Medical Management of Cushing’s Disease

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List of topics that we will cover

- The pertinent pituitary physiology
- An update on the medical management of ACTH producing pituitary tumours
- Details of surgical management will not be covered during the talk but you are welcome to ask about it in the Q&A session
Amy’s case

- Gained 50 lbs in 1 year
- Amenorrhea for 10 months
- New-onset hypertension
- Proximal muscle weakness
- Depression
Amy’s case

- Gained 50 lbs in 1 year
- Amenorrhea for 10 months
- New onset hypertension
- Seen by psychiatry for ‘psychosis’
Hypothalamo-pituitary system
Hypothalamic pituitary hormones
Goals of therapy for functioning sellar tumors

- Remove (or shrink) the tumour
- Normalize hormone levels
During co-treatment with SSAs, PEG (being a competitive GHR blocker) has less GH to compete with, and less GHRs to block on the liver. Moreover, SSAs inhibit IGF-1 generation by liver directly. Leung et al. JCEM 2000. Murray RD et al. JCI 2004. SSAs, decreasing portal insulin concentration, may reduce the number of GHRs expressed in the liver, and may also directly inhibit liver IGF-1 generation.
Cortisol Synthesis

11-deoxycortisol

Pregnenolone

Cholesterol

ACTH

Feedback loop malfunctioning in Cushing’s

17-OH pregnenolone

17-OH progesterone

11-deoxycorticosterone

Dehydroepiandrosterone

Androstenedione

Estrone

18-OH corticosterone

Testosterone

Estradiol

Aldosterone

Corticosterone
First-line therapy: Transsphenoidal adenomectomy

First-line therapy for patients with Cushing’s disease is transsphenoidal adenomectomy to remove the ACTH-secreting pituitary adenoma

Treatment goals
- Normalization of cortisol levels
- Reversal of clinical features
- Long-term biochemical control
- Removal of tumor mass
- Preservation of normal pituitary function
Biochemical remission

- Post-operative biochemical assessment is used to:
  - Evaluate whether patients are in remission
  - Inform decisions about the need for further therapy, such as repeat surgery or medical therapy
  - Provide an idea of overall surgical success

- There are three possible outcomes of pituitary surgery:
  - **Success**
    - No ACTH
    - No cortisol
  - **Partial success**
    - ACTH+
    - ACTH –ve
    - Cortisol +
  - **Failure**
    - ACTH +++
    - ACTH –ve
    - Cortisol +++
Post-operative remission rates and long-term recurrence rates vary widely.

- Swearingen 1999 (n=161)
- Invitti 1999 (n=236)
- Sonino 1996 (n=103)
- Knappe 1996 (n=310)
- Bakiri 1996 (n=50)
- Favia 1994 (n=110)
- Trainer 1993 (n=45)
- McCance 1993 (n=57)
- Lindholm 1992 (n=48)
- Robert 1991 (n=78)
- Burke 1990 (n=41)
- Guilhaume 1988 (n=64)
- Mampalam 1988 (n=216)
- Nakane 1987 (n=93)
- Fahrbusch 1986 (n=101)
- Lüdecke 1985 (n=100)
- Boggan 1983 (n=100)

Newell-Price J. IPC 2011; abst P13
In 17 studies published from 1983 to 1999, remission rates ranged from 46–93% and recurrence rates ranged from 0–28%.
Similar rates reported in more recent studies

- Valassi 2010 (n=620)
- Alwani 2010 (n=79)
- Jagannathan 2009 (n=261)
- Fomekong 2009 (n=40)
- Atkinson 2008 (n=42)
- Jehle 2008 (n=193)
- Prevedello 2008 (n=167)
- Xing 2008 (n=266)
- Carrasco 2008 (n=68)
- Romanholi 2008 (n=57)
- Patil 2008 (n=215)
- Rollin 2007 (n=108)
- Pouratian 2007 (n=111)
- Acebes 2007 (n=44)
- Shah 2006 (n=65)
- Hoffmann 2006 (n=100)
- Esposito 2006 (n=40)
- Atkinson 2005 (n=63)
- Hammer 2004 (n=289)
- Rollin 2004 (n=41)
- Pereira 2003 (n=78)
- Chen 2003 (n=174)
- Flitsch 2003 (n=147)
- Shimom 2002 (n=82)
- Rees 2002 (n=54)
- Barbetta 2001 (n=68)
- Chee 2001 (n=61)
- Imaki 2001 (n=49)

