Recurrent Cushings disease
New medical options - role and limitations

Dr. Stan Van Uum, MD, PhD, FRCPC
10th Annual Canadian Endocrine Update

Dr. Stan Van Uum perceives no conflict of interest with this presentation but has worked with or consulted for:

Novartis
Genzyme
Abbott
Pfizer
Janssen
Lilly
Cushing Case – A 31-year old female

**History:**
- Symptoms since 5 years:
- Hypertension, not controlled
- Central adiposity
- ↑ facial redness/roundness
- ↑ weight
- Proximal muscle pain and weakness
- Difficulty work as finance manager

**Medications:**
- Labetalol, HCT, Furosemide, trazodone, clonazepam, prenatal vitamin.

**Physical exam:**
- Cushingoid
- BMI 28.7
- BP 149/114 mmHg
- Dorsal and supraclavicular fat pads
- Prox. Myopathy
- Multiple bruises
Patient High Likelihood Cushing’s Syndrome

**Laboratory:**
UFC 1386 and 1773 (N<275) nmol/day
1 mg DST: cortisol 477 nmol/L, ACTH, 6.6 pmol/L

**MRI:** somewhat unusual pituitary adenoma, 12 mm

**Pituitary surgery**

**Post surgery:**
UFC 1057, ACTH 10.3, cortisol 787
Pathology: nodular corticotroph hyperplasia
Consider resurgery either early (within weeks) or late
Careful discussion: why would now be successful?
Goals treatment for Cushing:

1. Control adrenal cortisol oversecretion
2. Ablate/destroy the primary tumoral lesion
3. Respect anterior pituitary functions and if possible restore normal pituitary-adrenal axis
4. Reverse peripheral manifestations of chronic steroid excess.

Only pituitary surgery can achieve all

Bertagna and Guignat
JCEM 2013,98,1307-18
Monitoring of Disease Activity

• 24 hour urine free cortisol (UFC) measurement
  – *Caveat: relies on complete collection*
• Risk of overtreatment: adrenal insufficiency (may go unrecognized)
• May require multiple serum measurements during single day
  – *Target mean serum 140-300 nmol/L*
• Perhaps use saliva cortisol
• Also need to monitor for side-effects specific for the medication.

*Trainer*
*Ind J Endocrin Met 2013,17*
After first pituitary surgery... five «tracks»

Persistent hypercortisolism («Immediate failure»)

- No adenoma
  - Mis-diagnosis
  - Adenoma totally unresected
    - 1

- Adenoma
  - Adenoma mostly unresected
    - 2

Eu- or hypo-cortisolism («Immediate success»)

- Adenoma
  - Adenoma mostly resected
    - 3
  - Adenoma totally resected
    - 4
    - Recurrent hypercortisolism
    - «Cure»

- Adenoma
  - 5

Figure 1. Assessing the outcome of pituitary surgery. The 5 tracks.
Figure 2. The therapeutic targets in Cushing’s disease and the corresponding therapeutic approaches.

Bertagna and Guignat
JCEM 2013,98,1307-18
Radiotherapy

- Conventional fractionated radiotherapy
- Stereotaxic radiosurgery (gamma knife/proton beam)

- In all cases, radiotherapy acts gradually on the tumors
- Success rates for controlling hypercortisolism are very different between series, depending in part on the doses administered and the time of observation.
- In general, it is not better than 50% at 2 years, although success increases further with time.
- There is no clear evidence that stereotaxic radio surgery accelerates the time to disease control.
- Does not ‘spare’ normal pituitary tissue, anterior pituitary function loss in up to 50% of patient.
- Potential risk cerebrovascular complications

Bertagna and Guignat
JCEM 2013,98,1307-18
Bilateral Adrenalectomy

Unequaled efficacy – 100% immediately.
Hypercortisolism may occur, sometimes after control for years, in up to 10%
Only to be done in referral centres, if necessary after medical preparation
Lifelong gluco- and mineralocorticoids
Pituitary tumor remains – risk for Nelson syndrome

Bertagna and Guignat
JCEM 2013,98,1307-18
When to Consider Medical Management for Cushing’s syndrome?

