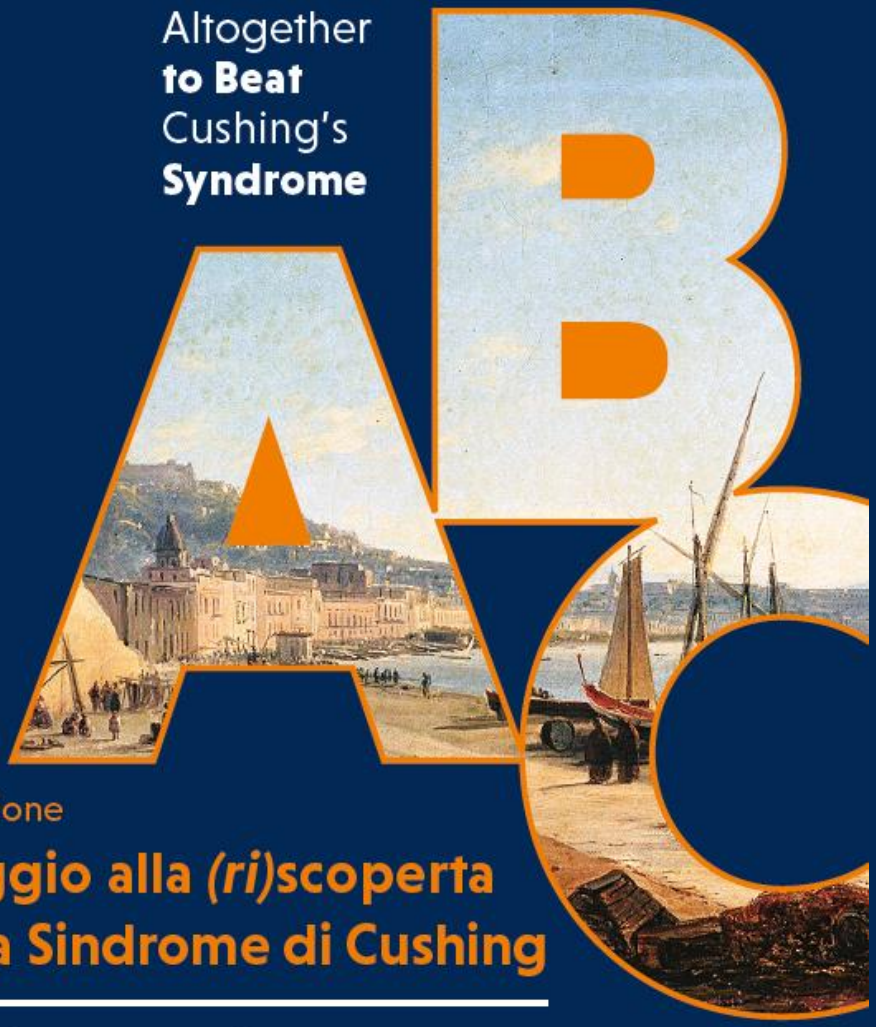
UNIVERSITA' DEGLI STUDI DI NAPOLI FEDERICO II
Dipartimento di Medicina Clinica e Chirurgia

Altogether
to Beat
Cushing's
Syndrome



5ª Edizione

Viaggio alla *(ri)*scoperta della Sindrome di Cushing

Napoli, 10-12 Aprile 2017
Centro Congressi Federico II - Via Partenope, 36

Coordinatori Scientifici
Annamaria Colao, Rosario Pivonello

LA TERAPIA MEDICA NELLA SINDROME DI CUSHING

GLI ANTAGONISTI RECETTORIALI: MIFEPRISTONE

Francesco Logoluso
U.O.C. Endocrinologia
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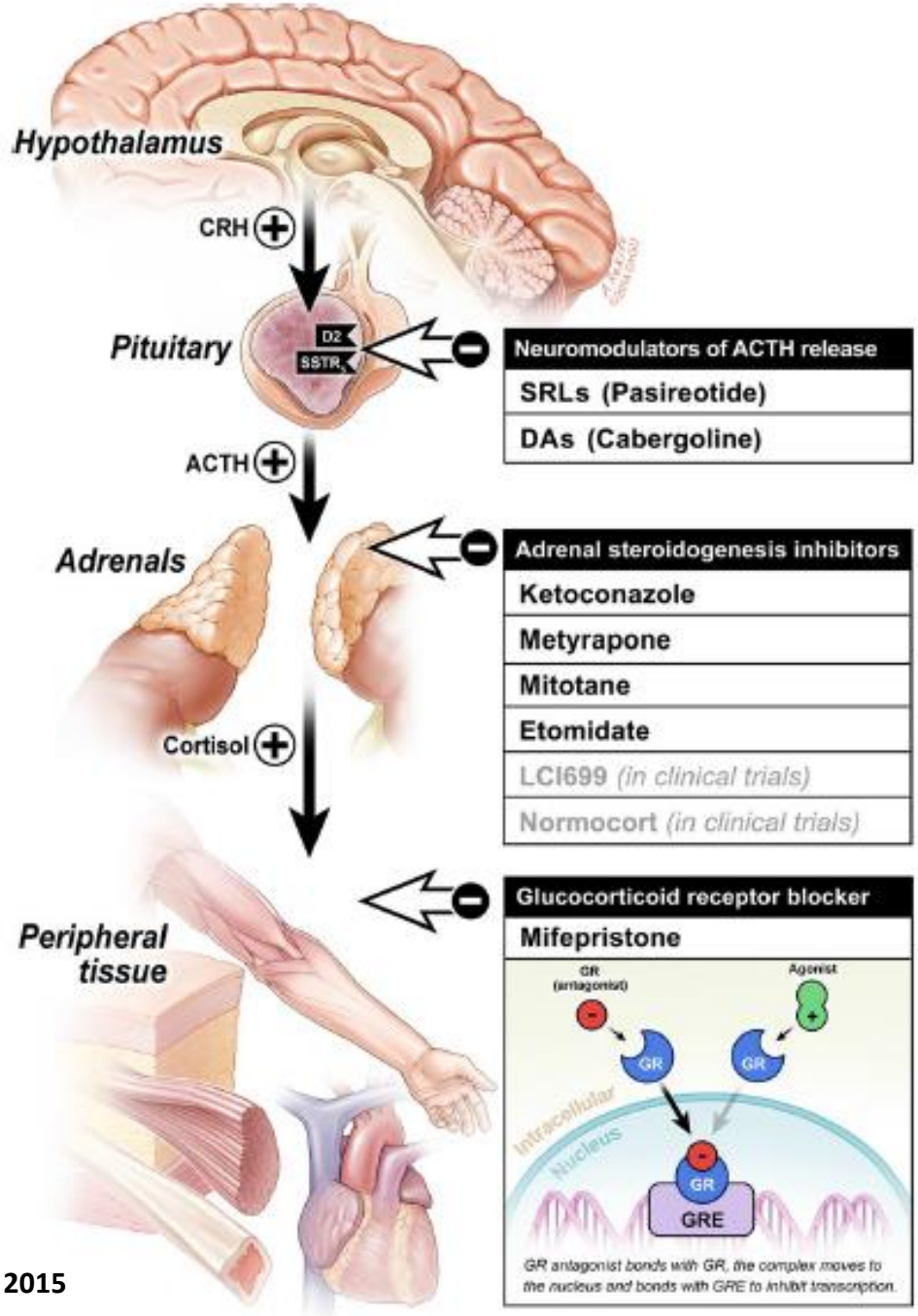
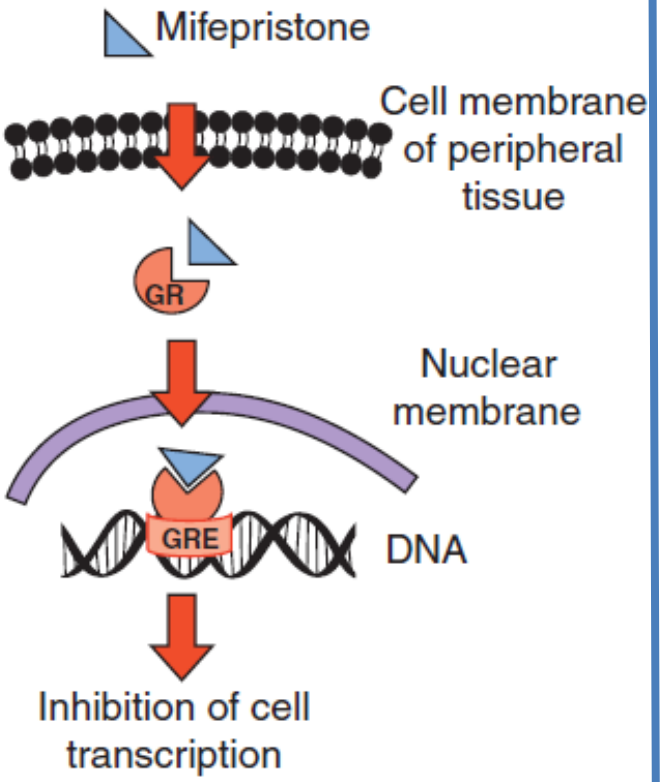
Policlinico Bari



