ACROMEGALY
Diagnosis and Management Options
MONDAY, JUNE 23, 2014
PROGRAM CHAIR
Roberto Salvatori, MD

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Learning Objectives

Upon completion of this educational activity, learners will be able to:

• Examine principle recommendations of the latest evidence-based clinical practice guidelines for the diagnosis and management of acromegaly
• evaluate surgery, radiotherapy, and pharmacological treatments, as well as the use of biochemical control, in the overall management of acromegaly
• Assess the effect of acromegaly and its comorbidities on patients’ quality of life to better assist and manage these patients
• Assess novel therapeutic targets and emerging drug formulations for the treatment of acromegaly
Disclosures

The Endocrine Society has reviewed all disclosures and resolved or managed all identified conflicts of interest, as applicable.

The following faculty reported relevant financial relationships:

Andrea Giustina, MD: Consultant, Ipsen, Novartis Pharmaceuticals, Pfizer, Inc.

Shlomo Melmed, MD: Consultant, Genentech, Inc.; Principal Investigator, Ipsen, Pfizer, Inc.

Roberto Salvatori, MD: Advisory Board, Novartis Pharmaceuticals, Pfizer, Inc.; Advisory Board and Investigator, Ipsen

The following faculty reported no relevant financial relationships: David R. Clemmons, MD

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The following SPC members reported no relevant financial relationships: Jeffrey Boord, MD, MPH; Larry Fox, MD; Ann Kearns, MD, PhD; Connie Newman, MD

Endocrine Society and Vindico Medical Education staff associated with the development of content for this activity reported no relevant financial relationships
COMORBIDITIES OF ACROMEGALY

Andrea Giustina
Chair of Endocrinology
University of Brescia
Italy
Consultant: Ipsen, Novartis Pharmaceuticals, Pfizer, Inc.
Comorbidities in Acromegaly

Hypertension, cardiomyopathy, valvular disease

- Na+ fluid retention
- Peripheral vasomotor dysfunction
- Endothelial disturbances
- Myocardial fibrosis

Cerebrovascular events, headache

- Hypopituitarism, hypogonadism

Respiratory complications, sleep apnea

- Craniofacial deformations
- Soft tissue hypertrophy

Insulin resistance
- Impairment of insulin secretion

Glucose intolerance/diabetes mellitus

Increased bone resorption
- Cartilage hypertrophy
- Osteophytosis

Osteoarthritis, osteoporotic fractures

Colon polyps

Mortality in Acromegaly
Biochemical Determinants

Mortality in Acromegaly
Clinical Determinants

Hypertension in Acromegaly

- Present in ≥40% of patients
  - Exacerbated by sleep apnea
- Baseline BP measurement recommended
- Early, aggressive treatment important
- Unclear effect of different medical treatments for acromegaly on hypertension

Cardiovascular Disease in Acromegaly

**Left ventricular mass index**
- **Cured**: Lower values
- **Controlled**: Intermediate values
- **Poorly controlled**: Higher values

**Interventricular septum thickness (cm)**
- **Cured**: Lower values
- **Controlled**: Intermediate values
- **Poorly controlled**: Higher values

*NEUROSURGERY + SOMATOSTATIN ANALOGS*

Sleep Apnea in Acromegaly

- Underassessed
  - Prevalence up to 70%
- All patients require careful assessment
  - Symptomatic
  - Laboratory
- Improved compliance with CPAP and other devices needed
- Maxillofacial consultation advised
- SAS only partially reversible with biochemical control of acromegaly

# Sleep Apnea in Acromegaly/2

<table>
<thead>
<tr>
<th>Paper</th>
<th>Type of therapy</th>
<th>N° of patients with improved SAS/Total</th>
<th>Mean AHI before therapy</th>
<th>Mean AHI after therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grunstein et al., 1994</td>
<td>SRLs</td>
<td>NA</td>
<td>39</td>
<td>19</td>
</tr>
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<td>Ip et al., 2001</td>
<td>SRLs</td>
<td>NA</td>
<td>29</td>
<td>13</td>
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<td>Herrmann et al., 2004</td>
<td>SRLs</td>
<td>9/14</td>
<td>NA</td>
<td>NA</td>
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<td>Berg et al., 2009</td>
<td>PEG</td>
<td>9/12</td>
<td>23</td>
<td>18</td>
</tr>
<tr>
<td>Pekkarinen et al., 1987</td>
<td>S</td>
<td>1/3</td>
<td>20,6</td>
<td>18,3</td>
</tr>
<tr>
<td>Sze et al., 2007</td>
<td>S</td>
<td>6/6</td>
<td>41</td>
<td>11,3</td>
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<tr>
<td>Davi et al., 2008</td>
<td>S, SRLs, RT</td>
<td>5/6</td>
<td>31,2</td>
<td>21,3</td>
</tr>
<tr>
<td>Rosenow et al., 1996</td>
<td>S, SRLs, RT, DA</td>
<td>24/32</td>
<td>NA</td>
<td>NA</td>
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</table>

