Martedì **11 Aprile 2017**

11:45-13:00 TAVOLA ROTONDA

LA TERAPIA MEDICA NELLA SINDROME DI CUSHING

Moderatori: Annamaria Colao, Marco Boscaro

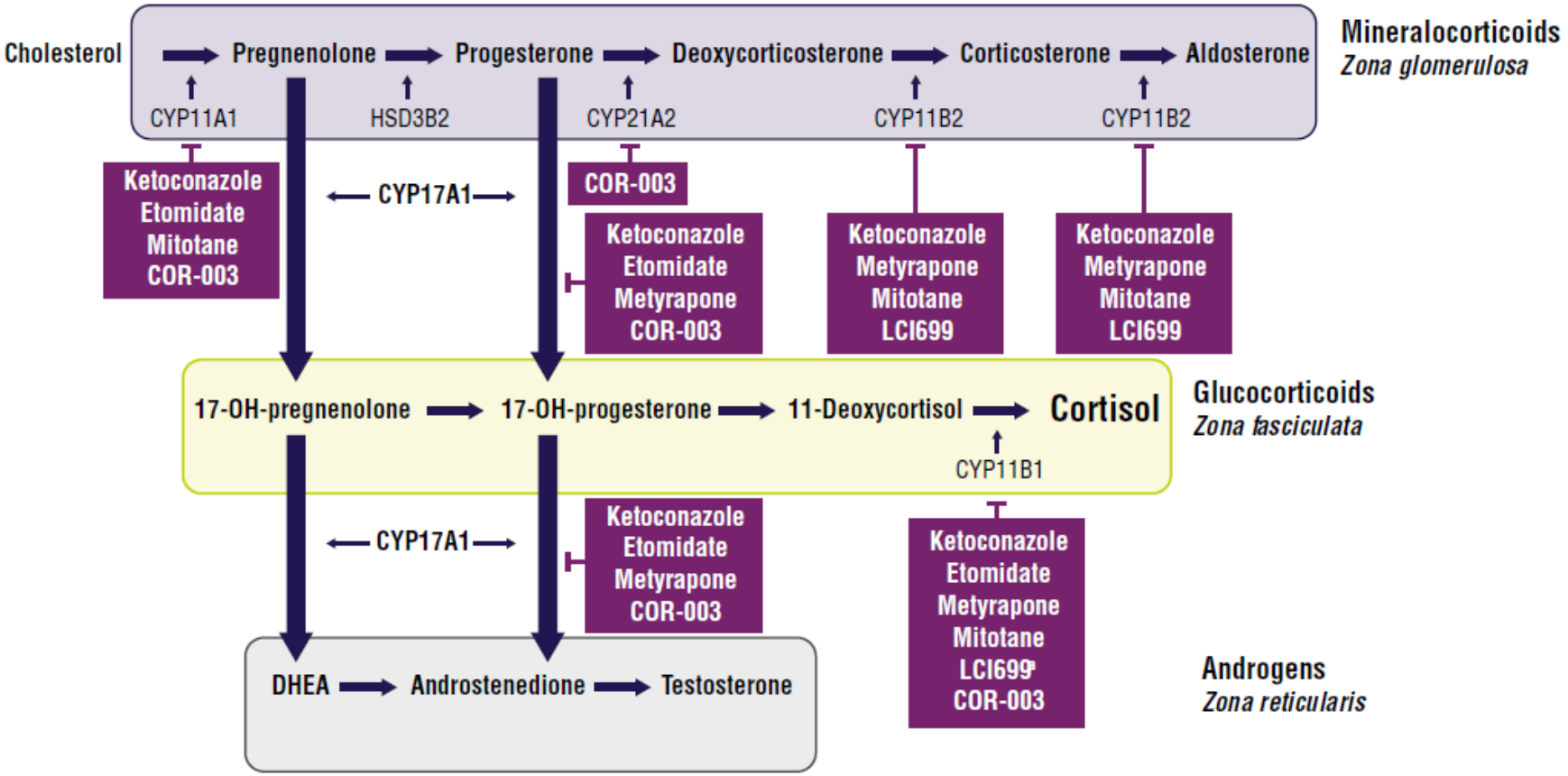
I farmaci ad azione surrenalica: Ketoconazolo e Levoketoconazolo

Laura Trementino

Goals of Treatment in Cushing's Syndrome

- Normalization of biochemical changes with minimal morbidity
- Reversal of clinical features
- Long-term control without recurrence

Adrenal-directed Drugs



Maria Fleseriu[1] · Frederic Castinetti[2]

Published online: 06 September 2016 Pituitary

Adrenal-directed Drugs

Mechanism of action: interference with cytochrome P450 (CYP) enzyme activities

Effective in the majority of cases and in a dose-dependent manner

- limited and no prospective clinical trials („old“ inhibitors)
- temporary/palliative treatment
- long-term use?
- publication bias?

Since selectivity is not high, extra-adrenal effects are likely to occur

- side effects/drug-drug interactions can limit their use

No effect on pituitary tumor

- however, upon prolonged use, no compensatory rise or even a decrease of ACTH levels may occur (*in vitro* studies suggested a role for Ketoconazole at pituitary level)

Adrenal-directed Drugs

Adrenal steroidogenesis inhibitors currently in clinical use

- Ketoconazole
- Metyrapone
- Mitotane
- Etomidate (not available in Italy)

Adrenal steroidogenesis inhibitors currently in clinical development

- Osilodrostat (LCI699) → Phase III study ongoing
- Levo-Ketoconazole (COR-003) → Phase III study ongoing

Ketoconazole

Antifungal drug (restricted use in 2013/2014 by EMA/FDA for hepatotoxicity)
Mechanism of Action: inhibition of P450 enzymes in adrenal gland (SCC, 17OH/17,20 lyase, 11β/18OH), testis, ovary, liver, kidney
Efficacy: most frequently drug used
Action: rapid, generally dose-dependent, fully reversible
Side Effects

