-IR	3.6 ± 0.5	3.1 ± 0.4	0.002	4.4 ± 0.5	4.0 ± 0.3	0.138
HOMA-B (%)	65.0 ± 7.2	65.4 ± 7.4	0.865	92.0 ± 17.1	94.0 ± 9.4	0.500
Plasma ACTH (pg/ml)	64.9 ± 3.3	56.3 ± 3.1	0.002	78.0 ± 10.3	78.6 ± 9.6	0.893
Serum cortisol (µg/liter)	239.3 ± 13.9	177.1 ± 13.4	0.001	288.8 ± 21.1	276.8 ± 14.5	0.686
Urinary cortisol (µg/d)	561.9 ± 52.5	192.0 ± 29.1	0.001	674.4 ± 100.5	642.2 ± 70.6	0.345
Tumor volume (mm^3)	246.5 ± 40.9	230.7 ± 41.5	0.047	565.3 ± 391.2	573.1 ± 394.3	0.109

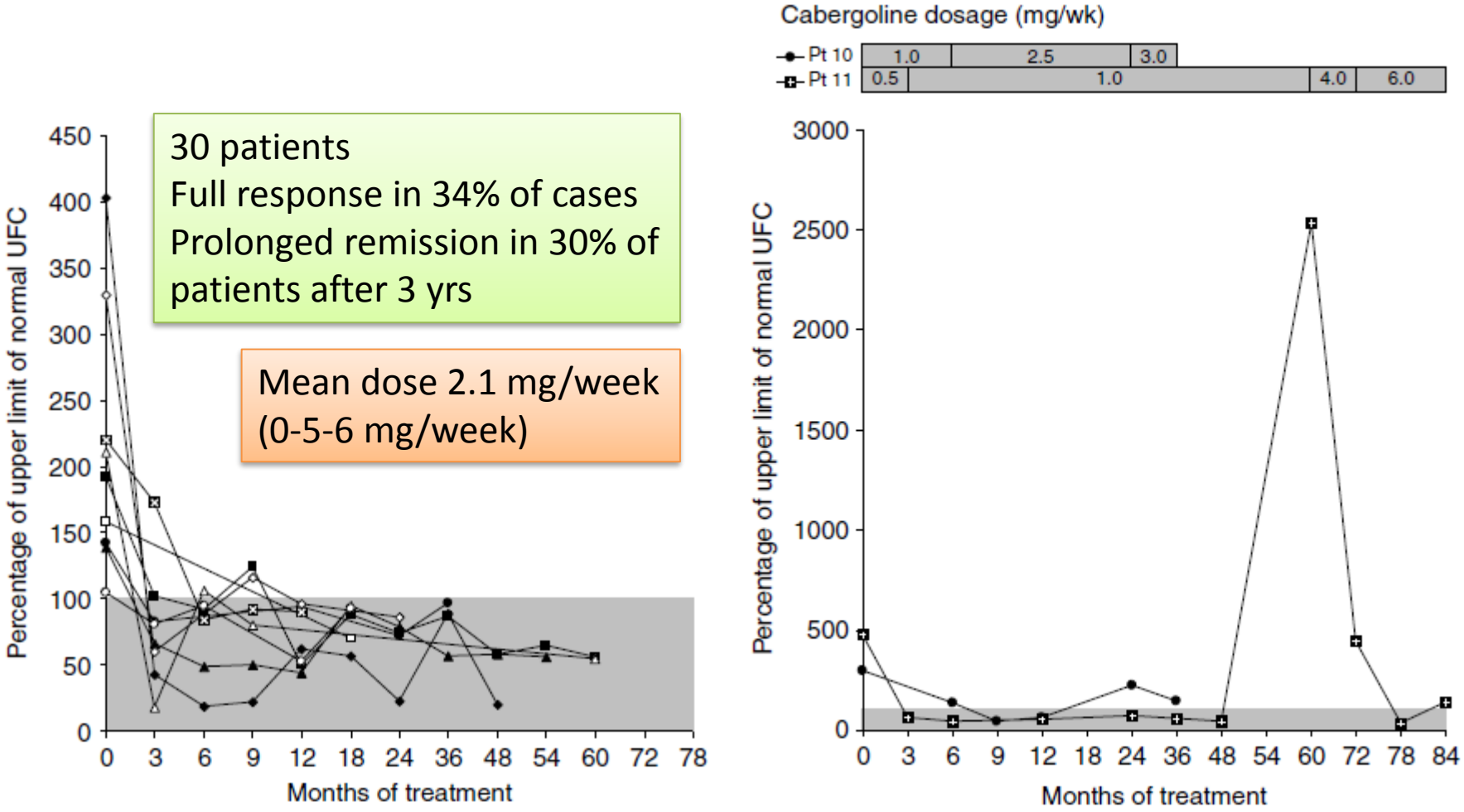
Pivonello, JCEM 2009

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

Ariane Godbout, Marcos Manavela[1], Karina Danilowicz[1], Hugues Beauregard, Oscar Domingo Bruno[1] and André Lacroix

30 patients
Full response in 34% of cases
Prolonged remission in 30% of patients after 3 yrs

Mean dose 2.1 mg/week (0-5-6 mg/week)

