Actualización en diagnóstico y tratamiento de síndrome de Cushing

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Conflictos de interés

- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Pfizer, **Novartis**, Siegfried
- Advisory Board: **Novartis Oncology**, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer, Siegfried
- Investigación clínica: Astra Zeneca, **Novartis Pharma Logistics Inc**., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

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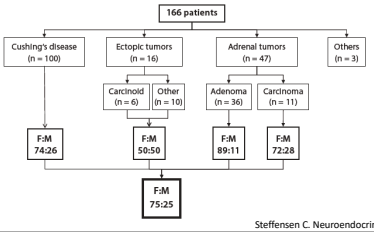
Agenda

- Cuándo tamizar?
- Algunas perlas en métodos diagnósticos
- Tratamiento
- Fármaco recientemente aprobado: osilodrostat

Dinamarca

- 1.2-1.7 casos por millón



Steffensen C. Neuroendocrinology. 2010;92(Supl 1):1

Mortalidad

	Period covered	Patients (mean age at treatment)	Remission of hypercortisolism	Follow-up duration, months[1]	Deaths	Overall SMR (95% CI)	p
Etxabe et al. [7]	1975–1992	49 (39)	36/41 (87%)	56 (6–210)	5/49[2]	3.8 (2.5–17.9)	<0.05
Swearingen et al. [8]	1978–1996	161 (38)	137/161 (85%)	96 (12–240)	6/159[3]	0.98 (0.44–2.2)	NS
Pikkarainen et al. [10]	1981–1994	63 (44)	20/20 (100%)[4] 25/43 (58%)[5]	84 (0–180)	2/20 6/43	1.35 (0.16–4.89) 2.67 (0.89–5.25)	NS NS
Lindholm et al. [1]	1985–1995	73 (41)[6] 26 (51)[7]	56/73 (77%) not stated	96 (36–168) 96 (36–168)	7/73 11/26	1.7 (0.7–3.5) 11.5 (5.7–20)	NS <0.001
Hammer et al. [9]	1975–1998	289 (37)	236/289 (83%)	132 (6–288)	17/236[8] 25/285 7/53	1.18 (no CI)[9] 2.8 (no CI)[10]	NS ?Sig.
Dekkers et al. [11]	1977–2005	74 (39)	59/74 (80%)	120 (36–204)	12/74	2.39 (1.2–3.9) 1.8 (0.71–3.37)[11] 4.38 (1.38–9.07)[12]	<0.05 NS <0.05

[1] Median (range); [2] no information on 8 patients; [3] two patients uncontactable; [4] adrenal adenoma; [5] CD; [6] proven CD at histology, [7] unproven CD – clinically/biochemically ACTH-dependent hypercortisolism; [8] four deaths in first 3/12 post-operatively – excluded as perioperative; [9] initial remission; [10] initial persistent disease; [11] remission after initial surgery; [12] persistent disease after initial surgery.

Clayton RN. Neuroendocrinology. 2010;92(Supl 1):71

	Predictors of increased mortality	Comment
Etxabe et al. [7]	older age at diagnosis, persistent hypertension; abnormalities of CHO metabolism	
Pikkarainen et al. [10]	no information	
Swearingen et al. [8]	older age at diagnosis	no information on HT or DM
Lindholm et al. [1]	persistent hypercortisolism after initial surgery	No information on HT or DM
Hammer et al. [9]	persistent hypercortisolism after initial surgery (but only after 10 years' follow-up)	No information on HT or DM
Dekkers et al. [11]	persistent hypercortisolism after initial surgery	No information on HT or DM

HT = Hypertension; DM = diabetes mellitus.

