Novel adrenal steroidogenesis inhibitors in the medical treatment of Cushing’s syndrome

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Disclosure

• Novartis, Millendo, Strongbridge
  – PI, Research funding to OHSU
• Novartis, Strongbridge
  – Scientific consulting fee
“Measure what is measurable, and to make measurable what is not so”

Galileo Galileo 1564-1642
On the horizon for Cushing’s syndrome
Levoketoconazole, phase III data published

Fleseriu M et al. Pituitary 2016
Fleseriu et al., Lancet Diabetes and Endocrinology, 2019
Significant improvements in quality of life and depression with levoketoconazole from baseline to end of maintenance

**P<0.01 versus baseline; ***P<0.001 versus baseline

BDI-II, Beck Depression Inventory II; QoL, quality of life
On the horizon for Cushing’s disease
**Osilodrostat**, phase III data available

Fleseriu M *et al.* *Pituitary* 2016, Pivonello, Fleseriu *et al.*, ICE 2018

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- Oral inhibitor of 11β-hydroxylase (responsible for catalysing final step of cortisol synthesis) ; also inhibits aldosterone synthesis
Osilodrostat phase II study- 22 weeks

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

Overall response (N=19):
- Controlled, n=15 (78.9%)
- Uncontrolled, n=2 and discontinued, n=2 (21.1%)

Change in mean ACTH over time

Fleseriu M et al, Pituitary 2015
# Osilodrostat in Cushing’s disease (CD): Results from a Phase III, multicenter, double-blind, randomized withdrawal study (LINC 3)

Rosario Pivonello, Maria Fleseriu, John Newell-Price, Xavier Bertagna, James Findling, Akira Shimatsu, Feng Gu, Richard Auchus, Rattana Leelawattana, Eun Jig Lee, Jung Hee Kim, Andre Lacroix, Audrey Laplanche, Paul O’Connell, Libuse Tauchmanova, Alberto M Pedroncelli and Beverly MK Biller

*International Congress of Endocrinology, Cape Town, Oral presentation on Dec 1st 2018*

<table>
<thead>
<tr>
<th></th>
<th>All patients N=137</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>40.0 (19.0–70.0)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>106 (77.4)</td>
</tr>
<tr>
<td>Median time since diagnosis, months (range)</td>
<td>47.2 (2.1–286.7)</td>
</tr>
<tr>
<td>Any previous pituitary surgery, n (%)</td>
<td>120 (87.6)</td>
</tr>
<tr>
<td>Any previous treatments for Cushing’s disease, n (%)</td>
<td>131 (95.6)</td>
</tr>
<tr>
<td>Any previous pituitary irradiation, n (%)</td>
<td>22 (16.1)</td>
</tr>
</tbody>
</table>

Baseline UFC

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Mean, x ULN</td>
<td>7.3</td>
</tr>
<tr>
<td>Median, x ULN</td>
<td>3.5</td>
</tr>
</tbody>
</table>

ULN for mUFC is 138 nmol/24 h
Summary: Cushing’s Disease treatment

- Surgery is first-line treatment, but is associated with high recurrence rates and is not a viable option in some patients.
- Repeat pituitary surgery, bilateral adrenalectomy and radiotherapy can result in control of hypercortisolism, but they are associated with variable response rates and significant risks.
- Medical therapy plays an increasing role.

**PROS**
- Agents with different actions
- Rapid & sustained effects
- Treatment adjustable & reversible
- Tumor shrinkage

**CONS**
- Long-term
- Costs
- AEs

**Individualized therapy!**

Which drug/target?