Diabetes in Acromegaly

Skeletal Fragility in Acromegaly

Clinical evidence!
# Skeletal Fragility in Acromegaly

<table>
<thead>
<tr>
<th>1° Author (year)</th>
<th>Non vertebral (Clinical)</th>
<th>Vertebral (RX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vestergaard (2002)</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Vestergaard (2004)</td>
<td>↔</td>
<td>-</td>
</tr>
<tr>
<td>Bonadonna (2005)</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Mazziotti (2008)</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Wassenaar (2011)</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Padova (2011)</td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td>Madeira (2013)</td>
<td></td>
<td>↑</td>
</tr>
</tbody>
</table>

All cross-sectional studies
Skeletal Fragility in Acromegaly

OUTCOME OF ACROMEGALY DURING 3-YEAR FOLLOW-UP

Incidence of VF (%)

Controls
Controlled/Cured for 36 months
Active for 1-12 months
Active for 13-24 months
Active for 25-36 months

Median of total duration of active acromegaly (months)

\[\text{a, } p<0.05 \text{ vs. control subjects; } \text{b, } p<0.05 \text{ vs. controlled/cured disease; } \text{c, } p<0.05 \text{ vs. active disease for 1-12 months}\]

### Outcome of Comorbidities in Acromegaly

<table>
<thead>
<tr>
<th>Generally improved with medical treatment</th>
<th>Variable or uncertain response to medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Left ventricular hypertrophy</td>
<td>• Arthropathy</td>
</tr>
<tr>
<td>• Left ventricular dysfunction</td>
<td>• Diabetes/glucose intolerance</td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• No reversal of skeletal changes</td>
</tr>
<tr>
<td>• Obstructive sleep apnea</td>
<td></td>
</tr>
</tbody>
</table>

Summary

• Severe comorbidities make acromegaly a life-threatening disease heavily impairing quality of life of affected patients
• Early diagnosis and effective and sometimes aggressive treatment is mandatory to avoid the onset, stop the progression, or reverse comorbidities
• All patients with acromegaly, including those in biochemical remission, should undergo structured follow-up in order to monitor evolution of comorbidities
CHALLENGES IN DIAGNOSING AND FOLLOWING ACROMEGALY

David R. Clemmons, MD
Sarah Graham Kenan Professor of Medicine
Director, Diabetes Center of Excellence
University of North Carolina-Chapel Hill
Chapel Hill, NC
Diagnosis of Acromegaly

- Single measurement of growth hormone (GH) is not an accurate indicator of elevation since secretion is pulsatile
  - Random GH sampling results in both false-positive and false-negative results
  - Patients can have active disease even though GH levels fall within normal range
  - Diagnosis can be confirmed by demonstrating failure to suppress GH <1 ng/mL after glucose administration

- Measurement of insulin-like growth factor (IGF)-I levels is a reliable marker for the diagnosis of acromegaly
  - Representative of average daily GH secretion
  - Levels remain stable throughout the day; not affected by meals

Correlation Between IGF-I and Clinical Indices

- IGF-I (ng/mL)

<table>
<thead>
<tr>
<th>Heel Pad Thickness (mm)</th>
<th>Fasting GH: r = 0.12</th>
<th>Fasting GH: r = 0.08</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r = 0.73</td>
<td>r = 0.74</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.00001</td>
<td>P&lt;0.00001</td>
</tr>
</tbody>
</table>

- Fasting Blood Glucose (mg/dL)

<table>
<thead>
<tr>
<th>Fasting Blood Glucose (mg/dL)</th>
<th>Nadir GH: r = 0.34</th>
<th>Nadir GH: r = 0.36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>360</td>
<td>360</td>
</tr>
</tbody>
</table>

Why Measure GH?