Fleseriu M. & Petersenn S., Pituitary 2015



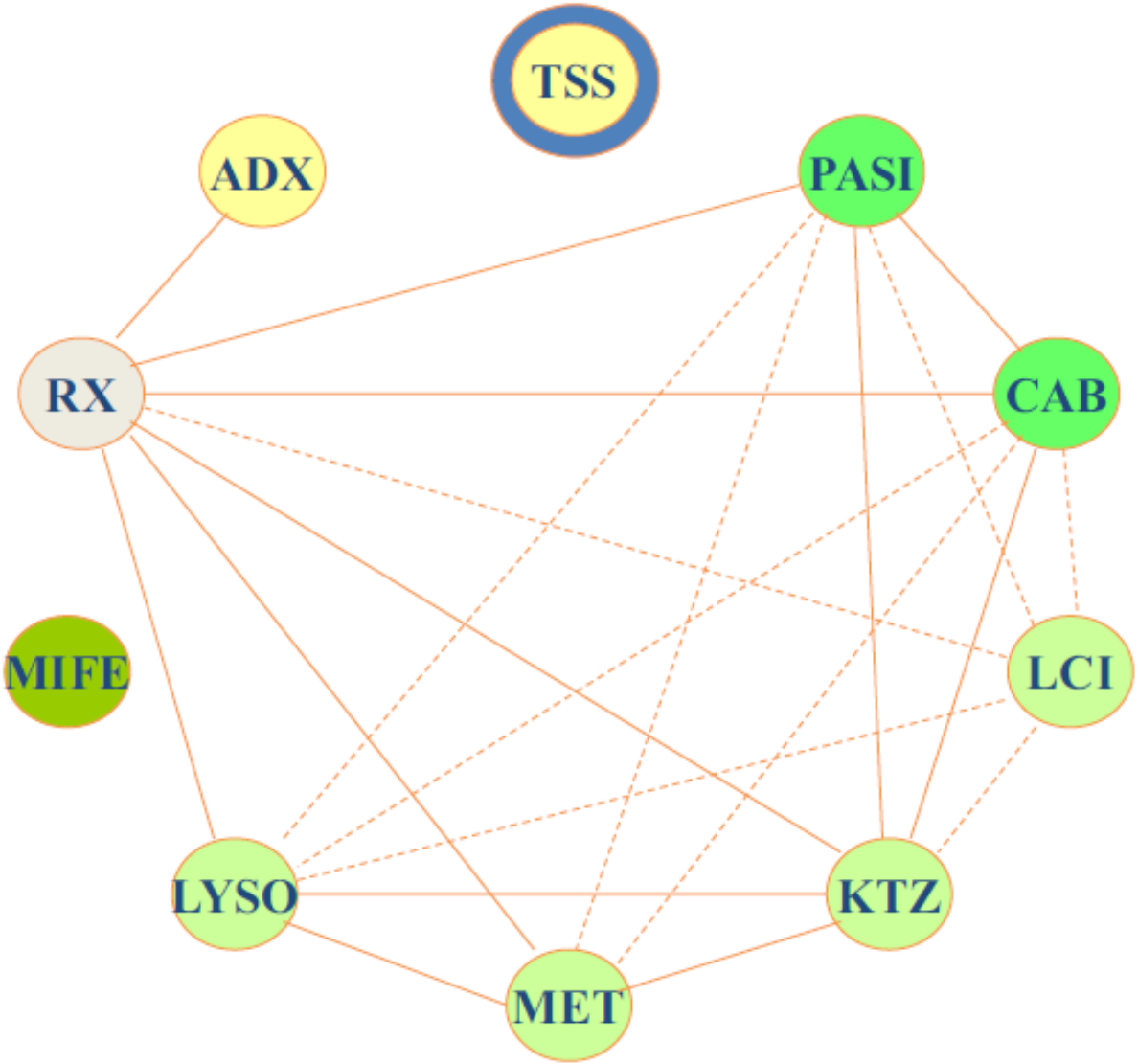
Antagonista non-selettivo del Glucocorticoid Receptor type II

Affinità per il recettore 3 volte quella del DEX
18 volte quella del cortisolo

Blocco centrale e periferico dell'azione del cortisolo

Attività anti-progestinica

CUSHINGAME



Successful Treatment of Cushing's Syndrome with the Glucocorticoid Antagonist RU 486*