Single or combination?
Cushing’s disease: tumor directed medical therapy

Eliza B. Geer, M.D.
CSRF conference
October 4-6th, 2019
## Financial relationships

<table>
<thead>
<tr>
<th>Commercial Interest(s)</th>
<th>Nature of Relationship</th>
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<tbody>
<tr>
<td>Novartis</td>
<td>Institution-directed research support for clinical trial participation</td>
</tr>
<tr>
<td>Strongbridge</td>
<td>Institution-directed research support for clinical trial participation; medical advisory board</td>
</tr>
<tr>
<td>Chiasma</td>
<td>Institution-directed research support for clinical trial participation</td>
</tr>
<tr>
<td>Ionis</td>
<td>Institution-directed research support for clinical trial participation</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>Research grant for a phase II trial investigating ipilimumab and nivolumab in the treatment of aggressive pituitary tumors.</td>
</tr>
</tbody>
</table>
Drug targets for Cushing’s disease

Somatostatin analogs
Dopamine agonists
(Retinoic acid)

Ketoconazole
Etomidate
Metyrapone
Mitotane (LCI699)

Glucocorticoid receptor antagonists
Mifepristone
# Table 1: Review of Literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Dose (mg/week)</th>
<th>Response criteria</th>
<th>Patients with controlled hypercortisolism (%)</th>
<th>Maximal duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivonello (2004) (4)</td>
<td>Retrospective, multicenter, monotherapy</td>
<td>10</td>
<td>2.2 (1.0–3.0)</td>
<td>UFC</td>
<td>40</td>
<td>3 months</td>
</tr>
<tr>
<td>Pivonello (2009) (6)</td>
<td>Prospective, multicenter, monotherapy</td>
<td>20</td>
<td>3.5 (1.0–7.0)</td>
<td>UFC</td>
<td>35 (short term) 40 (long term)</td>
<td>2 years</td>
</tr>
<tr>
<td>Lila (2010) (17)</td>
<td>Prospective, multicenter, monotherapy</td>
<td>20</td>
<td>3.6 (1.0–5.0)</td>
<td>Midnight cortisol and/or LDDST</td>
<td>28</td>
<td>12 months</td>
</tr>
<tr>
<td>Godbout (2010) (7)</td>
<td>Retrospective, multicenter, monotherapy</td>
<td>30</td>
<td>2.1 (0.5–4.0)</td>
<td>UFC</td>
<td>37 (short term) 30 (long term)</td>
<td>3 years</td>
</tr>
<tr>
<td>Vilar (2010) (8)</td>
<td>Prospective, monocenter, bitherapy</td>
<td>12</td>
<td>2.5 (1.0–3.0)</td>
<td>UFC</td>
<td>25</td>
<td>6 months</td>
</tr>
<tr>
<td>Barbot (2014) (9)</td>
<td>Prospective, monocenter, bitherapy</td>
<td>14</td>
<td>2.3 (0.5–3.0)</td>
<td>UFC</td>
<td>33 (short term, monotherapy) 100 (long term, bitherapy)</td>
<td>12 months</td>
</tr>
<tr>
<td>Burman (2016) (10)</td>
<td>Prospective, monocenter, monotherapy</td>
<td>20</td>
<td>4.7 (2.5–5.0)</td>
<td>UFC</td>
<td>0</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

n, number of patients; UFC, urinary free cortisol; LDDST, low-dose dexamethasone suppression test.
Summary of cabergoline for CD

- No clinical trials; only small, observational, mostly short term studies
- 24 hr UFC control in 25-40% of patients treated > 1 month
- Modest response due to low doses used? (2 mg/wk, range 0.5-6 mg)
- No clear predictive factors
- Variable time to control, lag of 3 months in some
- Treatment escape/intolerance in 40%

Ferriere A Eur J Endo 2017
A 12-Month Phase 3 Study of Pasireotide in Cushing’s Disease

Annamaria Colao, M.D., Ph.D., Stephan Petersenn, M.D.,
John Newell-Price, M.D., Ph.D., James W. Findling, M.D., Feng Gu, M.D.,
Mario Maldonado, M.D., Ulrike Schoenherr, Dipl.-Biol., David Mills, M.Sc.,
Luiz Roberto Salgado, M.D., and Beverly M.K. Biller, M.D.,
for the Pasireotide B2305 Study Group*
Pasireotide treatment for Cushing’s disease

At month 12:
13% of 600 μg group
25% of 900 μg group
Achieved normal UFC

**Figure 1. Absolute Change in Urinary Free Cortisol Levels from Baseline to Month 6.**
Urinary free cortisol was available at baseline and at month 6 in a total of 103 patients; 61 patients had a reduction of at least 50% in urinary free cortisol levels at month 6. The black dashed line represents the upper limit of the normal range (ULN) (145 nmol per 24 hours [52.5 μg per 24 hours]).
SC Pasireotide treatment for Cushing’s disease