• Provides a direct measure of tumor output
• Necessary to exclude the diagnosis in 2.5% of normal population who have an elevated IGF-I
• Correlates with degree of improvement after surgery
• Predicts long term mortality outcome
Summary of Criteria for Selecting IGF-I Assays

1. Adequate age-adjusted normative data
2. Interassay variability is stated
3. Method is adequate to eliminate binding protein interference
4. Assay results show proven GH dependence
5. Reference values are available that allow comparison of results to other commercial assays
IGF-I Age Adjusted Reference Ranges

Summary of Criteria for Selecting IGF-I Assays

1. Adequate age-adjusted normative data
2. Interassay variability is stated
3. Method is adequate to eliminate binding protein interference
4. Assay results show proven GH dependence
5. Reference values are available that allow comparison of results to other commercial assays
## Interlaboratory Agreement of Insulin-like Growth Factor 1 Concentrations Measured by Mass Spectrometry

Comparison of a central calibrator vs a local calibrator.

- **a** One laboratory generated a single calibration curve and distributed it.
- **b** Each laboratory generated its own calibration curve using rat plasma and reference material.
- **c** Average CV was calculated from the CV of all 4 samples.

<table>
<thead>
<tr>
<th>Sample</th>
<th>Mean concentration, ng/mL</th>
<th>Central calibrator, CV, %\textsuperscript{a}</th>
<th>Local calibrator, CV, %\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>85</td>
<td>4.0</td>
<td>16.4</td>
</tr>
<tr>
<td>2</td>
<td>90</td>
<td>5.6</td>
<td>19.3</td>
</tr>
<tr>
<td>3</td>
<td>210</td>
<td>6.1</td>
<td>10.6</td>
</tr>
<tr>
<td>4</td>
<td>356</td>
<td>6.9</td>
<td>5.5</td>
</tr>
<tr>
<td>5</td>
<td>179</td>
<td>3.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Mean CV, %\textsuperscript{c}</td>
<td></td>
<td>5.2</td>
<td>12.8</td>
</tr>
</tbody>
</table>

## Results from a HGH Recovery Study


<table>
<thead>
<tr>
<th>Background matrix</th>
<th>Recovery value, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hGH, μg/ml</td>
</tr>
<tr>
<td>PBS</td>
<td>5.05</td>
</tr>
<tr>
<td>hGH-depleted serum</td>
<td>5.18</td>
</tr>
<tr>
<td>Charcoal-stripped serum</td>
<td>5.09</td>
</tr>
<tr>
<td>SRM 971 male</td>
<td>5.03</td>
</tr>
<tr>
<td>Sheep serum Reconstitution in PBS-BSA</td>
<td>5.12</td>
</tr>
<tr>
<td>PBS-BSA</td>
<td>4.94</td>
</tr>
<tr>
<td>hGH-depleted serum</td>
<td>5.01</td>
</tr>
<tr>
<td>Charcoal-stripped serum</td>
<td>5.03</td>
</tr>
<tr>
<td>SRM 971 male</td>
<td>4.91</td>
</tr>
<tr>
<td>Sheep serum</td>
<td>4.97</td>
</tr>
</tbody>
</table>
Comparison of LC-MS and Immunoassay Techniques with Respect to hGH Quantification

<table>
<thead>
<tr>
<th>Sample</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>[hGH] by LC-MS, μg/L Peptide T12</td>
<td>7.250 (0.023)</td>
<td>5.205 (0.010)</td>
<td>4.365 (0.019)</td>
</tr>
<tr>
<td>Peptide T6</td>
<td>6.348 (0.005)</td>
<td>4.458 (0.017)</td>
<td>3.675 (0.012)</td>
</tr>
<tr>
<td>[GHBP], μg/L</td>
<td>42.2 (1.8)</td>
<td>21.2 (1.6)</td>
<td>24.7 (1.4)</td>
</tr>
<tr>
<td>Decrease in [hGH] upon addition of 10 μg/L GHBP, %</td>
<td>9.7</td>
<td>10.6</td>
<td>14.8</td>
</tr>
<tr>
<td>[hGH] by immunoassay, μg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Siemens</td>
<td>9.78 (0.31)</td>
<td>7.14 (0.44)</td>
<td>4.21 (0.18)</td>
</tr>
<tr>
<td>Roche</td>
<td>9.29 (0.21)</td>
<td>7.26 (0.12)</td>
<td>4.10 (0.11)</td>
</tr>
<tr>
<td>Mediagnost</td>
<td>7.91 (0.17)</td>
<td>5.62 (0.06)</td>
<td>3.14 (0.07)</td>
</tr>
<tr>
<td>DiaSorin</td>
<td>6.90 (0.87)</td>
<td>5.60 (0.30)</td>
<td>2.87 (0.15)</td>
</tr>
<tr>
<td>IDS</td>
<td>7.99 (0.76)</td>
<td>6.18 (0.25)</td>
<td>3.25 (0.13)</td>
</tr>
</tbody>
</table>

