

Altogether
to Beat
Cushing's
Syndrome



SESSION 7: THE COMBINED THERAPY IN CUSHING'S DISEASE
Chairs: Emanuela Arvat, Franco Grimaldi

4^a Edizione / 4th Edition

COMBINATION OF STEROIDOGENESIS INHIBITORS

Maria Chiara Zatelli

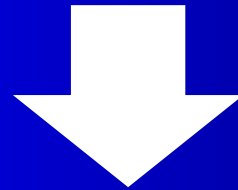
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Combination of Steroidogenesis inhibitors

Combination therapy with drugs that have additive or potentiating effects seems a rational approach to treat CS and may allow for lower dosages of drugs with serious adverse events like ketoconazole.

Feelders et al. Neuroendocrinology 2010;92(suppl 1):111



drug doses reduction
fewer adverse events
additive or synergistic effects

Combination of Steroidogenesis inhibitors

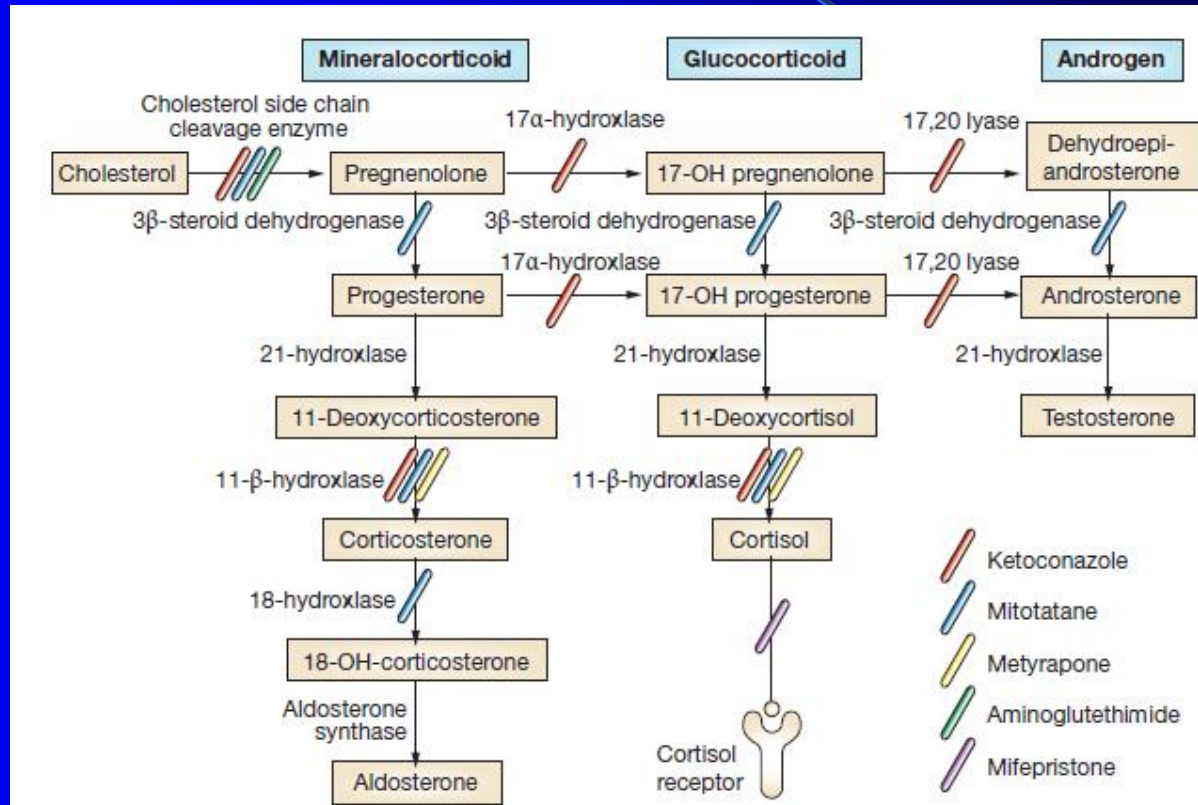
Steroidogenesis inhibitors

Drug	Mechanism	Dose	Efficacy	Adverse events
Ketoconazole	inhibition of SE	400-1200 mg/day	70%	Hepatotoxicity, gastrointestinal, hypogonadism
Mitotane	Adrenolytic effects	0.5-8 g/day	80%	Neurological, gastrointestinal
Etomidate	inhibition of SE	0.03-0.3 mg/kg/h	Unknown	Hypocortisolism
Metyrapone	inhibition of SE	0.5- 6 g/day	75%	Hypertension, acne, hirsutism
Aminoglutetimide	inhibition of SE	250 -1750 mg/day	45-50%	
LCI699	inhibition of SE	4 - 100 mg/day	92%	Fatigue, nausea, headache