LYNNETTE K. NIEMAN, GEORGE P. CHROUSOS, CHARLES KELLNER, IRVING M. SPITZ, BRUCE C. NISULA, GORDON B. CUTLER, GEORGE R. MERRIAM, C. WAYNE BARDIN, AND D. LYNN LORIAUX

ABSTRACT. A patient with Cushing's syndrome due to ectopic ACTH secretion was treated successfully with the new glucocorticoid antagonist RU 486 [17β-hydroxy-11β-(4-dimethylamino phenyl)17α-(1-propynyl)estra-4,9-dien-3-one]. This compound is a 19-nor steroid with substitutions at positions C11 and C17 which antagonizes cortisol action competitively at the receptor level. Oral RU 486 was given in increasing doses of 5, 10, 15, and 20 [illegible] was monitored [illegible] several gluco[illegible] sugar, blood [illegible] and plasma concentrations of TSH, corticosteroid-binding globulin, LH, testosterone-estradiol-binding globulin, and total and free testosterone. With therapy, the somatic features of Cushing's syndrome (buffalo hump, central obesity, and moon facies) ameliorated, mean arterial blood pressure normalized, suicidal depression resolved, and libido returned. All biochemical glucocorticoid-sensitive parameters normalized. No side-effects of [illegible] drug toxicity were observed. We conclude that RU 486 may provide a safe, well tolerated, and effective medical treatment for hypercortisolism. (*J Clin Endocrinol Metab* **61:** 536, 1985)

Medical Treatment of Cushing's Syndrome: Glucocorticoid Receptor Antagonists and Mifepristone

Neuroendocrinology 2010;92(suppl 1):125–130

Frederic Castinetti Bernard Conte-Devolx Thierry Brue

Table 1. Individual data of patients treated with mifepristone for adrenal carcinoma (patients 1–17), ectopic ACTH secretion (18–29), Cushing's disease (30–34) or other causes (35–37)

Patient No.	Sex/ age	Dose mg/day	Previous treatments	Duration months	High BP	Hypoka-lemia	Adrenal insufficiency	Diabetes
1	F/45	5–22 mg/kg		2				
2	F/32	400		2				
3	F/NA	20–30 mg/kg		4				
4	M/62	400		9			↑	
5	M/43	400–800 mg		0.5				
6	M/63	1,000	M	6	↓	↔		↓
7	F/39	400	M	2.5	↔	↑		–
8	F/52	400–600	M	3	↓	↑		–
9	F/52	400–600	M	3	↓	↑		↔
10	F/45	400–2,000	M+K	1	–	↑		–
11	F/63	600	M+K	2	↔	–	↑	–
12	M/20	600–1,200	M+K	1	↓	↑	↑	↔
13	F/47	400–1,200	M+K	2	↔	↑		–
14	F/38	400–600	M+m	3	–	–		–
15	F/44	200–600	M+m	2	–	–		–
16	M/64	200–400	M+m	1.5	–	–		–
17	M/52	600	M+E	0.25	–	↑		↔
18	M/36	5–22 mg/kg		10			↑	
19	M/42	5–22 mg/kg		12				
20	F/63	5–22 mg/kg		4			↑	
21	F/55	5–22 mg/kg		2.5				
22	F/46	800–1,600		0.3				
23	M/25	5–20 mg/kg	m+chemotherapy	2.5	↓	↓		↓
24	F/2	75–300	none	2	↓	–		↓
25	F/46	600	chemotherapy	2	↑	↑		↓
26	F/37	800	chemotherapy	10	↑	↑		–
27	M/55	400–600	E+m	1	↓	↑		↓
28	F/43	600	K	2	↑	↑		↓
29	F/38	400–800	K	18	↑	↑		–
30	M/45	400–800	K	12	–	–		–
31	M/56	600–1,200	K	24	–	–	↑	–
32	F/50	600	–	0.5	–	↔		–
33	F/45	600	–	3	↑	↑		–
34	M/51	400–2,000	K	18	↔	↑	↑	–
35	F/38	5–22 mg/kg	–	1.5				
36	F/52	600	K	6	–	↔		↓
37	F/14	400	–	8	–	–		–

Previous treatments are treatments administered before the start of mifepristone therapy: M = mitotane; K = ketoconazole; m = metyrapone; E = etomidate. High blood pressure (BP), hypokalemia, adrenal insufficiency and diabetes: ↓ = alleviation or improvement on mifepristone; ↑ = worsening or onset on mifepristone; ↔ = unchanged on mifepristone; – = absent before treatment, unchanged on mifepristone; blank space for patients 1–5 = not available.

Medical Treatment of Cushing's Syndrome: Glucocorticoid Receptor Antagonists and Mifepristone

Frederic Castinetti Bernard Conte-Devolx Thierry Brue

Neuroendocrinology 2010;92(suppl 1):125–130

Mifepristone represents a rapidly effective treatment to control signs of hypercortisolism with the main drawback of the impossibility to follow blood cortisol levels.

Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome

J Clin Endocrinol Metab, June 2012, 97(6):2039–2049

SEISMIC **Study of the Efficacy and Safety of Mifepristone in the Treatment of Endogenous Cushing's Syndrome**

Studio multicentrico, open-label, 24 settimane

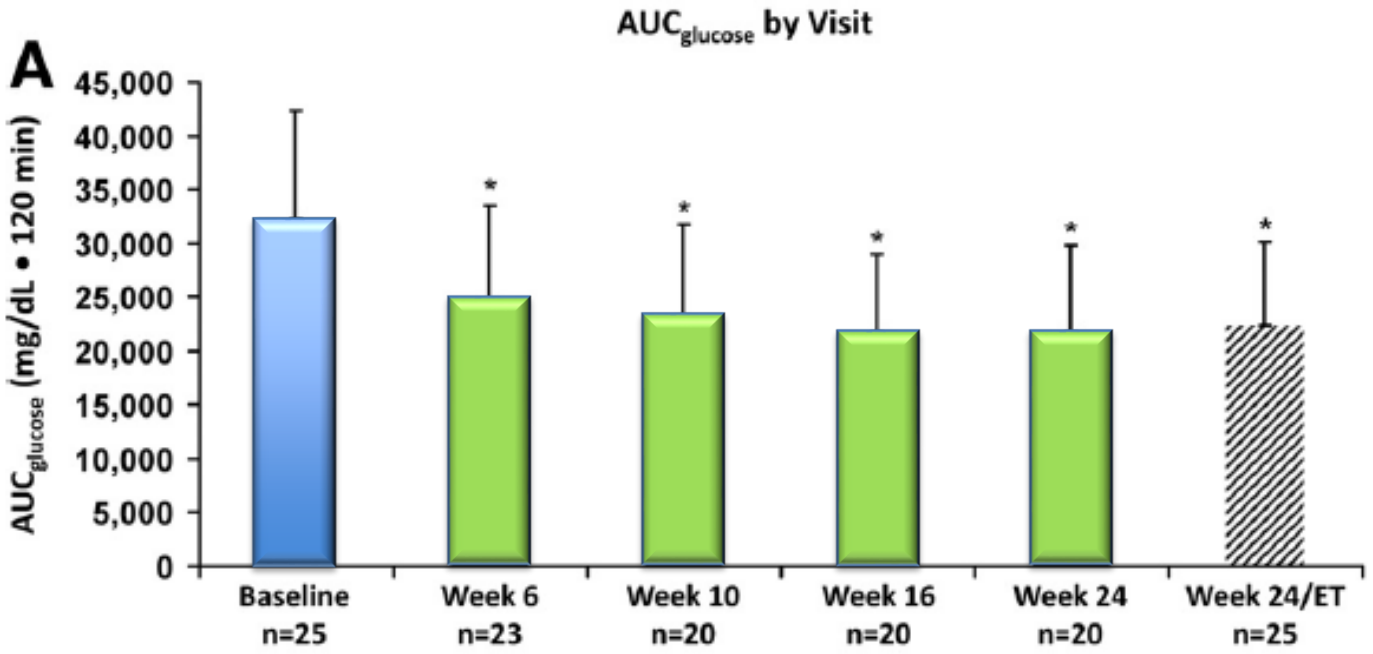
50 pazienti adulti con Cushing's syndrome, dopo fallimento di terapie combinate, con associato Diabete mellito/alterata tolleranza ai carboidrati o Ipertensione arteriosa

