Quantitative and qualitative determination of natural occuring regulatory t cells in blood and bronchoalveolar lavage fluid of patients with pulmonary sarcoidosis and healthy volunteers.

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The primary goal of this research is to characterize the regulatory Treg population in peripheral blood and bronchoalveolar lavage in patients with sarcoidosis compared to healthy controls. What is the frequency of these cells, what is the phenetype...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON29919

Source
ToetsingOnline

Brief title
Role of regulatory t cells in patients with pulmonary sarcoidosis.

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Besnier Boeck disease, Sarcoidosis

Research involving

Human

Sponsors and support

Primary sponsor: St. Antonius Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: immunology, lofgren, regulatory t cells, sarcoidosis

Outcome measures

Primary outcome

phenotypical analysis: 1 - expression of protein (absolute en percentual)

2 - intensity of protein expression per

cel

both in lavage-fluid and peripheral blood

functional analysis: 1 - suppression of proliferation (%)

2 - cytokine measurement (concentration)

in peripheral blood

physiological analysis: measurement of auto-antibodies in peripheral blood

genetic analysis: when abovementiones analyses show significant differences

with respect to protein expression or cytokine production relevant genes

(PTPN22, CTLA4, CD103, TGFβ-1) will be genotyped and screened for present

polymorphisms.

Secondary outcome

not applicable

Study description

Background summary

Pulmonary sarcoidosis is a chronic inflammatory disorder of unknown aetiology, characterized by non-caseating granulomas and compartmentalized inflammation with accumulation of activated CD4+ lymphocytes in the lung [1,2]. Untill now an antigen at which the inflammation is directed, has not been discovered although a possible role of bacteria in saroidosis has been extensively studied. Especially Gram-positive and intracellular bacteria, such as mycobacteria and propionibacteria, have been suggested to play a role in the aetiology of sarcoidosis [3-5].
Persistant antigen stimulation may result in chronic inflammation and can cause immune pathology to surrounding lung tissue. The balance between protective and immunopathological effects of the Th1-type cellular immune response may determine a good prognosis in patients with sarcoidosis, ie Löfgren syndrome or a chronic manifestation with severe lung fibrosis and destruction of lung tissue.

It has been well documented that a unique population of lymphocytes, regulatory T cells, are responsible for suppression of cellular immune responses. In addition to cell-intrinsic peripheral tolerance mechanisms such as anergy induction and peripheral deletion, CD4+CD25bright Tregs play indispensible roles in the maintaince of natural tolerance, in averting autoimmune responses, as well as controlling inflammatory reactions [6-12].
Regulatory T cells suppress both Th1- and Th2-mediated immune responses in such a way that suficient immunity remains for clearing infectious agents while unwanted immunopathology is prevented. In case of shortage of regulatory T cells the potential amplitude of Th1 and Th2 responses is increased resulting in excessive T cell immunity as associated with autoimmune disease, asthma and allergy, allograft rejection, and some cases of early pregnancy loss. Abundance of regulatory T cells, on the other hand, will reduce the potential amplitude of Th1 and Th2 responses and therefore may prevent adequate immunity to tumours and infectious diseases, but also effective vaccination against infections [6,13].

In the past few years, intensive research has led to numerous publications describing the role of Tregs in a variety of autoimmune or chronic inflammatory diseases [14-19]. With respect to sarcoidosis, Planck et al 2003 [20] found an increased percentage of peripheral blood CD4+CDbright lymphocytes in patients

with active Löfgren syndrome compared to those with resolved disease and healthy controls and increased CD4+CDbright lymphocytes in BAL compared to healthy controls, suggesting accumulation of Tregs during inflammatory conditions as a strategy for down-regulating harmful inflammatory reactions. And very recently, an article published in february 2006, Miyara et al [21] found an expanded but functional impaired global Treg subset in sarcoidosis patients with active disease. Specifically, they demonstrate that CD4+CDbright cells isolated from the peripheral blood of patients with active sarcoidosis can suppress the responder CD4+ T cell proliferative response but not the secretion of inflammatory cytokines TNFa and IFNg.

While both studies point towards an explicit role of Tregs in active disease compared to resolved disease or healthy controls, differences in Treg pupulations between acute and chronic manifestations of sarcoidosis, associated with specific clinical and radiogical characteristics, are not described.

As mentioned above, an insufficient Treg populatin (in number or functional inadequate), may lead to chronic inflammation in sarcoidosis patients and finally to irreversible scar tissue or fibrosis.

We hypothesise that regulatory T cells are increased in patients with sarcoidosis and that patients with Löfgren syndrome have a distinct Treg lymphocyte population compared to sarcoidosis patients with chronic manifestations. Phenotypical analysis of Treg cells from peripheral blood and BAL as well as functional ex vivo stimulation assays will elucidate the role of Tregs in sarcoidosis, in particular their involvement in chronic disease course.

References

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Study objective

The primary goal of this research is to characterize the regulatory Treg population in peripheral blood and bronchoalveolar lavage in patients with sarcoidosis compared to healthy controls. What is the frequency of these cells, what is the phenetype of these cells and are these cells functional competent. The secundary goal is the comparison between patients with an acute form of sarcoidosis, i.e. Löfgren syndrome, and patients with chronic manifestations of sarcoidosis. The hypothesis is that the latter patient group has a deviant Treg population.

Answers to these questions give insight to the immune (patho) physiology of the disease and possible therapeutical opportunities to treat the disease.

Study design

The design of this study is observational. Bronchoalveolar Lavage and venapuncture are once performed in included patients for diagnostic purposes, extra blood is drawn from existing venapuncture.

Study burden and risks

The BAL and venipuncture are performed for diagnostic puposes. Risks of drawing extra blood from existing venapuncture are minimal.
This research will benefit future patients.

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

Clinical strong suspicion of sarcoidosis
Alveolar lymphocytosis (>=15%)
Histological confirmed sarcoidosis
firstly presenting

Exclusion criteria

previous steroid use , smoking

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):	27-02-2007
Enrollment:	70
Type:	Actual

Ethics review

Approved WMO

Date:	20-07-2006
Application type:	First submission
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
CCMO	NL11549.100.06