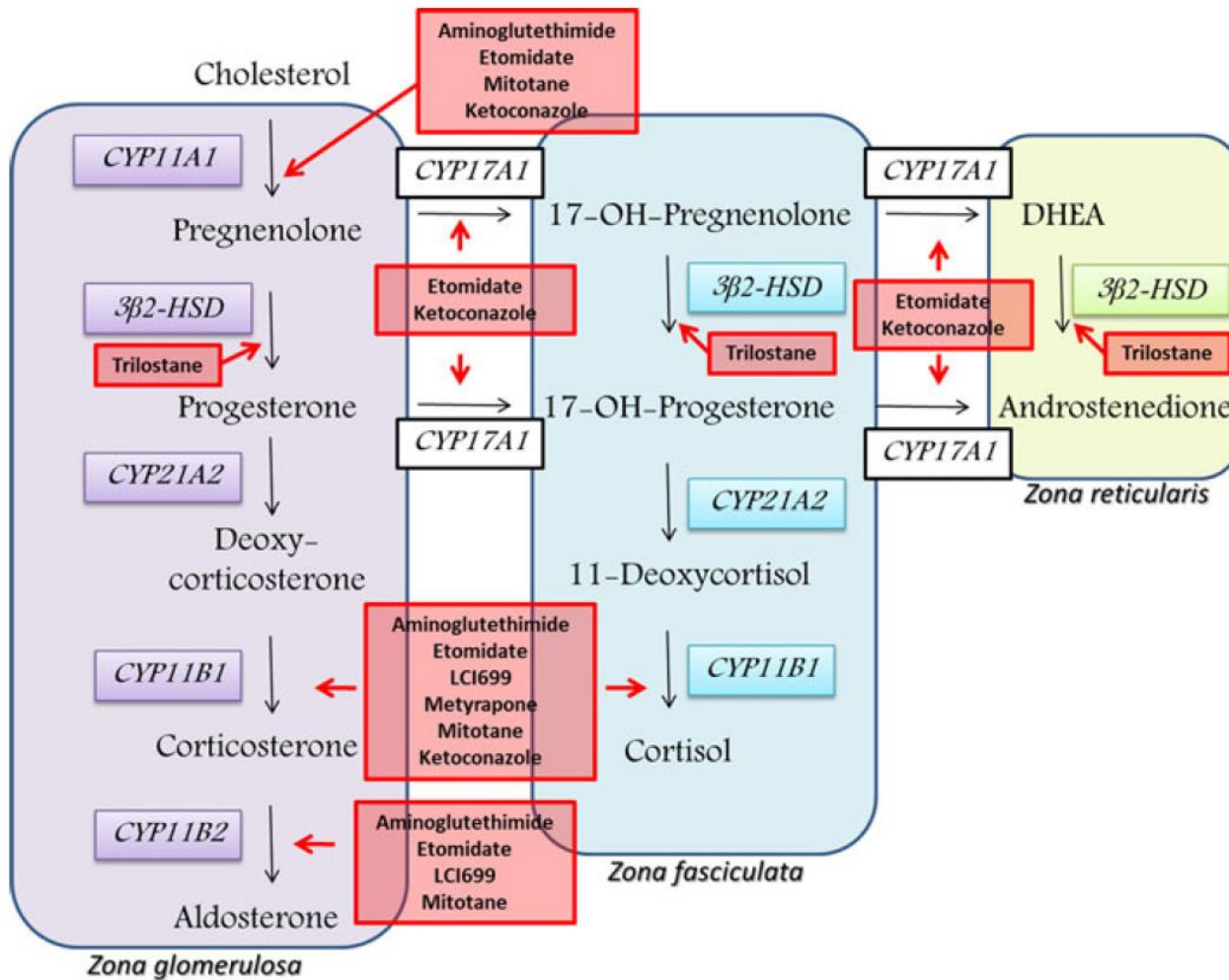
Combination of Steroidogenesis inhibitors

