Evolution of Human Growth Hormone Therapy: Are We Going the Right Direction?

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Disclosure

Steven Chernausek is an investigator in a trial sponsored by Versartis, a producer of long-acting growth hormone.
Objectives

- Review GH biology and action
- Examine traditional GH regimens
- Explore status of long-acting GH preparations
  - Biochemistry/PK
  - Efficacy/Safety
- Future Considerations
Primary Modes of Regulated GH Secretion

Veldhuis, JD et al. Endocrine Reviews 2006
Pubertal Augmentation GH Burst Mass

Veldhuis, JD et al Endocrine Reviews 2006
GH Receptor Function

- Fat & CHO Metabolism
- Growth
- GH Feedback

GHR

IGF-1

- Insulin-like
- Growth
- GH Feedback

IGFBP-3

- IGF Clearance & Distribution
- Cell Proliferation
GH Deficiency

- Slow Linear Growth
- Severe Short Stature
- Decreased Muscle Mass
- Low Bone Mineral
- Increased Fat
- Hypoglycemia
- Micropenis
- Hypogonadism
- CNS changes
Treating GH Deficiency

To provide human growth hormone to the patient in a way that restores all biological actions of GH in the safest and most acceptable manner.
Who was the first to use hGH in a human?

A) Maurice Raben ✔️
B) Ron Rosenfeld
C) William Daughaday
D) Mark McGwire
Fig. 1. Response of a pituitary dwarf to treatment with human growth hormone.
Things We Thought We Knew

- hGH has to be given IM
- Thrice weekly was optimal frequency
- Only the truly GH deficient should benefit
- No need for GH after epiphyseal fusion
GH as Therapeutic Agent Today

- **Positive Attributes**
  - Clean preparation
  - Highly effective in GHD
  - Wide therapeutic window
  - Administration uncomplicated
  - Excellent Safety Record
  - Abundant

- **Challenges and Concerns**
  - Daily injection - pain and compliance
  - Optimal dosing ?
  - Long-term adverse effects
  - Cost
GH Rx in Isolated GHD

Reiter et al J Clin Endocrinol Metab 2006
GH treatment in Children - Compliance with current regimens

  - Non-adherence = 5-82 % depending on nature of assessment etc

- Cutfield et al (*Plos One* 6:e1623, 2011)
  - 177 patients
  - Vial counting method
  - 66% of patients missed > 1 injection per week
Effect of Compliance on Growth Response

Cutfield et al (Plos One 6:e1623, 2011)
Alternatives to daily injections

- Inhaled GH
- Nasal GH
- Rectal GH
- Transdermal GH
- Long Acting GH

How to Make Long-acting GH

- Delay absorption
  - Matrix (Lupron)
  - Physical-chemical change e.g. crystal
  - Patch equivalent

- Prolong plasma clearance
  - Make it bigger (fusion)
  - Bind it to something

- Combination of above
Advancing GH Therapy with Long Acting Product

- Efficacy (Growth and Metabolic) equal or better than daily GH
- Minimum frequency is weekly
- Simple preparation/administration
- No more painful than standard injection
- Non-antigenic
- Safety profile equal of better than daily GH
Response to sc GH in normal adults

Keller et al. EJE 2007
1\textsuperscript{st} Long Acting GH
Nutropin Depot PK

Kemp SF et al J Clin Endocrinol Metab 2004
Sustained Release GH: LB03002
PK and PD in GHD children

- GH in matrix (Na hyaluronidate/lecithin)
- Dispersed in oil base (MCT) prior to injection
- Compared 3 doses LB03002 to standard sc GH 0.030 mg/kg

Peter F et al. EJE 2009
PK measures on LB03002

Peter F et al.  EJE 2009
PK measures on LB03002

<table>
<thead>
<tr>
<th>Agent</th>
<th>$T_{\text{max}}$ (h)</th>
<th>$C_{\text{max}}$ (ng/ml)</th>
<th>$T_{\frac{1}{2}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sc 0.03 mg/kg</td>
<td>3.4</td>
<td>25</td>
<td>2.6</td>
</tr>
<tr>
<td>LB 0.2 mg/kg</td>
<td>10.5</td>
<td>37</td>
<td>12</td>
</tr>
<tr>
<td>LB 0.5 mg/kg</td>
<td>14.4</td>
<td>75</td>
<td>10</td>
</tr>
<tr>
<td>LB 0.7 mg/kg</td>
<td>17.6</td>
<td>109</td>
<td>12</td>
</tr>
</tbody>
</table>