Clayton RN. Neuroendocrinology. 2010;92(Supl 1):71

RETOS DIAGNÓSTICOS

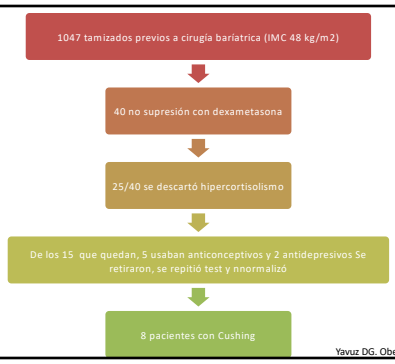
Manifestaciones clínicas

Signos/síntomas	Frecuencia (%)
Obesidad central	97
Cara luna llena	89
Hipertensión	76
Atrofia cutánea y equimosis	75
Diabetes o intolerancia a glucosa	70
Disfunción gonadal	69
Debilidad miscular	68
Hirsutismo, acné	56
Trastornos del ánimo	55
Osteoporosis	40
Edema	15

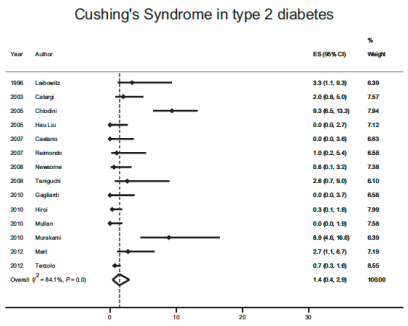
1. Boscaro and Arnaldi. J Clin Endocrinol Metab. 2009;94:3121-3131

Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and > 1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		
Menstrual abnormalities		
In children, slow growth	In children, abnormal genital virilization	
	In children, short stature	
	In children, pseudoprecocious puberty or delayed puberty	

Nieman LK. J Clin Endocrinol Metab. 2008;93:1526



Yavuz DG. Obes Surg. 2020; online Aug 15



Steffensen C. Eur J Endocrinol. 2016;175:R47

Cushing en diabetes

	Study	Number of diabetic participants (%)	Male/ female	Number of patients with hypercortisolism (%)	Test used, number of positives (%)						Pituitary adenoma (%)	Adrenal adenoma (%)	Ectopic adenoma (%)	Number of patients with CS (%)
					MSC (%)	MPC (%)	OD (%)	LDDST (%)	ACTH elevated (%)	UFC (%)				
1	(14)	90 (100)	26/64	3 (3.3)			4 (4.4)	3 (3.3)	0 (0)	3 (3.3)	2 (2.2)	1 (1.1)	0 (0)	3 (3.3)
2	(12)	200 (100)	49/151	17 (8.5)	2 (1)	17 (8.5)	52 (26)			17 (8.5)	3 (1.5)	8 (4)	0 (0)	4 (2)
3	(25)	289 (100)	124/165	35 (12.1)			51 (17.6)		5 (1.7)	8 (2.7)	4 (1.4)	21 (7.1)	2 (0.7)	27 (9.3)
4	(24)	141 (100)	141/0	4 (2.8)	28 (19.9)			4 (2.8)	3 (2.1)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
5	(21)	103 (100)	34/69	8 (7.8)	12 (11.7)		29 (28.2)	1 (0.9)	2 (1.9)	0 (0)	1 (0.9)	4 (3.9)	0 (0)	0 (0)
6	(18)	100 (100)	67/37	1 (1)		1 (1)	5 (5)	1 (1)	1 (1)	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)
7	(17)	171 (100)	102/69	1 (0.6)			31 (18.1)			3 (1.8)	0 (0)	0 (0)	0 (0)	1 (0.6)
8	(19)	77 (100)	47/30	6 (7.8)		27 (35)	7 (9)		6 (7.8)		2 (2.6)	0 (0)	0 (0)	2 (2.6)
9	(13)	100 (100)	60/40	0 (0)	3 (3)	0 (0)	0 (0)		0 (0)	0 (0)				0 (0)
10	(22)	304 (100)	181/123	1 (0.3)			1 (0.3)	1 (0.3)	1 (0.3)	0 (0)	0 (0)	14 (4.6)	0 (0)	1 (0.3)
11	(23)	201 (100)	119/91	7 (3.5)	47 (23)		7 (3.5)	0 (0)		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
12	(16)	90 (100)	53/37	9 (10)		57 (63.3)	9 (10)		0 (0)					8 (8.9)
13	(15)	148 (100)	35/113	4 (2.6)			9 (6.2)	4 (2.6)			2 (1.4)	2 (1.4)	0 (0)	4 (2.7)
14	(20)	813 (100)	428/385	6 (0.7)			40 (4.9)	6 (0.7)	1 (0.12)		0 (0)	3 (0.4)		6 (0.7)