Newell-Price J. IPC 2011; abst P13
Currently used medical therapies in Cushing’s disease

Steroidogenesis inhibitors

- Mitotane, metyrapone, ketoconazole, etomidate
- Reduce cortisol levels via inhibition of steroid synthesis in the adrenal gland
- Temporary, palliative treatment

During co-treatment with SSAs, PEG (being a competitive GHR blocker) has less GH to compete with, and less GHRs to block on the liver. Moreover, SSAs inhibit IGF-1 generation by liver directly.

Leung et al. JCEM 2000

Murray RD et al. JCI 2004

SSAs, decreasing portal insulin concentration, may reduce the number of GHRs expressed in the liver, and may also directly inhibit liver IGF-1 generation.
Ketoconazole

- **Efficacy as monotherapy (200–1200 mg/day):**¹
  - Retrospective study of 38 patients with active Cushing’s disease
  - Treatment was stopped in first week in 5 patients due to clinical or biological intolerance
  - **17 (51%)** had normalized UFC at follow-up (mean: 23 months)
  - Clinical regression of signs of hypercortisolism
  - 5 patients with no visible adenoma at baseline developed a visible tumor during follow-up

- **Adverse events associated with ketoconazole include:**²
  - GI events
  - Pruritus and rash
  - Liver toxicity
  - Gynecomastia
  - Impairment of testicular function
  - Adrenal insufficiency

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Murray RD et al. JCI 2004

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Cabergoline

- Potent dopamine type 2 receptor (DR2) agonist
- Approximately 80% of ACTH-secreting adenomas express the dopamine D$_2$ receptor$^1$
- Studies (n=20–27) have demonstrated the effective use of cabergoline in persistent or recurrent Cushing’s disease$^{2,3}$
- The phenomenon of escape has been described
- Studies in larger patient populations are required to establish efficacy and safety

The Medical Treatment of Cushing’s Disease: Effectiveness of Chronic Treatment with the Dopamine Agonist Cabergoline in Patients Unsuccessfully Treated by Surgery

Rosario Pivonello, Maria Cristina De Martino, Paolo Cappabianca, Monica De Leo, Antongiulio Faggiano, Gaetano Lombardi, Leo J. Hofland, Steven W. J. Lamberts, and Annamaria Colao

(J Clin Endocrinol Metab 94: 223–230, 2009)
The Medical Treatment of Cushing’s Disease: Effectiveness of Chronic Treatment with the Dopamine Agonist Cabergoline in Patients Unsuccessfully Treated by Surgery

Background: Cushing’s disease (CD) is the most common form of Cushing’s syndrome, and often complicated by hypertension and impaired glucose tolerance. The first-line treatment of CD is transsphenoidal surgery, with the objective of removing the pituitary tumor, associated with increased morbidity and mortality for cardiovascular diseases (1–3). The role of dopamine agonists in the treatment of CD has been described in the past, as a useful treatment option in patients with CD who are unsuccessfully treated by neurosurgery.

Aim: The aim of this study was to evaluate the effectiveness of chronic cabergoline treatment in patients with CD who are unsuccessfully treated by surgery, with the objective of removing the pituitary tumor, as a full response at short-term evaluation; persistence of normal cortisol excretion was the only criterion to evaluate the response at long-term evaluation.

Patients and Methods: Unsuccessfully treated patients with CD were included in the study. Cabergoline was administered at an initial dose of 1 mg/wk, with a monthly increase of 1 mg, until urinary cortisol levels normalized or the maximal dose of 7 mg/wk was achieved. The responsiveness of patients to cabergoline treatment was evaluated according to changes in urinary cortisol excretion. A decrease greater than 50% from baseline to 6–18 months was considered indicative of a response. Cabergoline was withdrawn in all resistant patients, except in one, who continued treatment for 12 months. Treatment escape was defined as a sustained control of cortisol secretion for 24 months. Cabergoline was withdrawn for intolerance in all resistant patients.

