Catch-up Growth During Tocilizumab Therapy for Systemic Juvenile Idiopathic Arthritis: 2-Year Data From a Phase 3 Clinical Trial

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Disclosures

• F. De Benedetti: Abbott, BMS, Novartis, Novimmune, Pfizer, Roche Pharmaceuticals, SOBI
• N. Ruperto: Abbott, ACRAF, BMS, Centocor, Novartis, Pfizer, Roche Pharmaceuticals, Xoma
• G. Horneff: Abbott, Chugai, Novartis, Pfizer, Roche Pharmaceuticals
• K. Onel: Merck, Roche Pharmaceuticals
• J. Frane: Consultant to Genentech and to Ipsen Biopharmaceuticals
• A. Kenwright: Roche Pharmaceuticals
• K. N. Bharucha: Genentech
• A. Martini: Abbott, ACRAF, BMS, Centocor, Novartis, Pfizer, Roche Pharmaceuticals, Xoma
• D. Lovell: Abbott, Amgen, Arthritis and Rheumatism, Astra-Zeneca, BMS, Centocor, Forest Research, Genentech, Hoffmann-La Roche, National Institutes of Health, Novartis, Pfizer, Regeneron, UCB, Wyeth, Xoma
• G. Espada, V. Gerloni, B. Flato, B. Myones, T. H. Lipman: Nothing to disclose

Systemic Juvenile Idiopathic Arthritis Growth Defect

“…general arrest of development when the disease begins before second dentition…” G. F. Still (1897)

Chronic Inflammation and Stunted Growth

• sJIA: occurs during periods of disease activity
• Crohn’s disease: growth defect before onset of intestinal symptoms and related to the inflammatory activity of the disease
• Cystic fibrosis: growth defect related to frequency and severity of pulmonary infections

A factor(s) produced during the inflammatory response affects linear growth

Impact of High Levels of IL-6 on the Growing Skeleton: Lessons From IL-6 Transgenic Mice

• Low levels of IGF-I secondary to increased IGFBP-3 proteolysis
• Impaired development and ossification of epiphysis
• Impaired mineralization apposition rate
• Increased osteoclast and increased osteoblast activity

IL-6TG

IL-6TG

Aim

- To evaluate in patients with sJIA treated with TCZ in the TENDER study:
  - Growth rates
  - Changes in IGF-I levels
  - Changes in soluble markers of osteoclast and osteoblast activities
  - Relationship with disease activity and with corticosteroid dose

TCZ, tocilizumab.

TENDER Study Design

Double-blind Period (Part 1)

- TCZ 8 or 12 mg/kg × 6
- 0 2 4 6 8 10 12 Weeks
- Day 3

- Escape with rescue therapy

Open-label Period (Parts 2 and 3)

- TCZ 8 or 12 mg/kg every 2 weeks for 92 weeks (subsequent 3-year extension added)

TENDER Baseline Growth Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N = 103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male, n</td>
<td>53/50</td>
</tr>
<tr>
<td>Age, yr, mean ± SD</td>
<td>10.0 ± 4.5</td>
</tr>
<tr>
<td>Tanner stage &lt;4, n (%)</td>
<td>86 (83)</td>
</tr>
<tr>
<td>Duration of sJIA, yr, mean ± SD</td>
<td>4.8 ± 4.0</td>
</tr>
<tr>
<td>Height SD score (WHO), mean ± SD</td>
<td>-2.0 ± 1.9</td>
</tr>
<tr>
<td>BMI SD score (WHO), mean ± SD</td>
<td>0.8 ± 1.4</td>
</tr>
</tbody>
</table>

BMI, body mass index; SD, standard deviation; WHO, World Health Organization.

Baseline height measured between 9 and 24 months before TCZ baseline.

Pretreatment Height Velocity versus Baseline Age

Patients with height measured between 9 and 24 months before TCZ baseline.

For each gender, the curve represents the expected height velocity based on WHO norms for height.
Majority of females (n = 41; 85%) and males (n = 36; 73%) experienced above-normal height velocities.

<table>
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<tr>
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<th>Value</th>
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BMI: body mass index; SD: standard deviation; WHO: World Health Organization.
Baseline = start of tocilizumab.
Excluding patients who received somatropin.

For each gender, the curve represents the expected height velocity based on WHO norms for height.

