The role of regulatory T cells in the pathogenesis of sarcoidosis.

Published: 18-10-2012
Last updated: 04-07-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Observational invasive

Summary

ID

NL-OMON45069

Source
ToetsingOnline

Brief title
SARTREG

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
sarcoidosis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: pathogenesis, regulatory T cells, sarcoidosis, Tregs

Outcome measures

Primary outcome

Number, distribution and phenotype of Tregs in peripheral blood, lung (BAL and EBBs) and lymph nodes (FNAs); the suppressive function of Tregs on allogenic T cell proliferation in the peripheral blood; viability and apoptotic susceptibility of Tregs in the peripheral blood; the cytokine and chemokine environment of the Tregs in peripheral blood, lung and lymph nodes; the gene expression profile of Tregs in the peripheral blood, lung and lymph nodes (including apoptosis-related and survival genes).

Secondary outcome

Clinical parameters indicating disease progression or resolution after two years.

Study description

Background summary

Sarcoidosis is a granulomatous disorder of unknown cause. Current therapy is immunosuppressive, not curative and often ineffective as we do not thoroughly understand the underlying pathogenesis of sarcoidosis. It is thought to arise from an exaggerated Th1/Th17-response upon exposure to one or more (unidentified) antigens in susceptible individuals. Failure of immunosuppressive regulatory T cells (Tregs), could contribute to an ongoing and uncontrolled Th1/Th17 response in sarcoidosis. Our preliminary data suggests an impaired immunosuppressive function of peripheral blood Tregs of sarcoidosis patients, possibly due to an intrinsic survival disadvantage. Therefore, we hypothesize that in sarcoidosis, Tregs are critically involved in the observed inflammatory response and that sarcoidosis originates from altered intrinsic properties of Tregs, leading to a common pathway of an exaggerated

Th1 and/or Th17 cell response with the characteristic granuloma formation and T cell alveolitis as result.

Study objective

Our primary objective is to identify which intrinsic defect in Tregs is crucial for sarcoidosis pathology. To this end we will examine the genetic and functional properties of Tregs in the peripheral blood and at the site of disease, i.e. the lung and draining lymph nodes. Our secondary objective is to identify a possible correlation between genetic and functional properties of Tregs and disease progression.

Study design

For this study we will compare the numbers, phenotype, function, viability and gene expression profile of Tregs from sarcoidosis patients with Tregs from healthy individuals in three different compartments of the immune system, i.e. blood, lungs and draining lymph nodes. To identify key aspects of the immunopathology specific for sarcoidosis compared to other granulomatous disorders, we will also investigate the blood from tuberculosis patients.

During routine diagnostic work-up, patients suspected of sarcoidosis will undergo a venapuncture and a bronchoscopy with a broncho-alveolar lavage (BAL) and endobronchial biopsy (EBB) or endoscopic ultrasound fine-needle aspiration (EUS/EBUS-FNA), depending on hospital protocols and physicians* preference. During these procedures, additional blood, residual BAL and two additional EBBs or EUS/EBUS-FNAs are obtained. Similarly, from healthy controls blood, BAL and EBBs will be obtained. From tuberculosis patients additional blood will be obtained during routine diagnostic venapuncture.

Study burden and risks

From patients suspected of sarcoidosis, during routine diagnostic procedures, two additional EBBs or FNAs are obtained, next to collection of residual material or withdrawal of extra blood during routine venapuncture. A small questionnaire is taken shortly before the bronchoscopy. After 2 years follow up the patient will be asked to donate extra blood during routine visits at the outpatient clinics. We estimate that participation in this study will pose a minimal additional risk of complications and patient discomfort. For healthy volunteers, a bronchoscopy together with a BAL and EBB is reported to be a safe procedure.
We do not expect increased discomfort for tuberculosis patients participating in this study as no additional intervention will be required to draw extra blood. Participants will not have direct personal benefit from participating in this study. The results from this study could be beneficial for the patient

population. Healthy volunteers will receive a financial compensation.

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

Sarcoidosis patients should have:
- Newly diagnosed pulmonary sarcoidosis, established using the criteria of the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG)
- Written informed consent
- Age > 18;Healthy controls should have:
- Written informed consent;
- Age > 18.;Tuberculosis patients should have:
- Newly diagnosed tuberculosis with pulmonary caseating granulomas.
o Diagnosis is based on European Respiratory Society (ERS) guidelines.

- Written informed consent;
- Age > 18.

Exclusion criteria

Sarcoidosis patients may not have:
- Used oral corticosteroids, antimycotica or antibiotics 1 weeks prior to the collection of materials.
- Used immunosuppressive medication or biologicals 3 months prior to the collection of materials.
- A possible infection of the upper- or lower respiratory tract 4 weeks prior to the collection of materials.
- Other diseases which could influence pulmonary function, granuloma formation and/or the immune system, such as:
o Chronic obstructive pulmonary disorder (COPD) or astma in the medical history;
o Auto-immune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), myasthenia gravis or Goodpasture*s syndrome;
o Malignancies;
o Human immunodeficiency virus (HIV);
o Pregnancy;
o Allergies such as allergic rhinitis. ;Healthy controls may not have:
- Sarcoidosis;
- An abnormal spirometry with a FVC or FEV1 below the 80% of the predicted value;
- A liaison with the coordinating or principal investigator, which could likely influence the decision to participate in this study voluntarily (in concordance with the WMO -article 5);
- See exclusion criteria sarcoidosis patients. ;Tuberculosis patients may not have:
- Sarcoidosis
- See exclusion criteria sarcoidosis patients.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-12-2012
Enrollment:	140
Type:	Actual

Ethics review

Approved WMO Date:	18-10-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-08-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-11-2017
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
CCMO	NL41353.078.12