Dose di 300-1200 mg/die

Endpoint primario: riduzione del 25% del $AUC_{glucosio}$ in OGTT
riduzione di 5 mmHg della DBP

Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome

J Clin Endocrinol Metab, June 2012, 97(6):2039–2049



Error bars in graph are SD.

* P<0.001 vs baseline.

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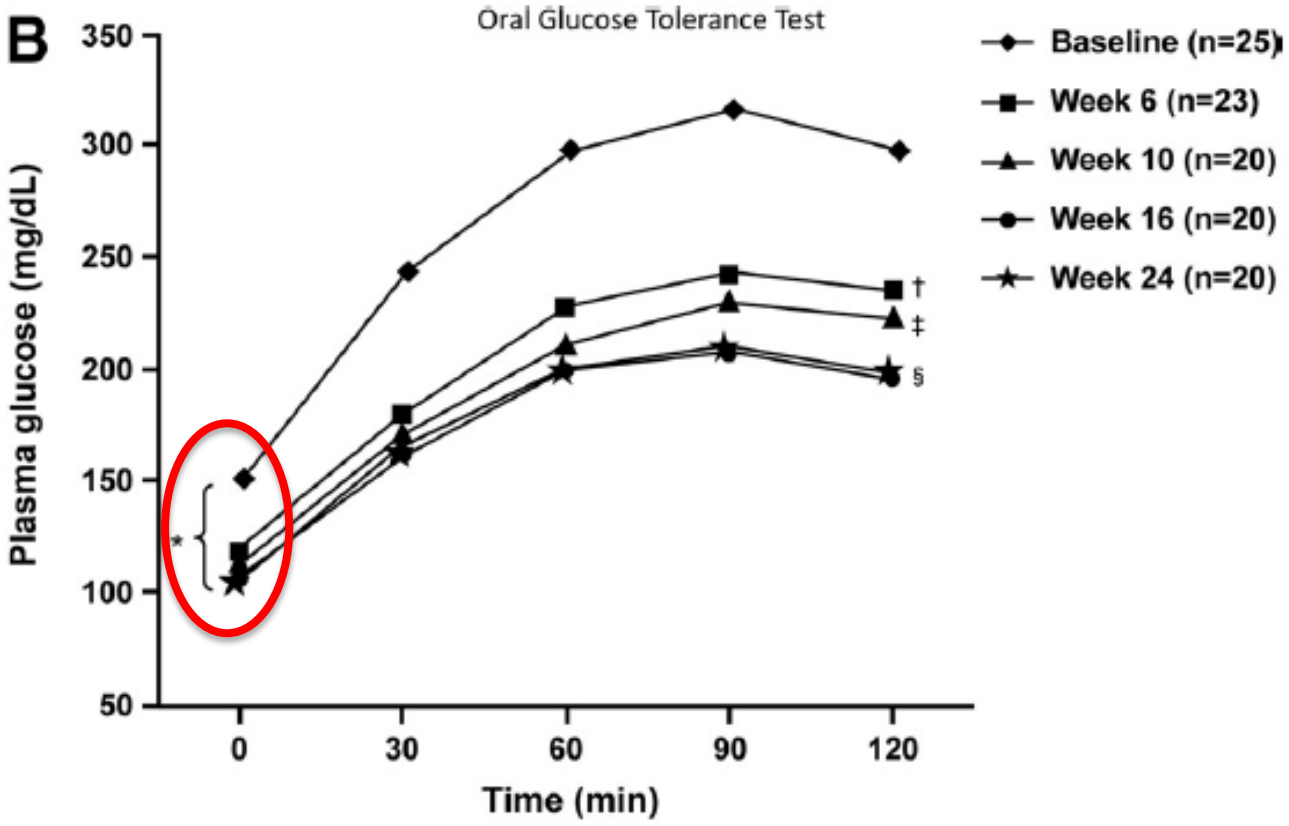

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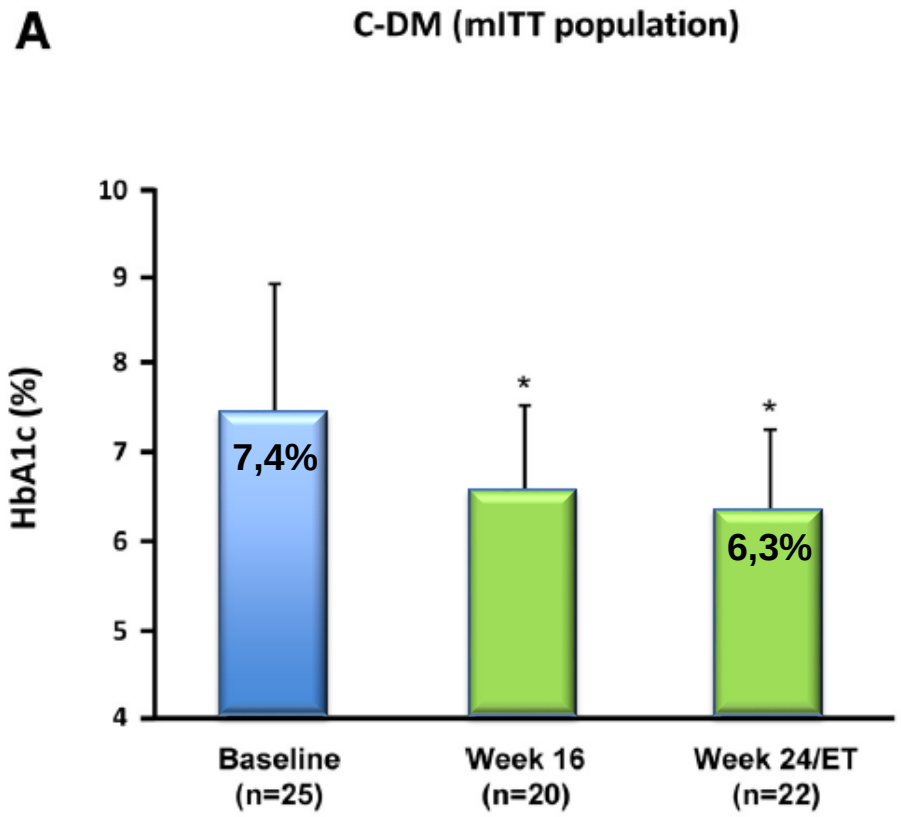