- **Gastrointestinal reactions**
- **Hepatotoxicity**
- Pruritus, skin rash (allergic reactions)
- **Gynecomastia , impairment of testicular function → second choice in men!**
- Adrenal insufficiency

May affect several physiologic functions:

- cholesterol syntesis (decreases cholesterol)
- vitamin D synthesis/metabolism

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

200 patients

40 as a presurgical treatment	32 as a primary treatment (CI or refusal to surgery)	128 as a secondary treatment - Unsuccesful surgery (n=93) - Following radiotherapy (n=35)
Antisecretory efficacy (n=39) - 19 Controlled (48.7%) - 14 Partially controlled (35.6%) - 6 Uncontrolled (15.4%)	**Antisecretory efficacy (n=32)** - 16 Controlled (50%) - 9 Partially controlled (28.1%) - 7 Uncontrolled (21.8%)	**Antisecretory efficacy (n=126)** - 62 Controlled (49.2%) - 28 Partially controlled (22.2%) - 36 Uncontrolled (28.5%)

	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%

Tolerance data in 190 patients

Dose mediana 600 mg/die (max duration 24 months)

- **49.3% UFC normalizzato**
- **25.6% UFC ridotto ≥50%**
- **25.4% UFC invariato**

Sospensione del trattamento per intolleranza nel 20.5% dei pz

Lieve ↑ delle transaminasi (<5 x ULN) nel 13% dei pz
↑ severo (>5 x ULN) nel 2.5% dei pz.
Nessun caso di epatite fatale.

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

Outcome of Ketoconazole in CD

First Author, Year (Ref.)	Study Drug	No. of Patients	Drug Dose, mg/d	Follow-up, mo	Remission Rate, %*	Escape (% of the Total Population)*	Escape (% of Initially Responsive Population) *	Adverse Effects, %
Sonino, 1991 (494)	Ketoconazole	28 (9 RT)	R:400–800; M: 564.3; m:600	R:0.13–36; M: 8.1; m:5	92.9	7.1	7.1	Transient increase in liver enzymes:10.7; GI disturbances:10.7; Skin rash:3.6; worsening of gynecomastia:25 (of men)
Moncet, 2007 (501)	Ketoconazole	52 (CS), 37 CD (16 S/RT)	R:200–1200; m:600**	R:0.5–156; M: 9.6**	84.6**	11.5**	12.8**	Adrenal insufficiency:18.5**; hepatotoxicity:11.1**; skin rash:5.5**; digestive intolerance:3.7**
Castinetti, 2008 (502)	Ketoconazole	38 (17 PS, 4 RT)	R:200–1200; M:636.8; m: 600	R:0.25–72; M: 15.2; m:12	44.7	13.2	22.7	Gastrointestinal disturbances:18.4; increase in gamma-glutamyl-transpherase:10.5; increase in liver enzymes:2.6
Van den Bosch, 2014 (507)	Ketoconazole	10	R:400–1000; M:720; m: 700	R:2.4–40.5; M: 9.5; m:5.5	50	NA	NA	Hepatotoxicity:18.7#; GI disturbances:18.7#; fatigue and malaise:12.5#; exanthema:6.2#; headache:6.2#
Castinetti, 2014 (508) (global population)	Ketoconazole	197 (93 PS, 35 RT)	R:200–1200; M:774.6; m: 600	R:0.03–135; M: 20.6	49.2*	na	na	Increase in liver enzymes:18.4§; gastrointestinal disturbances:13.1§ adrenal insufficiency:5.3§; pruritus:3.7§
Castinetti, 2014 (508) (long-term population)	*Ketoconazole*	*51*		*R:24.1–135; M: 108*	*64.7*	*11.8**	*15.4**	
Total	**Ketoconazole**	**310**	**R:200–1200; M:673.9; m:620**	**R:0.03–156; M:12.6; m: 7.5**	**R:44.7–92.9; M:64.3; m: 50**	**R:7.1–13.2; M:10.9; m: 11.6**	**R:7.1–22.7; M:14.5; m: 14.1**	**Hepatotoxicity:R:10.7–18.7; M:14.5; m: 13.6; GI disturbances:R:3.7–18.7; M: 12.9; m:13.1; skin rash:R:3.6–6.2; M: 5.1; m:5.5; adrenal insufficiency:R: 5.3–18.5; M:11.9; m:11.9**

Combination Therapy

Table 4 Overview of medications that have been tested as combination drug therapy for Cushing's disease

References	Combination therapy	Patients (n)	UFC normalization (%)	
			Monotherapy	Combination
Vilar et al. [10]	Cabergoline + ketoconazole	12	25	67
Pivonello et al. [53]	Cabergoline + ketoconazole	6	–	100
Barbot et al. [54][a]	Ketoconazole + cabergoline	14	0	79
Feelders et al. [12]	Pasireotide + cabergoline + ketoconazole	17	30 (P)	34 (P + C)75 (P + C + K
Total/average		49	19	77
Severe hypercortisolism/aggressive tumor				
Vignati and Loli [55]	Ketoconazole + octreotide	4	0	75
Bode et al. [62]	Temozolomide + pasireotide	1	0	100
Kamenicky et al. [50]	Mitotane + metyrapone + ketoconazole	11 CS (4 CD)	0	73
Total/average		16	0	75