Steroidogenesis



Combination of Steroidogenesis inhibitors

Steroidogenesis inhibitors



Combination of Steroidogenesis inhibitors

Steroidogenesis inhibitors

rarely used as long-term monotherapy
in Cushing's disease

nonpermanent adjuncts

- in preparation to pituitary surgery
- waiting for the full effects of radiotherapy
- in situations where surgery is contraindicated in the short term

particularly in combined treatment

Bertagna et al. J Clin Endocrinol Metab, 2013;98:1307



Combination of Steroidogenesis inhibitors

Steroidogenesis inhibitors

Cortisol levels reduction

No effect on pituitary mass

↳ increase in ACTH secretion

↳ possible escape

↓
secondary failure

Combination of Steroidogenesis inhibitors

These limitations of monotherapy can be addressed by combining ketoconazole with additional adrenal enzyme inhibitors in the following four-step sequence: first, ketoconazole 250 mg three times daily, increasing to 400 mg three times daily, if needed; second, the 11β -hydroxylase inhibitor metyrapone 250 mg three times daily, increasing to a total of 4 g per day if needed (while watching for increased ACTH secretion leading to increased adrenal androgen and mineralocorticoid production, leading, in turn, to hirsutism and hypertension); third, 250 mg aminoglutethimide three times daily, which inhibits cholesterol side-chain cleavage, reducing the excess androgen and mineralocorticoid production seen with ketoconazole plus metyrapone; and finally, the addition of mitotane, an inhibitor of four P450 enzymes, if a combination of ketoconazole, metyrapone, and aminoglutethimide fails to control hypercortisolemia (Figure 2).

NATURE CLINICAL PRACTICE ENDOCRINOLOGY & METABOLISM

2008 Oct;4(10):560-8

Manish K Aghi



Combination of Steroidogenesis inhibitors

Steroidogenesis inhibitors

combined treatment

**New developments in the medical treatment
of Cushing's syndrome**

R van der Pas, W W de Herder, L J Hofland and R A Feelders

"combination therapy is indicated when
symptomatology requires rapid reversal of
cortisol excess"

Ketokonazole + Metyrapone



Combination of Steroidogenesis inhibitors

Metyrapone

normalization of cortisol levels in up to 80 % of patients

↑ adrenal androgens and testosterone
hirsutism/mild acne

+ Ketokonazole

17,20 lyase (CYP17) inhibition
antiandrogenic properties
hypertension



Combination of Steroidogenesis inhibitors

Ketokonazole + Metyrapone

	KTZ (%)	MTP (%)	KTZ + MTP (%)
CO (<i>n</i> = 20)	9 (45)*	6 (30)	5 (25)
PC (<i>n</i> = 12)	0	7 (58) [†]	5 (42)
NC (<i>n</i> = 30)	8 (27)	10 (33)	12 (40)
Overall (<i>n</i> = 62)	17 (27)	23 (37)	22 (35)

CO, controlled; PC, partially controlled; NC, not controlled; KTZ, ketoconazole; MTP metyrapone.

Valassi et al. Clin Endocrinol 2012;77:735

“preoperative administration of KTZ, MTP or both normalize UFC in more than a half patients with CS, although concomitant clinical improvement was not reached in all”



