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NordiNet® IOS/ANSWER Noonan syndrome CV safety

Title:

Cardiovascular safety of growth hormone treatment in Noonan syndrome: real-world evidence

Short title:

Cardiovascular safety of GH in Noonan syndrome

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Keywords (min 4, max 5)

growth hormone, hypertrophic cardiomyopathy, Noonan syndrome, pulmonary valve stenosis, real-world data

Item	**Maximum count**	**Current count**
Word count	5,000	1,683
Figures/Tables	10	2
References	60	22

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ABSTRACT (245/250 words)

Objective: To assess cardiovascular (CV) safety of growth hormone (GH) treatment in patients with Noonan syndrome (NS) in clinical practice.

Design: Two observational, multicentre studies (NordiNet® IOS and the ANSWER Program) evaluating long-term effectiveness and safety of GH in >38,000 paediatric patients, of which 421 had NS.

Methods: Serious adverse events, serious adverse reactions (SARs), and non-serious adverse reactions (NSARs) were reported by the treating physicians. CV comorbidities at baseline and throughout the studies were also recorded.

Results: The safety analysis set comprised 412 children with NS (29.1% females), with a mean (standard deviation) baseline age of 9.29 (3.88) years, treated with an average GH dose of 0.047 (0.014) mg/kg/day during childhood. CV comorbidities at baseline were reported in 48 (11.7%), most commonly pulmonary valve stenosis and atrial septal defects. Overall, 22 (5.3%) patients experienced 34 safety events. The most common were the NSARs: headache (eight events in seven patients) and arthralgia (five events in three patients). Two SARs occurred in one patient (brain neoplasm and metastases to spine). No CV safety events were recorded in patients with NS. Five CV comorbidities in five patients were reported after initiation of GH treatment: three cases of unspecified CV disease, one ruptured abdominal aortic aneurysm and one pulmonary valve stenosis.

Conclusions: GH treatment had a favourable safety profile in patients with NS, including those with CV comorbidities. Prospective studies are warranted to systematically assess the safety of GH treatment in patients with Noonan syndrome and CV disease.

INTRODUCTION

Noonan syndrome (NS) is a genetic condition characterised by short stature, a characteristic facial appearance, skeletal anomalies and cardiovascular disease (1, 2). NS is an autosomal dominant disorder and has been associated with several genes related to the RAS/mitogen-activated protein kinase cascade (3, 4).

NS is one of the main syndromic causes of cardiovascular (CV) disease in children (5). CV anomalies commonly associated with NS include pulmonary valve stenosis (PVS; prevalence 50–60%), hypertrophic cardiomyopathy (HCM; 20%) and atrial septal defects (6–10%) (1).

Growth hormone (GH) treatment in patients with NS improves height velocity, height standard deviation score (SDS), and adult height, with a good safety profile (6, 7). Norditropin® (Novo Nordisk A/S, Denmark) is currently the only GH replacement therapy approved internationally for the treatment of short stature in children with NS (in the USA, Canada, European Union, UK, Japan, Israel, Brazil, South Korea, Switzerland and Argentina). Despite limited data showing low rates of CV events and no change in left ventricular wall thickness with GH treatment, some concerns persist about the role of GH in progression of CV disease in patients with NS (8-17).

The objective of this study was to describe the CV safety in patients with NS treated with GH in clinical practice using data from two large observational studies.

MATERIALS AND METHODS

Study design and ethics

The NordiNet® International Outcomes Study (IOS; NCT00960128) and ANSWER Program (NCT01009905) were observational, multicentre studies monitoring the real-world long-term outcomes of GH treatment (Norditropin®, Novo Nordisk A/S, Denmark) in children and adults. The studies were performed between 2002 and 2016 and involved 676 clinics in 23 countries across Europe, the Middle East and the USA (18, 19).

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The patient population reported here comprises the safety analysis set (SAS) including all patients with NS under 18 years of age with at least one Norditropin® prescription recorded. The SAS included both GH-naïve and non-naïve patients.

Both studies were conducted with approval from relevant ethics committees, written consent was obtained from all patients after full explanation of the purpose and nature of all procedures used, and pseudonymisation of all data was carried out in accordance with the Declaration of Helsinki, Guideline for Good Pharmacoepidemiology Practices, and regulatory requirements.