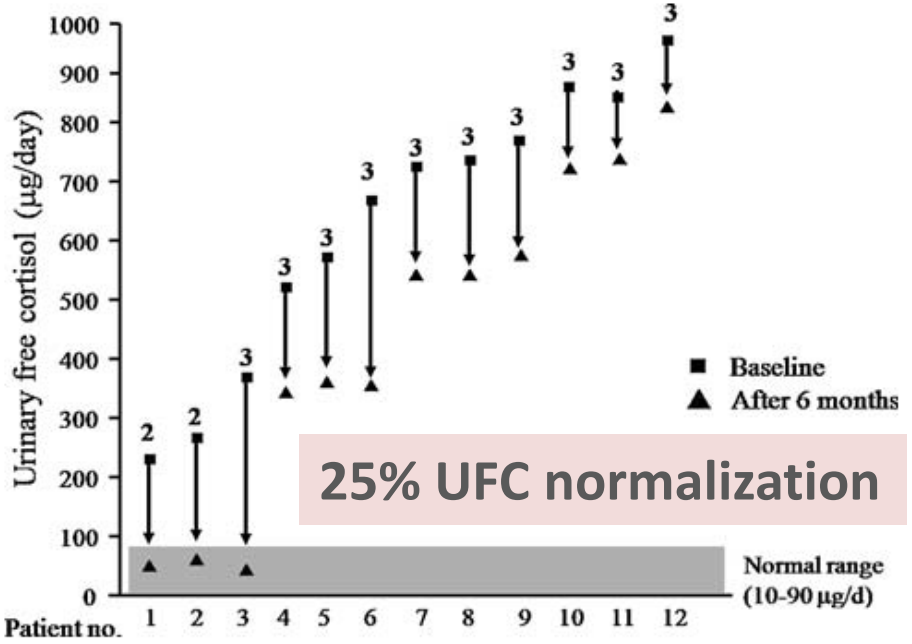
Lucio Vilar · Pituitary (2015) 18:253–262

Higher probability of longterm control of the hypercortisolism at lower doses, a lower incidence of side-effects, and possibly a lower rate of treatment escapes

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

CABERGOLINE



25% UFC normalization

Fig. 1 Changes in 24 h urinary free cortisol levels after treatment with cabergoline. The number on each *arrow* indicates the maximal dose of cabergoline expressed in mg/week administered to each patient

CAB + KETOCONAZOLE

66.7% UFC normalization

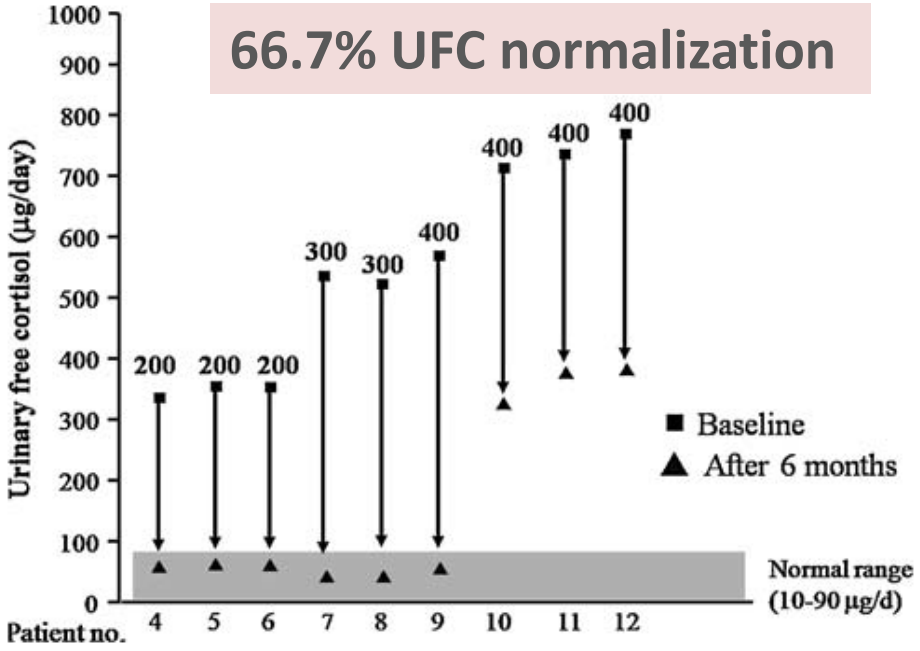
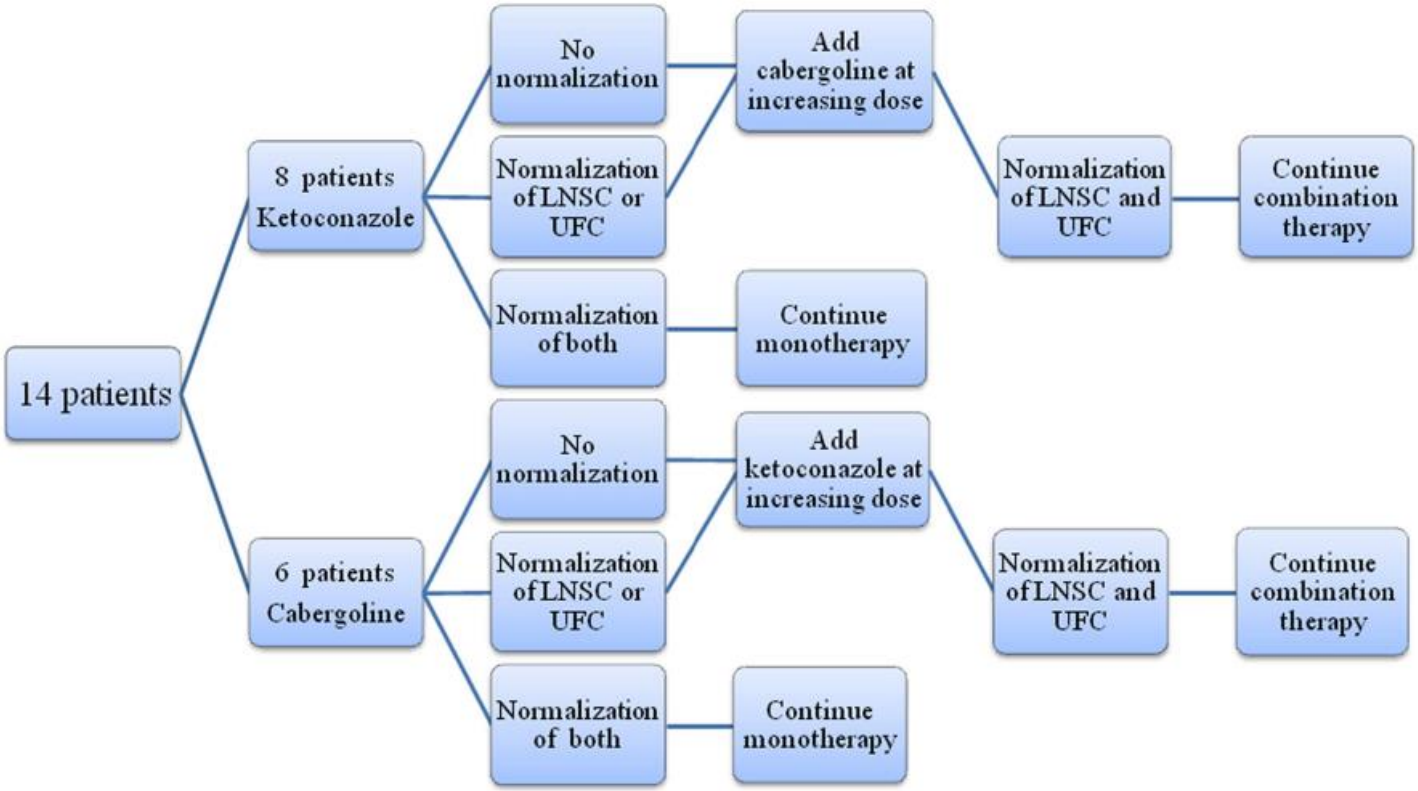


