BENEFIT study

No registrations found.

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

Summary

ID

NL-OMON27093

Source
Nationaal Trial Register

Brief title
BENEFIT

Health condition

IPF; Idiopathic pulmonary fibrosis; interstitial lung disease; lung fibrosis
Longfibrose; interstitiele longziekten
TNF-alpha; anti-TNF-alpha antibodies

Sponsors and support

Primary sponsor: Investigator's initiated study performed by BENEFIT study group
Source(s) of monetary or material Support: Centocor BV
Einsteinweg 92
2333 CD Leiden

Intervention

Outcome measures

Primary outcome

Change in FVC from baseline

Time to disease progression (ATS criteria)

Secondary outcome

Cytokines

-BAL: pro-inflammatory and pro-fibrotic cytokines; growth factors; MMP's; surface (activation) markers on resident cells

- Serum:pro-inflammatory and pro-fibrotic cytokines; growth factors; MMP's; surface markers on resident cells

- Blood: surface (activation) markers on white blood cells

Clinical secondary endpoints

- Six minute walk distance (6-MWD)

- Borg dyspnea score after 6-MWT

- Difference in O2 saturation and heart rate before and after 6-MWT

- PO2 and p(A-a)O2 at rest and room air

- HRCT: fibrosis and groundglass

Lung function (FVC,TLC,RV,DLco)

Study description

Background summary

Idiopathic Pulmonary Fibrosis (IPF) is a relatively rare interstitial lung disease of unknown etiology with a median survival between 2 and 4 years. Treatment of IPF is still a major therapeutic challenge;

standard treatment includes corticosteroids and azathioprine or cyclophosphamide. However, the available studies on standard treatment of IPF have not proven a significant effect on survival.
There is compelling evidence for an important role of tumor necrosis factor-alpha(TNF-a) in the pathophysiology of IPF. TNF-a has a direct pro-fibrotic potential by stimulation of (myo)fibroblast proliferation and collagen synthesis and its role involves additional activities

in regulation of inflammatory and immune responses. In animal models of fibrosis a pivotal role for TNF-a was demonstrated; induction of fibrosis could be inhibited by concomitant treatment with soluble TNF-a receptors.

Therefore, we hypothesize that the inhibition of TNF-a by the chimeric monoclonal anti-TNF-a antibody infliximab (Remicade®) will affect inflammatory and pro-fibrotic cytokine expression and thereby will slow-down disease progression in IPF.

Patients (n=18) treated with standard therapy (prednisolone and azathioprine) for at least three months will be randomly assigned to receive additional intravenous infliximab (5 mg/kg) or placebo at week 0,2,6,12,18,24,30,36,42 and 48.

Primary endpoints are change form baseline in Forced Vital Capacity and time to disease progression according to the ATS criteria. Secondary endpoints include among others analyses of pro-inflammatory and pro-fibrotic mediators and growth factors in broncholaveolar lavage fluid and serum.

Study objective

Inhibition of TNF-alpha in IPF (idiopathic pulmonary fibrosis) will affect inflammatory and pro-fibrotic cytokine expression and thereby will slow-down disease progression in IPF

Study design

Clinical assessments

- week 0,14 and 52

- if indicated (time to disease progression)

Bronchalveolar lavage at week 0 and 14

Serum at week 0,14,32 and 52

Blood at week 0,14 and 52

Intervention

Intavenous administration of infliximab (chimeric monoclonal anti-TNF-alpha; 5 mg/kg) vs placebo (2:1) next to standard treatment with prednsiolone and azathioprine; given at week

0,2,6,12,18,24,30,36,42, and 48.

Contacts

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Eligibility criteria

Inclusion criteria

1. Diagnosis of IPF(2):

a) If possible a thoracoscopic or open lung biopsy showing UIP. A thoracoscopic or open lung biopsy must be performed in patients <51 years old. Transbronchial biopsy is strongly advocated and should show no features to support an alternate diagnosis.

b) Insidious onset of otherwise unexplained dyspnea on exertion.

c) Presence of bibasilar, inspiratory crackles.

d) Abnormal lung function: VC < 90% predicted or TLC < 90% predicted, plus DLco < 90% predicted.

e) Parenchymal abnormalities on chest X-ray.

f) HRCT: bilateral parenchymal abnormalities with peripheral and bibasilar distribution showing linear and reticular opacities, usual in conjunction with subpleural honeycombing and architectural distortion.

g) Exclusion of other forms of interstitial lung diseases.

h) In patients > 50 years fulfilling all above mentioned criteria a BAL to exclude other causes of interstitial lung disease is sufficient and a lung biopsy is not necessary.

