Acromegaly: Management of the Patient Who Has Failed Surgery

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Disclosures

• Financial
  - Products used in the treatment of patients with acromegaly
    • Research support from Ipsen, Novartis, Chiasma
    • Consulting with Ipsen, Pfizer, Novartis, Novo Nordisk, Genentech, Chiasma

• Non-FDA approved uses of drugs
  - Cabergoline for acromegaly
  - Pasireotide for acromegaly
Acromegaly comorbidities

- Hypertension, cardiomyopathy, valvular disease
- Cerebrovascular events and headache
- Hypogonadism
- Arthritis
- Respiratory complications
  - Sleep apnea
- Glucose intolerance/DM
- Colon polyps
Acromegaly Impacts Survival

Life expectancy ↓ 10 years

General population

All acromegaly

Acromegaly + diabetes

Acromegaly + cardiac disease

Rajasoorya et al Clin Endocrinol 1994;41:95
Acromegaly (n=442)
Survival Curves According to Last GH Level

Mercado et al, JCEM 2014;99:4438
Acromegaly (n=442)
Survival Curves According to Last IGF-1 Level

Mercado et al, JCEM 2014;99:4438
Improvement in Morbidity in Patients With Acromegaly According to Their Last GH Level

The ultimate goal of surgery is complete restoration of normal GH and IGF-I levels and GH secretory dynamics with GH suppressed to < 0.4 ng/ml or lower by glucose.

Random GH levels < 1 ng/ml along with age-adjusted normal IGF-I levels are associated with normalization of mortality and considerable reduction of morbidity.

When glucose suppressed GH levels are > 1.0 ng/ml or random GH levels are > 2.5 ng/ml or IGF-I levels are greater than age-adjusted normal values, additional therapy is indicated to reduce morbidity and mortality with the goal of obtaining normal IGF-I levels.
## Surgical Cure Rates for Acromegaly

<table>
<thead>
<tr>
<th>Series</th>
<th>No. of Patients</th>
<th>Micros % Cured</th>
<th>Macros % Cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abosch et al</td>
<td>254</td>
<td>75%</td>
<td>71%</td>
</tr>
<tr>
<td>Swearingen et al</td>
<td>149</td>
<td>91%</td>
<td>48%</td>
</tr>
<tr>
<td>Freda et al</td>
<td>99</td>
<td>88%</td>
<td>53%</td>
</tr>
<tr>
<td>Beauregard et al</td>
<td>103</td>
<td>82%</td>
<td>47%</td>
</tr>
<tr>
<td>Shimon et al</td>
<td>98</td>
<td>84%</td>
<td>64%</td>
</tr>
<tr>
<td>Krieger et al</td>
<td>181</td>
<td>80%</td>
<td>31%</td>
</tr>
<tr>
<td>Mercado et al</td>
<td>332</td>
<td>75%</td>
<td>40%</td>
</tr>
</tbody>
</table>

Abosch et al., JCEM 1998;83:3411  
Swearingen et al., JCEM 1998;83:3419  
Freda et al., J Neurosurg 1998;89:353  
Beauregard et al., Clin Endocrinol 2003;58:86  
Shimon et al., Neurosurgery 2001;48:1239  
Krieger et al., J Neurosurg 2003;98:719  
Mercado et al, JCEM 2014;99:4438
Percentage of Transsphenoidal Operations in 3 Experience Groups Resulting in Each Complication: Results of National Survey

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>&lt;200 ops.</th>
<th>200-500 ops.</th>
<th>&gt;500 ops</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.2%</td>
<td>0.6%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1.9%</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>CSF Leak</td>
<td>4.2%</td>
<td>2.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Carotid injury</td>
<td>1.4%</td>
<td>0.6%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Loss of Vision</td>
<td>2.4%</td>
<td>0.8%</td>
<td>0.5%</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>20.6%</td>
<td>14.9%</td>
<td>7.2%</td>
</tr>
<tr>
<td>Diabetes Insipidus</td>
<td>19%</td>
<td>-</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

Ciric et al., Neurosurgery 1997;40:225
The Birmingham Pituitary Surgery Experience

8 surgeons, n=78
1 surgeon, n=66

% post-op GH <2.5 ng/ml

micros: 54 86
macros: 30 52
overall: 33 66

Gittoes et al. QJM 1999:92;741-5
Tumor MRI and Histologic Phenotypes and Outcomes

- **Densely Granulated** tumors (lower T2 intensity)
  - Higher GH and IGF-1 levels
  - Smaller, less invasive tumors
  - Better hormonal and tumor size response to somatostatin analogs

- **Sparsely Granulated** tumors (higher T2 intensity)
  - Lower GH and IGF-1 levels
  - Larger, more invasive tumors
  - Poorer hormonal and tumor size response to somatostatin analogs

Cytokeratin Staining: Densely Granulated
MRI T2 Imaging: Lower T2 Intensity

Cytokeratin Staining: Sparsely Granulated
MRI T2 Imaging: Higher T2 Intensity

Brzana et al., Pituitary 2013;16:490
Heck et al., Endocrine 2016;52:333
Potorac et al., Endocr Relat Cancer 2016;23:871
Therapy: Residual disease after surgery

