Long-Term Treatment with Recombinant IGF-1: Results in Patients with Severe Primary IGF-1 Deficiency (IGFD)

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Disclosure

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OBJECTIVES

• Review the efficacy data from nearly two decades of IGF-I therapy in children with severe primary IGF-I deficiency (IGFD)

• Discuss the safety information from nearly two decades of IGF-I therapy in children with severe primary IGFD
Physiologic actions of IGF-I

Mitogenesis
(Salmon and Daughaday, 1966)

Anti-lipolysis
(Underwood, 1972)

Paracrine/autocrine actions
(Van Wyk et al, 1980)
(Isaksson, 1982)

Increase insulin sensitivity
(Guler & Zapf, 1987)

Neurotrophic actions
(Glazner, 1994)

Inhibition of apoptosis
(Jung, 1996)
Hypothalamus

GHRH

Pituitary

GH

Liver: ‘endocrine’ effect

Intracellular signaling pathway

GH receptor

IGF-I

STAT5b

IGFBP-3

ALS

Ternary complex (circulation)

Local effects

Local IGF-I

IGF-I receptor

LINEAR GROWTH

Clemmons DR. Nat Rev Drug Disc 2007
The challenges we had...

• Would IGF-I produce **sustainable** anabolic effects in humans?

• If autocrine-paracrine IGF-I was a significant factor, would solely restoring the endocrine component of IGF-I be sufficient to stimulate statural growth?

• What about the lack of the independent specific GH action?

• Are the other components of the ternary complex necessary for optimal physiologic response to IGF-I?

• Would the insulin-like effects of IGF-I limit its use as a therapeutic agent?
**Anabolic and Metabolic Studies in Growth Hormone Insensitivity Syndrome (IGF-I Deficiency)**

- **8.9 year old male**
- **Ht: 50\textsuperscript{th} %ile for 4.5 y old**

Walker et al. NEJM, 1991
IGF-1 Therapy Trials in Severe Primary IGFD

- Backeljauw, Chernausek, et al. 80-120 mcg/kg twice daily
- Ranke, Savage et al. 40-120 mcg/kg twice daily
- Laron, Klinger et al. 150-200 mcg/kg once daily
- Guevara-Aguirre, Rosenbloom et al. 80 & 120 mcg/kg twice daily
- Several case reports with few patients each

- Baseline heights (SD) : - 5.6 to - 6.6 (- 8.0 for Ecuadoran patients)
- Baseline growth velocity (cm/year) : 3.0 to 4.7
- Year one growth velocity (cm/year) : 8.2 to 9.1
- Year two growth velocity (cm/year) : 5.6 to 6.4

- All initial studies with small n (7 - 17)
- Some now with 4-5 year follow-up data
Integrated Analysis of Long-Term IGF-1 Therapy

- Clinical program in consultation with USFDA
- 76 patients (46 M, 30 F) - 12 withdrew
- GH gene deletion in only 9 subjects
- Average treatment duration is 4.4 years
- 321 patient-years analyzed
- IGF-I at 60 – 120 mcg/kg/dose SQ twice daily

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>7.8 ± 4.5</td>
</tr>
<tr>
<td>Height SDS</td>
<td>-6.5 ± 1.8</td>
</tr>
<tr>
<td>Weight SDS</td>
<td>-6.6 ± 4.0</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>-0.2 ± 1.2</td>
</tr>
<tr>
<td>Height Velocity</td>
<td>2.8 ± 1.8</td>
</tr>
<tr>
<td>Bone Age (years)</td>
<td>5.1 ± 3.8</td>
</tr>
<tr>
<td>IGF-I SDS</td>
<td>-4.4 ± 1.8</td>
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</tbody>
</table>
Long Term Treatment with IGF-I in Children with Severe Primary IGF-I Deficiency due to GHIS

Inclusion Criteria

- **GH insensitivity due to**
  - GH receptor deficiency/dysfunction
  - GH gene deletion with GH antibodies

- **Biochemical validation**
  - Molecular defect GHR gene
  - GH excess, IGF-I and GHBP deficiency
  - Failure to respond to exogenous GH
  - GH binding capacity > 10 mcg hGH/mL (10 mg/L)
Long Term Treatment with IGF-I in Children with Severe Primary IGF-I Deficiency due to GHIS

First Year Growth Response

First-year height velocities versus year-one dosages and Pre-treatment height velocities versus pre-treatment height.

