An analysis of the safety of childhood growth hormone therapy: data from NordiNet® International Outcome Study

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Objectives

Data from NordiNet® International Outcome Study (IOS; NCT00960128) were analysed to identify the characteristics of patients receiving growth hormone (GH) therapy (Norditropin®, Novo Nordisk A/S, Denmark) at risk of second and subsequent adverse events (AEs). We also report AEs of special interest according to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms System Organ Class (SOC) classification 'Neoplasms benign, malignant and unspecified (incl cysts and polyps)', nervous system disorders and cardiac/vascular disorders.

Methods

- Safety data were analysed from 16,359 patients enrolled in NordiNet® IOS and treated with GH between 1998 and 2016.
- Patient diagnoses were based on physician's decision and were classified according to the International Classification of Diseases 10th Revision criteria.[7]
- Based on diagnosis at GH treatment start and associated risk for mortality, patients were classified into three risk groups:[5]
  - Low-risk: patients with diagnoses of idiopathic GHD, idiopathic short stature (ISS), SGA at birth, or isolated GHD in association with a minor craniofacial malformation such as cleft lip.
    - This risk group was subdivided into patients with GHD/ISS and children born SGA.
  - Intermediate-risk: patients with multiple pituitary hormone deficiency, clinically defined syndromes known to be associated with increased mortality risk (e.g. TS), benign pituitary tumours, severe craniofacial or other malformations, or severe or chronic paediatric disease.
  - High-risk: patients previously diagnosed with a malignancy, craniopharyngioma or chronic renal failure.
- AEs were classified using the MedDRA preferred terms SOC classification.

Statistical analyses

- Patient-years of exposure (PYE) were calculated from initiation of GH treatment to the end of GH treatment or patient's final visit.
- Incidence rates (IRs) defined as number of events/1000 PYE for adverse drug reactions (ADRs), serious ADRs (SADRs), and serious AEs (SAEs) were calculated, and comparisons, according to risk group in relation to the low-risk group, were carried out using Poisson regression (log-linear model).
- The proportions of patients with one AE, two (first and one subsequent) AEs and three or more (first and two or more subsequent) AEs were calculated.
- Occurrence of AEs of interest are presented using descriptive statistics only.

Introduction

- Recombinant human GH was first approved in 1985 as a safe and effective treatment for short stature in patients with GH deficiency (GHD)[1] and more recently in patients with Turner syndrome (TS) and born small for gestational age (SGA).[2]
- Despite a favourable safety profile, concerns have been raised over a potential link between GH therapy and increased morbidity and mortality.[3–6]
- NordiNet® IOS is a non-interventional study assessing the long-term effectiveness and safety of GH (Norditropin®) treatment in everyday clinical practice.

Results

- Baseline demographic and clinical characteristics are displayed in **Table 1**.
- In this study, a total of 428 AEs were reported for 372 patients.
- The overall proportions of patients with one, two, or three or more AEs were 91.1% (n=339), 6.7% (n=25) and 2.2% (n=8), respectively. The proportions of patients with one, two or three or more AEs according to risk group are shown in **Figure 1**.
- Overall IRs were 3.74 events/1000 PYE for ADRs, 3.77 events/1000 PYE for SAEs, and 1.08 events/1000 PYE for SADRs.
- IRs of ADRs, SADRs and SAEs were significantly higher in the intermediate-risk and high-risk groups in comparison to the low-risk group (**Figure 2**).
- Following the first AE, 50.4% of all patients remained on the same GH dose; proportionally more patients in the low-risk group (56.8%) and intermediate-risk group (52.0%) than in the high-risk group (28.0%) remained on the same GH dose after the AE.
- The proportion of all patients discontinuing treatment after the first AE was 25.1% with proportionally more patients in the high-risk group (46.0%) than in the low-risk (17.3%) or intermediate-risk (25.3%) groups discontinuing after the AE.

SAEs of interest

- Neoplasms/malignancies were more frequent in the intermediate-risk (15 events reported in 13 of 5336 patients [0.2%]) and high-risk (24 events reported in 19 of 859 patients [2.2%]) groups than in the low-risk group (three events, one event each in three of 10,164 patients [<0.1%]).
- One cardiovascular event was reported in the low-risk group (in one of 10,164 patients [<0.01%]), eight cardiovascular events were reported in the intermediate-risk group (five cardiac events in three of 5336 patients [<0.1%] and one vascular event each in three of 5336 patients [<0.1%]), and no cardiovascular events were reported in the high-risk group.
- The total number of reported nervous system disorders was 15 in the low-risk group (one event each in 15 of 10,164 patients [0.1%]), 37 in the intermediate-risk group (in 24 of 5336 patients [0.4%]), and 13 in the high-risk group (in 10 of 859 patients [1.2%]).