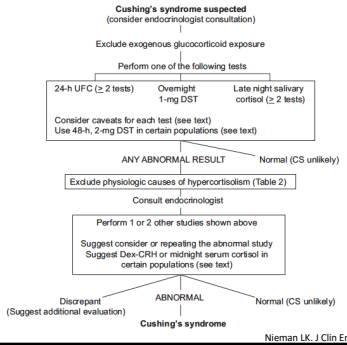
Steffensen C. Eur J Endocrinol. 2016;175:R47

Poblaciones con mayor prevalencia

- Osteoporosis y fracturas vertebrales: hasta 5%, principalmente por adenomas adrenales
- Incidentalomas adrenales: hasta 5% tienen secreción autónoma de cortisol

Barun LT. Front Endocrinol. 2019;10:1

TAMIZAJE, CONFIRMACIÓN Y LOCALIZACIÓN



Nieman LK. J Clin Endocrinol Metab. 2008;93:1526

Test de superesión de dexametasona

- Fundamento fisiológico
- Administración exógena de un glucocorticoide debe ser capaz de suprimir la producción endógena en condiciones fisiológicas normales
- Dar un glucocorticoide que no interfiera en la medición de cortisol
- Dar dexametasona 1 mg VO a las 11 PM
- Tomar cortisol sérico plasmático entre 7 y 8 AM de la mañana siguiente
- Respuesta normal: supresión a <1.8 ug/dl

Drugs
Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4
Phenobarbital
Phenytoin
Carbamazepine
Primidone
Rifampin
Rifapentine
Ethosuximide
Pioglitazone
Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4
Aprepitant/fosaprepitant
Itraconazole
Ritonavir
Fluoxetine
Diltiazem
Cimetidine
Drugs that increase CBG and may falsely elevate cortisol results
Estrogens
Mitotane
Drugs that increase UFC results
Carbamazepine (increase)
Fenofibrate (increase if measured by HPLC)
Some synthetic glucocorticoids (immunoassays)
Drugs that inhibit 11β-HSD2 (licorice, carbenoxolone)

Nieman LK. J Clin Endocrinol Metab. 2008;93:1526.

Cortisol salival

- Cortisol sérico libre difunde libremente a través de las células acinares de la glándula salival
- Saliva no contiene proteínas ligadoras
- Por lo tanto, cortisol salival está en equilibrio con el cortisol sérico libre
  - 4% de todo el cortisol circulante
- Muestra estable a temperatura ambiente hasta por 7 días o varias semanas refrigerado

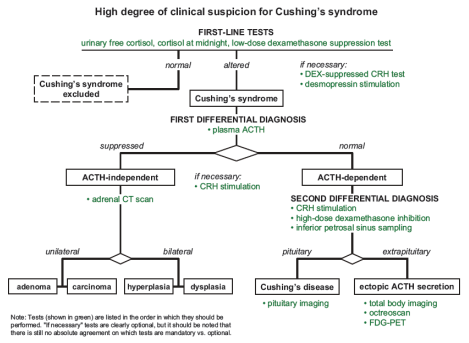
Alexandraki KI. Neuroendocrinology. 2010;92(Suppl 1):35.

Metanálisis test diagnósticos

Test	Studies	CS	Non-CS	Suspicion[a] (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	LR+ (95% CI)	LR– (95% CI)
UFC	76	2351	4764	54.7	94.0 (91.6-95.7)	93.0 (89.0-95.5)	13.3 (8.47-21.0)	0.065 (0.046-0.092)
LNSC	58	1868	5049	51.8	95.8 (93.8-97.2)	93.4 (90.7-95.4)	14.6 (10.3-20.7)	0.045 (0.030-0.066)
DST	50	1531	3267	76.4	98.6 (96.9-99.4)	90.6 (86.4-93.6)	10.5 (7.2-15.3)	0.016 (0.007-0.035)
MSC	37	1695	2048	60.2	96.1 (93.5-97.6)	93.2 (88.1-96.3)	14.2 (7.96-25.2)	0.042 (0.026-0.069)
2d DST	19	569	526	61.4	95.3 (91.3-97.5)	92.8 (85.7-96.5)	13.2 (6.47-27.1)	0.051 (0.027-0.095)
Dex-CRH	9	258	210	90.5	98.6 (90.4-99.8)	85.9 (67.6-94.7)	7.01 (2.80-17.6)	0.016 (0.002-0.118)