Surgical Cure Rates for Acromegaly According to Tumor Size and Criteria Used

<table>
<thead>
<tr>
<th>Series</th>
<th>% Cured</th>
<th>Micros</th>
<th>Macros</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abosch (n=254)</td>
<td></td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Swearingen (n=149)</td>
<td></td>
<td>91</td>
<td>48</td>
</tr>
<tr>
<td>Freda (n=99)</td>
<td></td>
<td>88</td>
<td>53</td>
</tr>
<tr>
<td>Beauregard (n=103)</td>
<td></td>
<td>82</td>
<td>47</td>
</tr>
<tr>
<td>Shimon (n=98)</td>
<td></td>
<td>84</td>
<td>64</td>
</tr>
<tr>
<td>Krieger (n=181)</td>
<td></td>
<td>80</td>
<td>31</td>
</tr>
</tbody>
</table>

## Correlation Between Tumor Size and Remission Rate After Surgery

<table>
<thead>
<tr>
<th></th>
<th>Microadenoma</th>
<th>Macroadenoma</th>
<th>Giant adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>142 (27%)</td>
<td>378 (70.7%)</td>
<td>12 (2.2%)</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td>2-9</td>
<td>10-37</td>
<td>41-60</td>
</tr>
<tr>
<td>Avg. Diameter (mm)</td>
<td>7.6±1.75</td>
<td>16.7 ± 5.6</td>
<td>50.9±9.5</td>
</tr>
<tr>
<td>GH level (µg/l)</td>
<td>1-142</td>
<td>4-357</td>
<td>10-398</td>
</tr>
<tr>
<td>Average GH level (µg/l)</td>
<td>16.4±15.2</td>
<td>42.6±38.4</td>
<td>102.4±64.3</td>
</tr>
<tr>
<td>Remission rate N</td>
<td>107 (75.3%)</td>
<td>186 (48.6%)</td>
<td>1(8.3%)</td>
</tr>
</tbody>
</table>

Odds Ratio for Presence of Left Ventricular Hypertrophy, Diastolic and Systolic Dysfunction in Patients with Estimated Duration of Acromegaly ≥10 Years Compared with Those with Estimated Disease Duration <10 Years

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IGF-I at Diagnosis Predicts OA Severity

Physician vs Computer Model

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>46</td>
<td>96</td>
<td>85</td>
<td>26</td>
</tr>
<tr>
<td>Worst</td>
<td>33</td>
<td>100</td>
<td>100</td>
<td>16</td>
</tr>
<tr>
<td>Best</td>
<td>83</td>
<td>96</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>Computer</td>
<td>71</td>
<td>100</td>
<td>100</td>
<td>86</td>
</tr>
</tbody>
</table>

Ten physicians, internists, or family practitioners, examined 49 8 × 10 color photographs and decided which represented patients with acromegaly or normal subjects. The same photographs were analyzed by the computer model. The computer was more accurate (86%) than all but one of the physicians (90%).

Case 1

- 46-year-old man referred for evaluation of enlarged thyroid
- Noted to have osteoarthritis
- Recalled hand and foot enlargement, sweaty palms, and change in facial features
- Sleep apnea, hypertension, and impaired fasting glucose
- GH 1.6 ng/ml IGF-I 609 ng/mL (87-267)
MRI and Histology
Case 2

- 44-year-old woman presented for evaluation of new onset diabetes
- BMI 26 kg/mm² and no family history of diabetes
- Reported changing ring size twice and shoe size once, modest increase in sweating
- IGF-I 804 ng/mL (110-368) GH suppression nadir 2.2 ng/mL
MRI: Microadenoma
Case 3

- 36-year-old man presented with clicking jaw symptoms of TMJ
- History revealed joint pain and weight gain
- Occupation: Barber, had to enlarge his scissors because fingers didn’t fit
- IGF-I 1600 ng/mL GH 13.9 ng/mL
Consensus Guidelines: Initial Evaluation

- Screening: There are no consensus guidelines for screening
- Diagnostic testing: Consensus recommendation is to measure IGF-I and growth hormone after glucose
- Initial evaluation should include: MRI, visual field (if large tumor), prolactin, testosterone/LH (males), FSH estrogen (females)
- Comorbidity evaluation: Fasting glucose; calcium assessment of arthritis; sleep study, if symptomatic ECG, followed by echocardiogram, if LVH is present; colonoscopy; dexa scan and radiographs of spine and hip films, if history of fracture or if hypogonadism is present; genetic analysis, if family is positive for pituitary tumors
Summary