**Osteocalcin/C-Telopeptide of Type 1 Collagen (OC/CTX-1) Ratio**

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<th>Osteocalcin</th>
<th>CTX-1</th>
<th>OC/CTX-1 Ratio</th>
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<tr>
<td>Baseline</td>
<td>35 ± 26</td>
<td>0.65 ± 0.34</td>
<td>54 ± 27</td>
</tr>
<tr>
<td>Year 2</td>
<td>95 ± 40*</td>
<td>1.45 ± 0.51*</td>
<td>66 ± 20*</td>
</tr>
</tbody>
</table>

* p < 0.01 vs baseline.
Patients with both baseline and year 2 OC and CTX-1 and Tanner <4 at baseline: n = 46.
First Year Height Velocity versus JADAS-71 at Year 1

Spearman Rank Correlation = -0.41
p = 0.0002

JADAS-71, juvenile arthritis disease activity score in 71 joints.

Multiple Regression for First Year Height Velocity

Regressor variables considered
- Gender
- Tanner stage at baseline
- BMI SD score at baseline
- Height SD score at baseline
- Age at baseline
- Duration of sJIA
- JADAS-71 at month 12
- Mean corticosteroid dose

Multiple Regression for First Year Height Velocity

Regressor variables not statistically significant (p > 0.05): Gender, Tanner stage at baseline, BMI SD score at baseline, Duration of sJIA, JADAS-71 at month 12
Regressor variables statistically significant (p ≤ 0.0020)

Conclusions
- Height was markedly reduced at study entry
- Height SD scores were significantly correlated with disease duration
- TCZ treatment was associated with catch-up growth
- TCZ treatment was associated with beneficial effects
  - on the growth hormone axis (increase in IGF-1 levels)
  - on bone metabolism (improved osteoblast and osteoclast activities)
- Height velocity during TCZ treatment is related to disease activity, CS dose, and age at baseline
**Height Velocity and Height SD Score**

<table>
<thead>
<tr>
<th></th>
<th>Height Velocity, cm/yr</th>
<th>Height SD Score</th>
<th></th>
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<tr>
<td></td>
<td>Mean ± SD (n)</td>
<td>WHO Normal Mean</td>
<td>p Value vs WHO</td>
<td>p Value vs Pre-TCZ</td>
<td>Mean ± SD (n)</td>
<td>p Value vs Previous Year</td>
</tr>
<tr>
<td><strong>TCZ baseline</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4 ± 2.2</td>
<td>(33)</td>
<td>6.0</td>
<td>&lt;0.0001</td>
<td>-2.2 ± 2.0 (81)</td>
<td>&lt;0.0001</td>
<td>-</td>
</tr>
<tr>
<td><strong>Year 1</strong></td>
<td></td>
<td>6.7 ± 2.5 (81)</td>
<td>&lt;0.0001</td>
<td>-1.96 ± 1.9 (81)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Year 2</strong></td>
<td></td>
<td>7.1 ± 2.9 (71)</td>
<td>&lt;0.0001</td>
<td>-1.61 ± 2.0 (71)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
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Patients with ≥1 year of TCZ who had Tanner stage <4 at baseline.
Baseline height velocity measured during period prior to TCZ baseline.
Comparisons made using paired t-tests.
Height velocities for year 1 and year 2 measured over at least 9 months.

**Osteocalcin/C-Telopeptide of Type 1 Collagen (OC/CTX-1) Ratio**

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<td>95 ± 40*</td>
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<tr>
<td><strong>Year 2 minus baseline</strong></td>
<td>60 ± 46</td>
<td>0.80 ± 0.51</td>
<td>12 ± 30</td>
</tr>
<tr>
<td><strong>Paired t-test p value</strong></td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0082</td>
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* p < 0.01 vs baseline.
Patients with both baseline and year 2 OC and CTX-1 and Tanner <4 at baseline: n = 48.
IGF-1 SD Scores

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<th>Paired t-Test p Value for Difference from 0</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>-0.9 ± 1.7 (70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Year 1</td>
<td>-0.3 ± 1.4 (81)</td>
<td>0.1300</td>
</tr>
<tr>
<td>Year 2</td>
<td>-0.5 ± 1.3 (56)</td>
<td>0.2936</td>
</tr>
<tr>
<td>Year 1 minus baseline</td>
<td>0.6 ± 1.5 (53)</td>
<td>0.0071</td>
</tr>
<tr>
<td>Year 2 minus baseline</td>
<td>0.8 ± 1.9 (48)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

Male Patient Treated With 8 mg/kg TCZ

Female Patient
Placebo -> 8 mg/kg TCZ

Female Patient
Placebo -> 8 mg/kg TCZ

Female Patient
8 mg/kg TCZ

Patients with ≥1 year of TCZ who had Tanner stage <4 at baseline.