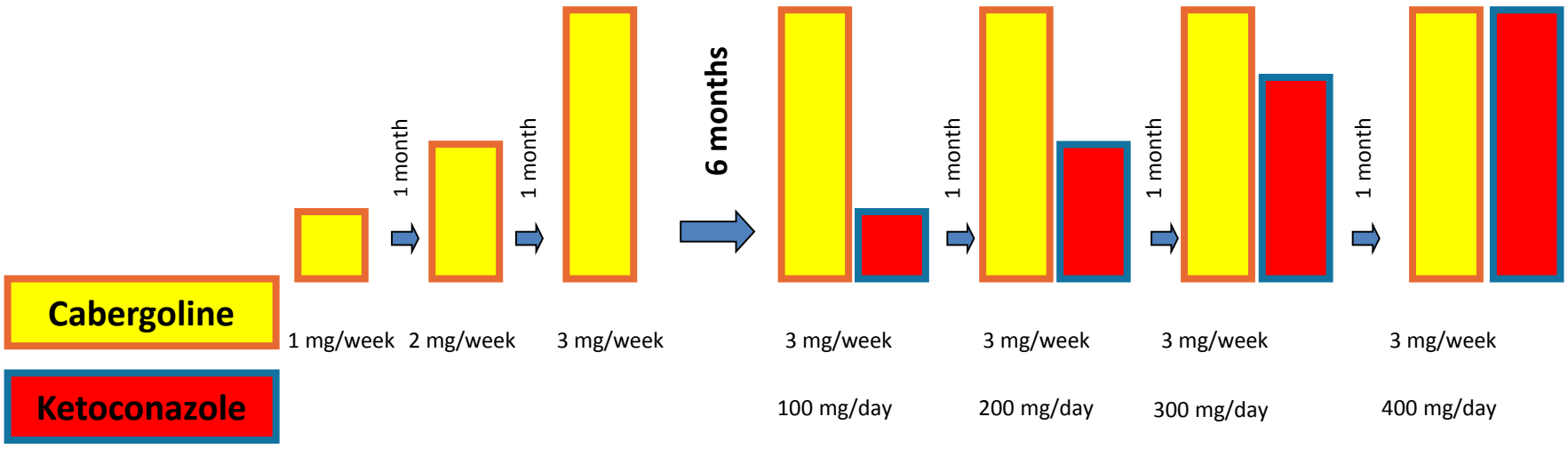


Godbout, EJE 2010

Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease

Lucio Vilar · Luciana A. Naves · Monalisa F. Azevedo · Maria Juliana Arruda · Carla M. Arahata · Lidiane Moura e Silva · Rodrigo Agra · Lisete Pontes · Larissa Montenegro · José Luciano Albuquerque · Viviane Canadas

12 patients with persistent CD



Vilar, Pituitary 2010

Effectiveness of cabergoline in monotherapy and combined with ketoconazole in the management of Cushing's disease

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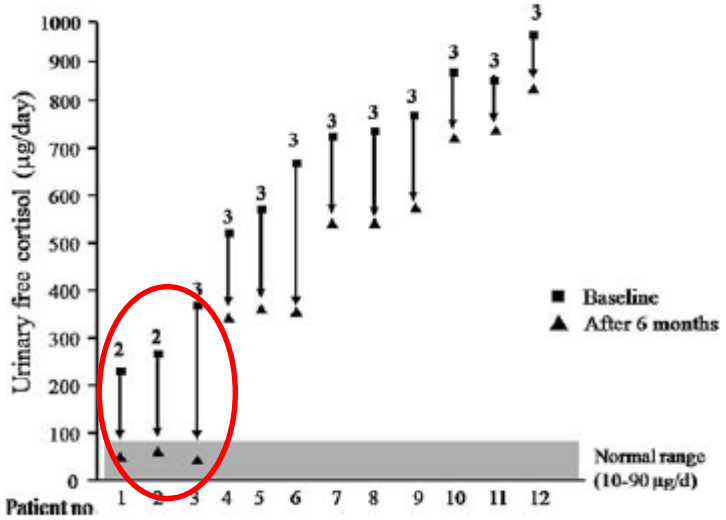
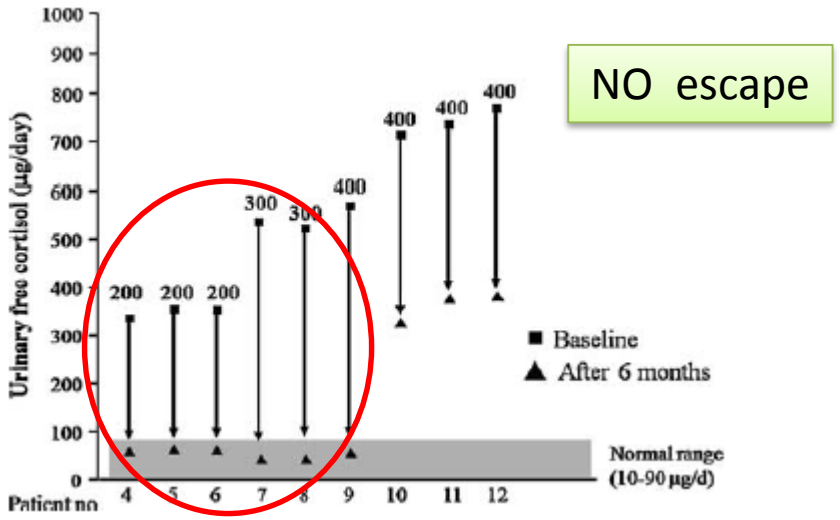
RESULTS