Combination of Steroidogenesis inhibitors

Steroidogenesis inhibitors

combined treatment

in severe cases
early use of combination therapy
should be considered

Mitotane + one of the rapid-acting
steroidogenesis inhibitors

early control of hypercortisolaemia
until the effect of mitotane takes place



Combination of Steroidogenesis inhibitors

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

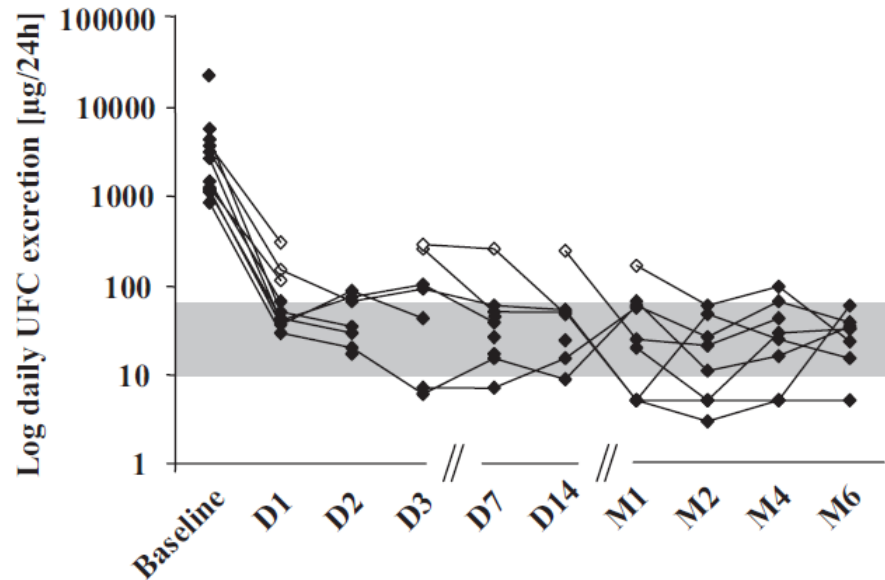
Kamenick et al. J Clin Endocrinol Metab, September 2011, 96(9):2796-2804

Prospective trial with 11 severe CD patients treated with mitotane, metyrapone and ketoconazole

Mitotane 3-5 g/day

Metyrapone 3 - 4.5 g/day

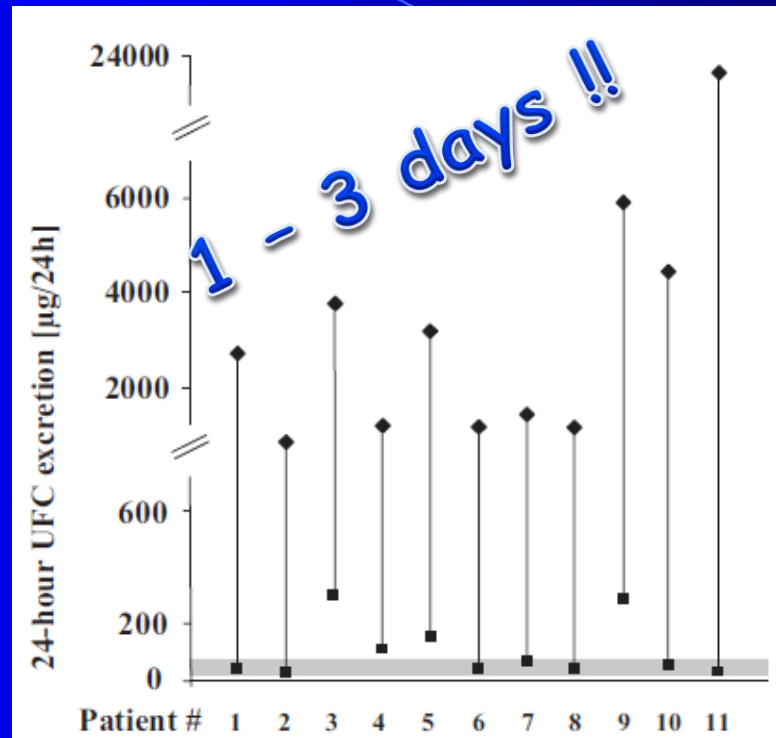
Ketoconazole 400 - 1200 mg/day



marked clinical improvement and important decrease in UFC



Combination of Steroidogenesis inhibitors



rapid decrease in UFC within 24 - 48 h

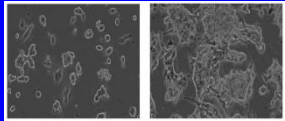
effective alternative to rescue
bilateral adrenalectomy

Kamenicky J Clin Endocrinol Metab, 2011, 96:2796

EFE 2015



Combination of Steroidogenesis inhibitors



A+T20

Research

E GENTILIN and others

Mitotane effects on
corticotrophs

218:3

275–285

Mitotane reduces human and mouse ACTH-secreting pituitary cell viability and function

Erica Gentilin^{1,2}, Federico Tagliati¹, Massimo Terzolo³, Matteo Zoli⁴,
Marcello Lapparelli⁵, Mariella Minoia¹, Maria Rosaria Ambrosio¹, Ettore C degli Uberti^{1,2}
and Maria Chiara Zatelli^{1,2}

Journal of Endocrinology
(2013) 218, 275–285

Mitotane directly reduces both
secretory activity and viability of
pituitary ACTH-secreting mouse cells

These data indicate that mitotane could have direct pituitary effects on corticotroph cells.