- First-year height velocities: n=61, p=0.0003

JCEM 2007; 92(3): 902-910
Linear Growth

Mean Height Velocity (cm/yr)

± 95% Confidence Interval

N = 58
N = 58
N = 48
N = 38
N = 23
N = 21
N = 20
N = 16
N = 13

Pretreatment
Year 1
Year 2
Year 3
Year 4
Year 5
Year 6
Year 7
Year 8

JCEM 2007; 92(3): 902-910
18 patients with severe primary IGFD treated with rhIGF-1 until final or near-final height

- Followed at the University of North Carolina or the University of Cincinnati, Cincinnati Children’s Hospital Medical Center
- Final or near-final height defined as an estimated bone age of $\geq 13.5$ years (females) or $\geq 15.5$ years (males)

Adult height was predicted using Laron syndrome growth charts

- Assumed growth at average rate for untreated Laron syndrome patients

Patients were treated for a mean of 10.7 years

Patients received a mean rhIGF-1 dose of 112 µg/kg twice daily
Mean Annualized HV by Treatment Year

Cumulative Mean Delta CDC Height SDS by Treatment Year

Bars = 95% confidence limits
Change in Height SDS From IGF-I Treatment Initiation

Mean gain in CDC height SDS during observation was 2.0

Recent Height Relative to the Expected Delta Height

Observed mean gain in height was 13.5 cm more than expected
Individual Patient Growth Curves

Males (n = 11)

Females (n = 7)
Other Effects

- Bone mineral content
- No adverse cardiac effects
- Kidney & spleen growth
- Renal function
- Lean body mass & body fat, insulin sensitivity, lipid metabolism

![Graph showing kidney length vs. height](image-url)

![Table showing metabolic parameters over years](table-url)
## Adverse Events Profile (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Hypoglycemia</td>
<td>49</td>
</tr>
<tr>
<td>Snoring</td>
<td>22</td>
</tr>
<tr>
<td>Hypo-accusis</td>
<td>22</td>
</tr>
<tr>
<td>Tonsillar hypertrophy</td>
<td>22</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>4</td>
</tr>
<tr>
<td>PE tube placement</td>
<td>16</td>
</tr>
<tr>
<td>T &amp; A</td>
<td>11</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td>4</td>
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<tr>
<td>Lipohypertrophy</td>
<td>32</td>
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<tr>
<td>Musculoskeletal pain</td>
<td>20</td>
</tr>
<tr>
<td>Thymus hypertrophy (n = 23)</td>
<td>35</td>
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</table>
Hypoglycemia

- Observed in 49% of subjects
- 47% had history of hypoglycemia PRIOR to therapy
- Most frequently noted in the first month of therapy
- More frequently in youngest patients
- Symptomatic hypoglycemia avoided when meal consumed at IGF-I administration
Facial Growth

Linear Measurements

Angular Measurements

Lateral Cephalogram \((n = 8)\)

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
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<tr>
<td>S-N</td>
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<td>0.0</td>
<td>0.4</td>
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<td>0.7</td>
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<tr>
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<td>0.7</td>
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<tr>
<td>ANS-N</td>
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<td>1.1</td>
<td>1.1</td>
<td>1.6</td>
<td>1.4</td>
<td>1.5</td>
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<tr>
<td>ME-ANS</td>
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<td>0.8</td>
<td>1.0</td>
<td>1.3</td>
<td>1.7</td>
<td>1.6</td>
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<tr>
<td>AR-GO</td>
<td>1.1</td>
<td>0.5</td>
<td>1.2</td>
<td>1.2</td>
<td>1.9</td>
<td>2.2</td>
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<tr>
<td>GO-PG</td>
<td>0.7</td>
<td>1.3</td>
<td>1.4</td>
<td>1.2</td>
<td>1.9</td>
<td>1.4</td>
</tr>
<tr>
<td>PTM-A</td>
<td>1.3</td>
<td>1.3</td>
<td>1.2</td>
<td>1.6</td>
<td>2.1</td>
<td>1.9</td>
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<tr>
<td>S-N-A</td>
<td>0.2</td>
<td>0.2</td>
<td>-0.3</td>
<td>-0.1</td>
<td>0.4</td>
<td>0.3</td>
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<tr>
<td>S-N-B</td>
<td>0.3</td>
<td>0.6</td>
<td>0.5</td>
<td>0.7</td>
<td>1.2</td>
<td>1.0</td>
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<tr>
<td>A-N-B</td>
<td>-0.2</td>
<td>-0.5</td>
<td>-1.0</td>
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<td>-0.9</td>
<td>-0.8</td>
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<tr>
<td>PO-OR / ME-GOI</td>
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<td>-0.3</td>
<td>-0.5</td>
<td>-0.7</td>
<td>-0.3</td>
<td>-0.6</td>
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</table>
Facial Growth
Facial Growth
Conclusion

- The safety and efficacy of rhIGF-1 was evaluated for more than 12 years in 76 subjects with Primary IGFD

- Doses of 80-120 µg/kg given BID by SC injection induced statistically significant increases in height velocity, height velocity SDS, and height SDS

- Statistically and clinically significant improvements in growth were maintained with prolonged dosing

- Hypoglycemia was present but manageable

- IGF-I appears to be effective and relatively safe as a replacement therapy in children with short stature due to severe Primary IGFD, and the availability of IGF-I has been an important development for the management of such patients
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