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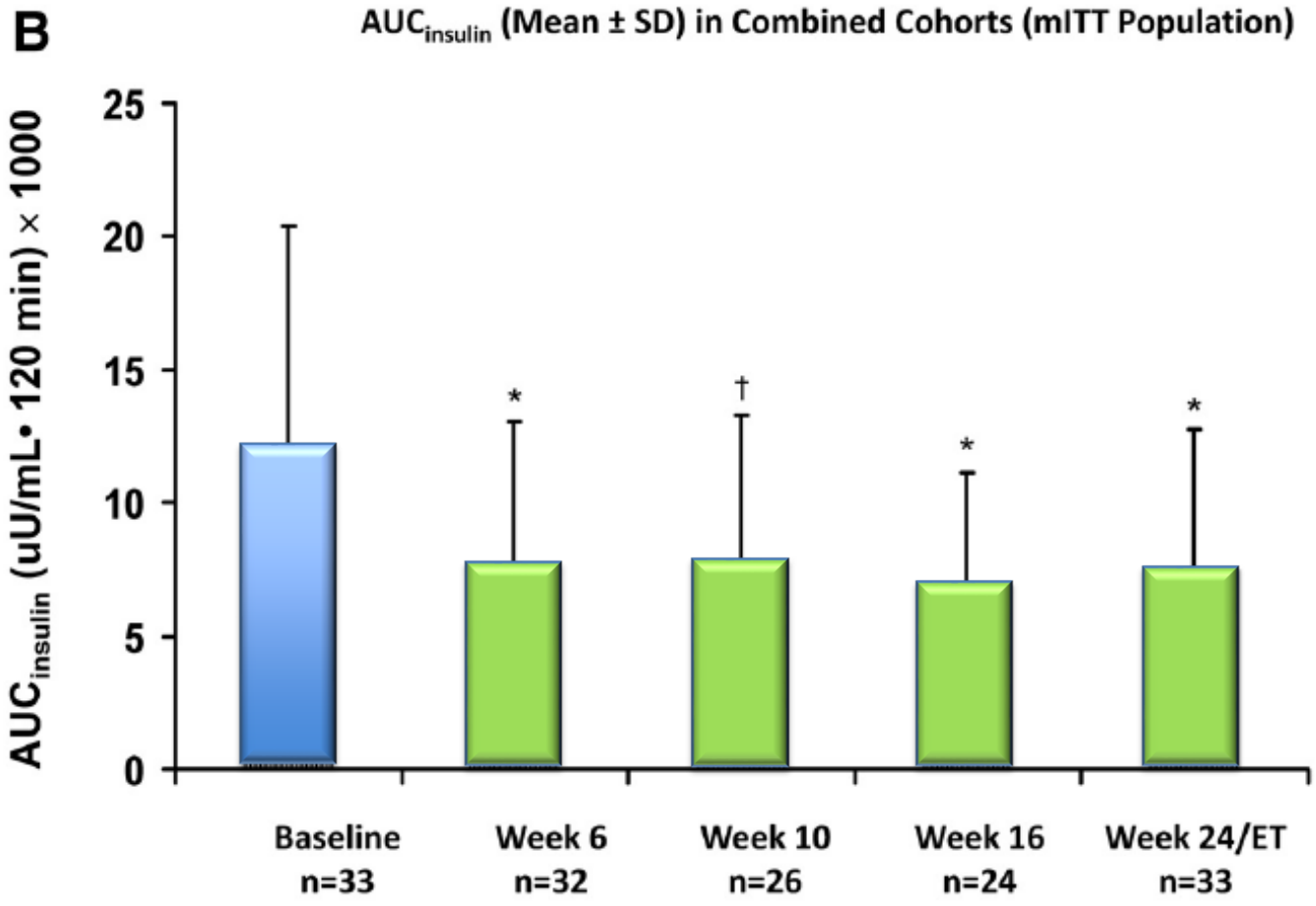

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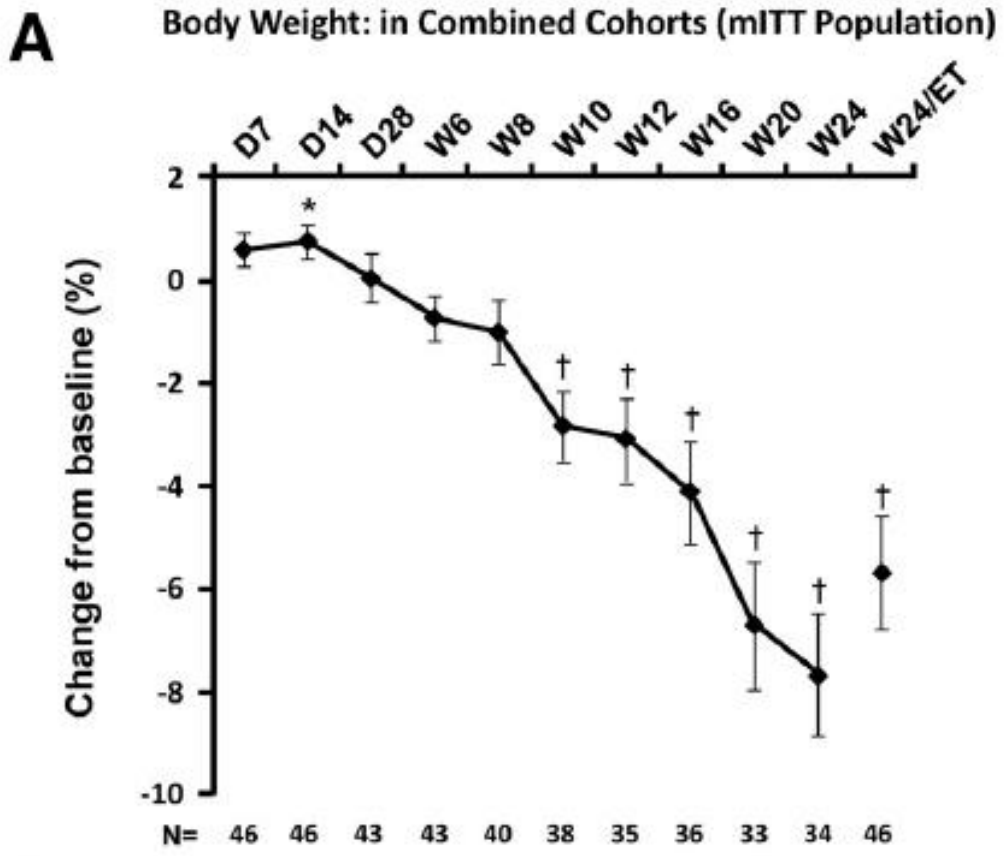