Abbreviations: CI, confidence interval; CRH, corticotropin-releasing hormone; CS, total number of patients with Cushing syndrome; dex-CRH, dexamethasone-suppressed CRH test; 2d DST, 2-day low-dose dexamethasone suppression test; DST, overnight 1-mg dexamethasone suppression test; LNSC, late-night salivary cortisol; LR–, negative likelihood ratio; LR+, positive likelihood ratio; MSC, midnight serum cortisol; non-CS, total number of patients without Cushing syndrome; UFC, 24-hour urinary free cortisol.
[a]Suspicion represents the percentage of patients without CS who had features of CS (as opposed to healthy controls).

Balm GP. J Clin Endocrniol Metab. 2020;105:2081



Giraldi FP. Horm Res. 2009;71 (Suppl 1):132

TRATAMIENTO ACTUAL

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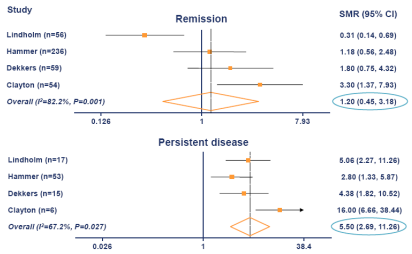
Mortalidad



1. Clayton RN et al. J Clin Endocrinol Metab 2011

Tratamientos disponibles

- Cirugía
  - Hipofisectomía
  - Adrenalectomía bilateral
- Radioterapia
- Terapia médica
  - Dirigido a adrenal
  - Dirigido a hipófisis
  - Dirigido al bloqueo del receptor de GC

Cirugía hipofisiaria

- Debería ser primera línea de tratamiento
- Como sucede con otras lesiones selares, los resultados son dependientes de la experiencia del cirujano y de las características del tumor
  - Microadenomas 82.4%, recurrencia 11.6%
  - Macroadenomas 60%, recurrencia 17.8%
  - Tumores invasivos 41%, recurrencia 25.3%

Pivonello R. Endocrine Rev. 2015;36:385

Adrenalectomía bilateral

- Es una alternativa para algunas situaciones
  - Riesgo de complicaciones quirúrgicas según vía de acceso
- Síndrome de Nelson
- Reemplazo con glucocorticoides y mineralocorticoides de por vida
- Estos pacientes tienen una tasa de mortalidad mayor comparado con la población general

Radioterapia

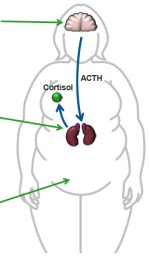
- Es una alternativa válida
- Efecto es lento en aparecer según la técnica empleada
  - Efectos adversos del hipercortisolismo deben ser manejados mientras se espera respuesta terapéutica
- Hipopituitarismo y enfermedad cerebrovascular

Medical therapies for Cushing's disease have different targets and mechanisms of action

Pituitary-targeted agents	
Cabergoline (dopamine receptor agonist)	Investigational use
Pasireotide (somatostatin analogue)	Cushing's disease*

Adrenal-directed agents	
Metyrapone	Investigational use
Ketoconazole	Investigational use
Mitotane	Investigational use
LCI699	Clinical development

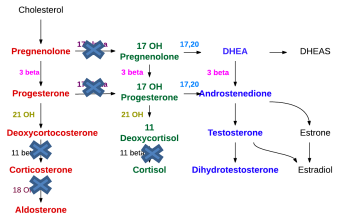
Glucocorticoid receptor antagonists	
Mifepristone	Hyperglycaemia in patients with Cushing's syndrome who have DM/IGT