Fig. 2 Changes in 24 h urinary free cortisol levels after treatment with cabergoline and ketoconazole. The number on each *arrow* indicates the maximal dose of ketoconazole expressed in mg/day administered to each patient

Pituitary (2010) 13:123–129

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

M. Barbot · N. Albiger · F. Ceccato · M. Zilio · A. C. Frigo · L. Denaro · F. Mantero · C. Scaroni



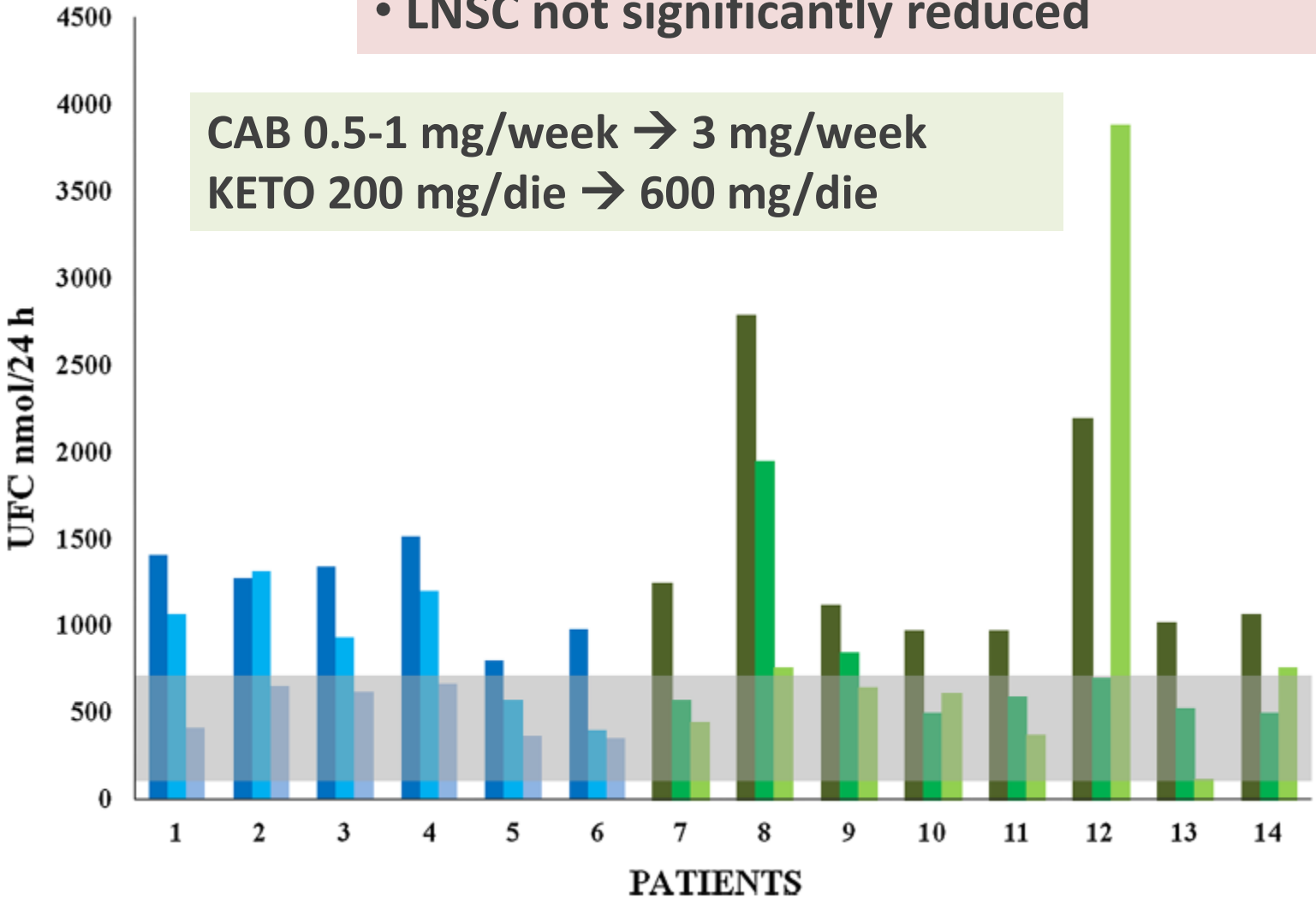
Baseline	*6 months*	*12 months*	*18 months*
Randomization	**Monotherapy**	**Combination therapy**	**Extension phase**