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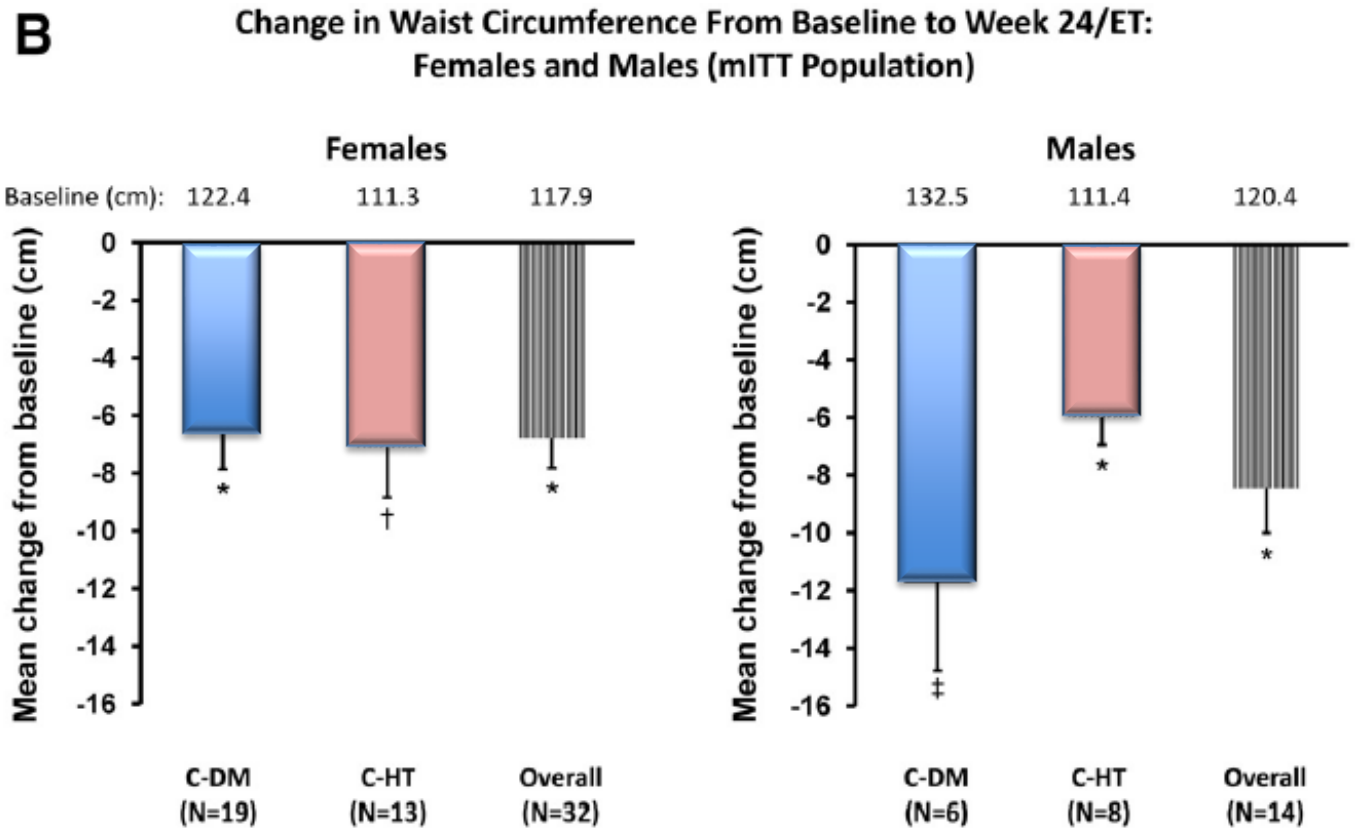


Mifepristone, a Glucocorticoid Receptor Antagonist, Produces Clinical and Metabolic Benefits in Patients with Cushing's Syndrome

J Clin Endocrinol Metab, June 2012, 97(6):2039–2049

TABLE 3. Summary of responder analyses (mITT population)

Statistics (mITT population)	Responder [n (%)]	Nonresponder [n (%)]	Lower bound one-sided 95% exact binomial CI (%)	*P* value
C-DM (n = 25)				
Participants with or without a 25% reduction from baseline in $AUC_{glucose}$ at wk 24/ET	15 (60)	10 (40)	41.7	<0.0001
C-HT (n = 21)				
Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	8 (38.1)	13 (61.9)	20.6	<0.05
C-HT and C-DM with HTN at screening (n = 40)				
Participants who had ≥5 mm Hg reduction from baseline in DBP at wk 24/ET	17 (42.5)	23 (57.5)		
Participants who had a reduction in antihypertensive medications at wk 24/ET	11 (27.5)	29 (72.5)		
Participants who had either ≥5 mm Hg reduction from baseline in DBP or had a reduction in antihypertensive medications at wk 24/ET	21 (52.5)[a]	19 (47.5)		
Median clinical improvement score of +1 at any reviewed visit[b]				
Combined cohorts (n = 46)	40 (87.0)	6 (13.0)	75.9	<0.0001
C-DM (n = 25)	23 (92.0)	2 (8.0)	76.9	
C-HT (n = 21)	17 (81.0)	4 (19.0)	61.6	

[a] 95% CI = 36.1–68.5.

[b] For overall clinical improvement (median DRB score +1) at any reviewed visit, the null hypothesis was to be rejected in favor of the alternative if the lower limit of the 95% exact one-sided binomial CI for the responder rate was at least 30%.

