Hypoglycaemic adverse events reported in children enrolled in the European Incrlex® Growth Forum Database (EU-IGFD) in Europe (5-year interim data)

Joachim Woelfler, Michel Polak, Peter Bang, Valérie Perrot, Caroline Sert on behalf of the EU-IGFD Registry study group

Children’s Hospital, University of Bonn, Bonn, Germany; Hospital Universitario de la Infanta Cristina, A Coruña, Spain; Université Paris Descartes, Paris, France; Faculty of Health Sciences, Linköping University, Linköping, Sweden; Ipsen Pharma, Boulogne Billancourt, France

INTRODUCTION

- In the Incrlex® Registry (420-P2), a 5-year-long (2010-2015) database, we evaluated the treatment of hypoglycaemia in children with severe primary IGF-1 deficiency, which is defined as: - Height >1.25 standard deviations (SD) below the mean - IGF-1<10% of the mean - Normal or elevated growth hormone (GH) secretion
- The EU Incrlex® Growth Forum Database (IGFD) Registry was initiated in December 2010 to monitor the safety and efficacy of Incrlex® in children, and is representative of the Incrlex®-treated patient population in 17 European countries.
- The most common adverse event observed with Incrlex® is hypoglycaemia, which may be caused by a lack of GH glucoregulatory actions due to severe primary IGF-1 deficiency and further augmented during height gain treatment.
- In clinical trials, hypoglycaemia occurred in up to 49% of children.
- However, in a real-world setting, data from the EU-IGFD Registry suggest a much lower frequency (7-8%).
- The EU-IGFD Registry is ongoing and recruiting new patients.

OBJECTIVES

- EU-IGFD Registry objectives:
  - To evaluate the impact of primary objective and efficacy (secondary objective) of Incrlex® in children with growth failure
- Objectives for this analysis:
  - To report the frequency of hypoglycaemia from 5-year interim data in the EU-IGFD Registry for patients who received at least one Incrlex® dose and who attended at least one follow-up visit for which there were data on hypoglycaemia.
  - To identify predictive factors for the occurrence of hypoglycaemia.
  - To compare first-year and third-year height SDSs in all children treated with Incrlex® who experienced hypoglycaemia and who had completed at least one follow-up visit (real-life population) with those in children who did not experience a hypoglycaemic event.

METHODS

- Ongoing, multi-centre, open-label, observational study monitoring the safety and efficacy of Incrlex® in children in the clinical setting.
- Children were eligible for enrollment if:
  - Received Incrlex® growth failure from a qualified practitioner
  - Gave informed consent, if appropriate, in addition to mandatory consent
- Data entered in the patients’ medical records as part of standard medical care were collected during visits:
  - Baseline characteristics
  - Incrlex® dose
  - Treatment outcomes, including height
  - Prior use of growth-promoting therapy, including concomitant human GH treatment
- Hypoglycaemia (arginine) was suspected or documented (blood glucose concentration <40 mg/dL).
  - Non-serious hypoglycaemic AEs considered to be treatment-related
  - Serious AEs (SAEs) relating to hypoglycaemia irrespective of relationship to treatment
- Logistic regression analysis was performed to identify predictive factors for the occurrence of hypoglycaemia at least one hypoglycaemic event in the safety population
- Covariates in the model: at age first Incrlex® dose (years), sex, pubertal group (pubertal status vs. prepubertal), Incrlex® dose at time of hypoglycaemia (mg/kg BIW or BIW/day) or mean dose during year 1 for those without hypoglycaemia, height of hypoglycaemia, prior use of growth-promoting therapy, age at diagnosis of Laron syndrome, baseline levels of insulin-like growth factor binding protein-3 (IGFBP-3; mg/mL).
- Variables with a p-value inferior to 0.2 were retained for multivariate analysis.

RESULTS

- Patients
  - The first patients were enrolled in the EU-IGFD Registry in December 2010
  - 205 patients (152 males, 53 females) were enrolled as of 2 October 2014
  - 200 patients (150 male, 50 females) were included in the safety population
  - 199 patients (129 male, 70 female) had at least one follow-up visit (real-life population)
  - Post-treatment safety data were only available for 1 patient
  - Baseline demographic characteristics are summarised in Table 1

HYPOGLYCAEMIA

- Hypoglycaemia (serious and non-serious) was the most common AE with 41 events occurring in 24 patients (4.36%).
  - Of these 24 events, 20 were documented by blood glucose measurement and 2 were reported for patients who did not specify whether they were verified or suspected.
  - 5-year data from the EU-IGFD Registry are similar to reports from 3-year and 4-year Registry data.
  - Of 29 patients who experienced an event, 19 were male and 10 females.
  - 14 patients had hypoglycaemic events per patient per treatment year (y.1).
  - 3 patients had hypoglycaemic events per patient per treatment year (y.1).
  - In these patients, hypoglycaemia occurred after fasting or eating or after exercise with poor intake of food.

Predictive factors for hypoglycaemia

- Table 2 provides the predictive factors for hypoglycaemia in a univariate and multivariate logistic regression analysis
- The hazard ratio (HR) of the independent variables included in the model is shown in Table 3.
- A model of a hazard ratio (HR) of 1.35 (95% CI 1.03–1.78) is considered to be serious and moderate of serious intensity.
- Incrlex® dose was the only predictive factor for hypoglycaemia in a univariate and multivariate analysis.

CONCLUSIONS

- It is still a question whether the proportion of patients treated with Incrlex® who experience hypoglycaemia is lower than that previously reported in clinical trials.
- Five-year data from the EU-IGFD Registry are similar to reports from 3- and 4-year Registry data.
- Laron syndrome was identified as an independent predictive factor for the occurrence of hypoglycaemia.
- The median Incrlex® dose was 100 mg/kg BIW at the first hypoglycaemic event.
- Age at time of first Incrlex® intake and Incrlex® dose were not related to hypoglycaemia.
- Incrlex® effectiveness (change in height SDS) was similar between those who did and those who did not experience hypoglycaemia.
- To reduce the potential for hypoglycaemia, Incrlex® should be administered in accordance with the product guideline, shortly before or after food intake.

ACKNOWLEDGEMENTS

- Thanks to all of the co-ordinators, investigators, centres, and patients who have contributed to the Incrlex® Registry, and to Ipsen Conference Communications Ltd supported by Ipsen for their assistance with poster development.

REFERENCES