Safety assessments

Safety events were reported by treating physicians in a case report form and are defined as a collection of serious adverse events (SAEs), serious adverse reactions (SARs; considered related to GH treatment either by the reporting physician or the study sponsor), and non-serious adverse reactions (NSARs; related to GH treatment). Events that were non-serious and not related to GH treatment were not included in this report to maintain compatibility of datasets from NordiNet® IOS and ANSWER Program. CV comorbidities reported at baseline and diagnosed throughout the duration of the studies were also recorded.

Statistical analysis

All code for statistical analyses was written using the SAS 9.4 software. Baseline and safety data were summarised using descriptive statistics. Statistical comparison of baseline characteristics between the SAS and patients who experienced at least one safety event was carried out with Fisher's test for categorical variables, and with *t*-test or Mann–Whitney U test (when the normality assumption was not met) for continuous variables. A statistically significant difference was defined as $p<0.05$.

RESULTS

Baseline characteristics

Of the 17,995 and 20,204 paediatric patients registered in NordiNet® IOS and the ANSWER Program, respectively, 156 and 265 had NS. Of these, nine children were excluded owing to missing valid data about GH dose (missing start or stop date of GH treatment or missing dose; n=7) or GH exposure (no treatment periods reported; n=2). Thus, the SAS comprised 154 patients in NordiNet® IOS and 258 in the ANSWER Program (**Supplementary Figure 1**).

The combined SAS of 412 children with NS consisted of 70.9% males and 29.1% females with a mean (standard deviation; SD) age of 9.29 (3.88) years and height SDS of −2.65 (0.95) at baseline (**Table 1**). Mean (SD) baseline GH dose was 0.044 (0.014) mg/kg/day, and average GH dose during childhood was 0.047 (0.014) mg/kg/day. There were no statistically significant differences in baseline characteristics between patients in the SAS and those experiencing safety events (n=22; **Table 1**), with the exception of baseline height SDS (p=0.0322).

The most common concomitant medications were central nervous system stimulants (12.4%), antihistamines (6.6%) and thyroxine replacement (5.1%) (**Supplementary Table 1**). Anti-hypertensive treatment was reported in four patients (1.0%) who received diuretics, of which three (0.7%) were also prescribed angiotensin-converting enzyme inhibitors. Steroid drugs were prescribed to 20 patients (4.9%).

Genotypes

Among the 61 patients with available genotypes, 66 genetic mutations in five genes were observed: *PTPN11* (n=56), *RAF1* (n=5), *KRAS* (n=2), *SOS1* (n=2) and *SHOC2* (n=1). Three patients had mutations in multiple genes, all including *PTPN11*. Of these, two patients had mutations in two genes (*PTPN11* and *SOS1*; *PTPN11* and *RAF1*) and one in four genes (*PTPN11, SOS1, RAF1,* and *KRAS*).

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Safety

Adverse events

In total, 22 (5.3%) patients with NS experienced 34 safety events (**Supplementary Table 2**). Adverse reactions (NSARs or SARs) occurred in 18 (4.4%) patients after initiation of GH treatment. Of the 24 NSARs, the most common were headache (eight events in seven patients) and arthralgia (five events in three patients).

Two SARs occurred in a single patient after 2.5 years of treatment: brain neoplasm (metastatic fourth ventricular pilocytic astrocytoma) and metastases to spine, possibly related to GH. The patient (aged 15.9 years) had a mutation in the *PTPN11* gene and had a history of headaches. Both events were reported as not resolved at the end of the follow-up period.

No CV safety events were recorded in a case report form by the investigating physicians during the studies. One cerebrovascular event (Moyamoya disease) was reported in one patient (female, 10.4 years) after 4.1 years of GH treatment. The event was considered serious and unlikely to be related to GH treatment.

Cardiovascular comorbidities

Forty-eight (11.7%) patients reported a CV comorbidity at baseline (**Table 2**). The most common CV comorbidities at baseline were PVS (18 patients) and atrial septal defects (four patients). In addition, three patients had HCM at baseline.

Five CV comorbidities in five patients were reported after initiation of GH treatment: three cases of unspecified CV disease, one case of PVS, and one ruptured abdominal aortic aneurysm. The first four patients had no reported SAEs. The abdominal aortic aneurysm was diagnosed in a patient with a *PTPN11* mutation 2.2 years after GH treatment initiation. This patient was also diagnosed with Crohn's disease (1.8 years after treatment initiation) and with a glioneuronal tumour (1 week after the aneurysm diagnosis).

