Real-world safety data in a cohort of children with Noonan syndrome treated with growth hormone: final results from NordiNet® International Outcome Study (IOS) and the ANSWER Program

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Objective
To describe real-world safety data on growth hormone (GH) therapy in paediatric patients with Noonan syndrome (NS) who were enrolled in NordiNet® IOS and the ANSWER Program.

Methods

- The long-term effectiveness and safety of NordiNet® (somatropin; Novo Nordisk A/S, Denmark), as prescribed in clinical practice, were evaluated in two complementary, non-interventional, multicentre studies (Figure 1).
- We report here safety results for 412 paediatric patients with NS. Patients for whom a valid NordiNet® exposure was not recorded were excluded from the safety evaluation (Figure 1).

Introduction

- Patients with NS have a high prevalence of cardiac defects1 and a higher risk than the general population for leukaemia and certain solid tumours.1
- Current safety data do not indicate an association of GH therapy with worsening of congenital cardiac defects or an increased risk for malignancies in individuals with NS; however, data are limited.1

Results

Patient characteristics

- Baseline characteristics and exposure information for all patients and for patients with safety events are presented in Table 1.
- Genotypes were only available for patients included in the ANSWER Program. Of 258 patients, data on mutations were available for 61 patients as follows: PTPN11, n=35; KRAS, n=3; SOS1, n=2; RAF1, n=1; SHOC2, n=1 (one patient could have more than one mutation).
- Cardiovascular (CV) comorbidities were reported in 35 (8.5%) patients prior to GH start; comorbidities reported in three or more patients are shown in Table 2.
- After start of GH treatment, (potentially pre-existing) CV comorbidities should have been considered as an SAE, based on medical judgement (see ‘Specific patients’ below).

Safety outcomes

- Overall, 31 safety events were reported in 21 patients (Table 2); of these, 68% (21/31) were deemed to be related to GH treatment. Most patients with safety events reported a single event (16/21). One patient reported two SARs (see ‘Specific patients’ below).
- Aside from the comorbidities listed above, no cardiac SAEs, NSARs or SAEs not related to GH therapy were reported. Under the MedDRA term ‘diabetes’, ‘impotence, benign and unspecified’ four events were reported in three patients (Table 3).

Specific patients

- The patient with two SAEs (Table 2) reported a brain neoplasm (metastatic fourth ventricular pilocytic astrocytoma) and metastases to spine, which were considered as possibly related to GH treatment by the reporter. This patient (PTPN11 mutation) had a history of headaches, which may suggest an underlying condition. A temporal association between brain neoplasm and GH treatment cannot be excluded, but further medical assessment was not undertaken.
- One patient (PTPN11 mutation) had a resected abdominal aortic aneurysm diagnosed 26 months after start of follow-up. This patient was also diagnosed with Crohn’s disease 22 months after start of follow-up and with a glomerulonephritis 1 week after the aneurysm diagnosis.

Discussion

- In the current analysis, one cardiac safety event (ruptured abdominal aortic aneurysm) was reported. A recent randomised, double-blind, clinical trial of Nordipin®, in which cardiac function was monitored (n=51), showed no evidence of a negative effect of GH on cardiac function or structure.2
- Furthermore, previous reports indicate that long-term GH treatment does not appear to have negative effects on the heart, in particular, ventricular wall thickness.1
- As there was no requirement in the protocol to report cardiac comorbidities at baseline, these baseline data may have been under-reported.
- The underlying pathophysiology of NS includes dysregulation of the RAS mitogen-activated protein kinase signalling pathway, which may increase the intrinsic risk of cancer development.1 NS is associated with a higher risk of benign and malignant proliferative disorders, including solid tumours,1 and glomerulonephritis and astrocitoma have both been reported in patients with NS.3 The available data on GH and cancer risk give no cause for concern, but underlying susceptibility to tumour growth should be considered when GH therapy is started.1

Conclusions

- Real-world data from NordiNet® IOS and the ANSWER Program support a favourable safety profile of GH therapy in patients with NS, specifically with regard to cardiac safety events.
- As with other real-world studies, assessment of safety events may be difficult owing to the unknown natural history of and/or under-reporting of comorbidities.

Table 1 Baseline characteristics of patients (all patients and patients with safety events) and GH exposure information

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=412)</th>
<th>Patients with safety events (n=21)</th>
</tr>
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<tbody>
<tr>
<td>Gender, %</td>
<td>Male = 57.1%</td>
<td>Male = 57.1%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.48 (3.92)</td>
<td>9.90 (4.23)</td>
</tr>
<tr>
<td>Height SDS†</td>
<td>–2.03 (1.31)</td>
<td>–2.57 (1.54)</td>
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<tr>
<td>Bone age/chronological age</td>
<td>0.83 (0.19)</td>
<td>0.86 (0.10)</td>
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<tr>
<td>GH-naïve at baseline, yes (%)</td>
<td>68.4%</td>
<td>57.1%</td>
</tr>
<tr>
<td>Duration of treatment follow-up (years)</td>
<td>3.1 (2.6)</td>
<td>3.06 (2.17)</td>
</tr>
<tr>
<td>GH dose during childhood (µg/kg/day)</td>
<td>46.6 (13.6)</td>
<td>47.6 (16.8)</td>
</tr>
</tbody>
</table>

1Unless otherwise specified. Weight and height SDS were calculated using age- and gender-specific national references. Baseline GH at all times (n=412), 53-90, GH, growth hormone; SDS, standard deviation score; SD, standard deviation; SDI, standard deviation index.

References

Conflict of interest disclosures
FJ received travel support from Novo Nordisk for a presentation at a Novo Nordisk meeting. JH received travel support 2015;112:1392–7. This study was supported by Novo Nordisk. NordiNet® IOS is registered at Clinkscales CA et al. Horm Res Pediatr 2015;83:157–66. This study was supported by Novo Nordisk A/S, Søborg, Denmark. Pétur Benedikt Júlíusson, M. Jennifer Abuzzahab, Birgitt Tonnes Pedersen, Sebastian Röhrich, Alicia Romano, Johanna Dahlgren. Pétur Benedikt Júlíusson is a consultant for Genetec and Novo Nordisk. Matthew Abuzzahab is an employee of Novo Nordisk, Health Care AG, all of the sponsor’s business for NordiNet, Novo Nordisk, and Genetec, and a consultant for Genetec and Naace Ltd, and Novo Nordisk.

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