Predictive value of baseline and stimulated serum IGF-1 and IGFBP-3 during a dose-escalation IGF-1 generation test with NutropinAq for the 1 year growth response to growth hormone (GH) therapy in short children with low IGF-1 and a normal GH peak in a provocation test

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Primary objective: Assessment of the value of the short-term (2 weeks) response of IGF-I (peak IGF-I SDS) to GH in a dosage of 1.4 mg/m2/day (as part of a dose-escalation IGF-I generation test) in comparison to baseline IGF-I to predict the 1 year...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON36350

Source
ToetsingOnline

Brief title
PRED-IGF

Condition

- Hypothalamus and pituitary gland disorders

Synonym
children with short stature of unknown cause, idiopathic short stature

Research involving
Human

Sponsors and support

Primary sponsor: Ipsen Pharmaceuticals
Source(s) of monetary or material Support: Ipsen Farmaceutica

Intervention

Keyword: GH (growth hormone), IGF-I generation, predictive value, response

Outcome measures

Primary outcome

Assessment of the value of the short-term response of IGF-I (peak IGF-I SDS) to different two weeks dose regiments (0.7 and 1.4 mg/mm2/day respectively) of GH (somatropine) in comparison to baseline IGF-I to predict the 1 year growth response to GH in a dose of 1.4 mg/m2/day.

Two approaches will be taken.

First, in a multiple regression analysis the explained variance will be calculated of the studentized residual of growth response (according to Ranke et al (1) (dependent variable) and baseline IGF-I SDS and peak IGF-I (after 1.4 mg/m2/day for 2 weeks) will be calculated.

The second approach is to define a good response as a studentized residual > -1, and prepare ROC curves for clinical predictors, baseline IGF-I SDS, and peak IGF-I SDS after 1.4 mg/m2/day.

The IGF-I generation test in this study is a modification of the test currently used in clinical practise (two weeks per dose instead of one), with measurements of IGF-I, IGFBP-3 and IGFBP-2 before and after 2 weeks of GH in dosages of 0.7, 1.4 and (if these dosages result in an insufficient response (IGF-I SDS < 0) 2.8 mg/m2/day. During long-term therapy serum IGF-I, and IGFBP-3 will be assessed shortly before the start (time 0) and after 3, 6 and 12 months.

Secondary outcome

Assessment of the value of other parameters of the dose-escalation IGF-I generation test (peak values and changes versus baseline of IGF-I, IGFBP-3, IGF-I/IGFBP-3 ratio, and IGF-I/IGFBP-2 ratio) in comparison to baseline IGF-I to predict the 1 year growth response to GH in a dose of 1.4 mg/m2/day. The other parameters include peak values and changes (before-after 2 weeks of GH) of IGF-I, IGFBP-3, IGF-I/IGFBP-3 ratio and IGF-I/IGFBP-2 ratio, on the dosages of 0.7 and 1.4 mg/m2/day.

Explorative objectives:

a) Assessment of the value of the various parameters of the dose-escalation IGF-I generation test in comparison to baseline IGF-I to predict the 1 year growth response.

b) Assess the predictive value of the short-term IGF-I SDS response to the highest GH dosage in those children in whom serum IGF-I does not sufficiently respond to the two lower dosages.

c) The correlation between serum GHBP and long-term growth response will be

assessed.

d) Biochemical and genetic analysis of the GH-IGF-I axis and genome-wide SNP-array.

Besides IGF-I and IGFBP-3, patients will be tested for an ALS defect.

Genetic analysis of the GH-IGF-I axis: for all participating patients DNA will be collected from blood lymphocytes for genetic studies.

Safety Endpoints and Evaluations: Patients will be seen by the paediatric endocrinologist before the IGF-I generation test, at start of long-term GH therapy, and after 3, 6, 9, and 12 months.

Study description

Background summary

In the Netherlands, the diagnostic strategy for non GH (growth hormone) deficient short children with very low IGF-I levels is to perform an IGF-I generation test (IGT), to select possible candidates for GH (growth hormone, somatropin) treatment. here is a need for an accurate test with which a better separation could be made between children who would benefit from therapy, and those who would not. Such test would offer the first group an effective therapy, and prevent the second group from being subjected to ineffective and expensive treatment consisting of numerous injections.

Study objective

Primary objective: Assessment of the value of the short-term (2 weeks) response of IGF-I (peak IGF-I SDS) to GH in a dosage of 1.4 mg/m2/day (as part of a dose-escalation IGF-I generation test) in comparison to baseline IGF-I to predict the 1 year growth response.

Secondary objective: Assessment of the value of other parameters of the dose-escalation IGF-I generation test in comparison to baseline IGF-I to

predict the 1 year growth response.

Study design

Open label, multicentre, evaluation of a newly designed standardized diagnostic test to predict the growth response in a 1 year trial with GH (somatropin) treatment (carried out in the context of regular patient care) in non GH deficient short children with low serum IGF-I.

Intervention

The intervention consists of a diagnostic procedure to assess GH responsiveness: the dose-escalation IGF-I generation test. This procedure will be followed by GH treatment in the context of regular patient care for children with a positive IGF-I response during an IGF-I generation test. Children whose IGF-I response is below the current cut-off (1 SD increase) GH will be made available by the sponsor for the study period of one year; It is assumed that a maximum of 2 children will fall in this category.