Feelders RA & Hofland LJ. *J Clin Endocrinol Metab* 2013;98:425–438

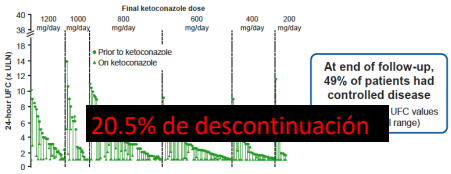
*Approved in the US, EU and other countries for adult patients for whom surgery is not an option or has failed
ACTH, adrenocorticotropic hormone; DM, diabetes mellitus; IGT, impaired glucose tolerance

Ketoconazol



Recent insights into the efficacy and safety of ketoconazole in Cushing's disease

- A multicentre, retrospective study on ketoconazole in 200 patients with Cushing's disease (1995–2012); mean treatment 25 months



20.5% de descontinuación

- Improvements also reported in diabetes, hypertension, and hypokalaemia

Castinetti F et al. *J Clin Endocrinol Metab* 2014;99:1623–1630 EndoDrChen.com Reproduced with permission from The Endocrine Society

Levoketoconazol: SONICS

- Ketoconazol: mezcla de 2 enantiómeros
  - 2S,4R-ketoconazole: levoketoconazol
  - 2R,4S-ketoconazole
- Levoketoconazol:
  - Más potente para inhibir (aproximadamente 2x más potente que ketoconazol)
    - 17-hidroxilasa
    - 11-hidroxilasa
  - Permitiría usar dosis más bajas

Flesseriu M. Lancet Diab Endocrinol. 2019;7:855

SONICS: eficacia

	Response rate	Response rate LS mean
mUFC normalisation without a dose increase* †		
Month 1	41/85	0·48 (0·37–0·59)
Month 2	44/88	0·50 (0·39–0·61)
Month 3	41/92	0·44 (0·34–0·55)
Month 4	31/90	0·35 (0·25–0·46)
Month 5	32/90	0·36 (0·26–0·47)
Month 6 (primary endpoint)	29/94	0·30 (0·21–0·40)
mUFC normalisation at month 6 (irrespective of dose increase)* ‡	34/94	0·36 (0·26–0·46)
mUFC normalisation at month 6 (irrespective of dose increase, with imputation)* ‡§	36/94	0·38 (0·28–0·49)
Analysis of observed rate at month 6 with imputation for missing mUFC after month 3‡¶	40/94	0·43 (0·32–0·53)
≥50% mUFC decrease or normalisation at month 6 (irrespective of dose increase)* ‡	43/94	0·46 (0·35–0·56)
≥50% mUFC decrease or normalisation at month 6 (irrespective of dose increase, with imputation)* ‡§	45/94	0·48 (0·37–0·58)
Participants who completed the maintenance phase with mUFC data and mUFC normalisation at month 6 (irrespective of dose increase)‡‖	34/55 (62%)	--
Participants who completed the maintenance phase with mUFC data and a 50% mUFC decrease or normalisation at month 6 (irrespective of dose increase)‡‖	43/55 (78%)	--

Flesseriu M. Lancet Diab Endocrinol. 2019;7:855

Eficacia: SONICS

- Eficacia según UFC inicial
  - <2x LSN: 71%
  - 2-5x LSN: 49%
  - >5x LSN: 56%
- Mejoría en otros parámetros como Hba1c, peso, lípidos, scores de hirsutismo, acné y QOL
- Aumento de ACTH en pacientes con enfermedad de Cushing

Flesseriu M. Lancet Diab Endocrinol. 2019;7:855

Eventos adversos

	Patients (n=94)
Any adverse event	92 (98%)
Serious adverse event	14 (15%)
Drug-related adverse event*	40 (43%)
Adverse event leading to discontinuation	12 (13%)
Intensity of adverse events	
Mild	21 (22%)
Moderate	54 (57%)
Severe	15 (16%)
Life-threatening	1 (1%)
Death	1 (1%)
Most common adverse events†	
Nausea	30 (32%)
Headache	26 (28%)
Peripheral oedema	18 (19%)
Hypertension	16 (17%)
Fatigue	15 (16%)
Diarrhoea	14 (15%)
ALT increased‡	14 (15%)
GGT increased‡	12 (13%)
AST increased‡	11 (12%)
Nasopharyngitis	11 (12%)
Urinary-tract infection	11 (12%)
Arthralgia	10 (11%)
Dizziness	10 (11%)
Dry skin	10 (11%)
Hypokalaemia	10 (11%)
Myalgia	10 (11%)
Vomiting	10 (11%)