Pituitary (2014) 17:109–117

Combination Therapy:

- **79% UFC normalization (no differences between the group)**
- **LNSC not significantly reduced**

CAB 0.5-1 mg/week → 3 mg/week
KETO 200 mg/die → 600 mg/die

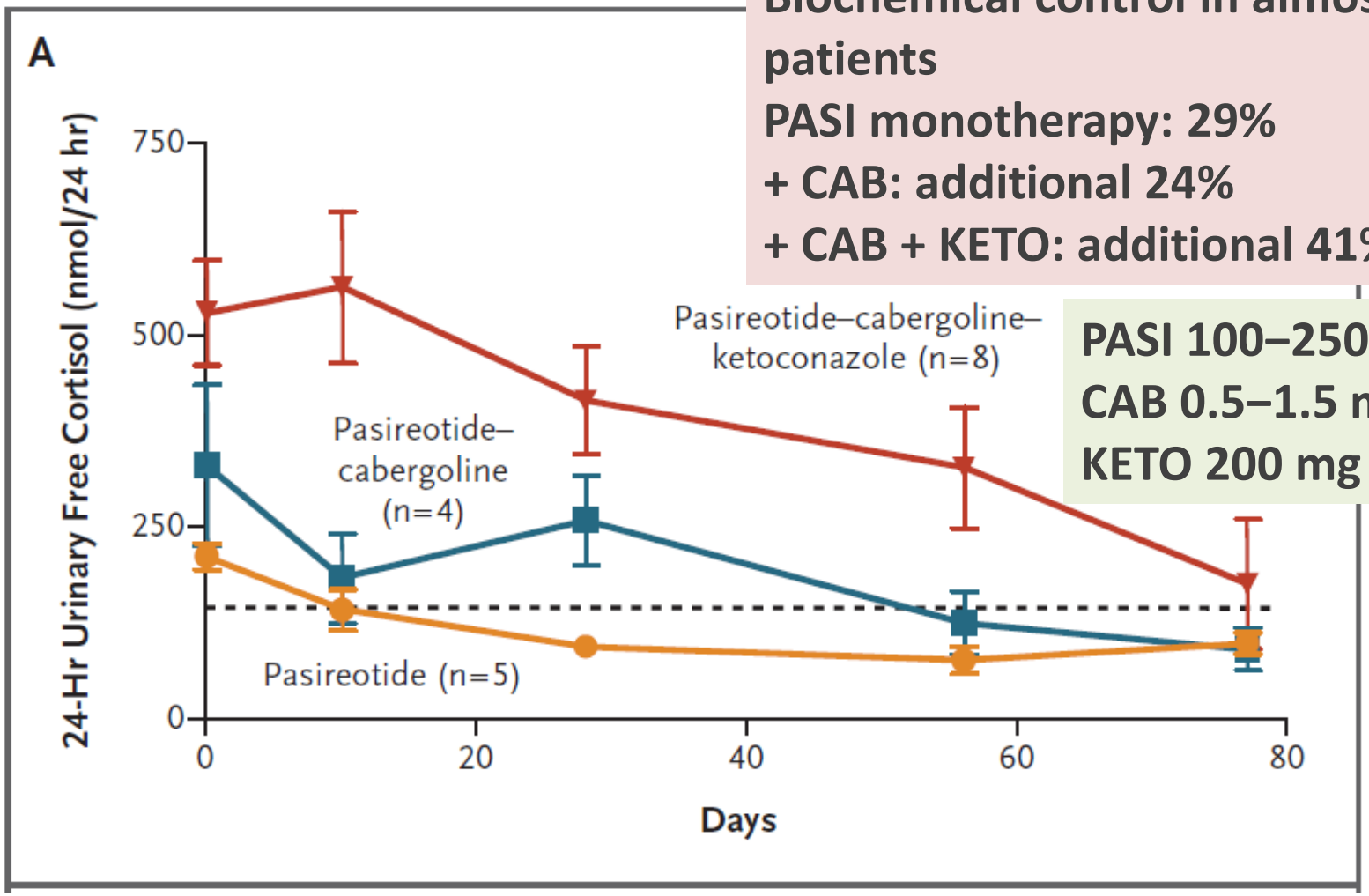


Pituitary (2014) 17:109–117

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