- Blood pressure, cholesterol, weight, and QoL improved

- Tumor volume decreased by 44% in 75 patients with a lesion in MRI in the 900 mcg group

- Safety profile:
  - Gastrointestinal side effects
  - 73% elevated glucose; 43% became prediabetic, 34% became diabetic

- Predictors? 50% response in mild Cushing’s; 90% of nonresponders at 2 months did not normalize later

FDA approved for CD in December, 2012
Efficacy and safety of once-monthly pasireotide in Cushing’s disease: a 12 month clinical trial

• 150 patients randomized to pasireotide LAR 10 or 30 mg monthly

• 40% achieved normal 24 hr. UFC

• Side effects: high glucose/diabetes, nausea, diarrhea, gallstones

• Patients had milder CD than in SC pasireotide trial could explain higher proportion that achieved remission

Lacriox, Lancet Endocrinology 2018
Long acting Pasireotide for CD: Phase III extension study

- Open label extension study, 81/150 pts from primary study
- Eligible if nl UFC or clinical benefit
- 53% nl UFC at last assessment
- 51.9% people discontinued; high glucose levels in 39.5%
- Improvements in BMI & WC maintained, QOL improved
- No new safety concerns

Fleseriu, Clinical Endocrinology 2019
Thank you
Cortisol Receptor Blockers

Adriana Ioachimescu, MD, PhD
Mifepristone: FDA-approved in 2012

• “to control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery.”

• Contraindications: pregnancy (abortifacient)
• Oral administration, 300-1,200 mg/day
Mechanism: (b)locks the cortisol receptors
Adverse Events

• Excess cortisol activates other receptors
  – Mineralocorticoid effects
    • leg swelling, ↓ potassium, sometimes ↑ blood pressure

• Mifepristone blocks other receptors
  – Progesterone
    • Vaginal bleeding, uterine endometrial thickening

• Manifestations of low cortisol
  – Treated with high dose dexamethasone (rescue medication)

• Nausea, fatigue, headaches, joint pain, dizziness
Mifepristone does not target the tumor and MRI surveillance is important
Efficacy

- Improves glucose control
- Improves BP in 38% of hypertensive patients
- Improves other manifestations of high cortisol
  - Body weight and composition
  - Waist circumference
  - Appearance
  - Strength
  - Moods
  - Quality of life
% Changes in body weight

SEISMIC study
- 34% patients lost ≥ 10%
- 62% patients lost ≥ 5%

Long-term Extension Study
- 80% maintained the weight loss
Dose titration

• Clinical evaluation
  – Feeling better? Tolerating the new medication?
  – Weight
  – Blood pressure
  – Home glucose records
• Are cortisol and ACTH levels helpful?
• What tests should be done?
  – Chemistry panel: potassium, creatinine, glucose
  – HbA1c
  – Thyroid tests
  – Lipids
  – EKG
Changes in concomitant medications

- Potassium supplements (especially with increasing mifepristone dose)
  - Both low and high potassium levels can be dangerous

- Blood pressure medications
  - Diuretics that decrease aldosterone effects are helpful
  - The usual diuretics that work for high blood pressure (HCTZ) may be stopped
  - Blood pressure medications that can cause edema may be decreased or stopped

- Insulin and oral antidiabetic medications are usually reduced
Proactive attitude – seek immediate advice

- Acute illness
- Procedures under general anesthesia
- New medications started by other physicians
- Vaginal bleeding
- Significant weight loss
- Low potassium
Clinical trials with cortisol-receptor blockers

• A Study of the Efficacy and Safety of Relacorilant in Patients With Endogenous Cushing Syndrome (GRACE)

• This is a Phase 3, double-blind, placebo-controlled, randomized-withdrawal study to assess the safety and efficacy of relacorilant in patients with endogenous Cushing syndrome and concurrent 1) Type 2 diabetes mellitus/impaired glucose tolerance and/or 2) uncontrolled hypertension

• Recorilant does not block the progesterone receptor

• https://clinicaltrials.gov
• Thank you!