2. Show stable disease or failure to respond to standard medication (i.e. azathioprine and prednisolone) (as defined by the ATS/ERS criteria(2)) during a minimum of 3 months prior to the study, with a minimum dose of prednisolone (or equivalent) of 20 mg daily, and azathioprine 2 mg per kg with a maximum of 200 mg daily during 3 months.

3. Men and women between 40 and up until 79 years.

4. Diagnosis of IPF within the past 36 months

5. Men and women must use adequate birth control measures (eg, abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) for the duration of the study and should continue such precautions for 6 months after receiving the last infusion.

6. The screening laboratory test results must meet the following criteria:

a. Haemoglobin > 8.5 g/dL (5.3 mmol/L)

b. WBC > 3.5 x 109/L

c. Neutrophils > 1.5 x 109/L

d. Platelets > 100 x 1012/L

e. SGOT (AST) and alkaline phosphatase levels must be within 3 times the upper limit of normal range for the laboratory conducting the test.

7. Patient must be able to adhere to the study visit schedule and other protocol requirements.

8. Patient must be able to communicate meaningfully with the study personnel.

9. The patient must be capable of giving informed consent and the consent must be obtained prior to any screening procedures.

10. Must have a chest radiograph within 3 months prior to first infusion with no evidence of malignancy or infection.

11. Are considered eligible according to the tuberculosis (TB) eligibility assessment, screening, and early detection of reactivation rules defined in Section 4.3

Exclusion criteria

1. Critical low lung function: FVC < 50%.

2. Artificially ventilated.

3. Inability to undergo a broncho-alveolar lavage.

4. Patients that were treated with IFN-alpha

5. Women who are pregnant, nursing, or planning pregnancy within 1,5 years after screening (ie, approximately 6 months following last infusion).

6. Use of any investigational drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.

7. Treatment with any other therapeutic agent targeted at reducing TNF (eg, pentoxifylline, thalidomide, etanercept, adalimumab etc.) within 3 months of screening.

8. Previous administration of infliximab.

9. History of receiving human/murine recombinant products or known allergy to murine products.

10. Serious infections (such as pneumonia or pyelonephritis) in the previous 3 months. Less serious infections (such as acute upper respiratory tract infection [colds] or simple urinary tract infection) need not be considered exclusions at the discretion of the investigator.

11. Documented HIV infection.

12. Active hepatitis- B or hepatitis-C.

13. Are considered ineligible according to the TB eligibility assessment, screening, and early detection of reactivation rules defined in Section 4.3.

14. Have or have had an opportunistic infection (eg, herpes zoster [shingles], cytomegalovirus, Pneumocystis carinii, aspergillosis, histoplasmosis, or mycobacteria other than TB) within 6 months prior to screening.

15. Have current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, cardiac, neurologic, or cerebral disease (including demyelinating diseases such as multiple sclerosis).

16. Concomitant congestive heart failure and/or cor pulmonale, including medically controlled asymptomatic patients. Criteria for cor pulmonale are based on cardiac sonography:

estimated systolic pulmonary artery pressure > 40 mmHg at rest.

17. Presence of a transplanted organ (with the exception of a corneal transplant > 3 months prior to screening).

18. Malignancy within the past 5 years (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence).

19. History of lymphoproliferative disease including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (such as nodes in the posterior triangle of the neck, infra-clavicular, epitrochlear, or periaortic areas), or splenomegaly.

20. Known recent substance abuse (drug or alcohol).

21. Poor tolerability of venipuncture or lack of adequate venous access for required blood sampling during the study period.

22. Have a chest radiograph at screening that shows evidence of malignancy, infection, or any abnormalities suggestive of TB as described in Section 4.3.2.1

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-07-2004
Enrollment:	18
Type:	Anticipated

Ethics review

Positive opinion
Date: 12-04-2008
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	NL1229
NTR-old	NTR1274
Other	MEC : 04/043
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results
N/A