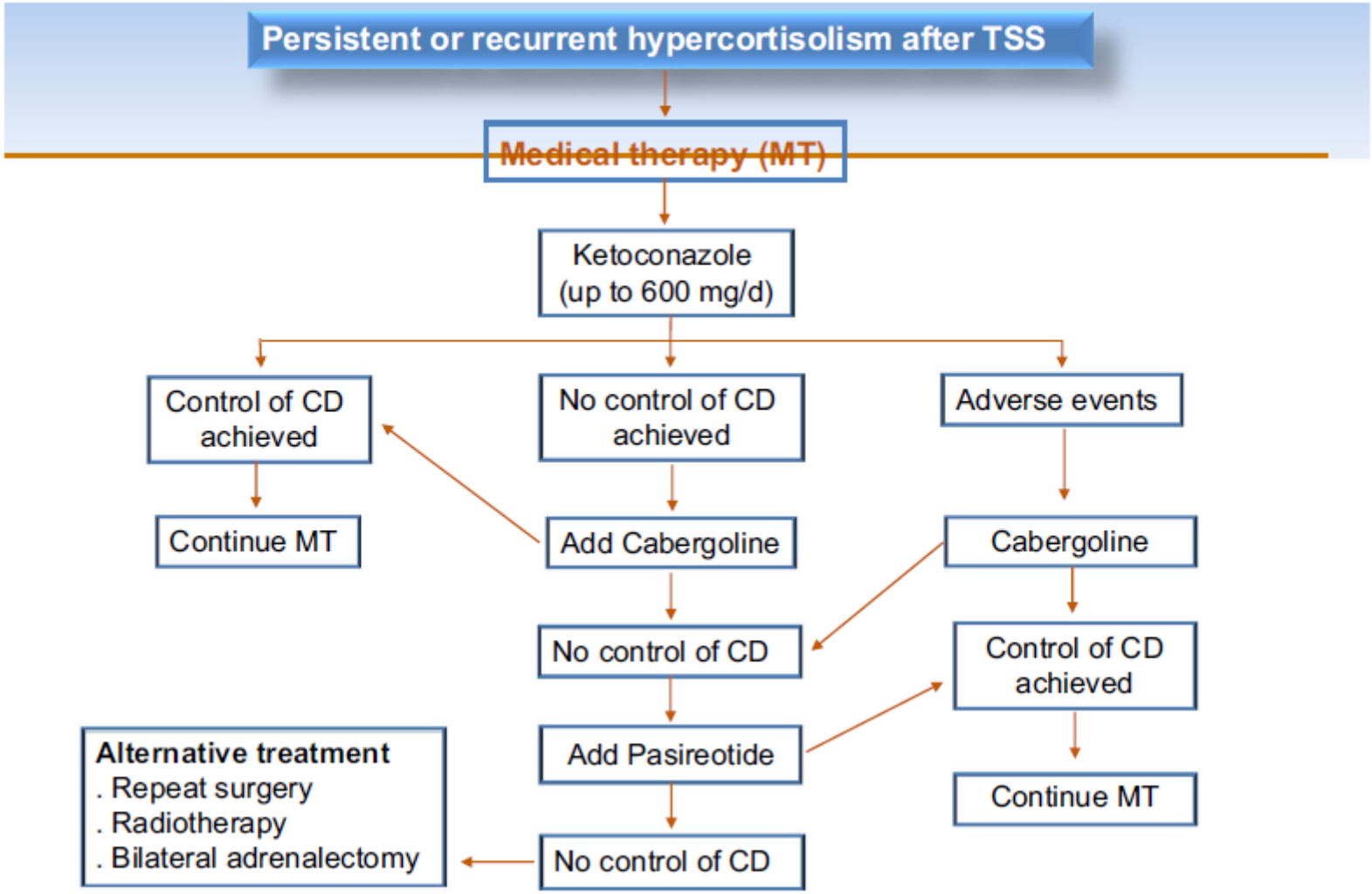
Biochemical control in almost 90% of patients
PASI monotherapy: 29%
+ CAB: additional 24%
+ CAB + KETO: additional 41%

PASI 100–250 mcg tid
CAB 0.5–1.5 mg qod
KETO 200 mg tid



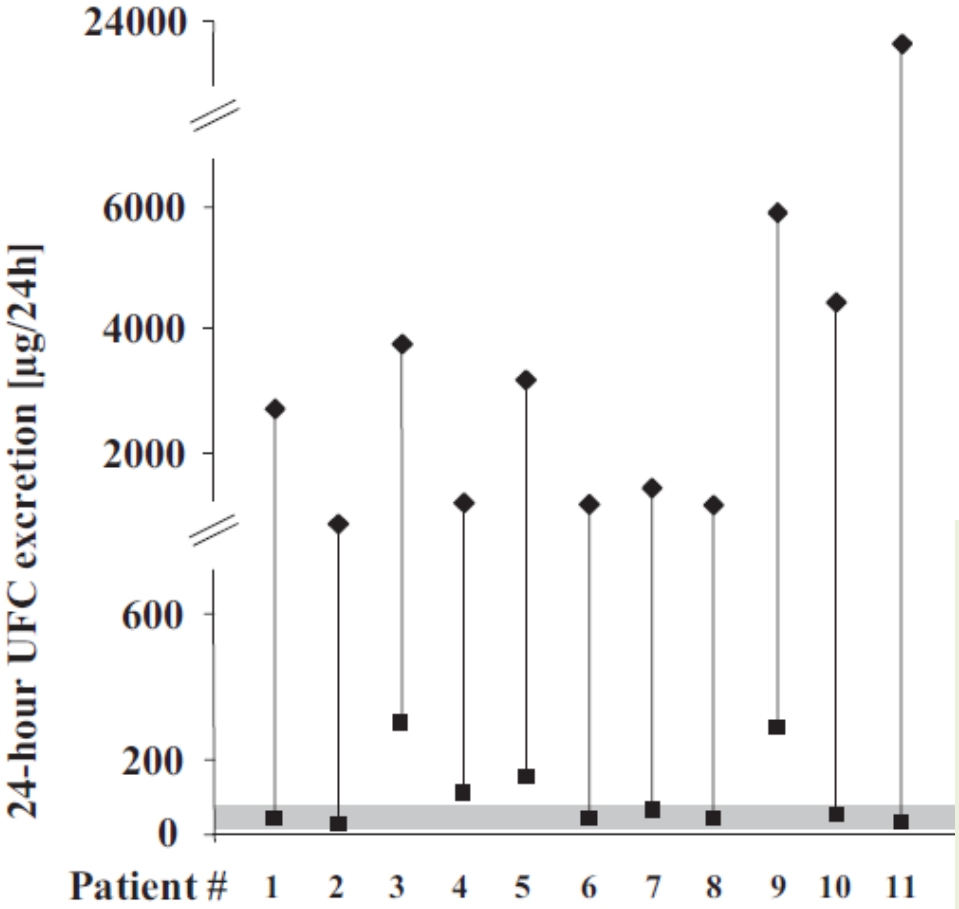
Medical combination therapies in Cushing's disease