- Repeat Surgery
- Irradiation
- Medical Therapy
- Observation
Therapy: Residual disease after surgery

- Repeat Surgery
- Irradiation
- Medical Therapy
- Observation
## Second Surgery for Acromegaly

9 series reviewed

<table>
<thead>
<tr>
<th>Original # of Patients</th>
<th># of Second Surgeries</th>
<th># in Remission</th>
<th>% in Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>181</td>
<td>21</td>
<td>6</td>
<td>28.6%</td>
</tr>
<tr>
<td>212</td>
<td>34</td>
<td>7</td>
<td>20.6%</td>
</tr>
<tr>
<td>29</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>-</td>
<td>10</td>
<td>3</td>
<td>30%</td>
</tr>
<tr>
<td>315</td>
<td>90</td>
<td>16</td>
<td>18%</td>
</tr>
<tr>
<td>303</td>
<td>26</td>
<td>4</td>
<td>15.4%</td>
</tr>
<tr>
<td>-</td>
<td>29</td>
<td>14</td>
<td>48.2%</td>
</tr>
<tr>
<td>212</td>
<td>16</td>
<td>3</td>
<td>19%</td>
</tr>
<tr>
<td>270</td>
<td>28</td>
<td>16</td>
<td>57.1%</td>
</tr>
<tr>
<td>Total</td>
<td>257</td>
<td>69</td>
<td>26.8%</td>
</tr>
</tbody>
</table>

Abe T, Ludecke DK. Neurosurgery 1998;42;1013-1022
Effects of Gamma Knife and Conventional Radiotherapy in Acromegaly

Landolt et al., J Neurosurg 1998;88:1002
Stereotactic Radiotherapy for Acromegaly

• Summary of 1303 patients treated in various series since 2000
  – Mean/median follow-up of 51.5 mos
  – Biochemical remission – 43.5% (range 17 – 82%)
  – Hypopituitarism – 14.9% (range 0 – 40%)

Sheehan et al., Neurosurg Clin N Am 2012;23:571
Adverse Effects of Conventional Radiotherapy for Pituitary Adenomas

• Hypopituitarism – up to 80%
  - GH > LH/FSH > ACTH-TSH
  - Likely also true for Gamma Knife RT
• Second Brain Tumors – 2 – 3% by 20 yrs
• Stroke – increased 2-fold
• Cognitive dysfunction – rare
• Encephalomalacia – very rare
Medical Therapy Targets of the GH/IGF-I Pathway

- **Somatostatin Analogos (SSAs)**
  - Directly inhibit GH secretion

- **Dopamine Agonists (DAs)**
  - Directly inhibit GH secretion

- **GH Receptor antagonist**
  - Blocks the GH receptor, negating effects of GH in periphery
  - Directly inhibits IGF-I secretion

Increased somatic growth & metabolic dysfunction
## Effects of Adjunctive Therapy With Cabergoline Following Surgery and/or Irradiation on IGF-I Levels in Patients With Acromegaly

<table>
<thead>
<tr>
<th>Series</th>
<th>N</th>
<th>% with Normal IGF-I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colao (1997)</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Abs (1998)</td>
<td>64</td>
<td>39</td>
</tr>
<tr>
<td>Cozzi (1998)</td>
<td>18</td>
<td>27</td>
</tr>
<tr>
<td>Moyes (2008)</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>TOTAL</td>
<td>108</td>
<td>32</td>
</tr>
</tbody>
</table>

Colao et al., *JCEM*. 1997;82:518.  
Abs et al., *JCEM*. 1998;83:374.  
Human somatostatin

- Inhibits multitude of hormones
- $T_{1/2}$ 3 minutes
- Binds all 5 receptor sub-types

Somatostatin Analogs

- Lanreotide
  - Dphecysphecysphecysphecys
  - Dtrpbnalcys
  - Dtrplys
  - Dtrplys

- Octreotide
  - Dphecysphecysphecysphecys
  - Dtrplys
  - Dtrplys
  - Dtrplys
  - Dtrplys
Comparison of Octreotide LAR to Lanreotide Autogel

Summary of 5 Studies

Murray RD, Melmed S. JCEM 2008;93:2957
Tumor Changes After Octreotide Therapy Expressed as a Percentage of the Pre-treatment Volume in 20 Macroadenomas

Bevan J. et al., J Clin Endocrinol Metab. 2002; 87:4554-4563.
Benefits of Adding Cabergoline to Somatostatin Analogs

IGF-I percent change during SA + CAB compared to SA alone

Patients are ranked by PRL (µg/l) level shown on the x-axis

Cozzi et al Clin Endocrinol 2004;61:209
Extension of Time Between 20 mg Octreotide LAR Doses in Patients With Acromegaly

Final Dose Frequency

No. of Patients

Weeks Between Injections

4 6 8 10 12 off

Turner et al Clin Endocrinol 2004;61:224
Prospective, Randomized Study Comparing Pasireotide to Octreotide in Patients with Acromegaly