Peter F et al. EJE 2009
IGF-1 response to LB03002

Peter F et al. EJE 2009
Long-acting GH Trial in GHD
LB03002 once-weekly

- Prepubertal children with GHD
- Naïve to GH
- 0.03 mg/k/d sc GH (n=91)
- or 0.5 mg/k/wk LB03002 (n=89)
- 1st 12 months comparison
- 2nd 24 months extension on LB03002

Khadilkar et al J Clin Endocrinol Metab 2014
IGF-I with LB03002

Khadilkar et al J Clin Endocrinol Metab 2013
Growth with LB03002

Khadilkar et al. *J Clin Endocrinol Metab* 2013
Growth with LB03002

Khadilkar et al *J Clin Endocrinol Metab* 2013
A novel long-acting human growth hormone fusion protein (vrs-317):

- Fusion protein GH + hydrophilic amino acids on C and N termini (119kDa)
- Decreased bioactivity relative to native
- Prolonged action due to decreased clearance
VRS-317

PK

PD
In vitro bioactivity VRS-317
MOD-4023: hGH with HCG
c terminal peptide extension

12 month treatment in childhood GHD

<table>
<thead>
<tr>
<th></th>
<th>MOD-4023</th>
<th>Daily GH</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Age</td>
<td>7.1 ± 2.5</td>
<td>6.6 ± 1.7</td>
</tr>
<tr>
<td>Dose (mg/k/wk)</td>
<td>0.66</td>
<td>0.24</td>
</tr>
<tr>
<td>Baseline Ht (SDS)</td>
<td>-4.1 ± 1.6</td>
<td>-4.4 ± 1.7</td>
</tr>
<tr>
<td>Baseline HV (SDS)</td>
<td>-3.0 ± 1.5</td>
<td>-3.0 ± 1.9</td>
</tr>
<tr>
<td>Growth Response (cm/yr)</td>
<td>11 ± 1</td>
<td>11 ± 1</td>
</tr>
</tbody>
</table>

Hart et al  ENDO 2015
## Long-acting GH Preparations

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mech to Prolong</th>
<th>Frequency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutropin-Depot</td>
<td>Sustained Release</td>
<td>1-2X/mo</td>
<td>Approved/Withdrawn 2004</td>
</tr>
<tr>
<td>LB03002</td>
<td>Sustained Release</td>
<td>Weekly</td>
<td>40 % GH Aby ? significance</td>
</tr>
<tr>
<td>PEGylated-GH</td>
<td>Prolonged T1/2</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>VRS-317</td>
<td>Prolonged T1/2</td>
<td>2X/mo</td>
<td>C &amp; N term ext</td>
</tr>
<tr>
<td>ACP-001/Trans Con</td>
<td>Sustained Release</td>
<td>Weekly</td>
<td>Prodrug: linked to PEG</td>
</tr>
<tr>
<td>MOD-4023</td>
<td>Prolonged T1/2</td>
<td>Weekly</td>
<td>hGH-CTP-HCG</td>
</tr>
<tr>
<td>ALTU-238</td>
<td>Sustained Release</td>
<td>?</td>
<td>crystalline GH ? status</td>
</tr>
<tr>
<td>NNC0195-0092</td>
<td>Prolonged T1/2</td>
<td>Weekly</td>
<td>Albumin bound</td>
</tr>
<tr>
<td>HM10560A</td>
<td>Prolonged T1/2</td>
<td>q1-2 weeks</td>
<td>hGH- fc IG</td>
</tr>
</tbody>
</table>
GHBP & GH as Long-acting Agonist

1. Extracellular receptor
   Flexible GHR N-terminus
   Ligand
   GH linked to GHBP (expressed as single construct)

2. Intermolecular interaction
   Physiological pool of protected GH (dynamic equilibrium)

3. GH available to bind to natively expressed receptor (long acting in vivo effect)

Transdermal GH Delivery

(a) ZP-Drug coated Patch

(b) ZP-Patch and applicator

(c) 60× Magnified section of a rhGH coated microneedles

(d) Front view of an individual rhGH coated microneedle (250× magnification)

Considerations for Long-acting GHs

- Interaction with circulating GH BP
- Lactogenic properties
- Lack of diurnal variation
- Lack of pulsatility
- Differential effect on GH target tissues
Intermittent vs. Continuous GH in mice (daily sc vs. minipump)

Diaz et al J Endocrinol 2014
Intermittent vs. Continuous GH in mice (daily sc vs. minipump)