UFC after 6 months of cabergoline



3 full responders

UFC after 6 months of cabergoline+ketoconazole



NO escape

6 full responders

At the end of the study, 9/12 patients (75%) had normal UFC

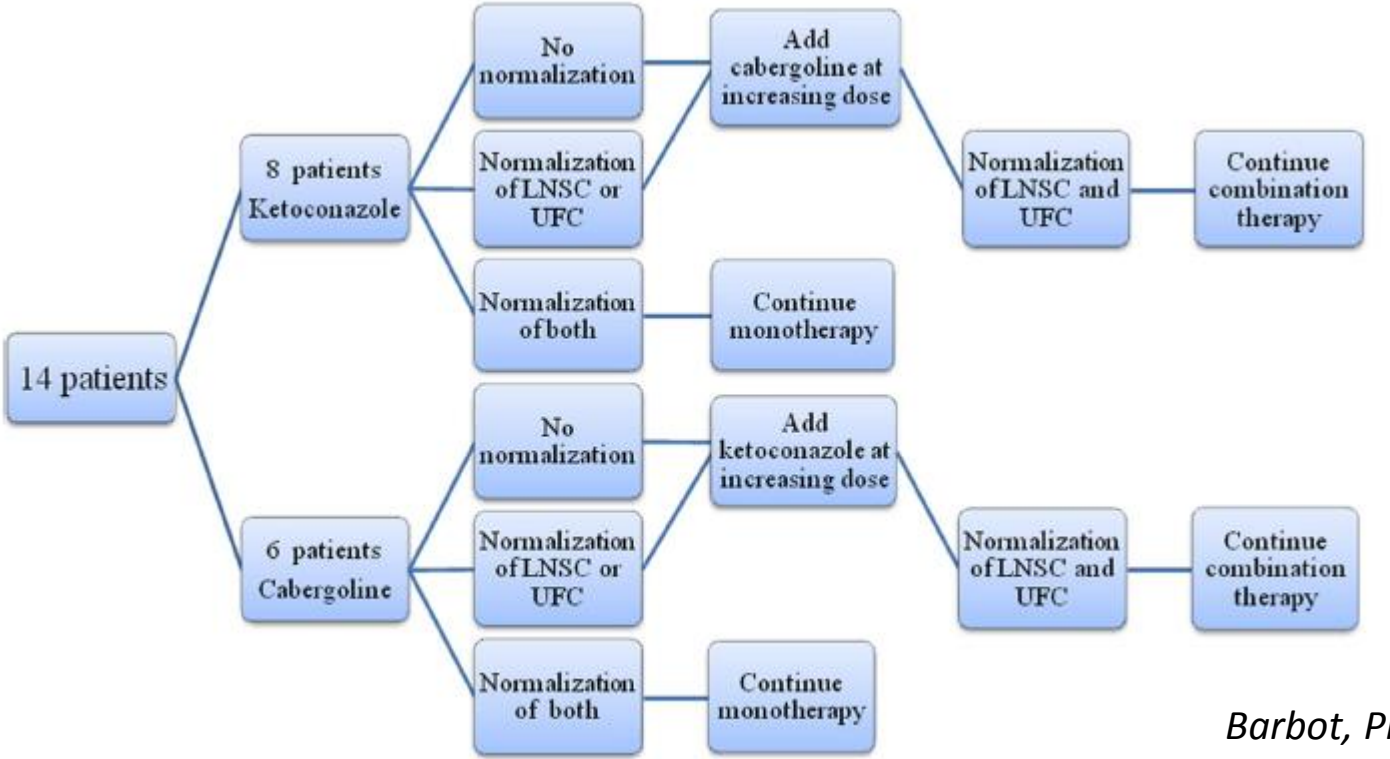
Vilar, Pituitary 2010

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

14 patients with CD

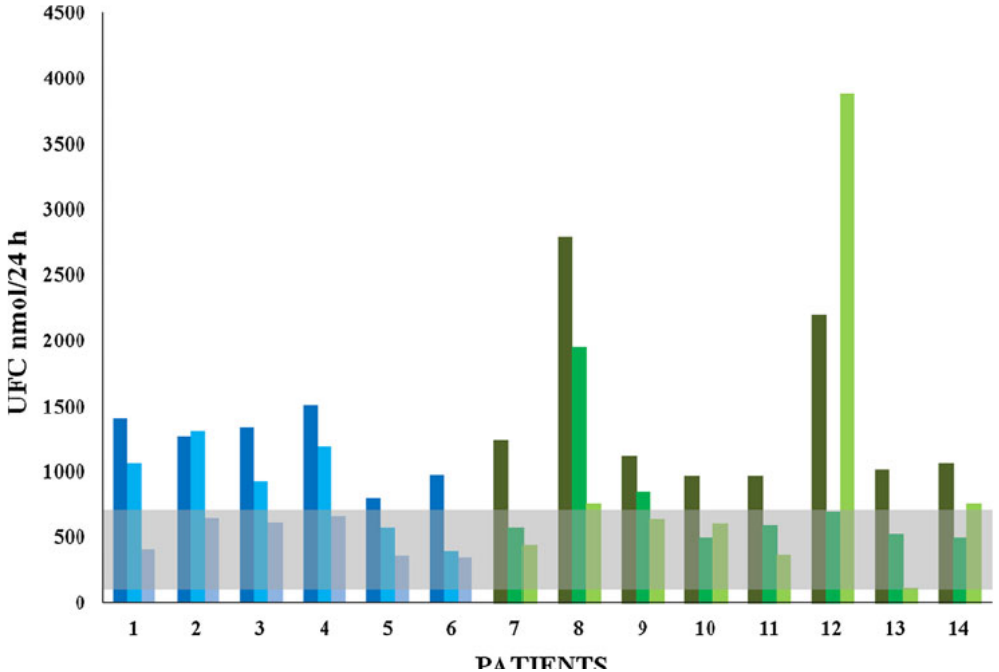
- 6 persistences
- 4 *de novo*
- 4 recurrences

