Measuring Control
Growth Hormone and IGF-I After Surgery For Acromegaly

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Introduction

- Overview of Acromegaly
  - Epidemiology
  - Clinical Features
  - Management

- Protocol
  - Prospective Study
  - Measures of biochemical control during the first year after surgery for acromegaly
Overview-Acromegaly

- Growth hormone (GH) excess usually from a pituitary adenoma
- Annual incidence of 3-4 cases per million people
- Mean age of diagnosis is 40-45 years
- Most patients have had symptoms for 9-10 years
Clinical Features

- Symptoms attributable to both elevated concentrations of GH and Insulin-like Growth Factor-I (IGF-I)
  - Arthropathy
  - Cardiovascular Disease, Cardiomyopathy
  - Hypertension
  - Respiratory disease, obstructive
  - Neuropathy
  - Glucose intolerance
Symptoms and Signs

- Acral Enlargement
- Prognathism
- Coarse Facial Features
- Excessive Sweating
- Carpal Tunnel Syndrome
- Headache, Bitemporal Hemianopsia
Somatotropic Axis

- **Biochemical Feedback Loop**
- **GH secretion stimulated by GHRH and inhibited by somatostatin**
- **IGF-I produced in response to GH**
- **Feeds back to pituitary and hypothalamus**
Therapy

Goals:

• Control pituitary tumor mass
• Control symptoms of GH excess
• Improvement in morbidity and mortality
• Preservation of pituitary function
Therapy: Modalities

- One or a combination of three therapies:
  - Surgery
  - Medications
    - Somatostatin Analogs
    - GH receptor antagonists
    - Dopamine Agonists
  - Radiation
Morbidity and Mortality

- Decreased survival rate compared to matched population controls of 2-3 fold

- Predictors of Mortality
  - Last GH
  - Hypertension
  - Cardiac Disease
  - Diabetes
  - Duration of Symptoms
Decreased Survival in Acromegaly: GH and IGF-I

Assessing Control

- Disease activity measured based on biochemical parameters
- Normalization of IGF-I (age and gender matched)
- GH suppression after oral glucose challenge to less than 1µg/L

Consensus Statement; 2004; JCEM 89(7): 3099-3102
Protocol Background

- Arbitrary cutoff points and assay methodologies have changed
- Currently two biochemical measures of control that are related but not always in agreement
- Discordant results of OGTT and IGF-I can be seen in approximately 30% of patients with acromegaly
"Abnormal" GH in Controlled Patients

- 76 subjects with acromegaly post surgery
- All with normal IGF-I
- 50 with normal nadir GH in response to OGTT
- 26 "abnormal"

Freda, P. U. et al. J Clin Endocrinol Metab 2004;89:495-500
Nadir GH levels after OGTT and IGF-I levels in postoperative patients in remission as defined by normal IGF-I levels

Freda, P. U. et al. J Clin Endocrinol Metab 2004;89:495-500
Longitudinal Follow-up

- 49 Subjects [30 with normal GH (Group 1)/19 with abnormal GH (Group 2)]
- Mean follow up time 3.2 years
- Patterns of GH/IGF-I similar in each group over time
- Five subjects in group 2 had biochemical evidence of recurrence: elevated IGF-I >15% of ULN
- MRI evidence of tumor recurrence in 2
- IGF-I remained normal in all subjects in group 1
OGTT and IGF-I in the first year after surgery

- Prospective study of 17 patients
- IGF-I and OGTT at several time points after surgery
- OGTT results at 1 week post op highly reproducible (measured until week 12)
- Week 12 IGF-I predicted IGF-I results at 1 year
- All controlled subjects had normal IGF-I at 2 weeks

Early, Intermediate and Late Stabilization

Protocol

- **Hypothesis** – There is a disparity between subjects with low normal IGF-I results after surgery and high-normal IGF-I results
  - Subjects with low-normal IGF-I and GH nadir > 1 µg/L will normalize GH over time
  - Subjects with high-normal IGF-I and GH nadir > 1 µg/L will have a higher rate of recurrence
Protocol - Objectives

- **Primary Objective** – prospectively assess the natural course of acromegaly treated by surgery in subjects with non-suppressed GH nadir values and normal IGF-I

- **Secondary Objective** – Reliability of GH nadir, free IGF-I, total IGF-I and IGF binding proteins on post op day 1 in predicting long term control of acromegaly
Secondary Objective - Assess the inter assay reliability of GH and IGF-I measurement using commercial and non-commercial assays
Study Population

- Pilot Study limited to 20 subjects
- Subjects diagnosed with acromegaly who will be undergoing surgical treatment of acromegaly
Inclusion Criteria

- Male or Female age 18+
- Diagnosis of acromegaly from a pituitary adenoma visualized by MRI
- Elevated IGF-I levels (age and gender matched)
- GH response to OGTT > 1 μg/L
- Plan to undergo surgical resection of pituitary adenoma
- Informed Consent
Exclusion Criteria

- Subjects receiving pre-operative octreotide LAR will be excluded.

- Washout periods
  - Short acting – 2 weeks
    - Bromocriptine, octreotide
  - Long acting – 4 weeks
    - Pegvisomant, cabergoline
Exclusion Criteria

- Hormone replacement (estrogen, progesterone, testosterone, thyroid) stable during trial
- Insulin use
Visit Schedule

- Testing of the GH-IGF-I axis during the first year after surgery
  - IGF-I, total and free
  - GH response to OGTT
  - IGF binding proteins
- Testing done at Day 1, 6 weeks, 3 months, and 12 months
- MRI obtained as part of standard of care at 3 months and 12 months
- Duplicate samples of each time point for GH and IGF-I will be drawn on each subject
Study Design

- Subjects divided into 1 of 4 groups based on values of Total IGF-I and GH nadir at 6 week time point
- Age and Gender Matched IGF-I
- GH nadir < 1 μg/L

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<tr>
<th>Normal IGF-I</th>
<th>Elevated GH</th>
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<td>Normal GH</td>
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<td>- Elevated IGF-I</td>
<td>- Elevated GH</td>
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Endpoints

- Primary endpoints – GH and IGF-I normalization at 3 months and 1 year
  - For subjects with normal IGF-I
    - Is there a difference in the high normal and low normal IGF-I groups regarding GH normalization?
  - Are GH results and IGF-I results concordant?
  - Does a normal result at any time point predict outcome at 1 year?
Secondary Endpoints

- Do measures of the GH-IGF-I axis on day 1 predict surgical outcome?
- How reliable are measures of GH and IGF-I between different assays?