- Intermittent in females
  - Increased hepatic EGF R
  - Augmented response to EGF
  - Increased cell-proliferation proteins

- Continuous GH in males
  - Decreased Hepatic EGF R
  - Decreased response to EGF
  - Decreased early gene expression

Diaz et al J Endocrinol 2014
Pulsatile vs. Continuous GH in Obese Adults

- 4 men and 5 women
- GH 0.5 mg/m²/d for 3 days

Assessed
- Lipolysis
- Hepatic glucose production
- Insulin sensitivity
- Plasma IGF1
- Skeletal muscle IGF1 mRNA

Surya S et al J Clin Endocrinol Metab 2009
Pulsatile vs. Continuous GH in Obese Adults

Surya S et al J Clin Endocrinol Metab 2009
Pulsatile vs. Continuous GH IGF-1 response

Surya S et al J Clin Endocrinol Metab 2009
Pulsatile vs. Continuous GH: CHO measures

Surya S et al J Clin Endocrinol Metab 2009
Pulsatile vs. Continuous GH: Lipolysis

Surya S et al J Clin Endocrinol Metab 2009
Continuous vs. Intermittent GH

- 14 GHD on standard GH Rx as hs injection
- 7 switched to continuous sc by pump for 6 mo
- Evaluated various metabolic and hormonal parameters

Laursen et al J Clin Endocrinol Metab 2001
## Continuous vs. Intermittent GH

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pump</th>
<th>6 mo</th>
<th>Injections</th>
<th>6 mo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Base</td>
<td></td>
<td>Base</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum IGF-I</td>
<td>175 ± 36</td>
<td>209 ± 50</td>
<td>217 ± 23</td>
<td>205 ± 30</td>
<td>0.34</td>
</tr>
<tr>
<td>Serum IGFBP-3</td>
<td>3186 ± 295</td>
<td>3076 ± 362</td>
<td>3342 ± 232</td>
<td>3146 ± 210</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>FFA (μmol/L)</strong></td>
<td>610.4 ± 71.5</td>
<td>510.6 ± 85.8</td>
<td>388.4 ± 33.9</td>
<td>393.4 ± 38.5</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>4.90 ± 0.39</td>
<td>4.89 ± 0.37</td>
<td>4.50 ± 0.13</td>
<td>4.71 ± 0.12</td>
<td>0.57</td>
</tr>
<tr>
<td>Fasting serum insulin (pmol/L)</td>
<td>87.4 ± 27.9</td>
<td>83.6 ± 42.7</td>
<td>47.1 ± 10.4</td>
<td>36.6 ± 6.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Si (10^{-5}(pmol/L)·min)</td>
<td>5.35 ± 1.90</td>
<td>9.55 ± 3.45</td>
<td>5.24 ± 1.49</td>
<td>6.89 ± 1.27</td>
<td>0.71</td>
</tr>
<tr>
<td>Urine NTX (nmol)/creatinine (mmol) ratio</td>
<td>70.9 ± 11.8</td>
<td>64.3 ± 11.0</td>
<td>62.3 ± 11.5</td>
<td>56.7 ± 9.6</td>
<td>0.77</td>
</tr>
<tr>
<td>Fat mass (kg (%))</td>
<td>23.3 ± 3.9  (28.6)</td>
<td>23.7 ± 3.5  (28.7)</td>
<td>17.3 ± 1.5  (23.6)</td>
<td>18.2 ± 1.5  (24.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>53.8 ± 5.0</td>
<td>54.7 ± 5.4</td>
<td>54.1 ± 3.6</td>
<td>54.2 ± 3.5</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Laursen et al J Clin Endocrinol Metab 2001
Body Comp Effects of LB03002: GHD adults for 26 weeks

*B < 0.001 for treatment difference

Biller BMK, et al J Clin Endocrinol Metab 2011
OUCH!
Adherence in Dental Hygiene

- What percentage of 14-18 year olds don’t floss at all?
  A. 20
  B. 40
  C. 50
  D. 70  ✓
  E. 90

- What percent brush twice a day?
  64

Ashkenazi et al; Odontology 2012
Bisphosphonates in Women with Osteoporosis (n = 10,000)

### Daily
- Adherence = 54%
- Persistence = 19%

### Weekly
- Adherence = 63%
- Persistence = 22%

Take Home Messages

- Long-acting GH preparations show promise and would be advance
- Though understudied, pulsatile vs. continuous doesn’t seem to be major issue
- Ease of administration and efficacy will be very important
- Need to examine all effects, not just skeletal growth
- Long term safety paramount
Thank you