Characteristics of two, or three or more AEs

- In patients with two AEs, in the intermediate-risk (n=14) and the high-risk group (n=4):
  - The most frequently reported AE according to SOC was nervous system disorders (12 events), with headache (five events [41.6%]) being the most frequent AE.
  - The second most frequently reported AE according to SOC was infections (eight events), for which all cases were considered as not related to GH treatment.
- In patients with three or more AEs, in the intermediate-risk (n=3) and high-risk group (n=2):
  - The most frequently reported AEs according to SOC was nervous system disorders, with seizures (13 events in one patient in the intermediate-risk group and two events in one patient in the high-risk group) being the only type of reported event.
  - The second most frequently reported AEs according to SOC were neoplasms benign, malignant and unspecified (three neoplasm recurrence events in one patient in the high risk group) and cardiac disorders (three events of myocardial ischaemia in one patient in the intermediate-risk group).

Conclusions

- These results are consistent with previous reports from NordiNet® IOS and reconfirm the overall favourable safety profile of GH treatment.
- Patients in the intermediate-risk and high-risk groups seemed to be more likely to have a second AE than those in the low-risk group.
- A low proportion of patients with three or more AEs was reported across all risk groups.

Figure 1. Proportion of patients with one, two and three or more adverse events by risk group.

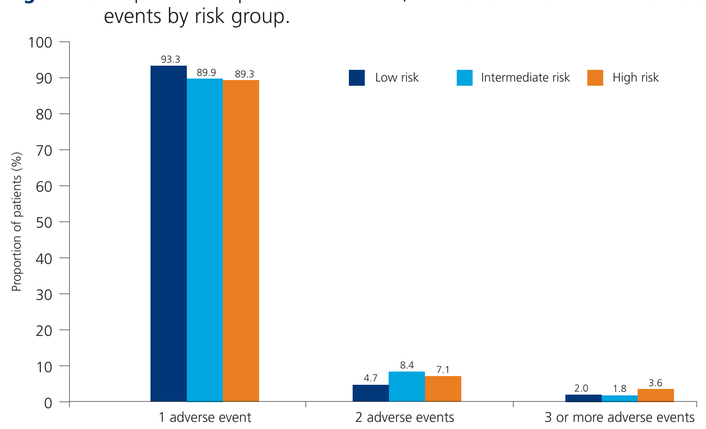


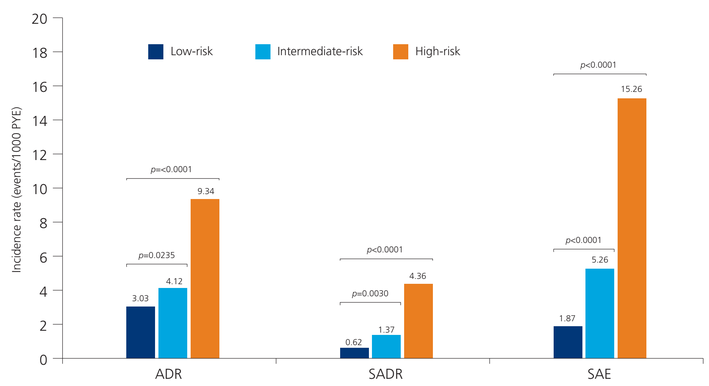
Table 1. Baseline demographic and clinical characteristics by risk group.

Trial	*Low-risk*			*Intermediate-risk*	*High-risk*	*Overall*
	Total low-risk group	*GHD/ISS subgroup*	*SGA subgroup*			
Number of patients (%)	10,164 (62.1)	6341 (62.4*)	3823 (37.6*)	5336 (32.6)	859 (5.3)	16,359 (100.0)
Sex, male/female, %	62.5/37.5	67.5/32.5	54.3/45.7	46.6/53.4	57.0/43.0	57.1/42.9
Mean age at treatment start, years (SD)	8.81 (3.66)	9.33 (3.77)	7.93 (3.28)	8.31 (4.25)	10.19 (3.88)	8.72 (3.90)
Mean height SDS at baseline (SD)	–2.59 (0.91)	–2.47 (0.92)	–2.79 (0.86)	–2.56 (1.29)	–2.00 (1.31)	–2.55 (1.08)
Mean duration of GH treatment, years (SD)	3.79 (2.81)	3.76 (2.81)	3.84 (2.82)	4.63 (3.24)	3.74 (2.71)	4.06 (2.98)
Mean GH dose until first event, µg/kg/day (SD)	34.98 (9.02)	32.46 (6.91)	39.48 (10.57)	33.75 (11.18)	31.46 (10.40)	33.91 (10.26)

*Percentage of low-risk group. †Norditropin approved for ISS in South Korea only.

GH, growth hormone; GHD, growth hormone deficiency; ISS, idiopathic short stature; SGA, small for gestational age; SD, standard deviation; SDS, standard deviation score.

Figure 2. Incidence rates of reported ADRs, SADRs and SAEs by risk group.



ADR, adverse drug reaction; PYE, patient-years of exposure; SADR, serious adverse drug reaction; SAE, serious adverse event.

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Disclosure statement

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