- In preparation for surgery in the belief that normalizing circulating cortisol reduces peri-operative morbidity and mortality.
- When doubt persists after initial investigation about the source of ACTH secretion, treatment can be withdrawn after a suitable interval and the patient can be re-investigated.
- After unsuccessful surgery, while considering further surgery such as bilateral adrenalectomy.
- To reduce morbidity in patients with inoperative metastatic adrenocortical carcinoma
- While waiting for pituitary radiotherapy to be effective, this may be several years.
- If the psychiatric complications of hypercortisolemia are an immediate threat to the patient’s safety.

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*Ind J Endocrin Met 2013,17*
<table>
<thead>
<tr>
<th>Glucocorticoid receptor antagonist</th>
<th>Not in Canada</th>
</tr>
</thead>
<tbody>
<tr>
<td>RU486 (mifepristone)</td>
<td></td>
</tr>
<tr>
<td>Adrenal-directed</td>
<td>Except Access Program</td>
</tr>
<tr>
<td>metyrapone</td>
<td>200 mg $1.03/tab</td>
</tr>
<tr>
<td>ketoconazole</td>
<td>500 mg $ 4.97/tab</td>
</tr>
<tr>
<td>mitotane</td>
<td>Not in Canada</td>
</tr>
<tr>
<td>trilostane</td>
<td></td>
</tr>
<tr>
<td>etomidate</td>
<td></td>
</tr>
<tr>
<td>Pituitary-directed</td>
<td>CBG 0.5 mg $9.26/tab</td>
</tr>
<tr>
<td>rosiglitazone</td>
<td>$95 0.6 mg (BID)</td>
</tr>
<tr>
<td>dopamine agonists</td>
<td></td>
</tr>
<tr>
<td>pasireotide</td>
<td></td>
</tr>
</tbody>
</table>

*Table 1: Medical options for the management of Cushing’s syndrome*

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*Ind J Endocrin Met 2013,17*
Ketaconazole

Inhibits cortisol synthesis
Start 200 mg BID → 400 mg TID (or 300 QID)
Takes several weeks for full effect
SE: Gastro-intestinal, skin rash, LFTs ↑10%, rare acute liver failure and death.
Excess mineralocorticoids and adrenal androgens.
Men: gynaecomastia and decreased libido.
Women hirsutism.
Also decrease TC and LDL

Note: 11-deoxy cortisol may cross react!

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Metyrapone

Inhibits conversion 11-deoxycortisol to cortisol

Potent

Rapid onset (<2 hr)

Starting dose 250 TID

Reassess cortisol at 72 hours, target mean cortisol 150-300 nmol/L

SE: Nausea, anorexia, abdominal pain (usually reflecting overdose). Hirsutism and acne in women

*Note: 11-deoxycortisol may cross react!*

*Trainer Ind J Endocrin Met 2013,17*
Mitotane

Cytotoxic agent for adrenocortical carcinoma
\( \downarrow \) cholesterol side-chain cleavage + 11\( \beta \)-hydroxylase
Takes several months for full effect, often transient
Start dose 0.5-1 g/day, increase by similar dose every few weeks (required dose highly variable)
SE: Nausea, anorexia, diarrhoea (common for >2g/day, universal for >4 g/day). Adrenal insufficiency, neurological side effects, LFTs↑, increased cholesterol.
Less effective and less tolerated than ketoconazole and metyrapone

*Note: changes hormone binding globulins*
Mifepristone

Potent glucocorticoid (and progesterone) receptor blocker
Dose up to 20 mg/kg
Negative feedback at HPA axis → ↑ACTH + ↑cortisol

How to monitor disease? (UFC ↑ 7-fold on average)
How to diagnose adrenal insufficiency?

Used in ectopic ACTH

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Mifepristone – SEISMIC study

• 24-week, open-label, multicenter study in 50 patients with endogenous Cushing S and DM2.
• mifepristone single daily PO dose (300-1200 mg/d)
• Outcomes: AUC for 2 hr OGTT, change DBP
• 87% of patients clinical improvement

**A**

<table>
<thead>
<tr>
<th>Visit</th>
<th>AUC_{glucose} (mg/dL • 120 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td><img src="https://via.placeholder.com/150" alt="Bar chart" /></td>
</tr>
<tr>
<td>Week 6</td>
<td><img src="https://via.placeholder.com/150" alt="Bar chart" /></td>
</tr>
<tr>
<td>Week 10</td>
<td><img src="https://via.placeholder.com/150" alt="Bar chart" /></td>
</tr>
<tr>
<td>Week 16</td>
<td><img src="https://via.placeholder.com/150" alt="Bar chart" /></td>
</tr>
<tr>
<td>Week 24</td>
<td><img src="https://via.placeholder.com/150" alt="Bar chart" /></td>
</tr>
<tr>
<td>Week 24/ET</td>
<td><img src="https://via.placeholder.com/150" alt="Bar chart" /></td>
</tr>
</tbody>
</table>

Error bars in graph are SD.
* P<0.001 vs baseline.