Flesseriu M. Lancet Diab Endocrinol. 2019;7:855

LCI699: OSILODROSTAT

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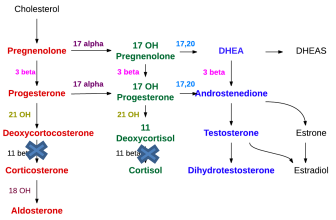
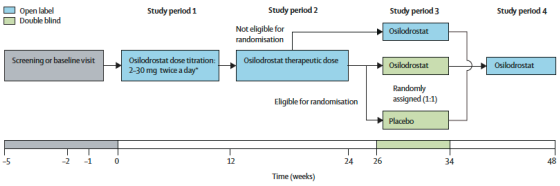
Osilodrostat

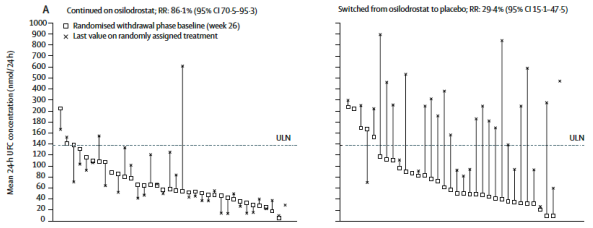


LINC3



Pivonello R. Lancet Diab Endocrinol. 2020;8:748

Respuesta terapéutica



Pivonello R. Lancet Diab Endocrinol. 2020;8:748

Respuesta terapéutica

	Responders	Odds ratio (95% CI)	Two-sided p value
All participants randomly assigned to treatment			
Osilodrostat	31/36 (86·1%; 70·5–95·3)	13·7 (3·7–53·4)	<0·0001
Placebo	10/34 (29·4%; 15·1–47·5)	..	..

Pivonello R. Lancet Diab Endocrinol. 2020;8:748

Eventos adversos

	Osilodrostat (n=36)		Placebo (n=35)	
	All grades	Grade 3–4	All grades	Grade 3–4
Most common study-emergent adverse events*				
Nausea	4 (11%)	0	0	0
Anaemia	3 (8%)	0	3 (9%)	0
Arthralgia	3 (8%)	0	0	0
Headache	3 (8%)	0	0	0
Asthenia	2 (6%)	0	0	0
Blood corticotropin increased	2 (6%)	0	1 (3%)	1 (3%)
Constipation	2 (6%)	0	0	0
Depression	2 (6%)	0	1 (3%)	0
Dizziness	2 (6%)	0	1 (3%)	0
Fatigue	2 (6%)	0	3 (9%)	1 (3%)
Hirsutism	2 (6%)	0	1 (3%)	0
Nasopharyngitis	2 (6%)	0	1 (3%)	0
UFC decreased	2 (6%)	0	1 (3%)	0
Cough	1 (3%)	0	2 (6%)	0
Insomnia	1 (3%)	0	2 (6%)	0
Urinary tract infection	1 (3%)	0	2 (6%)	0
Diarrhoea	0	0	2 (6%)	0
Gastro-oesophageal reflux disease	0	0	2 (6%)	0

Pivonello R. Lancet Diab Endocrinol. 2020;8:748

First Approval for Osilodrostat for Cushing Syndrome, in EU

Miriam E. Tu
DISCLOSUR
0 Read (

FDA Approves New Treatment for Adults with Cushing's Disease

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For Immediate Release: March 06, 2020

The U.S. Food and Drug Administration today approved Isturisa (osilodrostat) oral tablets for adults with Cushing's disease who either cannot undergo pituitary gland surgery or have undergone the surgery but still have the disease. Cushing's disease is a rare disease in which the adrenal glands make too much of the cortisol hormone. Isturisa is the first FDA-approved drug to directly address this cortisol overproduction by blocking the enzyme known as 11-beta-hydroxylase and preventing cortisol synthesis.