Colao A et al, JCEM 2014;99:791–799
Worsening of Glucose Tolerance with Pasireotide in Acromegaly
Prospective Randomized Study Comparing Pasireotide to Octreotide

• Change in HbA1c levels:

<table>
<thead>
<tr>
<th></th>
<th>Pasireotide</th>
<th>Octreotide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic pts</td>
<td>+0.87%</td>
<td>+0.03%</td>
</tr>
<tr>
<td>Prediabetic pts</td>
<td>+0.64%</td>
<td>+0.11%</td>
</tr>
<tr>
<td>Nondiabetic pts</td>
<td>+0.75%</td>
<td>+0.37%</td>
</tr>
</tbody>
</table>

• Antidiabetic medication required:
  - Pasireotide – 44.4%
  - Octreotide - 26.1%

Colao et al., JCEM 2014;99:791
Clomiphene Citrate for Treatment of Acromegaly Not Controlled by Conventional Therapies

Clomiphene Citrate 50 mg per day added to other therapies for 3 months

Duarte et al., J Clin Endocrinol Metab. 2015;100(5):1863
Oral Octretide
Transient Permeability Enhancer (TPE)
Induces increased intestinal paracellular permeation
Oral Octreotide Inhibits GH Secretion in Rats

**GH Levels in Individual Rats (N=6)**

- **Octreolin Treated**
  - Rat GH (ng/mL)
    - Time (min)
    - Octreolin
    - Saline

- **Naive Rats**
  - Rat GH (ng/mL)
    - Time (min)

**Mean AUC of GH**

- AUC of GH Curves (pg/mL * min)
  - Octreolin Treated
  - Naive Rats

Chiasma
Oral Octreotide
Pharmacokinetic Results in Normal Subjects
Plasma Octreotide Levels after Single Oral Administration or Single SC Octreotide Injection in Healthy Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Oral Octreotide 20 mg</th>
<th>SC Injection Octreotide 100 mcg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>3.77</td>
<td>3.97</td>
</tr>
<tr>
<td>Tmax (hrs)</td>
<td>2.67</td>
<td>0.64</td>
</tr>
<tr>
<td>AUC</td>
<td>16.2</td>
<td>12.1</td>
</tr>
<tr>
<td>Half-life (hrs)</td>
<td>2.38</td>
<td>2.25</td>
</tr>
<tr>
<td>Time ≥ 1 ng/ml (hrs)</td>
<td>6.00</td>
<td>3.92</td>
</tr>
</tbody>
</table>

Tuvia et al., JCEM 2012;97;2362
Primary Efficacy Endpoint: Responders (IGF-1 < 1.3 x ULN and GH < 2.5 ng/mL) at End of Core Treatment

<table>
<thead>
<tr>
<th>Dose at End of Core Treatment, mITT (7 months, n=151*)</th>
<th>40 mg (n=61)</th>
<th>60 mg (n=33)</th>
<th>80 mg (n=57)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>53 (87%)</td>
<td>22 (67%)</td>
<td>23 (40%)</td>
<td>98 (65%)</td>
</tr>
</tbody>
</table>

*mITT = subjects having at least one set of values after beginning treatment

- 88 of 98 responders entered the extension phase
- 85% of patients entering the extension phase as responders maintained response through 13 months

Melmed et al. *JCEM* 2015;100:1699
Growth hormone receptor antagonist (Pegvisomant) design

Site-1 binding to GH receptor enhanced, preventing hGH from binding to the receptor

Functional dimerization is prevented; signal transduction and IGF-I production do not occur
Mechanism of GH Binding & Signal Transduction

GH binding to dimerized receptor cause rotational conformational change that causes receptor activation with transduction through JAK/STAT pathways

IGF-I at baseline and after 12 months pegvisomant

97% normalisation of IGF-I

van der Lely et al Lancet 2001:358:1754
Tumor Volume Changes in 92 Patients Receiving Daily Pegvisomant for > 6 Months

van der Lely et al Lancet 2001:358;1754
Tumor Enlargement and Liver Tests While Receiving Pegvisomant in ACROSTUDY for mean of 3.8 years

- 710 subjects had $\geq$ 2 MRI’s done over 3.8 years
  - 12/542 (2.2%) – tumor size increased confirmed with central reading
- 8/670 (1.2%) patients had $>3x$ ULN transaminases (ALT or AST)

Freda et al., Endocrine Practice 2015;21:264
Weekly Pegvisomant Added to Somatostatin Analogs in Resistant Patients Normalizes IGF-I

*9 pts required > 100 mg/wk & 4 pts required 160 mg/wk

n=31
Therapy (35–149 wk)

Neggers SJ, et al. JCEM 2007;92:4598
Summary: Medical Therapy of Acromegaly

• **Somatostatin analogs** - remain the mainstay of medical therapy
  - *On the Horizon: oral somatostatin analogs*

• **Cabergoline**
  - Worth a try in mild cases
  - Often helpful added to somatostatin analogs

• **Pegvisomant**
  - Can switch from somatostatin analogs
  - Can add to somatostatin analogs (especially if large tumor residual)
  - Watch out for transaminase abnormalities
Thank you!