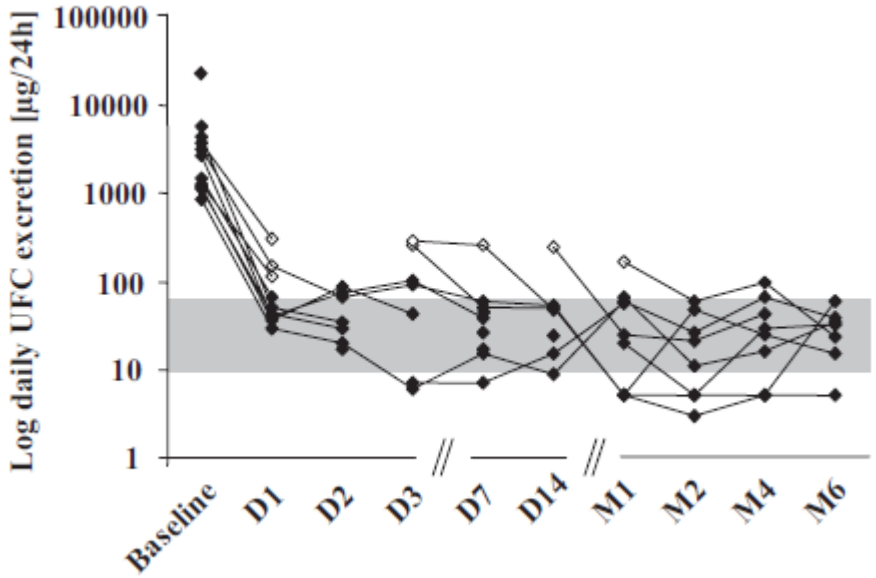
Lucio Vilar · Luciana A. Naves · Márcio C. Machado · Marcello D. Bronstein



Pituitary (2015) 18:253–262

Mitotane, Metyrapone, and Ketoconazole Combination Therapy as an Alternative to Rescue Adrenalectomy for Severe ACTH-Dependent Cushing's Syndrome





Median doses:
Mitotane 3 gr/24h (3-5 mg/24h)
Metyrapone 3 gr/24h (3-4.5 mg/24h)
KETO 800 mg/24h (400-1200 mg/24h)

AEs tolerable
(GI and CHOLE and ϒ-GT increase)

Ketoconazole

Indicazione:

- Trattamento della Sindrome di Cushing endogena in adulti e adolescenti di età superiore ai 12 anni
  (prescrivibile con ricetta non ripetibile limitativa –RNRL– di centri ospedalieri o di specialisti endocrinologi e internisti)

Dosaggio:

- Start dose 400–600 mg/die , frazionato in 2-3 dosi/die,

(necessità di ambiente acido gastrico per assorbimento)

- Max dose 1200 mg/die

Monitoraggio biochimico/clinico:

- Funzione epatica, surrenalica e QTc
- Interruzione trattamento per incremento enzimi epatici

≥ 3xULN (non iniziare se enzimi epatici >2xULN)

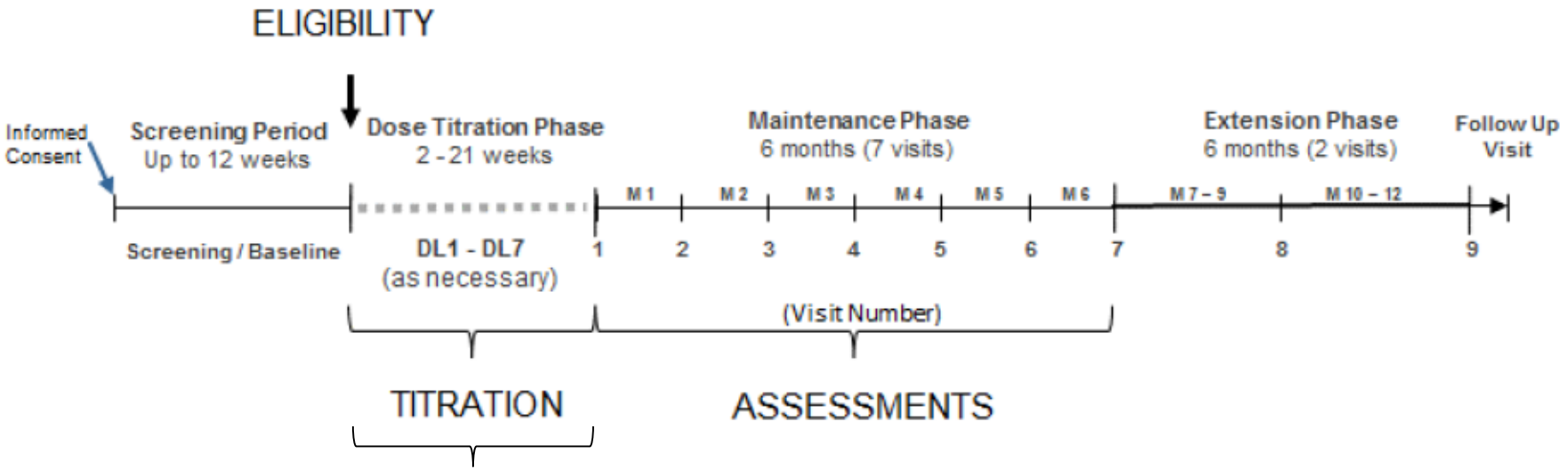
Levo-Ketoconazole (COR-003)

- Phase III study in CS ongoing
- More effective than Ketoconazole in adrenal cortisol inhibition
- Lower risk of hepatotoxicity
- Positive effect in c-LDL (DM2 patients)

CLINICAL STUDY PROTOCOL

An Open Label Study to Assess the Safety and Efficacy of COR-003 (2S, 4R-Ketoconazole) in the Treatment of Endogenous Cushing's Syndrome