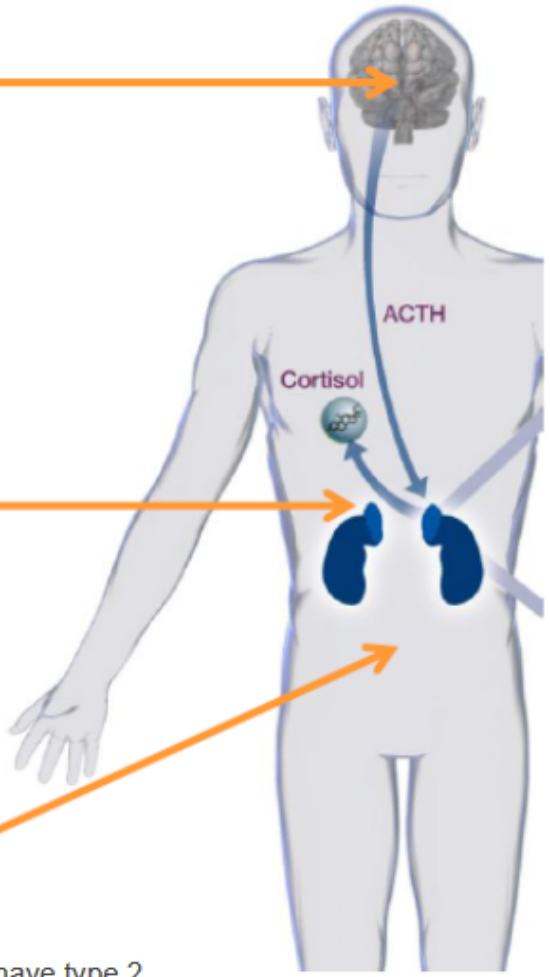
Pituitary-targeted agents	
	Indication
Cabergoline	Off-label
Pasireotide	Approved SSN

Adrenal-directed agents	
	Indication
Metyrapone	**Approved SSN**
Ketoconazole	**Approved SSN**
Mitotane	**Law 648/96***

* Sindrome di Cushing grave (trattata con terapia radiante o in preparazione all' intervento chirurgico)

Glucocorticoid receptor antagonists	
	Indication
Mifepristone	Off-label

Approved in patients with endogenous Cushing' s syndrome who have type 2 diabetes or glucose intolerance and are not candidates for surgery or who have not responded to prior surgery

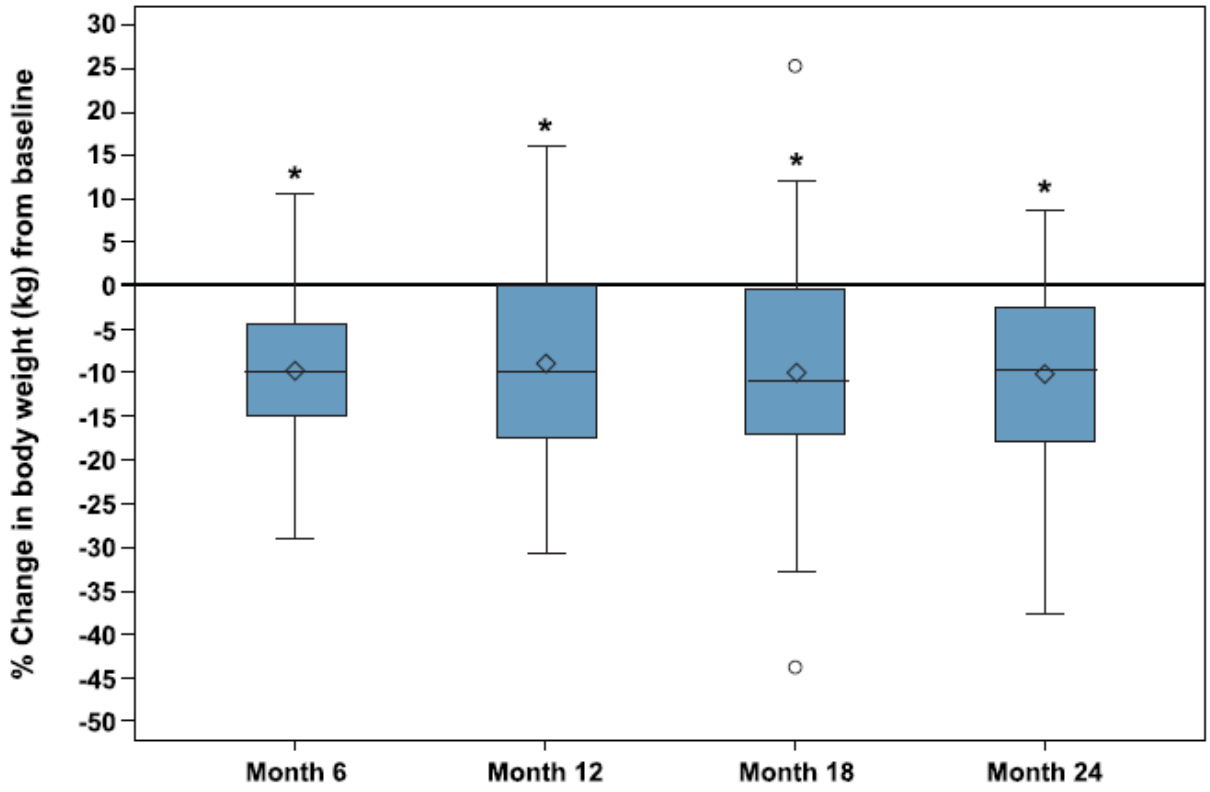


Sustained weight loss in patients treated with mifepristone for Cushing's syndrome: a follow-up analysis of the SEISMIC study and long-term extension

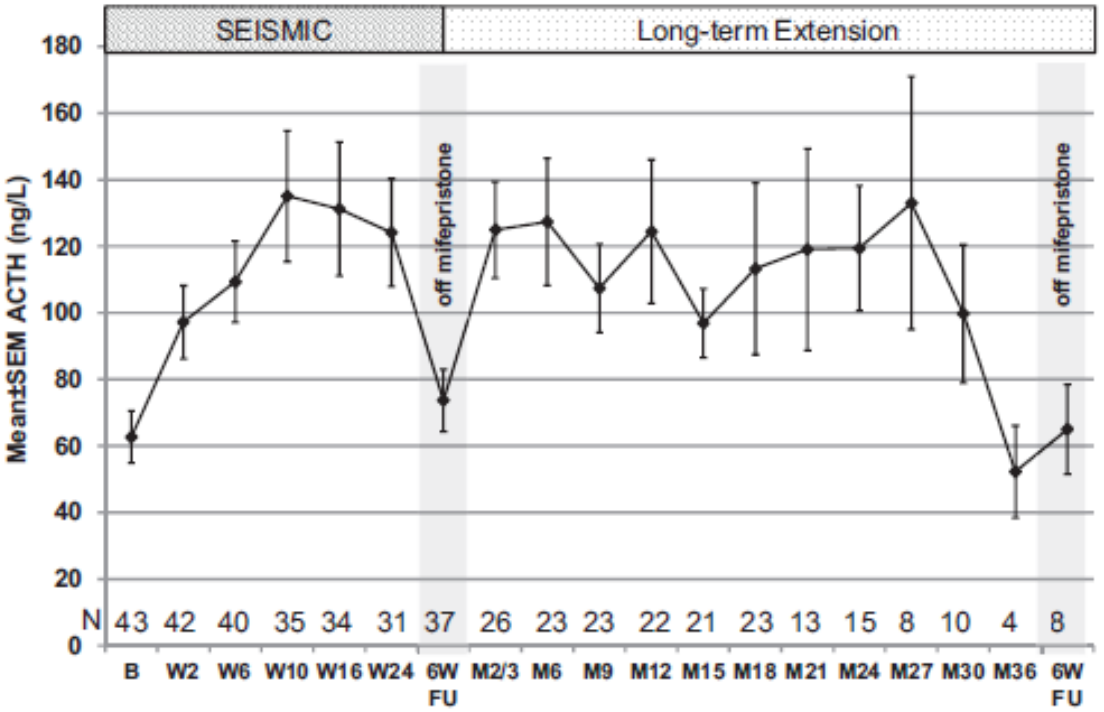
Henry G. Fein[1*], T. Brooks Vaughan III[2], Harvey Kushner[3], David Cram[4] and Dat Nguyen[4]

