Strategies to Maximize Growth in Puberty

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Dr. Mauras has disclosed the following financial relationships. Any real or apparent conflicts of interest related to the content of this presentation have been resolved.

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<tr>
<th>Affiliation / Financial Interest</th>
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<td>Drug Supply Agreement</td>
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Dr. Mauras has documented that this presentation involves comments or discussion of off-label, or investigational use of aromatase inhibitors.
Starting treatment of children with significant short stature during puberty is limited by the tempo of epiphyseal fusion as impacted by sex steroids.

Estrogens are principally responsible for growth plate fusion in puberty, decreasing progenitor cells in the resting zone chondrocytes and increasing structural senescence.
Martha P, JCEM 1989
High Dose Recombinant Human Growth Hormone (GH) Treatment of GH-Deficient Patients in Puberty Increases Near-Final Height: A Randomized, Multicenter Trial

NELLY MAURAS, KENNETH M. ATTIE, EDWARD O. REITER, PAUL SAENGER, JOYCE BAPTISTA, AND THE GENENTECH, INC., COOPERATIVE STUDY GROUP

JCE&M, 85; 2000

Growth Velocity

Height SDS

3yrs: +3.6cm
4yrs: +5.7cm
Effects of GH/GnRHa vs. GH only Rx in GHD pubertal children

adult height gain ≈10 cm

N=21

Mericq et al, JCEM 2000
Effects of Combined Gonadotropin-Releasing Hormone Agonist and Growth Hormone Therapy on Adult Height in Precocious Puberty: A Further Contribution*  Pucarelli I, JPEM 2003

Adult Height in Short Children Born SGA Treated with Growth Hormone and Gonadotropin Releasing Hormone Analog: Results of a Randomized, Dose-Response GH Trial  Lem AJ, JCEM 2012

Effectiveness of the Combined Recombinant Human Growth Hormone and Gonadotropin-Releasing Hormone Analog Therapy in Pubertal Patients with Short Stature due to SHOX Deficiency  Scalco RC, JCEM 2010

In GH-treated children for GHD, SGA, SHOX, with low PAH, adding GnRHa results in 5-10 cm gain
Sex Steroids Dual Effects on Growth

Estrogen

GH (IGF-I)

progenitor cells in the resting zone chondrocytes
structural senescence


+ ERα

Linear Growth

Linear Growth

Linear Growth
Anastrozole  
![Chemical structure of Anastrozole](image1)  
1mg

Letrozole  
![Chemical structure of Letrozole](image2)  
2.5mg

Exemestane  
![Chemical structure of Exemestane](image3)  
25mg
Pharmacokinetics and Dose Finding of a Potent Aromatase Inhibitor, Aromasin (Exemestane), in Young Males

NELLY MAURAS, JOHN LIMA, DEVAL PATEL, ANNIE RINI, ENRICO DI SALLE, AMBROSE KWOK, AND BARBARA LIPPE

Pharmacokinetics and Pharmacodynamics of Anastrozole in Pubertal Boys with Recent-Onset Gynecomastia

Nelly Mauras, Kim Bishop, Debbie Merinbaum, Ugochi Emeribe, Felix Agbo, and Elizabeth Lowe
Anastrozole vs GnRHa: Comparison

Inhibition of Estrogen Biosynthesis with a Potent Aromatase Inhibitor Increases Predicted Adult Height in Boys with Idiopathic Short Stature: A Randomized Controlled Trial

Matti Hero, Ensio Norjavaara, and Leo Dunkel

N=31 boys with ISS
Age: 9-14.5 yrs, 27/31 prepubertal
Rx 2.5mg/d of Letrozole or Placebo x 2yrs

Bone age progression (deltaBA/deltaCA)

Predicted adult height

$P < 0.001$
N=52 boys with GHD
Age: 14.0 ± 0.2 yrs, all pubertal
Rx 1.0mg/d of Anastrozole or PL x 3yrs or cessation of growth
Net gain in predicted height vs. baseline