DISCUSSION

Our report of GH treatment in patients with NS in a real-world setting did not reveal substantial clinically significant CV safety signals. No CV safety events were reported, which is encouraging, particularly given the pre-existing CV comorbidities in some patients. Of 18 patients with PVS and three with HCM at baseline, no worsening of these conditions during treatment with GH was reported. Among the commonly used concomitant medications, most were not relevant from a cardiac perspective.

The overall number of CV comorbidities at baseline was low (11.7%), considering that up to 80% of individuals with NS have been reported to have a cardiac anomaly (5). This contrast in prevalence suggests that patients with pre-existing CV disease may have been under-represented owing to a selection bias in GH prescribing practices, and/or the conditions may have been under-reported at baseline. Thus, as active screening of participants was not required prior to enrolment in the study, the five CV comorbidities reported after GH treatment initiation may have also been pre-existing. Because of the low prevalence of reported CV disease, the findings in relation to CV safety for patients with pre-existing CV disease need to be interpreted with caution. In particular, as there was no requirement to perform or report results of echocardiograms in children with NS to monitor for development or worsening of cardiomyopathy, and as only three children had recorded HCM at baseline, these data do not readily offer guidance for treatment of children with NS and HCM. Another limitation of the study is the scarce availability of CV data (e.g., blood pressure and heart function), which may have contributed to the underreporting of CV safety events, including worsening of existing conditions. However, the real-life setting of the study can be considered a strength.

Our findings are in agreement with previous studies, reporting no clinically significant change in cardiac function in children with NS treated with GH for 1–3 years (8, 9, 14, 17). We have identified 11 studies published between 1995 and 2019 reporting adult height outcome results from 1,288 patients with NS, only 16 CV adverse events were reported. Of these events, pulmonary valve-

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related events comprised two cases of PVS (16), two mild progressions of PVS unlikely related to GH (11), and one increased pulmonary regurgitation (15). Among hypertrophy-related events, one case of HCM (12) and one worsening of HCM (15) were reported. In addition, there was one case of left ventricular hypertrophy (16), two cases of mild left ventricular wall thickening within the normal limit (9), and one increased biventricular hypertrophy (12). Rhythm-related events included one case each of atrial fibrillation (16), mild tachycardia lasting 1 day, and mild ventricular extra-systoles, from which the patient recovered (14). The remaining events involved a supravalvular aortic stenosis (12) and a successful surgical right ventricular outflow tract procedure without complication (9).

While no CV events were reported in our study, one serious cerebrovascular event was reported (Moyamoya disease). A concern about mortality due to cerebral haemorrhage has been raised previously in the SAGhE study, in adults without Noonan syndrome who were treated with GH during childhood (20). However, it was later shown that such concern was mainly driven by results from the French sub-cohort of SAGhE (21). Additionally, the investigating physician considered the event unlikely to be related to GH treatment.

In conclusion, the evidence suggests a favourable safety profile of GH treatment in patients with NS, including those with CV comorbidities and those receiving concomitant medications. However, the low prevalence of CV comorbidities in our patient population highlights the importance of baseline cardiovascular assessments before initiating GH therapy, particularly in patients with genotypes associated with a higher CV risk. Prospective studies are warranted to systematically assess the safety of GH treatment in patients with NS and pre-existing CV disease.

Declaration of interest:

AR: consultant and speaker for Novo Nordisk; consultant for Ascendis Pharma. JPK: consultant and speaker for Novo Nordisk. JD: speaker for Novo Nordisk. NK: employee of Novo Nordisk and stockholder in Novo Nordisk and Pfizer. AP: employee of Novo Nordisk and stockholder in Novo

Nordisk. TRR: consultant and speaker for Novo Nordisk. MP: Novo Nordisk growth international advisory board member and has received grants from Novo Nordisk.

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Supplementary Figure 1: Patient disposition

The safety analysis set includes all patients with available birthdate information who were

<18 years of age and with at

least one Norditropin® prescription recorded.

*Reasons for exclusion for the combined studies: no valid mean GH dose, n=7; no valid GH

exposure: n=2.

IOS, international outcomes study.

