Towards optimizing infliximab therapy in severe sarcoidosis patients: personalized medicine

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To assess the percentage of patients with at least one subtherapeutic infliximab trough serum concentration, being < 1 mg/l.To assess the percentage of patients positive for AIAs at a minimum of one timepoint.To assess the percentage of patients...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Ocular infections, irritations and inflammations
Study type	Observational non invasive

Summary

ID

NL-OMON39486

Source
ToetsingOnline

Brief title
Infliximab in sarcoidosis patients

Condition

- Ocular infections, irritations and inflammations
- Respiratory tract infections
- Skin and subcutaneous tissue disorders NEC

Synonym
Besnier Boeck Disease, Interstitiel Lungdisease, Sarcoidosis

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: anti-infliximab antibodies, Infliximab, Sarcoidosis, TNF-&alfa

Outcome measures

Primary outcome

Infliximab trough serum concentrations and the number of patients with at least one subtherapeutic concentration, being < 1 mg/l.

AIAs and the number of patients who are positive for AIAs at a minimum of one timepoint.

The number of patients that have both a subtherapeutic serum concentrations of infliximab and are positive for AIAs at a minimum of one timepoint.

Baseline, trough and peak TNF-α, TACE, and TNF-α receptors concentrations.

Symptoms, ACE-, CRP-, IL-2R-concentrations at baseline and during infliximab treatment (at 3 months and after 6 months) and concentration changes from baseline.

FVC and DLCO at baseline and after 6 months of treatment and parameter changes from baseline.

Response i.e. presence/absence of disease progression and/or changed/unchanged

abnormalities, assessed by X-thorax, HRCT and PET scanning at baseline and

after 6 months of treatment.

The number of patients clinically classified as a responder to infliximab

treatment after 6 months of treatment.

Secondary outcome

Expression of TNF-α, TACE, and TNF-α receptors at mRNA and protein levels at

basline, 3 and 6 months.

Study description

Background summary

Sarcoidosis is a systemic granulomatous disease that primarily affects the lung and lymphatic systems of the body. The cytokine tumor necrosis factor (TNF)-α is critical to the development of the granulomatous inflammation. Corticosteroids and methotrexat are considered to be the standard treatment for sarcoidosis. Due to the non-specificity, long-term toxicity and unproven efficacy of these therapies (5, 6), there is a clinical need in some cases for more effective and safer therapies such as infliximab. This is a TNF-α inhibitor that binds to TNF-α and neutralizes its biological activities. Infliximab is not registered as a treatment for sarcoidosis yet. However, CVZ has classified sarcoidosis as an orphan indication for which the drug is considered to be rational pharmacotherapy. Although most of RA and CD patients are achieving at least partial clinical response to infliximab, 30-40% of them are not responding (10, 11). This is also recognized in the treatment of sarcoidosis in daily clinical practice. Those patients are classified as responders and nonresponders, due to the interindividual variation in response to infliximab

So far, the relationship between infliximab concentrations and response in sarcoidosis patients has not been studied and the optimal dosing regimen is still unknown. Infliximab serum trough level of < 1 mg/l has been considered as a sub-therapeutic level, higher trough levels are associated with improved response in RA (15) and lower level of anti-infliximab antibody development (16). Researchers have shown that the response to infliximab in RA patients follows the trough levels of infliximab and the formation of anti-infliximab

antibodies (17). Recently, more data became available regarding the association between low infliximab serum concentrations and the failure of infliximab in RA (18,19).
The hypothesis to be tested in this study is that serum infliximab concentrations, anti-infliximab antibodies, TNF-α levels, and the genetic background of the patients are responsible to the interindividual variation in response to infliximab.

Study objective

To assess the percentage of patients with at least one subtherapeutic infliximab trough serum concentration, being < 1 mg/l.

To assess the percentage of patients positive for AIAs at a minimum of one timepoint.

To assess the percentage of patients with both a subtherapeutic infliximab trough serum concentration and positive for AIAs at a minimum of one timepoint.

To assess the percentage of patients classified as responder after 6 months of infliximab treatment.

To assess the correlation between TNF-α, TNF-α receptors versus TACE concentrations.

To study the pharmacokinetics of infliximab.

To study the TNF-α concentrations in course of the infliximab treatment and to compare concentrations with baseline values.

Study design

This is a prospective observational study in patients who are diagnosed with sarcoidosis and routinely treated with infliximab.

Study burden and risks

Blood will be drawn from the patients prior to each infusion and one hour after their completion at each visit. The risks of drawing blood from a vein are minimal. Patients are requested to visit the hospital at two additional timepoints.

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

- patients diagnosed with sarcoidosis.
- patients treated with infliximab
- capability of giving informed consent

Exclusion criteria

· vaccination with live viral or bacterial vaccines within the previous 3 months, or within the next 3 months of the last doses.
· cases of active or untreated latent tuberculosis (by mantoux-Elispot/TBC-IGRA)
· serious infections within the past 2 months
· serious right-sided heart failure or cor polmunale

· known malignancy
· Hepatitis B
· paitients with allergic reactions to the monocolonal antibodies or their fragments
· oppotunistic infections last 6 months
· HIV
· transplantation
· pregnancy or bearstfeeding

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-01-2011
Enrollment:	52
Type:	Actual

Ethics review

Approved WMO

Date:	08-10-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	06-01-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	11-06-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
Other	99
CCMO	NL31842.100.10