Combination of Steroidogenesis inhibitors

Steroidogenesis inhibitors

combined treatment

in milder cases
use of combination therapy is
reasonable only after a few months
of ineffective treatment
with each drug in monotherapy

Starkman et al. Psych Res 1986;19:177

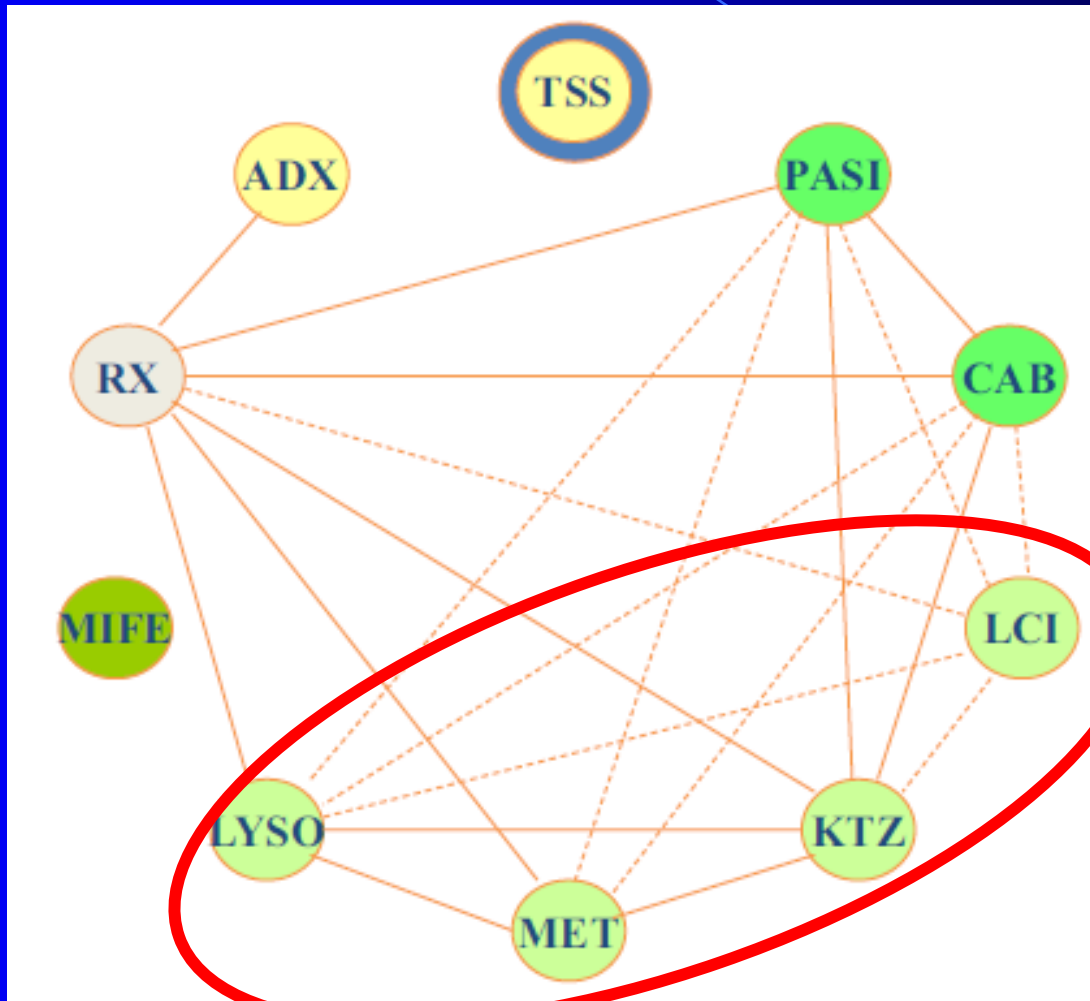
Castinetti et al. J Endocrinol 2008;158:91

Daniel et al. Eur J Endocrinol 2015; 172:R263



Combination of Steroidogenesis inhibitors

"Cushinggame"



Bertagna et al. J Clin Endocrinol Metab, April 2013, 98(4):1307–1318

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Combination of Steroidogenesis inhibitors

Predictors of response ?

degree of hypercortisolism at baseline determined the amount of drugs needed to control cortisol excess

Feelders et al. N Engl J Med 2010;362:19

patients not reaching biochemical remission had the highest UFC excretion at baseline

Vilar et al. Pituitary 2010;13:123



Combination of Steroidogenesis inhibitors



THANKS!

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