Osilodrostat is an effective and well-tolerated treatment for Cushing's disease (CD): results from a Phase III study with an upfront, randomized, double-blind, placebo-controlled phase (LINC 4)

Mônica Gadelha,[1] Marie Bex,[2] Richard A Feelders,[3] Anthony Heaney,[4] Richard J Auchus,[5] Aleksandra Gilis-Januszewska,[6] Przemyslaw Witek,[7] Zhanna Belaya,[8] Yerong Yu,[9] Zhihong Liao,[10] Chih Hao Chen Ku,[11] Davide Carvalho,[12] Michael Roughton,[13] Judi Wojna,[14] Georg Hofstetter,[13] Alberto M Pedroncelli,[15] Peter Snyder[16]

BLOQUEADORES RECEPTORES DE GLUCOCORTICOIDES

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Mifepristone

- 10x más afin por el receptor GC comparado con el cortisol
- Se une al receptor de progesterona y andrógenos

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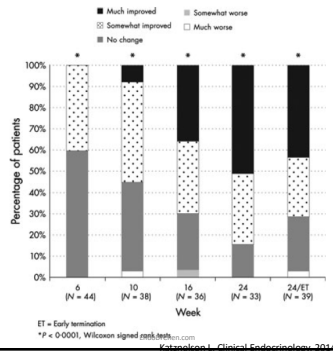
Castinetti F. Neuroendocrinology. 2010;92 (Supl 1):125



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Katznelson L. Clinical Endocrinology. 2014;80:863

Mifepristone

- Mejoría en hba1c, peso, presión arterial, circunferencia abdominal
- Náusea 48%, fatiga 48%, cefalea 44%, hipokalemia 34%, artralgia 30%, vómitos 26%, edema periférico 26%, hipertensión 24%, mareos 22%, hiporexia 20%, engrosamiento endometrial 20%

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Fleseriu M. J Clin Endocrinol Metab. 2012;97:2039

TRATAMIENTO DIRIGIDO A HIPÓFISIS

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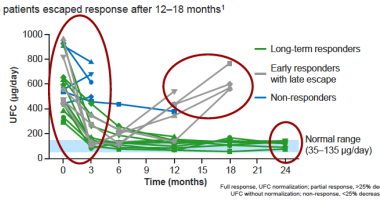
Previous studies have shown that cabergoline is effective in some patients with mild cortisol elevations[1–3]

- After 3 months of cabergoline (1–7 mg/week):
  - Seven (35%) full and eight (40%) partial responders; five (25%) non-responders[1]
- 40% remained controlled after 24 months
  - Five patients escaped response after 12–18 months[1]



Full response, UFC normalization; partial response, >25% decrease in UFC without normalization; non-response, <25% decrease in UFC

Reproduced with permission from The Endocrine Society

AE, adverse event; UFC, urinary free cortisol

1. Pivonello R *et al. J Clin Endocrinol Metab* 2009;94:223–230; 2. Vilar L *et al. Pituitary* 2010;13:123–129; 3. Godbout A *et al. Eur J Endocrinol* 2010;163:709–713

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PASIREOTIDE

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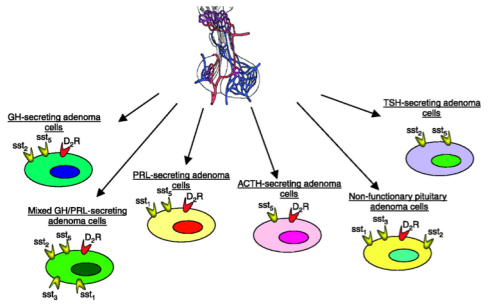
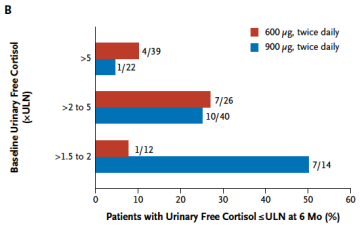


Quiénes son más probable que respondan?



