Stepwise Medical Treatment of Cushing*s Disease: a prospective open label multi-center trial with SOM230 mono- and combination therapy with dopamine agonists and ketoconazole

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

Summary

ID

NL-OMON30660

Source
ToetsingOnline

Brief title
Stepwise Medical Treatment of Cushing's disease

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Cushing's disease, hypercortisolism

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: Cabergoline, Cushing, Ketoconazole, SOM230

Outcome measures

Primary outcome

The primary outcome measure of the study is normalization of cortisol production which is assessed by measurement of urinary cortisol excretion and plasma and salivary cortisol levels.

Secondary outcome

Secundary utcome measures include quality of life scores and bone metabolism- and clotting parameters.

Study description

Background summary

Cushing*s disease is caused by an ACTH-producing pituitary adenoma leading to cortisol overproduction. Currently, there is no medical treatment modality available which combines optimal clinical efficacy with minimal toxicity. Cushing's disease is therefore primarily treated by pituitary surgery, with a success rate of 60-70 %, eventually followed by radiotherapy. The mean period after which radiotherapy becomes effective is two years. Medical treatment is temporarily applied as pre-treatment before pituitary surgery and after radiotherapy, but the clinical utility of available drugs such as ketoconazole is limited due to lack of efficacy or serious toxicity.
The currently available somatostatin analogs, which suppress hormone overproduction by various neuroendocrine tumors, have no inhibitory effects on ACTH production in Cushing's disease. This is explained by the fact that these somatostatin analogs preferentially bind to somatostatin receptor subtype (sst) 2, whereas corticotroph adenomas predominantly express sst5. SOM230 is a novel somatostatin analog that binds with high affinity to sst 1, 2, 3 and 5. In

vitro, SOM230 suppresses ACTH secretion and the combination of SOM230 and ketoconazole has additive effects on ACTH secretion and cell growth of corticotroph tumor cells. In a pilot study SOM230 decreased cortisol production in patients with Cushing's disease with complete normalization of cortisoluria in a minority of patients. Higher SOM230 dosages (1200 mcg daily), however, can induce a (transient) worsening of glucose tolerance in Cushing's disease.
In addition to sst 5 expression, about 80 % of corticotroph adenomas express dopamine subtype 2 receptors (DA2). Both in vitro and in vivo dopamine agonists have inhibitory effects on ACTH production by corticotroph tumor cells. Dopamine agonist monotherapy normalizes cortisol production in about 40 % of patients. So the majority of corticotroph adenomas simultaneously express sst5 and DA2 to a variable degree. It is anticipated that these adenomas will respond beneficially to a combination of SOM230 and DA2-agonists.
Ketoconazole is currently the standard therapy for pre-treatment in high dosages of 800 to 1200 mg daily. This is, however, frequently accompanied by gastro-intestinal side effects and hepatotoxicity. In dosages of 400-600 mg daily, ketoconazole plasma concentrations are reached (between 10-6M and 10-5M) which combined with SOM230 had additive inhibitory effects on ACTH secretion by corticotroph tumor cells in vitro. The combination of SOM230 and low-dose ketoconazole may therefore be more effective and less toxic than high-dose ketoconazole monotherapy.

Study objective

The objective of the study is to improve medical treatment of Cushing's disease by combining partially independent medical therapies which act through differential mechanisms. Given the high affinity of SOM230 to sst5 and considering the facts that patients with Cushing*s disease are prone to develop glucose intolerance and that in the majority of patients ACTH production can only partially be controlled by SOM230, there seems a rationale to treat patients with Cushing*s disease with low to moderate dosages of SOM230 and to combine this, when control of hypercortisolism is not accomplished, with agents with additive or potentiating effects, i.e. dopamine agonists and ketoconazole. Therefore, this study uses a stepwise approach of medical treatment of patients with Cushing*s disease with SOM230 as basic treatment modality, sequentially extended with cabergoline and low-dose ketoconazole, according to parameters of hypercortisolism. As such, maximum clinical efficacy will be coupled to minimum toxicity.

Study design

The total study period is estimated at 60 days which compares to the period which is currently used to treat patients with cortisol lowering drugs before pituitary surgery. All patients will be treated with the same medication schedule. Treatment starts with administration of SOM230 s.c. 100 mcg three times daily. If after 10 days urinary free cortisol excretion (UFC) is

normalized, this SOM230 dosage will be continued. If UFC is not normalized, the dosage SOM230 will be increased to 250 mcg s.c. three times daily. At day 20, patients will again be evaluated and if UFC is normalized, patients will continue to receive SOM230 250 mcg three times daily. In case of persistent hypercortisolism, cabergoline will be added to SOM230 in a dosage of 0.5 mg every other day which is increased to 1 respectively 2 mg every other day in 15 days. At day 45, patients will again be evaluated and if hypercortisolism is not controlled, ketoconazole will be added to SOM230 and cabergoline in a lower dose (600 mg daily) than the standard dose (800-1200 mg). The last evaluation will be performed at day 60, after which patients can continue medication or can undergo transsphenoidal adenomectomy.

Intervention

Intervention consists of medical therapy (see study design)

Study burden and risks

The burden for patients includes subcutaneous administration of the study medication (SOM230), 4 additional admission days during the study period, filling in of quality of life questionaires and more frequent collection of 24 hour urine.
Higher dosages of SOM230 can induce a transient worsening of glucose tolerance. Therefore, in this study a lower dose is applied with careful monitoring of glucose levels. Finally, during cortisol-lowering therapy hypocortisolism can theoretically develop for which patients are instructed and monitored.

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

Patients with Cushing's disease, i.e. with hypercortisolism due to an ACTH-producing pituitary adenoma. Eligible for enrolment are: naive patients with Cushing*s disease, patients with residual hypercortisolism after recent transsphenoidal adenomectomy and patients with recurrent Cushing*s disease.

Exclusion criteria

- Patients with poorly controlled diabetes mellitus indicated by a HbA1c % > 8.5 %.
- Patients with a disturbed liver function indicated by serum bilirubin, ALAT, ASAT or alkaline phosphatase levels > 2.5 x ULN.
- Patients with renal insufficiency indicated by serum creatinine levels > 2.0 x ULN
- Patients with symptomatic cholelithiasis.
- Pregnant patients or patients who desire to become pregnant during the study period.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-09-2007
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dostinex
Generic name:	Cabergoline
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nizoral
Generic name:	Ketoconazole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	volgt
Generic name:	Pasireotide

Ethics review

Approved WMO Date:	27-02-2007
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-04-2007
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: 20587
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2006-004080-55-NL
CCMO	NL13656.078.07
OMON	NL-OMON20587