TABLES

Table 1: Baseline characteristics

	All patients		Patients with safety events	
	Number of patients	**Mean (SD)[a]**	**Number of patients**	**Mean (SD)[a]**
Female/male, n and %	120/292	29.1% / 70.9%	9/13	40.9% / 59.1%
Age, years	412	9.3 (3.9)	22	9.7 (4.1)
Height SDS[b]	371	–2.65 (0.95)	17	–3.13 (0.79)
Weight SDS[b]	308	–2.03 (1.31)	13	–2.57 (1.54)
Bone age/chronological age	163	0.83 (0.19)	8	0.87 (0.10)
IGF-I SDS[c]	162	–1.13 (1.62)	7	–1.22 (1.98)
GH dose at baseline (mg/kg/day)	404	0.044 (0.014)	21	0.040 (0.019)
GH-naïve at baseline, yes (%)	282	68.5%	12	54.6%
Duration of treatment (years)	412	3.1 (2.6)	22	3.3 (2.5)
GH dose during childhood (mg/kg/day)	412	0.047 (0.014)	22	0.047 (0.016)

[a]Unless otherwise specified.

[b]Height and weight SDS were calculated using age- and gender-specific national references.

[c](22)

GH, growth hormone; IGF-I, insulin-like growth factor I; SD, standard deviation; SDS, standard deviation score

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Table 2: Cardiovascular comorbidities

Diagnosis	At baseline	After GHT start
Pulmonary valve stenosis	18	1
Atrial septal defect	4	–
Cardiac murmur, unspecified	3	–
Hypertrophic cardiomyopathy	3	–
Cardiovascular disease, unspecified	1	3
Cardiac disease, unspecified	2	–
Coarctation of aorta	2	–
Ventricular septal defect	2	–
Benign and innocent cardiac murmurs	1	–
Cardiac arrest with successful resuscitation	1	–
Cardiomegaly	1	–
Cardiovascular disorder originating in the perinatal period, unspecified	1	–
Atrioventricular septal defect	1	–
Mitral valve disease, unspecified	1	–
Other pulmonary valve disorders	1	–
Aortic valve disorder, unspecified	1	–
Ruptured abdominal aortic aneurysm	–	1
Stenosis of pulmonary artery	1	–
Tetralogy of Fallot	1	–

GHT, growth hormone treatment.

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SUPPLEMENTARY MATERIAL

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Supplementary Table 1: Concomitant medication

Concomitant medication class	Patients (n)
Central nervous system stimulant	51
Antihistamine	27
Thyroxine replacement	21
Dietary supplements	15
Vitamin D_3	14
Proton pump inhibitor	13
Selective serotonin reuptake inhibitor	11
Leukotriene inhibitor	10
Alpha2-adrenoreceptor agonist	9
Circadian hormone; non-steroidal anti-inflammatory analgesic	8
Anticonvulsant; calcium replacement	7
GnRH agonist; steroid/anti-inflammatory agent; vitamin D_2	6
Antibiotic; hormone	5
Alpha-agonist; antibiotic	4
ACE inhibitor; antipsychotic; beta2-agonist (bronchodilator); histamine 2 receptor blocker; loop diuretic; steroid/anti-inflammatory/immunosuppressant; topical steroid	3
5-HT_1 agonist; aminosalicylates; antacid (H2 blocker); anticholinergic bronchodilator; antidepressant; antispasmodic; benzodiazepine; beta blocker; cardiac glycoside; fluoride replacement; gastric motility stimulant; haemostatic agent; insulin replacement; laxative; laxative (PEG); norepinephrine re-uptake inhibitor; oestrogen; opioid analgesic; phenylpiperazine; antidepressant; anabolic steroid	2
Anti-fungal; anti-oestrogen; antimetabolite; aromatase inhibitor; central nervous system depressant; carnitine replacement; co-enzyme Q10; disaccharide (sugar); IGF-I; local anaesthetic; neurotransmitter; pituitary hormone; probiotic; steroid/anti-inflammatory; thiazide diuretic; vitamin A	1

5-HT_1, 5-hydroxytryptamine (serotonin) receptor, ACE, angiotensin-converting enzyme; GnRH, gonadotropin-releasing hormone; IGF-I, insulin-like growth factor I; PEG, polyethylene glycol.

