Ketoconazole and octreotide as medical treatment for Cushing's disease.

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20862

Source
Nationaal Trial Register

Health condition

Cushing's disease
Ziekte van Cushing

Sponsors and support

Primary sponsor: Erasmus MC Rotterdam
Source(s) of monetary or material Support: None

Intervention

Outcome measures

Primary outcome

Urinary free cortisol excretion.

Secondary outcome

1. Parameters of coagulation and fibrinolysis;

2. Parameters of bone turnover;

3. Quality of life.

Study description

Background summary

N/A

Study objective

Octreotide, a somatostatin analog that preferentially binds with sst2, is frequently used in the treatment of somatotropic pituitary adenomas and neuroendocrine tumors. The glucocorticoid-mediated sst2 downregulation in corticotroph adenoma cells explains why octreotide is hardly effective with respect to inhibition of ACTH production in patients with Cushing’s disease. In contrast, octreotide does inhibit ACTH production in Nelson’s syndrome, a condition in which patients with Cushing’s disease have undergone bilateral adrenalectomy and hence, the corticotroph adenoma cells are not exposed to high levels of cortisol (9). From this, it can be hypothesized that cortisol-lowering therapy with adrenal blocking agents like ketoconazole may induce upregulation of sst2 in corticotroph adenomas of patients with Cushing’s disease. Indeed, preliminary data show that corticotroph adenomas from patients with normalized preoperative UFC excretion (after medical pre-treatment) have significantly higher sst2 mRNA expression levels compared to adenomas from patients with elevated preoperative UFC concentrations. This could potentially have consequences for the efficacy of octreotide in lowering ACTH production by corticotroph tumor cells.

Study design

Baseline, followed by monthly evaluation untill the end of the study period (ie 9 months).

Intervention

The total study period is estimated at 9 months. Treatment starts with administration of ketoconazole 200 mg four times
daily. Urinary free cortisol (UFC) excretion will be measured after 1, 2 and 3 months. As soon as UFC excretion has normalized, octreotide treatment will be initialized at a dose of 20 mg every 4 weeks. Before start of octreotide treatment, an octreotide test will be performed with serial measurement of ACTH concentrations. If UFC has not normalized after 2 months of ketoconazole monotherapy, the ketoconazole dosage will be increased to 3 times 400 mg daily. If after two months of ketoconazole-octreotide combination therapy UFC levels are still normal, ketoconazole will be stopped. Patients are then treated with octreotide monotherapy until the end of the study period. If UFC excretion (mean of 2 collections) increases again (>125% the upper limit of normal (ULN)) under octreotide/ketoconazole combination therapy or octreotide monotherapy, the octreotide

dosage will be increased to 30 mg every 4 weeks. If UFC excretion does not normalize under ketoconazole monotherapy, combination therapy with cabergoline (0.5 mg every other day (qod), which is gradually increased to 1 to 2 mg qod in 15 days) will be started. After 15 days, the ketoconazole dosage will then be decreased from 1200 mg daily to 800, 600 and 400 mg daily, respectively, in 4 weeks. These patients will not be treated with octreotide.

Contacts

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Eligibility criteria

Inclusion criteria

Both naïve patients with Cushing’s disease and patients with residual hypercortisolism after recent transsphenoidal adenomectomy are eligible for enrolment. Finally, patients with recurrent Cushing’s disease can also be included.

Exclusion criteria

1. Patients with a disturbed liver function indicated by serum bilirubin, ALAT, ASAT or alkaline phosphatase levels > 2.5 x ULN;

2. Patients with renal insufficiency indicated by serum creatinine levels > 2.0 x ULN;

3. Patients who are already treated with cortisol lowering therapy can only be included after a wash-out period of 4 weeks followed by re-assessment for hypercortisolism;

4. Patients with symptomatic cholelithiasis;

5. Patients with a history of pituitary irradiation;

6. Pregnant patients or patients who desire to become pregnant during the study period.

Study design

Design

Study type:	Interventional
Intervention model:	Factorial
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-12-2011
Enrollment:	10
Type:	Anticipated

Ethics review

Positive opinion

Date:	08-12-2011
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 36055
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL3038
NTR-old	NTR3186
CCMO	NL37105.078.11
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON36055

Study results

Summary results
N/A