1.3 < UFC < 4 x ULN



Barbot, Pituitary 2014

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



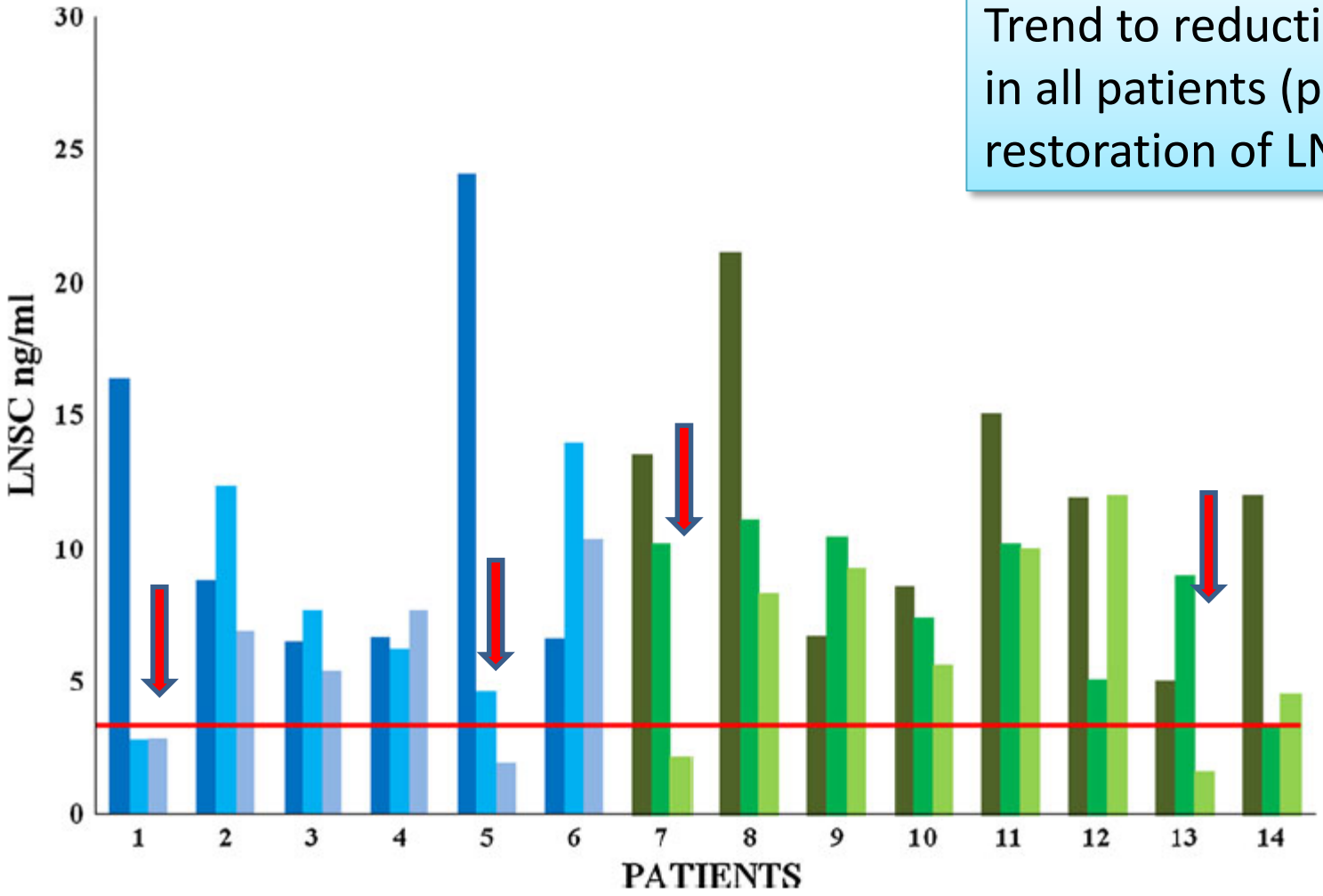
Normalization of UFC:
CAB monotherapy: 33%
KET monotherapy: 62%

Normalization of UFC in 10/14 patients (79%)