Results: Twenty patients with CD unsuccessfully treated by surgery entered the study. After short-term treatment, 15 (75%) patients were responsive to cabergoline treatment. Among these, normalization of cortisol excretion was maintained in 10, whereas treatment escape was observed in 5 patients after 6–18 months. Among the 10 long-term responsive patients, seven (28.6%) full responders and three of the eight (37.5%) resistant patients, except in one, who continued treatment for 12 months. Cabergoline was withdrawn in all resistant patients.

Conclusions: The results of this study demonstrated that cabergoline treatment is effective in reducing urinary cortisol levels during the entire period of treatment in all 20 patients treated with cabergoline. The patients long-term response to cabergoline treatment was evaluated as a useful treatment option in patients with CD who are unsuccessfully treated by surgery.
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 alone

Cabergoline plus Ketoconazole
During co-treatment with SSAs, PEG (being a competitive GHR blocker) has less GH to compete with, and less GHRs to block on the liver. Moreover, SSAs inhibit IGF-1 generation by liver directly. Leung et al. JCEM 2000. Murray RD et al. JCI 2004.

SSAs, decreasing portal insulin concentration, may reduce the number of GHRs expressed in the liver, and may also directly inhibit liver IGF-1 generation.
**Mifepristone**

- Glucocorticoid receptor (GR) antagonist blocks the action of cortisol by binding to the GR-II (cortisol) receptor
  - 3–4-fold higher affinity than dexamethasone
  - 18-fold higher affinity than cortisol

- In Phase III clinical development as a treatment for endogenous Cushing’s syndrome

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**Screening**
- 42 days
- n=84 screened

**Dose escalation until week 10**
- Day 1
- Week 6
- Week 10

**24-week treatment**
- Week 16
- Week 24
- n=34 completed

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Fleseriu M *et al.* *Endocr Rev* 2011;32:OR09-5
Mifepristone in Cushing’s disease: Conclusions

- Mifepristone treatment was associated with clinical improvements in patients with refractory Cushing’s syndrome
  - Glucose tolerance and hypertension improved in 60% and 38%, respectively
  - Body weight decreased by an average of 5.7 kg
  - Waist circumference decreased by an average of 7 cm in women and 8 cm in men

- However, mifepristone blocks the glucocorticoid receptor rather than targeting the underlying cause of Cushing’s disease

- Increases in ACTH and UFC levels were observed on mifepristone treatment
During co-treatment with SSAs, PEG (being a competitive GHR blocker) has less GH to compete with, and less GHRs to block on the liver. Moreover, SSAs inhibit IGF-1 generation by liver directly. Leung et al. JCEM 2000. Murray RD et al. JCI 2004. SSAs, decreasing portal insulin concentration, may reduce the number of GHRs expressed in the liver, and may also directly inhibit liver IGF-1 generation.
Pasireotide

- Multireceptor-targeted somatostatin analogue
  - 30-, 5- and 39-fold higher affinity for sst\(_1\), sst\(_3\) and sst\(_5\) than octreotide, and similar affinity for sst\(_2\)\(^1\)

- Expression of sst\(_5\) predominates in ACTH-secreting pituitary adenomas\(^2,3\)
  - sst\(_1\), sst\(_2\) and sst\(_3\) are also expressed

- Broad binding profile means that pasireotide may be an effective treatment for Cushing’s disease

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Change in UFC from baseline to month 6 in the 103 patients with baseline and month-6 UFC measurements

Median percentage UFC change from baseline was –47.9% in both groups

†Reference line is the upper limit normal UFC, which is 52.5 μg/24 h (145 nmol/24 h)
# Primary efficacy results

<table>
<thead>
<tr>
<th>Response status</th>
<th>600 µg bid (n=82)</th>
<th>900 µg bid (n=80)</th>
<th>Overall (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-month response, n (%)*</td>
<td>12 (14.6)</td>
<td>21 (26.3)</td>
<td>33 (20.4)</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(7.0, 22.3)</td>
<td>(16.6, 35.9)</td>
<td>(14.2, 26.6)</td>
</tr>
</tbody>
</table>

*NOTE: Responder was a patient with UFC ≤ULN who did not require up titration

| 12-month response, n (%)†        | 11 (13.4)         | 20 (25.0)         | 31 (19.1)       |

†NOTE: Responder was a patient with UFC ≤ULN irrespective of up titration

**Predetermined criterion for the primary efficacy endpoint:**
lower bound of the 95% CI >15% for either of the dose groups; this was met for the 900 µg group
Highly potent inhibitor of 11β-hydroxylase (Three times more potent then metyrapone for inhibiting 11β-hydroxylase