**Anastrozole**
- 12mo: +1.2 cm
- 24mo: +4.5 cm
- 36mo: +6.7 cm

**Placebo**
- 12mo: +0.3 cm
- 24mo: +1.0 cm
- 36mo: +1.0 cm

* vs. placebo

Mauras, et al JCEM 2008
Safety

Incidence of adverse events:
- Head & neck
- Respiratory
- GI
- GU
- Musculoskeletal

Safety labs:
- CBC
- UA
- Liver profile
- UA
- Glucose

were the same in both groups
CA = 5 7/12yrs
BA = 12yrs

Initial Testosterone:
185ng/dl
(16.8nmol/L)
CA = 5 7/12 yrs  
BA = 12 yrs

CA = 12 4/12 yrs  
BA = 15 yrs

Initial Testosterone:  
185ng/dl  
(16.8nmol/L)
<table>
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<tr>
<th>Adult HT</th>
<th>MPH</th>
<th>Dad’s HT</th>
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<tbody>
<tr>
<td>1) 186.5cm (73.4”)</td>
<td>179cm (70.5”)</td>
<td>188cm (74”)</td>
</tr>
<tr>
<td>2) 183.6cm (72.3”)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3) 168cm (65.3”)</td>
<td>167.6cm (66”)</td>
<td>165cm (65”)</td>
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Bicalutamide plus Anastrozole for the Treatment of GIP in Boys


*J Ped Endo Metab 23; 999, 2010*

- N = 14
- Age: 3.9 ± 1.9 yrs
- BA: 10.3 ± 3.8 yrs
Aromatase inhibitors have been studied in males with
- Idiopathic short stature
- GH deficiency
- Testotoxicosis
- Gynecomastia
- Oligospermia
A randomized controlled trial of the use of aromatase inhibitors, alone and in combination with GH in adolescent boys with idiopathic short stature

Nelly Mauras¹, Judith Ross², Priscila Gagliardi¹, Debbie Merimbaum¹, Jobayer Hossain³, Miles Yu⁴, Ravinder Singh⁵, Joseph Permuy¹, Ligeia Damaso¹, Ximena Gaete⁶, Veronica Mericq⁶

Jacksonville, FL¹, Philadelphia, PA², Wilmington, DE³, Orlando, FL⁴, and Mayo Clinic, Rochester, MN⁵ and University of Chile, Santiago, Chile⁶
Specific Aims

In adolescent boys with idiopathic short stature treated with AIs (anastrozole and letrozole), vs. GH, vs. AI/GH -

To assess -

Primary

- impact on increasing adult height potential
- bone density and morphology
- lean body mass accrual

Secondary

- degree of aromatase suppression using letrozole vs. anastrozole using highly sensitive LCMSMS assays
- differences in quality of life
Inclusion Criteria

- Males: Ages 12 – <18 years
- Bone age $\leq 14 \frac{1}{2}$ yrs
- ISS
  - HT $\leq -2SD$
  - No other identifiable pathology
- Presence of puberty
- Birth weight AGA
*Anthropometry, BA, DEXA, Lateral spine, Hormones, Safety Labs, QoL

ClinicalTrials.Gov NCT01248416
Results presented at Endocrine Society meeting
Boston, MA  April 2016
OR31-4
Summary:
In growth-retarded adolescents with ISS

AI: +14.0 ± 0.8 cm
GH: +17.1 ± 0.9 cm
AI/GH: +18.9 ± 0.8 cm
HTSDS -2.0 (CDC data): +10.2 cm

- Near final height gain (CA 17.3 yr, BA 15.3 yr)
  AI: +17.3 ± 1.5 cm
  GH: +20.0 ± 1.5 cm
  AI/GH: +22.4 ± 1.4 cm
  HTSDS -2.0 (CDC data): +12.8 cm
  Many of these subjects have residual height potential

- The combination of GH and AI appears more anabolic enhancing FFM accrual than each compound alone

- Safety profile for all programs was very good
In growth-retarded males who are in puberty:

- High dose GH, GnRHa+GH have been shown to increase height potential

- Aromatase inhibitors in combination with GH for 2-3 years also offer an alternative to the treatment of males with ISS who are in puberty
Supported by
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W.J. Wadsworth

Our thanks to the patients and their families