	Basal	Monotherapy	Combined therapy	*p* value Mono versus basal	*p* value Comb versus basal	*p* value Mono versus comb
UFC (nmol/24 h)	1180.5 (800–2,789)	646.5 (398–1,944)	617 (121–3,884)	0.0006	0.03	ns
LNSC (ng/ml)	10.38 (5.05–24.1)	8.34 (2.79-14.0)	6.28 (1.62-12.0)	ns	ns	ns
ACTH (pg/ml)	32 (15–84)	34.5 (15–84)	35 (12–76)	ns	ns	ns
Glycemia (mmol/l)	5.3 (4.1–1.8)	5.2 (3.9–11)	5.0 (3.2–8.9)	ns	ns	ns
HbAlc (mmol/mol)	54 (38–114)	51 (38–92)	44 (37–78)	ns	0.045	0.02
BMI (kg/m^2)	27.25 (22.8–41.6)	27.95 (22.8–42.4)	25.7 (23.2–40.5)	ns	ns	0.018
Waist (cm)	106 (78–126)	99 (75–125)	98.5 (76–126)	0.02	0.006	ns

Barbot, Pituitary 2014

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



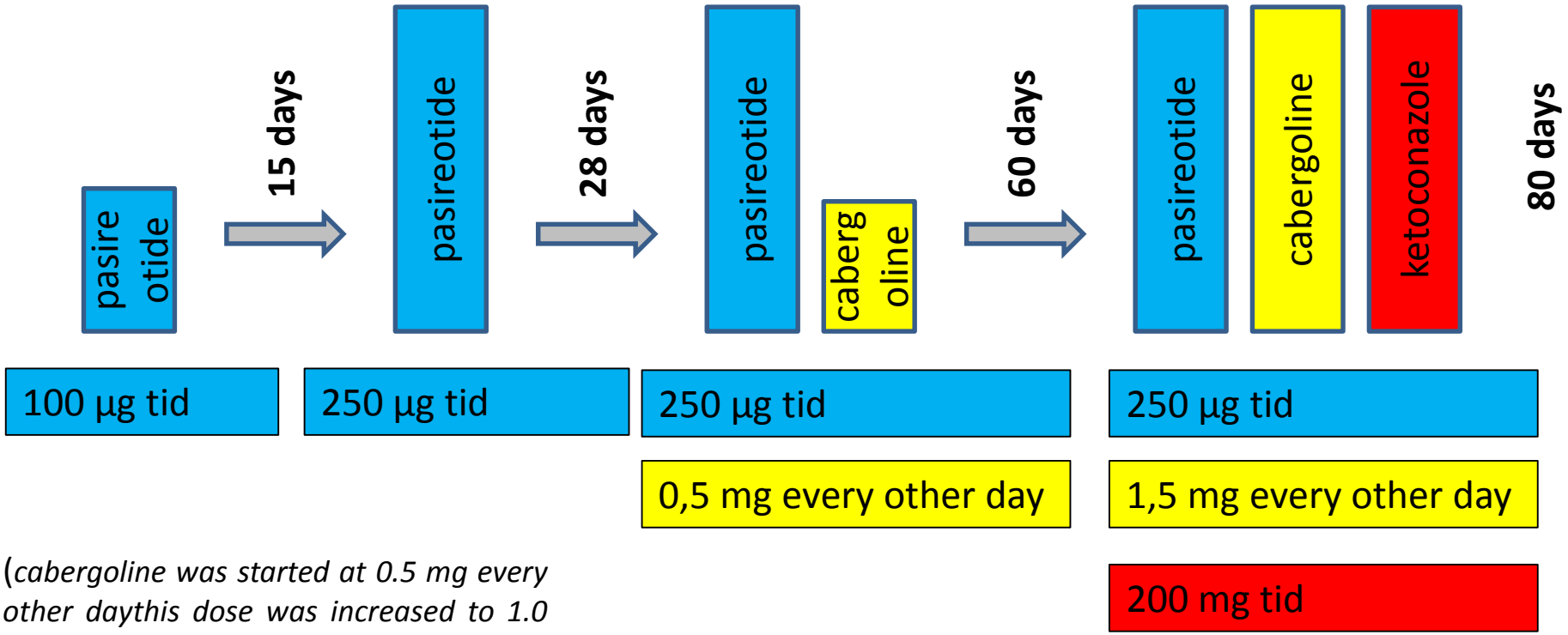
Trend to reduction of LNSC in all patients (p=0.06) but restoration of LNSC only in 4

