The Effects of Epidermal Growth Factor (EGFR) Inhibition on Pulmonary Arterial Hypertension Associated with Systemic Sclerosis.

No registrations found.

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

Summary

ID

NL-OMON27131

Source
NTR

Brief title
N/A

Health condition

18-year old patients with systemic sclerosis-associated pulmonary arterial hypertension (SScPAH)

Sponsors and support

Primary sponsor: VU University Medical Center
Source(s) of monetary or material Support: None

Intervention

Outcome measures

Primary outcome

Safety.

Secondary outcome

Efficacy, measured by effects on six minute walk test, stroke volume, changes n HRCT, NT-pro-BNP.

Study description

Background summary

Background of the study:
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.

Objective of the study:
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.

Study population:
> 18-year-old patients with scleroderma-associated PAH

Intervention (if applicable):
Cetuximab, loading dose 400 mg/m2 week 1. week 2 t/m week 11 maintainance dose of 250 mg/m2.

Primary study parameters/outcome of the study:
To describe the safety of cetuximab in scleroderma associated PAH.

Secundary study parameters/outcome of the study (if applicable):
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)

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable):
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.

Study objective

As EGFR plays a role in pathogenesis of both pulmonary arterial hypertension and systemic sclerosis, EGFR inhibition will lead to beneficial effects in disease course.

Intervention

All participants will receive cetuximab at a loading dose of 400 mg/m2 in week 1, followed by a weekly dose of 250 mg/m2 starting from week 2, up to a total of 12 weeks.

Contacts

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Eligibility criteria

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).

Study design

Design

Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Suspended
Start date (anticipated):	01-01-2007
Enrollment:	20
Type:	Anticipated

Ethics review

Positive opinion

Date:	29-12-2006
Application type:	First submission

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
NTR-new	NL844
NTR-old	NTR858

Register	ID
Other	: 155/2006
ISRCTN	ISRCTN75611179

Study results

Summary results
N/A