Figure 1 Study Design



Dose Level (DL)	Morning dosing	Evening Dosing
DL1	150 mg	150 mg
DL2	150 mg	300 mg
DL3	300 mg	300 mg
DL4	300 mg	450 mg
DL5	450 mg	450 mg
DL6	450 mg	600 mg
DL7	600 mg	600 mg

Keto/LevoKeto drug-drug interaction

Table 2 Drug–drug interactions with adrenal steroidogenesis inhibitors

Medical intervention	Interacts with	Potential for adverse event
Ketoconazole [24, 54, 69]	CYP3A4	Drug–drug interactions with oral anticoagulants,* statins, cyclosporine, and tacrolimus
	hERG	Possible QT prolongation
		Use acid-lowering and hepatotoxic drugs with caution
Metyrapone [68]	UGT1	Drug–drug interactions occur frequently
		Acetaminophen toxicity
Etomidate [70–73]	CYP11B1	Etomidate should be given carefully with calcium channel blockers, opioids, and benzodiazepines
Mitotane [35]	CYP3A4	Drug–drug interactions with oral anticoagulants, statins, cyclosporine, and tacrolimus
		Hydrocortisone dose increased
Osilodrostat (LCI699) [21, 60, 74]	CYP1A2 and CYP2C19 (moderate inhibition)	Drug–drug interactions
		Possible QT prolongation
	CYP2D6 and CYP3A4 (weakly inhibited)	
Levoketoconazole (COR-003) [21]	CYP3A4, CYP3A5	Drug–drug interactions with oral anticoagulants, statins, cyclosporine, and tacrolimus
	hERG	
		QT prolongation

CYP, cytochrome P450; hERG, human ether-a-go–go–related gene; UGT1, UDP-glucuronosyltransferase 1 family; NR, not reported

* Lovastatina, Simvastatina, Atorvastatina (substrato CYP3A4)

Table 9 Drugs That Have Been Shown to or Are Predicted to Have Their Plasma Concentrations Altered by COR-003

Systemic exposure to these drugs is increased significantly by the addition of COR-003, concomitant use is prohibited:	
Alprazolam, midazolam, triazolam Cisapride Dofetilide Eplerenone Ergot alkaloids (ergotamine, dihydroergotamine) Nisoldipine Pimozide Quinidine	HMG-CoA reductase inhibitors **except** pravastatin, fluvastatin and rosuvastatin
Systemic exposure to these drugs is increased by COR-003: Careful monitoring, with possible adjustment in doses, is recommended	
Alfentanil, fentanyl, sulfentanil Amlodipine, felodipine, nicardipine, nifedipine Bosentan Buspirone Busulfan Cilostazol Cyclosporine Digoxin Docetaxel, paclitaxel Indinavir, saquinavir	Oral anti-coagulants Rifabutin Sildenafil Sirolimus Tacrolimus Telithromycin Tolterodine Trimetrexate Verapamil Vinca alkaloids (vincristine, — vinblastine, vinorelbine)

Table 10 Drugs That Are Predicted to Reduce or Increase significantly The Plasma Concentration of COR-003 and Are Prohibited

Carbamazepine Gastric Acid Suppressants (histamine H2 -blockers, proton pump inhibitors, sucralfate) Nevirapine	Phenytoin Rifampin, rifabutin, isoniazid Ritonavir

No Untoward Effect of Long-Term Ketoconazole Administration on Electrocardiographic QT Interval in Patients with Cushing's Disease

Martina De Martin[1], Paola Maria Toja[2], Karine Goulene[3], Piero Radaelli[1], Francesco Cavagnini[1], Marco Stramba-Badiale[3] and Francesca Pecori Giraldi[1,4]

KETO 100-800 mg/die (1 month-12 years)

No significant QTc prolungation

Baseline						On ketoconazole					
Pt #	Sex/Age	LVH	Kalaemia	QTc	QT-prolonging drugs	Disease phase	Dose, mg	Length	Kalaemia	QTc	QT-prolonging drugs
1	M/36	No	3.9	436		Prior to TSS	800	5	3.8	426	
2	M/30	No	4.4	379		TSS failure	600	24	4.5	393	
3	M/23	Yes	**3.15**	**458**		TSS failure; after RT	100	132	3.8	375	
4	F/55	Yes	3.7	418	Fluoxetine 20 mg	TSS failure	200	60	4.0	406	Fluoxetine 20 mg
5	F/42	No	4.7	408	Paroxetine 20 mg	Prior to TSS	400	6	5.3	431	Paroxetine 20 mg
6	F/31	No	3.9	372		Prior to TSS	600	7	4.5	377	
7	F/40	No	3.9	424		Prior to TSS	600	1	4.4	408	
8	F/34	No	4.1	433		Prior to TSS	600	6	3.6	440	
9	F/59	Yes	3.5	391	Citalopram 20 mg Glibenclamide 15 mg	TSS failure	400	5	3.7	388	Citalopram 20 mg Glibenclamide 15 mg Ciprofloxacin 1 g (1 week)
10	F/34	No	4.2	402		TSS failure; after RT	600	7	4.0	392	Escitalopram 20 mg
11	F/27	No	4.4	367		TSS failure; after RT	400	18	4.4	388	
12	F/51	No	4.5	368		TSS failure; after RT	400	132	4.4	375	Ciprofloxacin 1 g (1 week)
13	F/29	No	3.8	375		Relapse	600	36	3.8	408	
14	F/41	No	4.1	360		TSS failure	800	12	4.3	400	
15	F/35	No	3.9	402		Relapse	400	144	**3.3**	450	Paroxetine 20 mg

Basic & Clinical Pharmacology & Toxicology, 2016, **118**, 279–283

Conclusion

Ketoconazole in Cushing's Syndrome
(as monotherapy or combined therapy)
is able to achieve:

- Normalization of biochemical changes with minimal morbidity
- Reversal of clinical features
- Long-term control without recurrence

thank you!