The Effects of Epidermal Growth Factor Receptor (EGFR) Inhibition on Pulmonary Arterial Hypertension Associated with Systemic Sclerosis
A phase II controlled open-label safety and efficacy study.

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The first objective is to evaluate the safety of cetuximab in patients with scleroderma associated PAH. The secondary objective is to assess efficacy.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON30491

Source
ToetsingOnline

Brief title
EGFR inhibition in SSc-PAH

Condition

- Heart failures
- Connective tissue disorders (excl congenital)
- Pulmonary vascular disorders

Synonym
high pulmonary vascular pressure associated with scleroderma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Epidermal Growth Factor Receptor Cetuximab, Pulmonary Arterial Hypertension, Systemic Sclerosis

Outcome measures

Primary outcome

To describe the safety of cetuximab in scleroderma associated PAH.

Secondary outcome

To explore the efficacy of cetuximab in terms of: stroke volume, 6 minute walk

test, changes on HRCT, changes in nailfold microcirculation, changes in

molecular parameters (NT-proBNP)

Study description

Background summary

The prognosis of Pulmonary arterial hypertension (PAH) associated with scleroderma continues to be poor with a 3-year survival of 56%, despite implementation of new therapies. Therefore, new therapeutic strategies are warranted. One such strategy could be pharmacological inhibition of the epidermal growth factor receptor (EGFR), as recent research shows that the EGFR plays an important role in the pathogenesis of both PAH and scleroderma. The chimeric monoclonal antibody Cetuximab (ErbituxÒ) against the extracellular domain of the EGFR is registered for the treatment of colorectal cancer and SCCHN. In this study, we evaluate the use of Cetuximab in the treatment of scleroderma associated PAH.

Study objective

The first objective is to evaluate the safety of cetuximab in patients with scleroderma associated PAH. The secondary objective is to assess efficacy.

Study design

This will be a phase II study, open-labelled, in one hospital in the Netherlands. The first phase consists of the successive enrollment of three patients. After evaluation, enrollment will be enhanced to a total number of 20 patients.

Intervention

Cetuximab, loading dose 400 mg/m2 week 1. week 2 t/m week 11 maintainance dose of 250 mg/m2.

Study burden and risks

Number of institutional visits: 15. Number of physical examinations 15. Number of blood samples: 15. Other invasive investigations: Right heart catheterization 1x; skin biopsy 2x.
Risks associated with investigations: risks associated with right heart catheterization (1:2000 major complications) and skin biopsies. Major risks associated with investigational product: 5% allergic side effects; severe infusion reactions 3% of subjects, fatal outcome < 1 in 1000; 5% conjunctivitis; 80% skin toxicity of which 15% severe (CTCAE Grade 3); 25 out of 100 patients report dyspnoea.
SSc-PAH is a severe disease with a poor prognosis, but this intervention methods may provide advantages over existing therapy in terms of efficacy and treatment burden compared with existing therapy.

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

A subject is eligible for inclusion in this study only if all of the following criteria apply:
1. Written informed consent
2. Systemic sclerosis
3. PAH with a mean PAP of above 25 mmHg measured during rest.
4. PVR above 300 dynes
5. TLC > 70 %
6. NYHA class III and/or 6 Minute Walk Test < 80% predicted
7.Conventional PAH treatment and/or bosentan and/or sildenafil treatment
8. Stability on medication during the previous 3 months (defined as stable or decrease of 6 MWT after 3 months of treatment).

Exclusion criteria

A subject will be excluded from this study in case of the following criteria:
1. Left ventricular dysfunction
2. Valvular heart disease
3. Pericardial constriction
4 Wedge pressure >/= 15 mmHg
5. Chronic thromboembolic pulmonary hypertension
6. Uncontrolled sleep apnea.
7. History of malignancies
8. Overt right heart failure
9. History or presence of skin ulcerations
10. Women of child-bearing potential (WOCB) who are unwilling or unable to use contraceptives
11. Sexually active fertile man not using effective birth control if their partners are WOCB
12. Severe abnormality of the cornea

13. Inadequate hematologic function defined by an absolute neutrophil count < 1,500/mm3, platelet count < 80.000/mm3 and hemoblobin level of < 9 g/dL
14.-Inadequate hepatic function defined by a total bilirubin level 1.5 times the upper limit of normal (ULN) and ASAT levels 2.5 times ULN
15. Inadequate renal function defined by a serum creatinine level > 1,5 times ULN (alternative: Cockroft <50 ml/min).
16. Substances that inhibit CYP3A4 activity, such as rifampicin, phenytoin, ketoconazole, itraconazole (see section 6.4.5)
17. Severe interstitial fibrosis on HRCT

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-10-2006
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Erbitux
Generic name:	Cetuximab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-10-2006
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2007
Application type:	Amendment
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	EUCTR2006-002081-19-NL
CCMO	NL12242.029.06