- Confirmation of the diagnosis of acromegaly is straightforward, the major problem is early detection.
- IGF-I measurements provide an index of disease severity and are useful for diagnosis and monitoring the response to treatment.
- GH suppression testing is useful for confirming that an elevated IGF-I is due to a GH-secreting tumor.
- Assays for both IGF-I and GH have improved, and further steps to improve the comparability of results among different reference labs are being undertaken.
- Abnormal enlargement of the hands and feet are the most common presenting symptoms of acromegaly and merit investigation.
- Early diagnosis predicts a much higher rate of surgical cure.
- Consensus guidelines recommend both GH and IGF-I measurements at diagnosis and proactive use of these tests to determine the need for further therapy.
Therapeutic Approaches to Acromegaly Management

Shlomo Melmed, MD
Cedars-Sinai Medical Center
Los Angeles, CA
Disclosure

- Consultant: Chiasma, Genentech
- Principal Investigator: Ipsen, Pfizer, Novartis
Acromegaly: Approach to Management
Treatment Outcomes

- **Unchanged**
- **Improved, with disease persistence**
- **Recurrence**
- **Spontaneous resolution**
- **Long-term normalization**

Variables:
- GH
- BP
- DM
- SA
- OA
- QOL
- ...etc

Timeline:
- Hours
- Days
- Weeks
- Months
- Years

Melmed 2014
Acromegaly Treatment

Goals:
• Eliminate morbidity
• Reduce mortality to expected rates

Strategy:
• Safe treatments
• Remove tumor or control growth
• Normalize GH secretion and action
• Preserve pituitary function

Assessment:
• Age-adjusted IGFI
• Nadir GH <1 mg/L after OGTT

Acromegaly Treatment Outcomes


If IGF-1 nl ... probably controlled!
If GH elevated ... likely sign of early relapse!
GH as a Postoperative Remission Biomarker

24-hour postop GH <1 µg/L has 98% predictive value

Caveats:

IGF-1 normalization might be delayed after surgery

Medication effects might be delayed and progressive

GH-secreting Adenoma: Remission Predictors

**Predictors for postsurgical disease persistence**

- Macroadenoma
- Parasellar extension
- Young age
- High GH/IGF1

…………Choice of surgeon


Hospital and Surgeon Volume Determine Outcome


Admissions/yr

Micro
Macro
Overall

% Post-op GH<2.5 ng/mL

408 hospitals

Mortality (%)

534 surgeons

Surgical skill as biomarker!!

Surgery

**Advantages**
- Rapid GH decrease
- One-time cost
- Potential cure
- Debulking may enhance adjuvant therapy

**Disadvantages**
- Tumor persistence
- Hypopituitarism
- Not all appropriate candidates

**Risks**

<table>
<thead>
<tr>
<th>Temporary vs permanent</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall complications</td>
<td>25</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>10</td>
</tr>
<tr>
<td>Electrolyte abnormalities</td>
<td>9</td>
</tr>
<tr>
<td>Neurologic deficit</td>
<td>5</td>
</tr>
<tr>
<td>CSF rhinorrhea</td>
<td>1.5</td>
</tr>
<tr>
<td>Mortality</td>
<td>1</td>
</tr>
</tbody>
</table>

More complications:
- *Low-volume surgeon*
- Comorbidity

Melmed 2014
Radiotherapy

**MORTALITY**

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>SMR (O/E)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>No</td>
<td>1.4</td>
<td>1.1, 2.4</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.1</td>
<td>1.6, 2.4</td>
<td>0.006</td>
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<tr>
<td>Cancer</td>
<td>No</td>
<td>1.1</td>
<td>0.8, 2.2</td>
<td>0.442</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2.4</td>
<td>1.6, 3.1</td>
<td>0.247</td>
</tr>
<tr>
<td>CV</td>
<td>No</td>
<td>1.7</td>
<td>0.8, 3.3</td>
<td>0.034</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4.1</td>
<td>2.3, 6.6</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Radiotherapy

- **Advantages**
  - Permanent
  - No long-term therapy
  - No drug-related adverse events
  - One-time cost
  - Patient compliance

