Bosentan (Tracleer®) in patients with Behçet*s disease: a Pilot Study.

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· To determine therapeutic efficacy of Tracleer in patients with active Behcet disease. Furthermore:· To study cytokine and immunological patterns and ET-1levels in those patients.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON31428

Source
ToetsingOnline

Brief title
Tracleer in Behcet

Condition

- Immune disorders NEC

Synonym
Amantiades-Behcets disease, Behcets disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Actelion BV,Actelion Pharmaceuticals

Intervention

Keyword: Behcet, bosentan, endothelin

Outcome measures

Primary outcome

Primary endpoint

· A decrease in the score in the BDCAF of > 10 in patients with BD with a BDCAF

score of > 20.

Secondary outcome

Secondary endpoints

· ET-1 levels in relation with BDCAF.

· Study of cytokine patterns in relation with therapy and BDCAF.

· T cell patterns in relation with therapy and BDCAF.

Study description

Background summary

Behçet*s disease (BD) is a vasculitis characterized by an inflammatory process of unknown etiology. It originates amongst countries alongside the Silk Route and is most common in Turkey with a prevalence of 430 per 100.000 in certain areas. In Western Europe approximately 2 of every 100.000 persons are affected. Patients present with aphthous oro-genital ulcers, inflammatory skin changes and uveitis, but may also demonstrate arthritis, thrombosis, neurological symptoms or colitis. BD can be diagnosed by fulfilling the criteria according to the International Study Group for BD. The disease specific pathergy test in which a sterile skin puncture yields a sterile pustule is one of theses criteria. In this light, BD may worsen after traumatic (skin) events provoking a Th-1 response in which (pro) inflammatory cytokines interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) are mainly involved2. The affected sites illustrate vaso-occlusive vasculitis with infiltration of predominantly activated T-cells and neutrophilic granulocytes. Therefore, therapy is mainly directed against T-cells, granulocytes or TNF-α. Toxicity and therapy failure limit the effect of immunosuppressive therapy.

The endothelin-1 (ET-1) receptor antagonist bosentan blocks vaso-occlusion and inhibits endothelial cell proliferation, inflammation and subsequent fibrosis in patients with pulmonary hypertension (PHT). This beneficial effect might also be relevant for patients with BD, because in those patients high levels of ET-1 have been shown in serum and BAL fluid samples comparable to patients with PHT. Furthermore, decreased or extremely elevated nitric oxide (NO) levels in serum and affected tissues in BD patients might reflect a dysfunctional balance with ET-1 and endothelial stress. These observations might be even more relevant since endothelial NO synthase (eNOS) polymorphisms have recently been described BD patients. The more than 100 treated BD patients in the ErasmusMC outpatient clinic (OPC) constitute the most significant BD population amongst Dutch Hospitals. It will therefore be very interesting to use the ET-1 inhibitor bosentan to provide new insight in the etiology and a novel treatment of inflammatory diseases such as BD in this patient cohort.

Study objective

· To determine therapeutic efficacy of Tracleer in patients with active Behcet disease. Furthermore:
· To study cytokine and immunological patterns and ET-1levels in those patients.

Study design

Double blinded randomized pilot study

Intervention

Randomization between placebo and Tracleer bid 125mg.

Study burden and risks

No additional risk or burden will be caused by participation with the study. Tracleer is a registered and safe treatment for various diseases.

Only 4-30cc extra of patient blood will be drawn for investigational purposes in a group that already provides blood samples during these routine blood checks.

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

1. Behcet disease (BD) patients classified according to the criteria according to the International study group for BD
2. BD patients not responding to their usual therapy (BDCAF > 20)
3. Non life -or sight threatening active disease.
3. Adequate birth control measures in women of childbearing age during and for 6 weeks after receiving the last administration.
4. The screening laboratory test results must meet the following criteria:
§ Hemoglobin >= 6.5 mmol/L.
§ WBC >= 3.0 x 109/L.
§ Neutrophils >= 1.5 x 109/L.
§ Platelets >= 100 x 109/L.
§ SGOT (AST), SGPT (ALT) and alkaline phosphatase levels must be within 3 times the upper limit of normal (ULN) range for the laboratory conducting the test.
§ Creatinine clearance > 20 ml/min.
5. Patient must be able to adhere to the study visit schedule and other protocol requirements.
6. The patient must be capable of giving informed consent and the consent must be obtained prior to any screening procedures.

Exclusion criteria

1. Age < 18 years.
2. Women who are pregnant, nursing, or planning pregnancy within 38 weeks after enrollment.
3. Hypotension, defined as systolic blood pressure less than 85 mm Hg
4. Use of any of the following drugs: glybenclamide, calcineurin inhibitors (eg, cyclosporine A, tacrolimus) or fluconazole. A.
5. Use of any investigational drug within 1 month prior to screening or within 5 half-lives of the investigational agent, whichever is longer.
6. Liver enzymes > 3 times the ULN, Creatinine clearance of < 20ml/min.
7. Patients with known hypersensitivity to Tracleer® or to drugs with similar chemical structures.
8. Current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurological, infectious or cerebral disease.
9. Malignancy within the past 5 years (except for treated squamous or basal cell carcinoma of the skin without evidence of recurrence).
10. Known recent substance abuse (drugs or alcohol).
11. Poor tolerability of venipuncture or lack of adequate venous access for required blood sampling during the study period.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-10-2008

Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tracleer
Generic name:	bosentan
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	26-02-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2008
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-09-2008
Application type:	Amendment
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-006714-42-NL
CCMO	NL20785.078.07