Also inhibits aldosterone synthase

LCI699 mechanism of action

Potent inhibitor of 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2)

Blocks last steps in cortisol and aldosterone production

- It is administered orally and it displays a half-life longer than metyrapone, allowing twice-daily dosing
- It has a three times higher potency (in vitro IC_{50} for CYP11B1 of 2.5 nM vs 7.5 nM) than metyrapone

\[ \text{IC}_{50}, \text{half maximal inhibitory concentration} \]
LCI699 early study

Inclusion
- Male or female patients aged 18–75 years
- Confirmed Cushing’s disease
- UFC >1.5x ULN (mean of three 24-hour urine samples)
- No other current medical treatment for Cushing’s disease

Exclusion
- Tumour with chiasmal compression
- Poorly controlled diabetes (HbA\(_{1c}\) >9%)

HbA, hemoglobin A; ULN, upper limit of normal

Pivonello R et al. Endocr Rev 2012;33:abst OR49-1
Demographics and baseline characteristics

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Mean age ± SD, years (range)</td>
<td>39.0 ± 10.3 (22–55)</td>
</tr>
<tr>
<td>Females: males</td>
<td>8:4</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Mean BMI ± SD, kg/m² (range)</td>
<td>33.8 ± 8.5 (23.8–48.7)</td>
</tr>
<tr>
<td>Prior pituitary surgery, n (%)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Mean UFC ± SEM, µg/24h (range)</td>
<td>345.8 ± 111.0 (115.0–1530.7)</td>
</tr>
<tr>
<td>Mean UFC ± SEM, fold ULN (range)</td>
<td>4.7 ± 1.3 (1.6–17.0)</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation; SEM, standard error of the mean
Pivonello R et al. Endocr Rev 2012;33:abst OR49-1
Urinary cortisol over time in all patients

- All 12 patients had normalized UFC or >50% reduction in UFC by day 70
  - 11/12 (92%) had normal 24-hour UFC at day 70
  - Urinary cortisol normalized at least once in all 12 patients

Pivonello R et al. Endocr Rev 2012;33:abst OR49-1
LCI699 doses required to normalize UFC

The doses most frequently associated with 24-hour UFC normalization were 10 and 20 mg/day.
## Changes in clinical and laboratory features during LCI699 treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=12)</th>
<th>Day 70 (n=12)</th>
<th>Change from baseline (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, mmHg</td>
<td>139.3 ± 4.4</td>
<td>129.3 ± 5.5</td>
<td>−10.0 ± 4.3</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>88.8 ± 3.8</td>
<td>82.8 ± 3.0</td>
<td>−6.0 ± 4.3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>96.8 ± 8.8</td>
<td>100.3 ± 9.5</td>
<td>3.5 ± 1.4</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.4 ± 0.5</td>
<td>5.7 ± 0.4</td>
<td>0.3 ± 0.3</td>
</tr>
<tr>
<td>Potassium, mEq/L</td>
<td>4.1 ± 0.1</td>
<td>3.8 ± 0.2</td>
<td>−0.3 ± 0.2</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>140.3 ± 1.1</td>
<td>140.8 ± 1.0</td>
<td>0.5 ± 1.1</td>
</tr>
</tbody>
</table>

**NOTE:** Data presented as mean ± SEM  
DBP, diastolic blood pressure; SBP, systolic blood pressure  

Pivonello R et al. *Endocr Rev* 2012;33:abst OR49-1
LINC 1: Most common AEs* during treatment with LCI699 (occurring in at least two patients)

<table>
<thead>
<tr>
<th>AEs</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>7 (58.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (41.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Arthropod bite</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (16.6)</td>
</tr>
</tbody>
</table>

*Assessed based on MedDRA definitions
Pivonello R et al. *Endocr Rev* 2012;33:abst OR49-1
Mitotane, Etomidate and Metyrapone

These drugs are only used in malignant cortisol producing tumours of the adrenal gland.

Long-term use of these agents in ACTH producing pituitary tumours is NOT indicated.
Amy’s case

- Underwent surgery
- In remission since then
- Lost over 75 lbs
- BP normal
- Working as a nurse
Watercolor – Fall River, NS
S. Ali Imran, 2011