BMC Endocrine Disorders (2015) 15:63

b



Changes in Plasma ACTH Levels and Corticotroph Tumor Size in Patients With Cushing's Disease During Long-term Treatment With the Glucocorticoid Receptor Antagonist Mifepristone



- Incremento ACTH 2/3 pazienti
- ACTH incrementa nelle prime settimane, dose-dipendente, stabile nel tempo
- Adenoma ipofisario può crescere o regredire
- Non sempre incremento ACTH significa progressione del volume tumorale

Table 2. Findings of Central MRI Reading

	Baseline	Progressed (C)[a]	Stable (A or B)[a]	Regressed (D)[a]
Nonvisible	20	1	19	
Microadenoma (<10 mm)	9	0	8	1
Macroadenoma (≥10 mm)	7	3	3	1

J Clin Endocrinol Metab, October 2014, 99(10):3718–3727

Global clinical response in Cushing's syndrome patients treated with mifepristone

Laurence Katznelson*, D. Lynn Loriaux†, David Feldman*, Glenn D. Braunstein‡, David E. Schteingart§ and Coleman Gross¶

Clinical Endocrinology (2014) 80, 562–569

Table 1. Clinical parameters assessed by raters for global clinical response

Glucose
Fasting plasma glucose test
Oral glucose tolerance tests*
Haemoglobin A1c test†
Change in glucose-lowering medications
Lipids
Total cholesterol and lipoprotein fractions and triglycerides
Blood pressure
Systolic blood
Diastolic bloo
Change in ant
Body compositi
Body weight
Body mass ind
Waist circumf
Bone resorption and formation markers
Clinical scores/appearance
Investigator-graded Cushingoid appearance‡
Investigator-graded acne scores[23]
Investigator-graded hirsutism scores (women only)[24]
Investigator-graded striae§
Strength
Sit-to-stand test (lower extremity function)[25,26]
Hand-grip strength test[27]
Psychiatric health/cognitive function
Beck depression inventory[28]
Trail making test (cognitive function)[29,30]
Quality of life
SF-36 health survey (quality of life)[31]

- **Peso corporeo**
- **OGTT**
- **Pressione diastolica**
- **Aspetto Cushingoide**

Predittori di Global Clinical Response

The Treatment of Cushing's Disease

Rosario Pivonello, Monica De Leo, Alessia Cozzolino, and Annamaria Colao

Endocrine Reviews, August 2015, 36(4):385–486

Table 12. Results of the Main Studies Evaluating the Outcome of Mifepristone in CD

First Author, Year (Ref.)	No. of patients	Drug Dose,	Remission
Castinetti, 2009 (757)	4		
Fleseriu, 2012 (758)	50 CS, 43 CD		
Total	**47**		

Nausea:48; fatigue:48; headache:44; hypokalemia:34; arthralgia:30; vomiting:26; peripheral edema:26; hypertension:24; dizziness:22; decreased appetite:20; adrenal insufficiency:4; endometrial thickening:38.5% (of the women)

Hypokalemia:R:25–34; M:29.5; m:29.5; hypertension:R:24–25; M:24.5; m:24.5; adrenal insufficiency:R:4–25; M:14.5; m:14.5

Mifepristone for Management of Cushing's Syndrome

Farah H. Morgan, and Marc J. Laufgraben

PHARMACOTHERAPY Volume 33, Number 3, 2013

Table 4. Drugs that Interact with Mifepristone Through CYP2C8/2C9 and CYP2B6[18]

Drugs Metabolized by CYP2C8/2C9	Drugs Metabolized by CYP2B6
Use lowest dose and monitor closely	Not studied—use lowest dose
Fluvastatin	Bupropion
NSAIDs	Efavirenz
Warfarin	
Repaglinide	

CYP = cytochrome P450; NSAIDs = nonsteroidal anti-inflammatory drugs.

Table 3. Sample List of Drugs or Foods that Interact with Mifepristone Through CYP4503A[18]

Drugs Metabolized by CYP3A	CYP3A Inhibitors	CYP3A Inducers
Use alternative drug or administer lowest dose and/or decrease frequency	Limit mifepristone to 300 mg/day	Do not use (has not been studied)
Cyclosporine	Azole antifungals	Rifabutin
Dihydroergotamine	Protease inhibitors	Phenobarbital
Ergotamine	Macrolides	Phenytoin
Fentanyl	Mibefradil	Carbamazepine
Pimozide	Nefazodone	St. John's wort
Quinidine	Conivaptan	Rifampin
Sirolimus	Caution—use lowest effective dose of mifepristone	
Tacrolimus	Imatinib	
Simvastatin	Aprepitant	
Lovastatin	Ciprofloxacin	
	Grapefruit juice	
	Nondihydropyridine CCBs	

CCBs = calcium channel blockers; CYP = cytochrome P450.

Conclusioni

Il Mifepristone è un antagonista del recettore dei glucocorticoidi (approvato dal FDA per il trattamento dell'iperglicemia associata alla CS)

Utile per il rapido controllo delle manifestazioni cliniche del Cushing (ectopico, psicosi)

Perdita di ogni markers ormonale per valutare l'efficacia del farmaco ed il controllo della malattia, mandatorio il controllo clinico del paziente

Importanti effetti collaterali: insufficienza surrenalica e ipokaliemia
(ipertensione arteriosa, edema, alcalosi,metrorragia)

Interazione con altri farmaci

L'efficacia a lungo termine ed il profilo di sicurezza del farmaco dovranno essere determinati in ulteriori studi


Grazie