Barbot, Pituitary 2014

Pasireotide alone or with cabergoline and ketoconazole in Cushing's disease

17 patients with CD

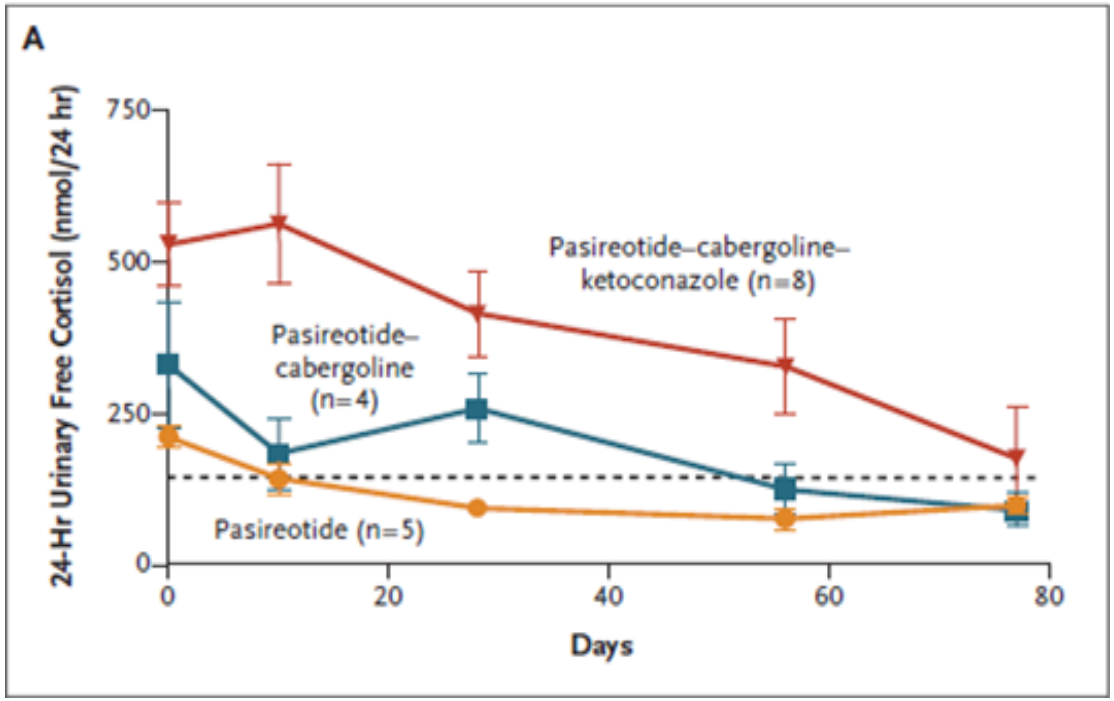
- 2 persistences
- 12 *de novo*
- 3 recurrences



(*cabergoline was started at 0.5 mg every other daythis dose was increased to 1.0 mg after 5 days and 1.5 mg every other day after 10 days*)

Feelders, NEJM 2010

RESULTS



pasireotide

pasireotide + cabergoline

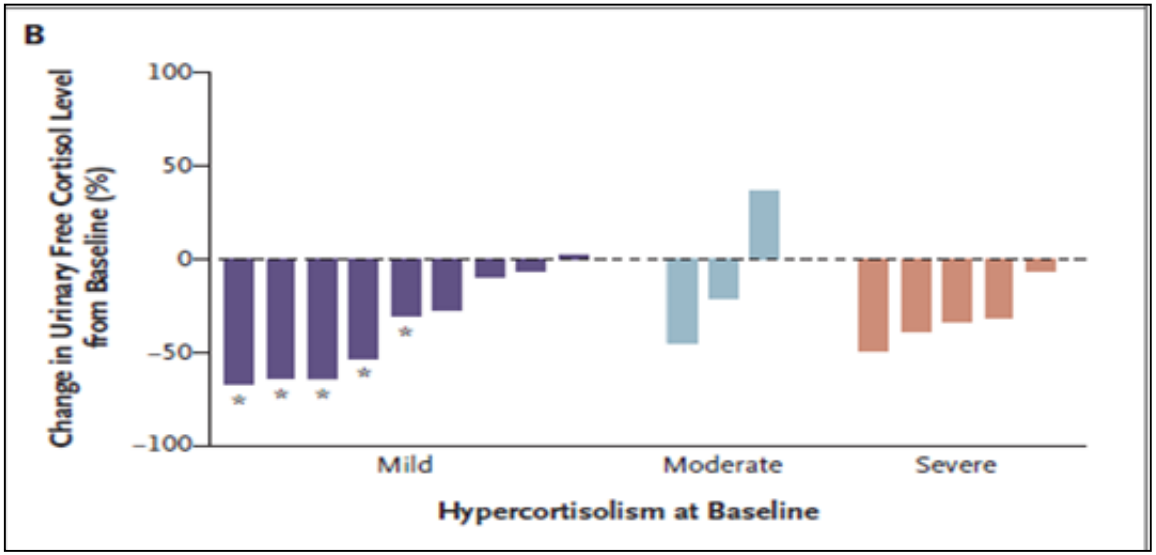
pasireotide + cabergoline + ketoconazole

- Pasireotide monotherapy→ normalization of UFC in 5/17 pazients (29%)
- Pasireotide + Cabergoline→normalization of UFC in 4/17 pazients (24%)
- Pasireotide + Cabergoline + Ketoconazole→ normalization of UFC in 6/17 pazients (35%)

At day 80, 15/17 patients (88%) had normal UFC

Feelders, NEJM 2010

RESULTS



Percent change from baseline in UFC levels in all patients after pasireotide monotherapy

Clinical improvements:

- ↓ body weight
- ↓ waist
- ↓ sistolic blood pressure
- ↓ diastolic blood pressure

