LA TERAPIA COMBINATA:
QUANDO E QUALE?

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“...Combination therapy or polytherapy is the use of more than one medication or other therapy. Typically, these terms refer to using multiple therapies to treat a single disease, and often all the therapies are pharmaceutical”
Combined therapy: when and which one?

1. Diagnosis of Cushing disease established
2. Transsphenoidal pituitary surgery
   - If in remission, monitor for relapse
   - If recurrent or persistent Cushing disease present
     - Consider second pituitary surgery
       - If recurrent or persistent Cushing disease present
         - Consider radiation therapy with interim medical therapy
         - Consider medical therapy
         - Consider bilateral adrenalectomy

*Nicholas A. Tritos, Beverly M. K. Biller and Brooke Swearingen*
Combined therapy: when and which one?

Maria Fleseriu
**Combined therapy: when and which one?**

<table>
<thead>
<tr>
<th>Table 1: A summary of drugs, commercially available and under clinical investigation</th>
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<td><strong>A</strong></td>
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| **B** | Modulate ACTH (act at the tumor level to modulate ACTH release) | Somatostatin receptor ligands:  
  - Pasireotide–SOM 230  
  - Octreotide  
  - Dopamine agonists  
  - Cabergoline  
  - Bromocriptine  
  - Other agents tried but not uniformly effective  
  - GABA agonists  
  - Valproic acid  
  - Serotonin antagonists  
  - PPAR gamma  
  - In vitro/animal models  
  - Alpha 1 adrenergic receptor antagonist  
  - Retinoic acid  
  - EGFR inhibitors |
| **C** | Inhibitors of steroidogenesis (blockage of adrenal enzymes implicated in cortisol synthesis) |  
  - Ketoconazole  
  - Mitotane (approved in Europe)  
  - Etomidate  
  - Metyrapone  
  - Ketoconazole + Metyrapone + Etomidate  
  - Aminoglutethimide (no longer available)  
  - Trilostane (no longer available)  
  - In clinical trials  
  - LCI (www.clinicaltrials.gov) |
| **D** | Combination therapy using drugs from different groups |  
  - Pasireotide + Cabergoline + Ketoconazole |
Combined therapy: when and which one?

Box 1
Clinical practice

- Ketoconazole at a dose of 200 mg two or three times daily, and check liver function and 24-hour UFC within 1 week.
- If clinical signs of adrenal insufficiency, measure morning cortisol as soon as possible, stop drug for 1 day. Start replacement glucocorticoids if needed.
- If UFC still high, increase to 400 mg twice daily.
- If not well tolerated or no effect in 2 to 3 months, switch to a different drug.
- Consider possible combination therapy.

Data from references.\textsuperscript{6,25,33,44}


Combined therapy: when and which one?

- **Steroidogenesis inhibitors**

- Cortisol levels reduction
- No effect on pituitary mass

  - increase in ACTH secretion

  - possible escape

  - secondary failure
Combined therapy: when and which one?

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).

Manish K Aghi
Combined therapy: when and which one?

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
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.
Combined therapy: when and which one?

Combining drugs with complementary pharmacological mechanisms:

- Higher chance of long-term hypercortisolism control
- Lower drug doses
- Lower side effects incidence

Hypothalamus
- CRH
- Pituitary
- ACTH
- Adrenals
- Cortisol
- Peripheral tissue

Neuromodulators of ACTH release:
- SRL’s (Pasireotide)
- DA’s (Cabergoline)

Adrenal steroidogenesis inhibitors:
- Ketoconazole
- Metyrapone
- Mitotane
- Etomidate
- LC1699 (in clinical trials)

Glucocorticoid receptor blocker:
- Mifepristone

Maria Fleseriu
Combined therapy: when and which one?

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

“monotherapy with either cabergoline or pasireotide induces complete biochemical remission in about 25% of patients”

Prospective open-label trial (80 days)
17 patients with CD treated in a stepwise manner with pasireotide mono or combination therapy with cabergoline and low-dose ketoconazole

- Pasireotide 100 μg x 3 daily
- Day 10: Pasireotide 250 μg x 3 daily
- Day 28: + Cabergoline 1.5 mg every other day
- Day 56: + Ketoconazole 200 mg x 3 daily
Combined therapy: when and which one?

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

Thus, stepwise medical therapy for Cushing’s disease with the use of three drugs that differentially target somatostatin-receptor subtype 5 and dopamine-receptor subtype 2 receptors in the adrenocorticotropic hormone-secreting adenoma and steroidogenic enzymes in the adrenal cortex resulted in biochemical control in nearly 90% of patients.
Combined therapy: when and which one?

Prospective trial (6 months) 12 CD patients [CLU > 2 x ULN] treated with cabergoline mono or combination therapy with ketoconazole

“.. (a) rationale for combination therapy may be to use lower drug dosages in order to reduce side effects of either agent”

Vilar et al. 2010 Pituitary 13 123–129
Combined therapy: when and which one?

Changes in 24 h UFC levels after treatment with cabergoline

Well tolerated

Vilar et al. 2010 Pituitary 13 123–129
Combined therapy: when and which one?

Changes in 24 h UFC levels after treatment with cabergoline and ketoconazole

Well tolerated

Vilar et al. 2010 Pituitary 13 123–129
Combined therapy: when and which one?

Prospective trial (6 months) 14 CD patients [persistent/recurrent] treated with

cabergoline and then in combination with ketoconazole

ketoconazole and then in combination with cabergoline

Cabergoline 1-3 mg/week

Ketoconazole 200-600 mg/day

Barbot et al.

**Combined therapy: when and which one?**

**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"

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**

Kamenicky´J Clin Endocrinol Metab, 2011, 96:2796
Combined therapy: when and which one?

1 - 3 days !!

rapid decrease in UFC within 24 - 48 h

effective alternative to rescue bilateral adrenalectomy

Kamenicky´ J Clin Endocrinol Metab, 2011, 96:2796
Combined therapy: when and which one?

Predictors of response?

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


Patients not reaching biochemical remission had the highest UFC excretion at baseline.

Vilar et al. Pituitary 2010;13:123
Combined therapy: when and which one?

Conventional antihypertensive therapy (thiazides, ACE inhibitors, and calcium antagonists are generally considered as first choice) may be only partially effective.

Additional therapies, such as calcium and vitamin D supplementation and sex hormone replacement in men or women with hypogonadism, may likely be beneficial.

Venous thromboembolic events

Thromboprophylaxis

Hypopituitarism in cured CD
Combined therapy: when and which one?

WARNING!

knowledge of combination therapy comes largely from case reports and small open-label studies
THANKS

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