Randomized double blind multi-centre study of the effects on low-dose pegvisomant treatment in acromegalic subjects in whom the IGF1 levels has been normalized by long-acting somatostatin analogues

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Primary Study Objective:To assess the efficacy and safety of the co-administration of low-dose pegvisomant (40 mg, administered via subcutaneous injection given once a week) and long-acting somatostatin analogs (administered once monthly) on the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON39522

Source
ToetsingOnline

Brief title
PEQoL

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Acromegaly, somatotrofinomas

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W,Pfizer

Intervention

Keyword: Acromegaly, insulin sensitivity, pevisomant, Quality of life

Outcome measures

Primary outcome

change in the AcroQol-physical score at the end of the treatment period

Secondary outcome

Secondary Study Objectives:

To assess the effect of low-dose pegvisomant co-administration on:

* Total body water / body weight.

* Blood pressure

* HbA1c

* BNP levels

* Ring-size

* IGF-I levels

* Safety based on:

* Adverse events, clinical examination, vital signs

* Glucose tolerance

* Standard hematology and biochemistry, including liver function tests

Study description

Background summary

Recent improvements in the medical treatment of acromegaly has resulted in better biochemical disease control in virtually every acromegaly patient. The current consensus on the goals of treatment of acromegaly has focused on normalization of IGF1 and GH and thereby a reduction in long-term morbidity and mortality [1-2]. However, normalization of levels of total serum IGF1 and GH do not necessarily reflect optimal quality of life (QoL) nor relief of symptoms, in acromegalic patients [3-7]. From the patient*s perspective an important parameter of disease control is QoL. To quantify the symptoms and QoL in patients with acromegaly, the Patient-Assessed Acromegaly Symptom Questionnaire (PASQ) [8-9] and the Acromegaly Quality of Life Questionnaire (AcroQoL) have been developed [10]. In a prospective, double-blind, placebo-controlled, crossover trial QoL was assessed by AcroQoL and PASQ to assess the effects of the addition of a weekly low dose of pegvisomant in patients with acromegaly whose levels of IGF1 were within the age-adjusted normal limits during long-term SRIF analog therapy [11]. After 16 weeks of treatment with 40 mg pegvisomant weekly, the patients' quality of life improved, as indicated by increases in the AcroQoL total score and the AcroQoL score's physical dimension. These improvements were accompanied by a reduction in the total PASQ score and in improvement of perspiration, soft-tissue swelling and overall health status. Moreover, these symptoms; perspiration and soft-tissue swelling can also be provoked during overdosing GH treatment in patients with GH deficiency.
The improvements in patients' quality of life, and signs and symptoms of acromegaly were not accompanied by a significant decrease in IGF1 level. Only change in body weight correlated with the improvement in the AcroQoL score's physical dimension, but the treatment-related decrease in body weight was not significant. The pegvisomant-related improvement in patients' quality of life might be also explained by the mode of action of somatostatin analogs. Somatostatin analogs reduce portal insulin concentration and the number of available growth hormone receptors in the liver, and can directly inhibit IGF1 production by hepatocytes. These mechanisms suggest that whereas the liver becomes relatively resistant to growth hormone during somatostatin analog treatment, acromegalic symptoms still persist in other parts of the body. One might expect that treatment of this 'extrahepatic acromegaly' with low-dose, weekly pegvisomant could improve the growth-hormone-dependent signs and symptoms and the patient's quality of life. The observed improvement in quality of life with combination therapy calls into question the widely used step-up approach, according to which patients are only treated with pegvisomant if somatostatin analog monotherapy is not able to normalize IGF1 levels. Although in some individuals IGF1 levels clearly decreased during PEG-V co-treatment, for the whole group, IGF1 did not decrease significantly. This observation might be explained by an observation by Segev et al. [12], who

reported that a GH receptor antagonist in rodents was able to block (in this case, renal) GH actions at lower concentrations than were necessary to decrease serum IGF1 and somatic growth. However, our study was powered to detect a difference in PASQ score and not designed to detect a difference in IGF1. Therefore, it is possible that studies in larger populations will observe a significant decrease.

The improvement in QoL can not be explained by a recall phenomenon of the questions. Our study assessed QoL over a 4-month period and it is internationally accepted that in
most studies, a 2-wk period between test and retest is enough to circumvent the memory effect [13-14].
Therefore we would like to conduct a study in a large group of patients. To assess the efficacy and safety of the co-administration of low-dose pegvisomant (40 mg, administered via subcutaneous injection given once a week) and long-acting somatostatin analogs (administered once monthly) on the Quality of Life over 16 weeks in 40 acromegalic patients.
The primary endpoint will be the change in the AcroQol-physical score at the end of the treatment period.
Secondary Study Objectives:
To assess the effect of low-dose pegvisomant co-administration on:
Total body water / body weight, Blood pressure, HbA1c, BNP levels, Ring-size and IGF-I levels.
Safety based on: Adverse events, clinical examination, vital signs, Glucose tolerance, Standard hematology and biochemistry and including liver function tests.
References:
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Study objective

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* Safety based on:
* Adverse events, clinical examination, vital signs
* Glucose tolerance
* Standard hematology and biochemistry, including liver function tests

Study design

This will be a multicentre, randomized double blind parallel study

Intervention

Treatment with Pegvisomant 40 mg weekly or placebo

Study burden and risks

there are little to no site effect with the administration of pegvisomant.
Other procedures are the same for every acromegaly patient, who visits the out patients clinic

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Acromegalic patients will be recruited in order to ensure 40 evaluable patients will enter the co-treatment period. All subjects should previously be treated with somatostatin analogues during which treatments their IGF-I levels should have normalized.

Inclusion criteria:
All patients must fulfill the following:
At the screening visit,
* Provision of written informed consent prior to any study related procedures.
* Male or female aged between 18 and 75 years inclusive
* The patient must have had documentation supporting the diagnosis of acromegaly based on elevated GH and/or IGF-1 levels.
* The patient is treated with lanreotide Autogel or octreotide LAR for at least 6 months and has a serum IGF-1 level above the 60th percentile and below ULN, 28 days after the last injection.

Exclusion criteria

Patients will not be included in the study if he/she:
* Has undergone pituitary surgery or radiotherapy within 6 months prior to study entry.
* It is anticipated that the patient will receive pituitary surgery or radiotherapy during the study.
* Has a history of hypersensitivity to lanreotide, octreotide or pegvisomant or drugs with a similar chemical structure.
* Has already been treated with a somatostatin analogue associated with pegvisomant.
* Has received a dopamine agonist within 6 weeks prior to study entry.
* Has been treated with any unlicensed drug within the last 30 days before study entry.
* Has abnormal hepatic function at study entry (defined as AST, ALT, gGT, alkaline phosphatase, or total bilirubin above 2 ULN).
* Is at risk of pregnancy or is lactating. Females of childbearing potential must provide a negative pregnancy test within 5 days before the start of the study and must be using contraception. Non-childbearing potential is defined as post-menopause for at least one year, surgical sterilization or hysterectomy at least three months before the start of the study.
* Has a history of, or known current, problems with alcohol or drug abuse.
* Has a 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 jeopardize the subject*s safety or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study.
* Renal insufficiency, clearance < 60 ml/min
* Participation in a clinical trail in the last 12 months

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-08-2013
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Somavert
Generic name:	Pegvisomant
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	18-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-07-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 24622
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
Other	3032
EudraCT	EUCTR2011-004231-31-NL
CCMO	NL37992.078.11
OMON	NL-OMON24622

Study results

Date completed: 22-05-2016

Summary results

Trial ended prematurely