- **Disadvantages**
  - Ineffective and slow onset
  - IGF-I not normalized
  - Hypopituitarism
  - CVA
  - Cost of interim medical therapy
  - Visual problems
  - Secondary brain malignancies
  - CNS damage
Tumor Shrinkage in 55 Patients Receiving Primary Octreotide Therapy

- Mean tumor volume reduction: 62%
- Reduction to empty sella
- Cavernous sinus resolution
- Tumor disappeared

11 patients

Tumor shrinkage: Progressive

%  
Before hormone normalization 45
Without GH control 35
None, with GH control 3

Primary Medical Treatment

- Poor likelihood of surgical cure
- Frailty
- Patient declines surgery
- Unacceptable anesthetic risk

Advantages

- Avoid noncurative surgery and radiation with attendant side effects
- Medications can be personalized
SRL Therapy

Advantages
- Rapid GH and/or IGF-I control and symptom relief
- No hypopituitarism
- Tumor mass control

Adverse effects
- Gallbladder
  - Gallstones or sludge
- Gastrointestinal
  - Diarrhea
  - Nausea
  - Abdominal discomfort
- Glucose
  - Hypo/hyperglycemia
- Cardiac
  - Sinus bradycardia
- Other
  - Injection site pain
  - Headache
  - Alopecia

Disadvantages
- Cure not permanent
- Long-term treatment
- Cost
- Patient compliance required

Doppman The Endocrinologist 1998
GH Receptor Antagonist

- **Goals**
  - Normalize IGF-I
  - Control symptoms

- **Efficacy Biomarker (nl IGF-I)**
  - >60% at 20-40 mg/day

- **Disadvantages**
  - Elevated liver enzymes
  - Lipodystrophy
  - Very rare increase in tumor volume; uncertain if due to drug or natural history

ACROSTUDY: Pegvisomant Biomarkers

<table>
<thead>
<tr>
<th>Diabetes Biomarkers</th>
<th>Baseline</th>
<th>6 Mos</th>
<th>24 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glucose Fasting</strong> (mg/dL)</td>
<td>141 ± 61</td>
<td>126 ± 56</td>
<td>102* ± 24</td>
</tr>
<tr>
<td>N=58</td>
<td>N=51</td>
<td>N=28</td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td>7.0 ± 1.4</td>
<td>6.5* ± 1.2</td>
<td>6.5 ± 1.3</td>
</tr>
<tr>
<td>N=71</td>
<td>N=65</td>
<td>N=41</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05.

Combined SRL and Pegvisomant

Morbidity
IGF-I
Pituitary function
Tumor size
Adverse effects
Avoiding other less safe Rx

Improved
Controlled ~80%
Uncompromised
Shrinkage ~50%
Similar to adjuvant Rx
Patient choice

Pasireotide* Control of Acromegaly

Adverse events (%)
- Gastro-intestinal: 25
- BS: 6
- HbA1c: 5
- Diabetes: 5

Pasireotide µg (bid)
- 200 (n=21)
- 400 (n=17)
- 600 (n=20)

GH inhibition %
- Octreotide 100 µg tid (n=58)
- Octreotide 250 µg bid (n=8)


*Not FDA approved
Comparing Treatment with Pasireotide* LAR and Octreotide LAR

- Overall, the number of patients with GH <2.5 µg/L and normal IGF-1 was significantly greater with pasireotide LAR compared to octreotide LAR (p=.007)
- Safety profile of pasireotide similar to octreotide, except for hyperglycemia-related AEs (57% vs 22%)

Effect of Octreolin* on Basal GH in 18 Healthy Subjects

83% inhibition of basal GH


*Not FDA approved
Effect of Oral Octreotide on GH Surge in 18 Healthy Subjects

Serum GH ng/mL

-1.0 0.0 1.0 2.0 3.0 4.0 5.0
Pre dose Basal Secretion GHRH-Stimulated

Octreolin
GHRH-Arg

79% inhibition of GHRH-induced GH

Control
OOA

Medical Management of Acromegaly

**Somatostatin Receptor Ligand**

- **Well controlled**
  - Consider reducing SRL dose or increasing dose interval
  - Monitor IGF-I
  - SRL + pegv
    - Pegv + cabergoline
    - SRL + dopamine agonist
  - Increase SRL dose or decrease dose interval
  - Increase pegv dose and/or add cabergoline
  - Consider reducing pegv dose and/or increasing dose interval

- **Partial response**
  - SRL + pegv
    - Increase pegv dose and/or add cabergoline
  - No response

- **No response**
  - Switch to pegv
  - Well controlled

ACROMEGALY
Diagnosis and Management Options

PANEL DISCUSSION