**B**

**Oral Glucose Tolerance Test**

<table>
<thead>
<tr>
<th>Week</th>
<th>Plasma glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td><img src="https://via.placeholder.com/150" alt="Graph" /></td>
</tr>
<tr>
<td>Week 6</td>
<td><img src="https://via.placeholder.com/150" alt="Graph" /></td>
</tr>
<tr>
<td>Week 10</td>
<td><img src="https://via.placeholder.com/150" alt="Graph" /></td>
</tr>
<tr>
<td>Week 16</td>
<td><img src="https://via.placeholder.com/150" alt="Graph" /></td>
</tr>
<tr>
<td>Week 24</td>
<td><img src="https://via.placeholder.com/150" alt="Graph" /></td>
</tr>
</tbody>
</table>

* P<0.03 FPG baseline to week 24: 149±75 mg/dL vs 105±38 mg/dL.
† P<0.004 vs baseline.
‡ P<0.003 vs baseline.
§ P<0.001 (week 16 and week 24) vs baseline.

* Fleseriu JCEM 2012,98:2039-49
Somatostatin Analogs

Pasireotide
Affinity for somatostatin receptor subtypes 1,2,3,5
Initial dose 600 microg s.c. BID for 15 days.
Initial ‘proof-of-concept’ study:
• Improvement in UFC in 76%
• Control UFC in 17%
SEs: similar to octreotide and lanreotide, in addition high rate of hyperglycaemia (118 of 163 patients)
12 month study.

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Ind J Endocrin Met 2013,17
Pasireotide for Cushing’s Disease

61% of patients reduction in UFC >50% at 6 months

Colao et al. NEJM 2012, 366, 10:914-24
Pasireotide, Cabergoline & ketoconazole for Cushing’s Disease

- Protocol for 17 patients, 80 day trial:
  - Pasireotide 100 ug sc TID to 250 ug TID
  - Day 28: add Cabergoline 0.5 mg every other day up to 1.5 mg every other day
  - Day 60: ketoconazole 200 mg TID

Feelders et al
NEJM 2010
Pasireotide, cabergoline & ketoconazole for Cushing’s Disease

Mild 1-2, moderate 2-4, severe > 4 xULN

Feelders et al
NEJM 2010
Mitotane, Metyrapone & ketoconazole for ACTH dependent CS

- 11 patients with severe Cushing S, ACTH dependent
- High dose mitotane, initially with metyrapone and ketoconazole
- Outcome: 24 hour UFC
- Evaluated as alternative to bilateral adrenalectomy

### Table

<table>
<thead>
<tr>
<th>Patient</th>
<th>Etiology</th>
<th>Tumor</th>
<th>Follow-up (months)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD</td>
<td>Micro</td>
<td>42</td>
<td>Surgery, remission</td>
</tr>
<tr>
<td>2</td>
<td>CD</td>
<td>Micro</td>
<td>14</td>
<td>Surgery, mitotane</td>
</tr>
<tr>
<td>3</td>
<td>CD</td>
<td>Micro</td>
<td>14</td>
<td>Surgery, remission</td>
</tr>
<tr>
<td>4</td>
<td>CD</td>
<td>Micro</td>
<td>25</td>
<td>Surgery, remission</td>
</tr>
<tr>
<td>5</td>
<td>EAS?</td>
<td>Occult</td>
<td>19</td>
<td>Mitotane</td>
</tr>
<tr>
<td>6</td>
<td>EAS?</td>
<td>Occult</td>
<td>9</td>
<td>Death (respiratory distress)</td>
</tr>
<tr>
<td>7</td>
<td>EAS</td>
<td>Occult</td>
<td>35</td>
<td>Surgery, remission</td>
</tr>
<tr>
<td>8</td>
<td>EAS</td>
<td>Metastatic</td>
<td>14</td>
<td>Death (tumor progression)</td>
</tr>
<tr>
<td>9</td>
<td>EAS</td>
<td>Metastatic</td>
<td>1</td>
<td>Death (myocardial infarction)</td>
</tr>
<tr>
<td>10</td>
<td>EAS</td>
<td>Metastatic</td>
<td>4</td>
<td>Death (tumor progression)</td>
</tr>
<tr>
<td>11</td>
<td>EAS</td>
<td>Metastatic</td>
<td>6</td>
<td>Surgery, remission</td>
</tr>
</tbody>
</table>