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Supplementary Table 2: Summary of safety events in patients with Noonan syndrome

System organ class	Preferred term	NSAR	SAR	SAE not related to GH	Total number of events (patients)
Cardiovascular	Any	0	0	0	0
Neoplasms	Brain neoplasm	–	1 (1)	1 (1)	2 (2)
	Metastases to spine	–	1 (1)	–	1 (1)
	Glioneuronal tumour	–	–	1 (1)	1 (1)
Musculoskeletal	Arthralgia	5 (3)	–	–	5 (3)
	Myalgia	2 (2)	–	–	2 (2)
	Scoliosis	2 (2)	–	1 (1)	3 (3)
Miscellaneous	Headache	8 (7)	–	–	8 (7)
	Giant cell epulis	–	–	1 (1)	1 (1)
	Epilepsy	–	–	1 (1)	1 (1)
	Condition aggravated	1 (1)	–	1 (1)	2 (2)
	Spinal fusion surgery	–	–	1 (1)	1 (1)
	Moyamoya disease	–	–	1 (1)	1 (1)
	Other*	6 (5)	–	–	6 (5)
	Total	**24 (17)**	**2 (1)**	**8 (5)**	**34 (22)**

Values are shown as number of events (number of patients). A patient may have experienced more than one event.

*Other NSARs included oedema, injection site erythema, growing pains, muscle spasms, off-label use and injection site extravasation.

GH, growth hormone; NSAR, non-serious adverse reaction; SAE, serious adverse event; SAR, serious adverse reaction.

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SUPPLEMENTARY MATERIAL

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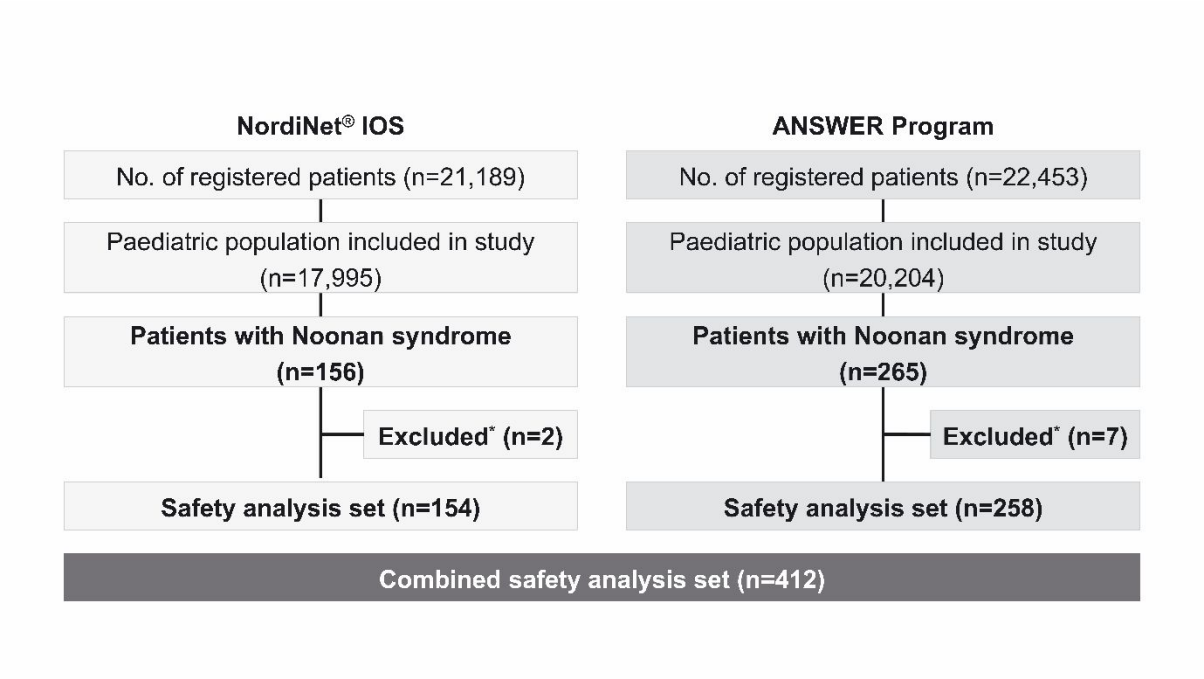
Supplementary Figure 1: Patient disposition



The safety analysis set includes all patients with available birthdate information who were <18 years of age and with at least one Norditropin® prescription recorded.

*Reasons for exclusion for the combined studies: no valid mean GH dose, n=7; no valid GH exposure: n=2.

IOS, international outcomes study.