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Colao A. N Engl J Med. 2012;366:914

Pasireotide sc Phase III trial: Perfil de seguridad

	Overall (N=162)	
AE	All grades n (%)	Grades 3 or 4 (%)
Hyperglycemia related	118 (72.8)	40 (24.7)
Diarrhea related	95 (58.6)	5 (3.1)
Nausea related	85 (52.5)	4 (2.5)
Gallbladder and biliary related	54 (33.3)	4 (2.5)
Liver chemistry related	26 (16.0)	7 (4.3)
Bradycardia related	23 (14.2)	3 (1.9)
Hypocortisolism related	13 (8.0)	4 (2.5)
QT prolongation related	13 (8.0)	4 (2.5)
Hypothyroidism related	7 (4.3)	0

Grading (1–4) of AEs follows the US HHS Common Terminology Criteria for Adverse Events (CTCAE) 2009
Common AE terms were pooled, for example, all terms relating to elevations in blood glucose or terms relating to diarrhea

QUÉ PASA SI NO SE CONTROLA CON MONOTERAPIA?
CUÁL ES EL ROL DE LA TERAPIA COMBINADA?

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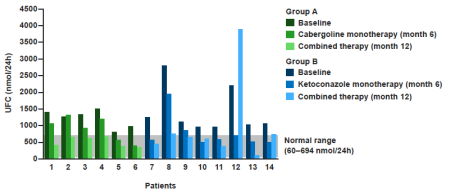
Addition of ketoconazole or cabergoline to the opposite treatment effectively controlled UFC levels after 6 months

- All 14 patients required combination therapy after 6 months of monotherapy; no patients achieved normal UFC and LNSC with caberoline or ketoconazole alone
  - 50% (7/14) of patients had normal UFC levels after 6 months of monotherapy
- 79% (11/14) of patients had normalized UFC after 6 months' combination therapy



Barbot M *et al. Pituitary* 2014;17:109–117

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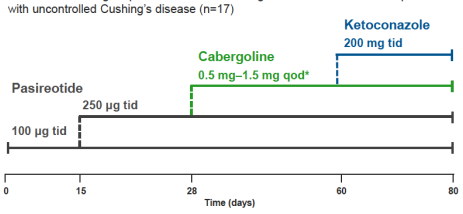
Stepwise combination of pasireotide, cabergoline and ketoconazole in patients with uncontrolled Cushing's disease

A prospective, open-label, multicentre study assessed the efficacy of pasireotide alone and following sequential addition of cabergoline and ketoconazole in patients with uncontrolled Cushing's disease (n=17)



*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
qod, once every other day; tid, thrice daily

Feelders RA *et al. N Engl J Med* 2010;362:1846–1848

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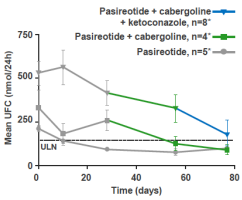
Stepwise combination of pasireotide, cabergoline and ketoconazole improved biochemical response rate



- UFC normalization was achieved by:
  - 5/17 (29%) patients receiving pasireotide monotherapy
  - 4 (24%) further patients after addition of cabergoline
  - 6 (35%) further patients after addition of ketoconazole
- Clinical features (eg blood pressure, weight) of Cushing's disease also improved

Stepwise medical combination therapy normalized UFC levels in 88% of patients with Cushing's disease at day 80

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Feelders RA *et al. N Engl J Med* 2010;362:1846–1848

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*Patient numbers at day 80
ULN, upper limit of normal

Conclusiones

- Es todo un reto diagnóstico
- Siempre hay que pensarlo
- Test de tamizaje con UFC, test de supresión con dexametasona 1 mg , o cortisol saliva nocturno
- Múltiples opciones de tratamiento disponibles

EndoDrChen.com

Preguntas…

chenku2409@gmail.com

Puede descargar la presentación en:

www.EndoDrChen.com