CD, Cushing’s disease; EAS, ectopic

2011; 96:2796-2804
## Summary I: Comparing the Various Therapeutic Approaches

### Table 1. Comparing the Various Therapeutic Approaches

<table>
<thead>
<tr>
<th>Option</th>
<th>Action</th>
<th>Success Rate, %</th>
<th>Adverse Events</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat pituitary surgery</td>
<td>Immediate</td>
<td>~50</td>
<td>Pituitary insufficiency</td>
<td>Fertility</td>
</tr>
<tr>
<td>Pituitary radiotherapy</td>
<td>Years</td>
<td>~40–70</td>
<td>Pituitary insufficiency, Cerebral complications</td>
<td></td>
</tr>
<tr>
<td>Cabergoline</td>
<td>Weeks</td>
<td>~40</td>
<td>Tolerability</td>
<td>Pregnancy?</td>
</tr>
<tr>
<td>Pasireotide</td>
<td>Weeks</td>
<td>~26</td>
<td>Diabetes</td>
<td>Not in pregnancy</td>
</tr>
<tr>
<td>Adrenal inhibitors</td>
<td>Immediate</td>
<td>~5</td>
<td>Escape, Liver, androgen defect, Tolerability, excess androgens/mineralocorticoids</td>
<td>Lifelong?</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metyrapone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lysodren</td>
<td>Delayed</td>
<td>~70</td>
<td>Central nervous system, gastrointestinal, liver enzymes, drug interactions...</td>
<td>Not in pregnancy</td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>Immediate</td>
<td>100</td>
<td>Lifelong adrenal insufficiency</td>
<td>Corticotroph tumor progression</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>Immediate?</td>
<td>~60</td>
<td>Nausea, fatigue, hypokalemia, high blood pressure, endometrial thickening, adrenal insufficiency</td>
<td>Women fertility, steroid coverage, monitoring, lifelong?</td>
</tr>
</tbody>
</table>

*Bertagna and Guignat*  
*JCEM 2013,98,1307-18*
### Summary II: Dosages and most important side effect of drugs for Cushing's Syndrome

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
<th>Dosage</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary-targeted drugs</td>
<td>Cabergoline</td>
<td>Up to 7 mg/week</td>
<td>Headache, dizziness, gastrointestinal discomfort, and cardiac valve fibrosis</td>
</tr>
<tr>
<td></td>
<td>Pasireotide</td>
<td>750–2400 µg/day</td>
<td>Hyperglycemia, GH deficiency, and gastrointestinal discomfort</td>
</tr>
<tr>
<td>Inhibitors of adrenocortical</td>
<td>Ketoconazole</td>
<td>400–1600 mg/day</td>
<td>Hepatotoxicity, gynecomastia, and gastrointestinal discomfort</td>
</tr>
<tr>
<td>steroidogenesis</td>
<td>Metyrapone</td>
<td>0.5–4.5 g/day</td>
<td>Dizziness, rash, gastrointestinal discomfort, worsening of hypertension, acne, and hirsutism</td>
</tr>
<tr>
<td></td>
<td>Mitotane</td>
<td>3–5 g/day</td>
<td>Gynecomastia, hepatotoxicity, hypercholesterolemia, prolonged bleeding time, gastrointestinal discomfort, dizziness, ataxia, confusion, dysarthria, and memory problems</td>
</tr>
<tr>
<td>Glucocorticoid receptor</td>
<td>Etomidate</td>
<td>0.1–0.3 mg/kg per h</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td>antagonists</td>
<td>Mifepristone</td>
<td>300–1200 mg/day</td>
<td>Hypokalemia, worsening of hypertension, clinical adrenal insufficiency, endometrial hyperplasia, and gastrointestinal discomfort</td>
</tr>
</tbody>
</table>

Feelders et al.  
*Endocr Related Cancer* 2012  
19 R205-23