The IMP in the IGF-I generation test is: NutropinAq (somatropin, 5 mg/ml, 2 ml per cartridge). Doses in the diagnostic protocol: 0.7 and 1.4 mg/m2/day sc administered for 2 weeks (divided by washout periods of preferably 4 weeks (accepted range 4-6 weeks)).
An additional period of 2 weeks on 2.8 mg/m2/day will be added if the IGF-I response is insufficient (serum IGF-I SDS <0 after two weeks on 0.7 and 1.4 mg/m2/week).

The long-term treatment regimen is GH (somatropine, any brand) in a dosage of 1.4 mg/m2/day s.c. administered for 1 year.

Study burden and risks

The burden associated with participation consists of 6 venipunctures in all subjects, and 2 additional venipunctures in the few subjects who do not show a proper IGF-I increase on the two lower doses. This is similar to the burden of the protocol that is currently used in regular care. In comparison to the current protocol, the number of GH injections in the diagnostic phase is doubled (2-3 times 14 injections versus 2-3 times 7 injections). The perceived burden of subcutaneous GH injections is considered small, as demonstrated in several clinical trials. The burden of the visits to the paediatric endocrine clinic is also considered small, and the number of visits is not different from regular care in such patients.

During long-term GH treatment 3 venipunctures will be performed, which is at most one additional venipuncture than usual in regular care.

The risk of GH injections is considered extremely low, on the basis of a history of 40 years and various large postmarketing surveillance databases. The only relevant possible adverse event is pseudotumor cerebri, caused by a temporary increase of intracerebral pressure, but this is extremely rare in children. Children and parents will be informed of this possibility, and about handling it (temporary stop of treatment, followed by a gradual re-introduction).

The primary goal of this protocol is to benefit future patients with short stature and low IGF-I, so that GH treatment will be available for those who need it, and not prescribed if the chances of success are small. The benefit for the patients themselves is that the diagnostic workup is intensified, including genetic analysis, and that GH treatment is secured for all participants for the duration of one year.
This study is group related, as growth and its treatment can only be studied in childhood.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

Prepubertal children aged 2.0-9.0 (females) or 2.0-10.0 (males) years, bone age <9 (females) or <10 (males) years, height SDS <-2.5 (for ethnically adequate references), peak GH after provocation >30 mU/L, IGF-I SDS < -2 (at least twice, one of which determined in UMCU), body mass index (BMI) SDS < -2

Exclusion criteria

* Has a history of hypersensitivity to growth hormone or phenol (conservative added to GH in NutropinAq), or drugs with a similar chemical structure.
* Was treated with any other Investigational Medicinal Product (IMP) within the last 30 days before study entry.
* Has any mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study, and/or evidence of an uncooperative attitude.
* Has abnormal baseline findings, any other medical condition(s) or laboratory findings that, in the opinion of the Investigator, might jeopardise the subject*s safety or decrease the chance of obtaining satisfactory data needed to achieve the objectives of the study.
* Has a birth weight and/or length below -2 SDS for Swedish reference charts. Patients will not be excluded due to an unknown birth weight or length.
* Has a known cause of short stature, or any significant concomitant disease that is likely to interfere with growth or with the study schedule/objectives, or is a known contraindication to GH treatment such as: chromosomal abnormalities (known syndromes associated with short stature, and skeletal dysplasias); growth failure due to high doses of glucocorticosteroids, hypothyroidism, chronic illnesses; malignancy, intra-cranial tumor; chronic disease such as insulin-dependent diabetes mellitus; chronic infectious disease; chronic renal insufficiency; chronic heart failure; chronic hepatic disease; celiac disease; chronic pulmonary disease; active rheumatic disease; psychosis; neurofibromatosis; McCune Albright syndrome; dysmorphic syndromes such as Russell-Silver syndrome, Leri-Weill syndrome, achondroplasia, etc; and emotional deprivation. Hypothyroidism adequately substituted with thyroid hormone replacement therapy is not an exclusion criterion. For girls, the karyotype, to eliminate a Turner syndrome, is mandatory. In case of a positive Rappold score (> 4), a SHOX defect has to be excluded.
* Has dysmorphic features suspect for chromosomal breakage syndromes.
* Has known causes of decreased IGF-I (e.g. undernutrition).
* Has an abnormal sitting height:height ratio SDS (<-2 or >+2), corrected for bone age, according to Dutch references.
* Has any abnormality at laboratory screening according to the Dutch consensus protocol (see appendix 3).
* Is likely to require treatment during the study with drugs that are not permitted by the study protocol (see appendix 4).

* Has active neoplasia or suspected neoplasia.
* The parents are investigator site personnel directly affiliated with the study, or are the immediate family of investigator site personnel directly affiliated with the study. Immediate family is defined as spouse, parent, child, or sibling, whether biological or legally adopted.
* Is unable or unwilling to comply with the study visits or the test schedule required by the protocol.
* Patients not affiliated to the health insurance system will not be allowed to participate in this trial.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NutropinAq
Generic name:	somatropin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	08-07-2011

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-019980-13-NL
CCMO	NL32198.029.11