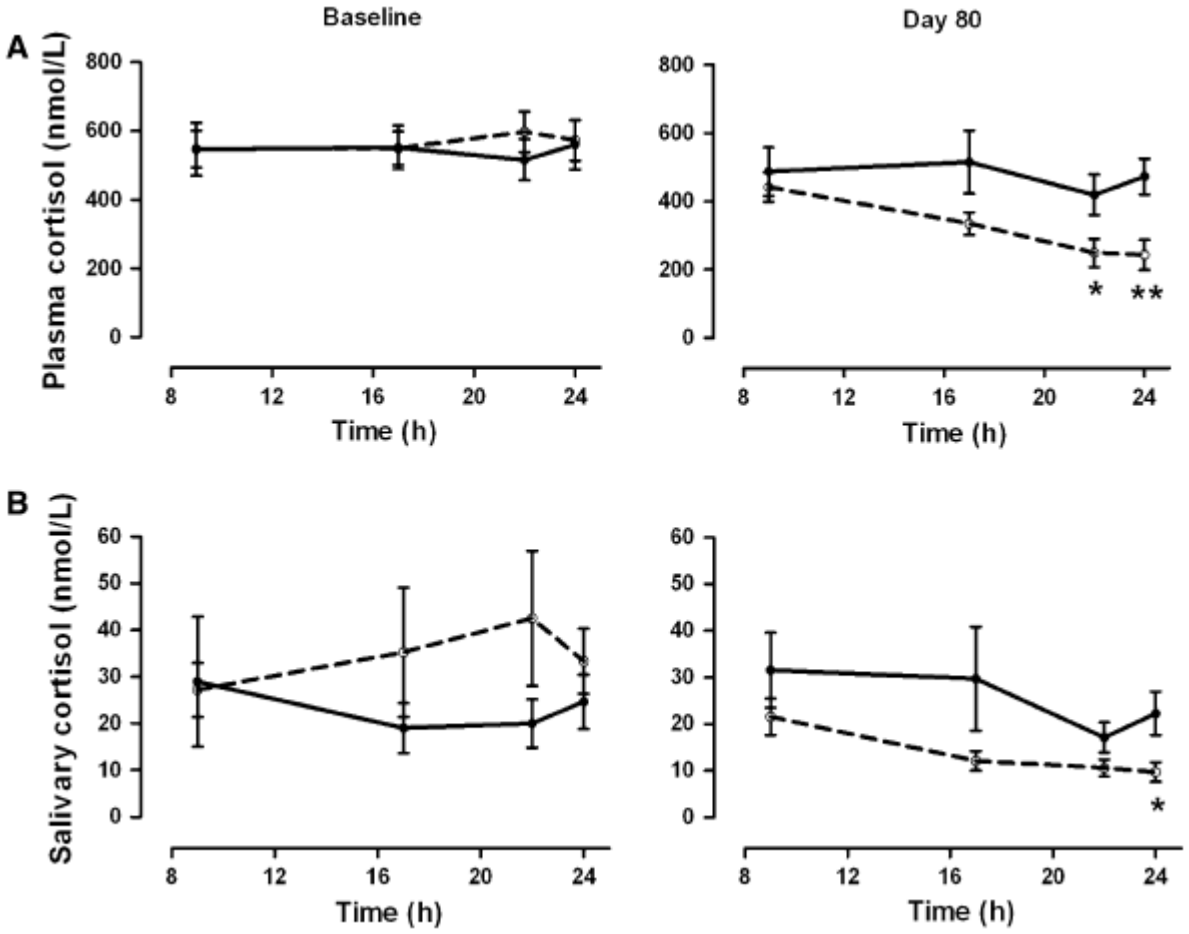
Adverse events:

- ↑ HbA1c
- ↓ IGF-1

Feelders, NEJM 2011

Cortisol diurnal rhythm and quality of life after successful medical treatment of Cushing's disease

R. van der Pas · C. de Bruin · A. M. Pereira · J. A. Romijn · R. T. Netea-Maier · A. R. Hermus · P. M. Zelissen · F. H. de Jong · A. J. van der Lely · W. W. de Herder · S. M. Webb · S. W. J. Lamberts · L. J. Hofland · R. A. Feelders



12/17 patients had elevated LNSC at baseline

In 6 /12 patients (1 mono, 1 duo and 4 triple therapy), recovery of serum and LNSC was observed after 80 days.

5/6 patients did not recover the circadian rhythm of serum- and salivary cortisol, despite normalization of UFC

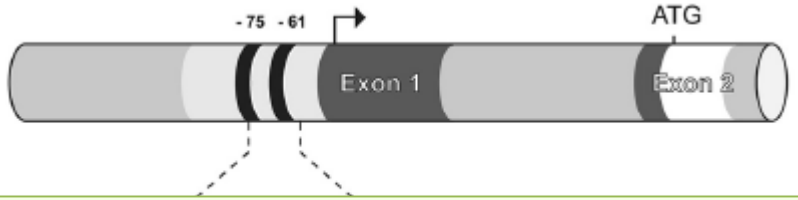
Van der Pas, JCEM 2014

OVERVIEW and CONCLUSIONS

Studies	N°	Type of patients	Agent and dose	Side effects	Overall success rate	Follow-up	Predictors of response
Pivonello et al 2009	6	Persistance (6)	CAB to 3.5 mg/week + KET 50-200/d	None	100%	12 months	N.A.
Vilar et al 2010	12	Persistance (12)	CAB 2-3 mg/week + KET 200-400/d	Transient dizziness and nausea with CAB; transient liver enzymes increase in 1 patient with KET	75%	12 months	Lower UFC
Feelders et al 2010	17	De novo (12) Persistance (2) Recurrence (3)	PAS 100-250 µg TID + CAB to 3 mg/week + KET 600/d	anorexia, nausea, dizziness, myalgia, arthralgia, hyperglycemia, decrease IGF-1	88%	80 days	Lower UFC (for PAS)
Barbot et al 2014	14	De novo (4) Persistance (6) Recurrence (4)	CAB to 3 mg/week + KET 200-600/d	2 patients had to reduce KET for skin rash and transient increase of transaminase respectively	79%	12 months	Previous TSS

