Characteristics of responders and poor responders to Increlex® therapy – data from children enrolled in the European Increlex® Growth Forum Database (EU-IGFD)

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Introduction

- The growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis is crucial for affecting post-natal growth and is defective in severe primary IGF-1 deficiency (SPIGFD) (Figure 1).
- Increlex® (mecasermin [rDNA origin] injection) is recombinant human IGF-1 (rhIGF-1) approved for the treatment of SPIGFD.
- European Medicines Agency (EMA) criteria for rhIGF-1 therapy in SPIGFD are:
  - Height standard deviation score (SDS) ≤ -3
  - IGF-1 serum concentration < 2.5th percentile
  - GH sufficiency
  - Exclusion of acquired forms of IGF-1 deficiency, such as malnutrition, hypothyroidism or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

Study population

- Cut-off date for the database: 6th October 2015.
- 221 patients enrolled from 10 countries (Figure 2).
- 93 NPP were eligible for this analysis.

- Responders defined as: Year 1 change in height SDS ≥ 0.3; n=55 (59%).
- Poor responders defined as: Year 1 change in height SDS ≤ 0.3; n=38 (41%).

- We have previously suggested to define a responder to rhGH therapy as anyone with a Year 1 change in height percentiles of ≥ 20.5. This difference should reflect the fact that patients with Laron syndrome (SPIGFD caused by a GH receptor defect) gain less height with rhIGF-1 treatment than do patients with severe GH deficiency receiving rhGH.

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=55)</th>
<th>Poor responders (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boys, n (%)</td>
<td>32 (58)</td>
<td>25 (66)</td>
</tr>
<tr>
<td>Larsons syndrome, n (%)</td>
<td>7 (13)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Age at first dose, mean (SD) years</td>
<td>7.2 (3.0)</td>
<td>10.1 (3.9)</td>
</tr>
<tr>
<td>Weight SDS at first dose, mean (SD)</td>
<td>-5.2 (2.0)</td>
<td>-5.5 (2.0)</td>
</tr>
<tr>
<td>Height SDS at first dose, mean (SD)</td>
<td>-5.2 (0.4)</td>
<td>-5.5 (0.3)</td>
</tr>
<tr>
<td>Mid parental adult height, mean (SD) cm</td>
<td>165.7 (8.2)</td>
<td>168.2 (5.3)</td>
</tr>
<tr>
<td>IGF-1 concentration, mean (SD) ng/ml</td>
<td>84.7 (69.1)</td>
<td>108.8 (78.9)</td>
</tr>
</tbody>
</table>

EU Increlex® Growth Forum Database registry

- As part of the Risk Management Plan, patients starting rhIGF-1 therapy should be registered on the European Increlex® Growth Forum Database (EU-IGFD) registry.
- Multicentre, open-label, observational study.
- Initiated in December 2008 to monitor long-term safety (primary objective) and effectiveness (secondary objective) of Increlex® (rhIGF-1) in children with growth failure in 10 countries in Europe.
- Ongoing and recruiting new patients, using electronic case report form (eCRF) data collection.

Objectives

- To better understand the determinants which are influencing the response to Increlex® therapy in treatment-naive prepubertal patients (NPP):
  - Describe baseline characteristics of patients according to the level of response to Increlex® therapy
  - Describe effectiveness and safety according to the level of response to Increlex® therapy.

Conclusions

- Response to treatment with Increlex® in NPP is positively related to a younger age at treatment initiation, poor responders being older.
  - No other predictor of response to Increlex® in NPP has been identified.
- The safety profile is consistent with previous reports, independent of the level of response to Increlex®.
- On a group level, poor responders do not show any significant catch-up growth over the second year of treatment.
  - The first-year response to Increlex® should be evaluated and a decision whether to continue treatment taken.

Treatment characteristics

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=55)</th>
<th>Poor responders (n=38)</th>
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<tbody>
<tr>
<td>Treatment duration, median (IQR) years</td>
<td>1.0 (1.0–1.0)</td>
<td>1.0 (1.0–1.4)</td>
</tr>
<tr>
<td>Dose at initiation, median (IQR) µg/kg/rd</td>
<td>40 (30; 50)</td>
<td>40 (30; 40)</td>
</tr>
<tr>
<td>Dose at Year 1, median (IQR) µg/kg/rd</td>
<td>100 (80; 100)</td>
<td>100 (80; 100)</td>
</tr>
<tr>
<td>Dose at Year 2, median (IQR) µg/kg/rd</td>
<td>100 (90; 100)</td>
<td>100 (90; 100)</td>
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</tbody>
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Effectiveness

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=55)</th>
<th>Poor responders (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 TEAE</td>
<td>30 (55)</td>
<td>18 (47)</td>
</tr>
<tr>
<td>Patients with ≥ 2 serious TEAE</td>
<td>5 (8)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Patients with ≥ 2 non-serious targeted TEAE</td>
<td>24 (44)</td>
<td>14 (37)</td>
</tr>
</tbody>
</table>

Safety

Conclusions

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Acknowledgements

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