The ZOMATRIP study
Four year combination therapy of GH and GnRHa in girls with a short predicted adult height during early puberty

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A 4 year combination treatment of GH and triptorelin in girls with a final height prediction below 2.5 SDS was safe and significantly increased height (mean 12.0 ± 2.6 cm) above the predicted adult height. This outcome must be weighed against the marked financial and psychological burden of the treatment.

Participants
24 girls age 8-13 y were recruited of which 18 girls completed the 4 year treatment phase and 16 girls completed the study per protocol (PP). Reasons to drop out were: doping concerns in sports (1), no wish to postpone puberty any further after 2.5 or 3 years (3), poor compliance (1), premature stop of GH injections (1) and loss of follow-up after the treatment phase.

Background
A combination of growth hormone and a GnRH agonist is sometimes used to improve adult height in children with a poor height prediction but there are few studies to support this practice.

Study Design
Open label, 6 study centers in Belgium

Participants:
inclusion criteria:
- female
- early puberty (breast stage M2-M3)
- bone age < 12.0 y
- adult height prediction < 151.0 cm (2.5 SDS)
- normal body proportions (SH/H within 2SDS (Gerver) informed consent
- exclusion criteria:
- syndromic short stature
- adopted children
- disease or chronic use of medication that interferes with growth

Intervention:
4 year combination therapy of GH (Zomacton) transcutaneous 50 µg/kg/day & Triptorelin (Decapetyl SR) IM injections 3.75 mg/month

Methods
standard anthropometric measurements every 6 months during the intervention period, then every year until final height
- height SDS calculations based on Flemish growth curves (Roelants 2009)
- patient diary for compliance, adverse events and medication use
- lab tests for safety and efficacy/compliance every year
- bone age readings (Greulich and Pyle method
- height predictions: Bayley-Pinneau method
- adult height definition: height at bone age ≥ 16 years

Results

Adult height outcome
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Table 1 Parameters at the start of treatment

<table>
<thead>
<tr>
<th>Girls per protocol n=16</th>
<th>median</th>
<th>range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth length (cm)</td>
<td>47.0</td>
<td>45-50.5</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2820</td>
<td>2390-3500</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39</td>
<td>35-41</td>
</tr>
<tr>
<td>Mother’s height(cm)</td>
<td>158.8</td>
<td>150-168</td>
</tr>
<tr>
<td>(SDS)</td>
<td>-1.53</td>
<td>-2.79 -0.26</td>
</tr>
<tr>
<td>Father’s height (cm)</td>
<td>170.0</td>
<td>162.0-181.1</td>
</tr>
<tr>
<td>(SDS)</td>
<td>-1.65</td>
<td>-2.80 -0.0</td>
</tr>
<tr>
<td>Age at start (year)</td>
<td>11.2</td>
<td>(8.0-13.2)</td>
</tr>
<tr>
<td>Height at start (cm)</td>
<td>132.4</td>
<td>(119.0-150.2)</td>
</tr>
<tr>
<td>(SDS)</td>
<td>-2.48</td>
<td>-3.62 -0.99</td>
</tr>
<tr>
<td>Bone age (year)</td>
<td>10.5</td>
<td>(9.0-12)</td>
</tr>
<tr>
<td>Predicted adult height(cm) (SDS)</td>
<td>147.9</td>
<td>(142.5-150.2)</td>
</tr>
<tr>
<td></td>
<td>-5.21</td>
<td>-10.72</td>
</tr>
</tbody>
</table>

Height evolution
In the PP group, height (mean ± SD) increased from 131.3 ± 4.1 cm to 155.3 ± 4.7 cm and an adult height of 159.8 ± 4.8 cm. Mean height SDS rose from -2.25 ± 0.73 the start of the treatment period to -1.36 ± 0.81 at the end of the treatment period and further increased to -1.10 ± 0.76 at adult height. (Fig.1).

Bone age
Bone age increased by 2.4 ± 0.5 yrs from 10.4 ± 0.6 yrs to 12.8 ± 0.6 yrs during the 4 y treatment phase. Bone age progression accelerated afterwards to about 1.3 yrs per calendar year.

Adult height prediction after 4 years of treatment
At the end of the treatment period, final height prediction (162.4 ± 5.5 cm) was 14.8 ± 4.2 cm above the predicted value at the start of treatment (147.6 ± 2.0 cm). Due to the bone age acceleration, adult height was 2.6 cm lower than predicted at the end of the treatment period.

Adverse events
The clinical adverse events consisted of injection site reactions (pain, bruising, scarring) and common health problems for this age group.

There were 3 serious adverse events (SAE):
- pyelonephritis needing IV antibiotics
- fracture of metatarsals in ballet dancer (possibly related to the intervention)
- depression, 2 years after the stop of treatment

Laboratory measurements
Mean serum IGF-1 levels peaked from 326 ± 128 ng/ml at start to 714 ± 228 ng/ml after 2 years of treatment. One year post treatment IGF-1 decreased again to 521 ± 164 ng/ml

Fasting insulin levels increased 2.5 fold but fasting glucose and HbA1C levels remained within the normal range. Fasting insulin normalized again after the stop of treatment. One obese patient had an impaired glucose tolerance at the start, which remained stable throughout the study.

References

Zomacton has EU/DACTR number 2007-002247-70 and is registered on Clinical Trials.gov NCT00402444

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