KET, ketoconazole; CAB, cabergoline; PAS, pasireotide; UFC, urinary free cortisol; LNSC, late night salivary cortisol

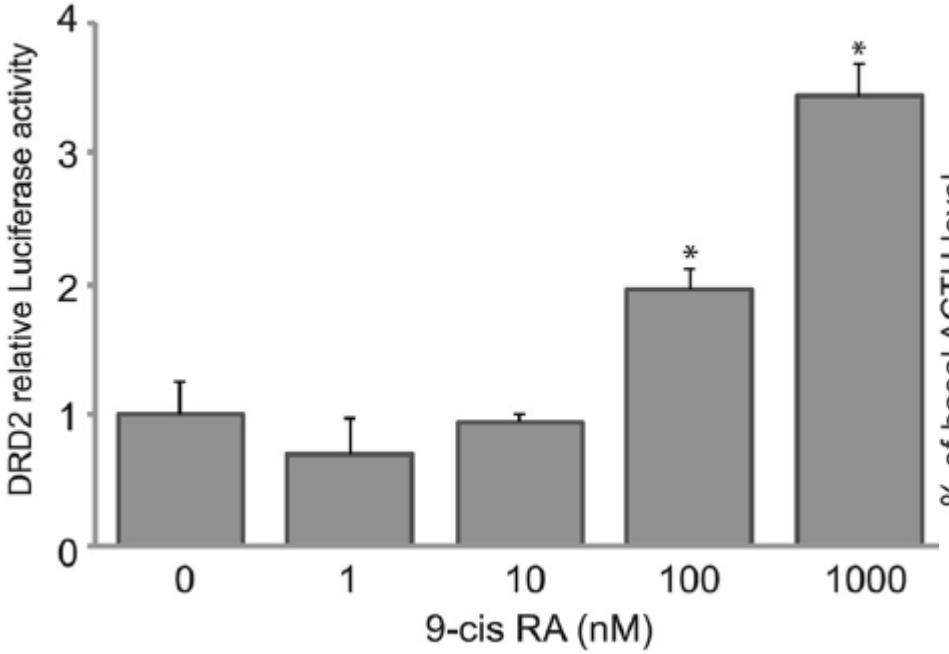
NEW INSIGHT: IMPROVING THE EFFECT OF CABERGOLINE

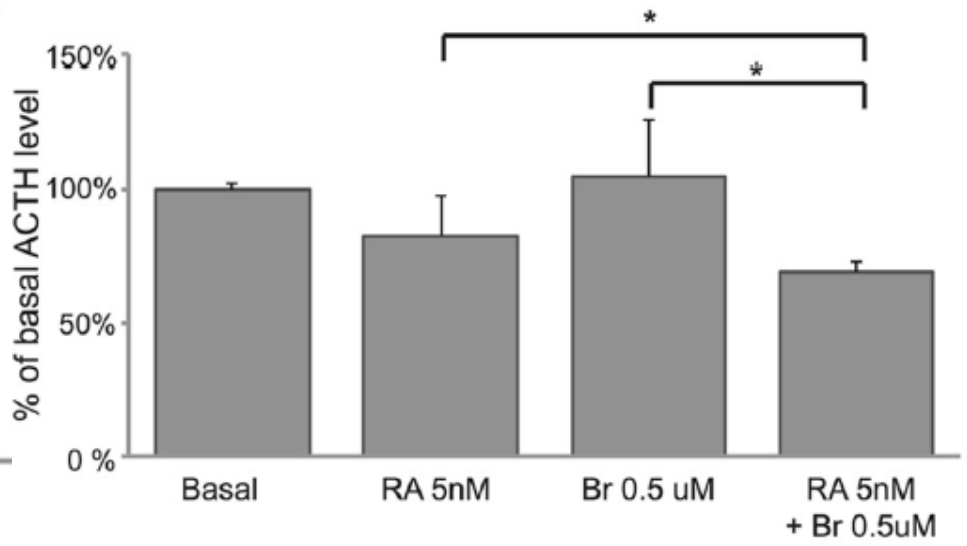


Retinoic acid induces DRD2 expression in the pituitary corticotroph-derived mouse cell line AtT20.

9-cisRA and Bromocriptine modulates more efficiently than either of the drugs alone:

- *POMC* transcriptional activity
- ACTH secretion
- cell viability





Occhi, Endocrinology 2014

CONCLUSIONS

- Data based on few small studies
- Cabergoline + ketoconazole is effective and safe
- Selected patients
- More effective in patients with mild hypercortisolism
- Combination therapy works better than each drug alone
- Less effective in restoring the circadian rhythm of cortisol
- Low cost and orally administred
- Positive effects on glucidic and lipid profile
- Both drugs are given off-label and so their combination
- Prospective studies warranted

Grazie dell'attenzione

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