CD4+ T cells and immune ageing; major players and predictors for disease activity in giant cell arteritis

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Primary Objective: to study the differences in CD4+ T cell subsets (Th1/Th2/Th17/Tregulatory/Tsenescent) between GCA patients and healthy controls at diagnosis and during follow up and in remission. Secondary Objective(s): - To characterize the cell...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Autoimmune disorders
Study type	Observational invasive

Summary

ID

NL-OMON44732

Source
ToetsingOnline

Brief title
CD4+ T cells and immune ageing in giant cell arteritis

Condition

- Autoimmune disorders
- Connective tissue disorders (excl congenital)

Synonym
Large vessel vasculitis and Polymyalgia rheumatica

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen

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

Intervention

Keyword: aging, frailty, giant cell arteritis, T lymphocyte

Outcome measures

Primary outcome

Is there a relation between CD4+ T cell subset diversity and GCA?

Secondary outcome

- Which cell subsets migrate into the arterial wall in GCA?

- Are there any biomarkers (CD4+ T cell subsets, cytokines, IRP) predicting

relaps in GCA patients?

- Is there a relation between the IRP and frailty?

- Are there any biomarkers (CD4+ T cell subsets, cytokines, IRP) that

distinguish PMR patients from GCA patients, or from patients that have both

diseases?

- Which cell subsets migrate into the joints of PMR patients?

- Are there shifts in the cell subsets in GCA and PMR patients in remission

- Which genes are involved in the pathogenesis of GCA and PMR

Study description

Background summary

Age-associated alterations of the immune system (immunosenescence) have a strong clinical impact and may contribute to susceptibility to infectious diseases, autoimmunity and cancer in the elderly. Instruments, such as the Groningen Frailty Index, have been devised to assess this general age-associated susceptibility to diseases, also named frailty.
Especially the adaptive arm of the immune system is affected by ageing.

Immunosenescence is the result of 1) thymus involution leading to a steady decline in the production of naïve T cells, 2) shrinkage of the T cell repertoire through continuous antigen stimulation favouring the development of functionally altered, oligolonal, senescent T cells (identified by CD28 loss and telomeric erosion) and 3) a chronic low degree of inflammation (termed inflamm-aging) evidenced by increased serum levels of inflammatory cytokines and acute phase proteins. Longitudinal studies (that included healthy octo-, nono- and centenarians) have identified a so called immune risk phenotype (IRP) that is associated with poor immune function and increased mortality risk: a CD4+/CD8+ T cell ratio < 1, low CD19+ B cell counts and a poor lymphocyte proliferative response.
In general the risk of developing autoimmune disease increases with age. This is particularly true for temporal arteritis or giant cell arteritis (GCA). GCA manifests as a vasculitis predominantly affecting medium and large arteries. Classically, this disease develops in older people (older than 50 years of age; mean age 72) with an almost similar incidence in men and women. In patients with GCA, a syndrome of systemic inflammation accompanies vascular manifestations such as occlusive vasculopathy causing stroke, blindness and aortic arch syndrome. Standard treatment of GCA is done with high dose corticosteroids. Relapse of GCA is frequently seen in 50% of patients within 1-25 months.
The etiology of GCA remains obscure, but progress has been made in clarifying the pathophysiology of the disease. Systemic inflammation in GCA is substantiated by reports showing elevated levels of TNFα and IL-6 in patients. Interestingly, like rheumatoid arthritis, GCA is associated with carriage of certain HLA-DR4 alleles (HLA-DRB1*0401 and HLA-DRB1*0404), although it has been suggested that different epitopes within these alleles are relevant in the two diseases. In RA the HLA-DR4 alleles are associated with production of the highly specific anti-citrullinated protein antibodies (ACPAs), but autoantibodies have not been found in GCA so far. Nonetheless, in both diseases a significant role for CD4+ T cells is suggested, since HLA-DR is involved in antigen presentation to these cells. Previously, Weyand and Gorozny, proposed a novel interpretation for the involvement of the HLA-DR4 haplotype in autoimmune disease. They noted that HLA-DR4+ individuals (both patients and healthy persons) experience premature ageing of their T cells as defined by shorter telomere lengths, decreased T cell receptor diversity and loss of CD28. Although studies have shown that aged T cells may demonstrate decreased proliferative responses, they are known to produce considerable amounts of IFN-γ, perforine and granzyme B. Further expansion of these aged cytotoxic T cells may be further enhanced in chronic inflammatory disease due to persistent immune activation, but it is also seen after CMV and EBV infection. In addition the functionality of aged T cells is altered due to acquisition NK cell markers. One of these molecules is CD161 that may identify T cells with tissue migratory properties.
As expected, CD4+ T cells appear to be major players in the pathophysiology of GCA. It is now appreciated that the naïve CD4 (helper) T cell is a multipotential precursor which can be triggered to differentiate towards Th1,

Th2, Th17 and T regulatory phenotypes dependent on APC function and the composition of the local cytokine milieu. Especially IFN-γ producing CD4+ T cells are found in large numbers in affected arterial walls. Whether these cells are Th1 cells or aged CD4+CD28- T cells is unknown. Recently IL-17 producing CD4+ T cells were also demonstrated in the inflamed arterial walls. Studies on the functional role of T regulatory cells in GCA are lacking.
It is currently unclear how aging affects the prevalence and functionality of different effector and regulatory T cell subsets. The altered cytokine milieu as a consequence of inflamm-aging may 1) accelerate replicative senescence in T cells and 2) favour a shift (away) from the T regulatory arm of the immune system towards the pro-inflammatory Th17 effector subset associated with tissue pathology. Both replicative senescence and the Treg to Th17 shift may be responsible for the decline in peripheral CD4 T cell numbers (an IRP parameter) as both senescent T cells and Th17 cells are thought to migrate to the tissues by virtue of CD161 expression and may promote autoimmune vascular injury.

In addition, an interesting feature of GCA is that it frequently associates (in 40-50% of cases) with polymyalghia rheumatica (PMR), although PMR may also present as an isolated disease. The annual incidence of PMR in persons > 50 years varies from 13 per 100 000 in Southern Europa to almost 70 per 100 000 in Scandinavia. Patients with PMR typically present with muscle stiffness/pain and a high ESR. However, the pathological substrate of PMR appear to be synovitis, instead of inflammation of muscles. Even in the absence of typical GCA symptoms, PMR patients may actually have GCA in 9-21% of cases, as population-based studies have shown. It*s feasible to think that the pathogeneses of GCA and PMR are somehow related, yet distinct at the same time. Interestingly, evidence is present suggesting that T cells may be the defining factor. It has been shown that resident dendritic cells in large/medium sized arteries of GCA patients are activated, resulting in attraction and activation of T cells in the artery wall. However, when the authors looked at the large/medium sized arteries of PMR patients, they surprisingly found activated dendritic cells in the artery walls as well. Yet, these activated dendrtic cells were not accompagnied by the presence of activated/differentiated T cells. So the vessel wall of PMR patients may actually be *ready* to receive T cells, but the T cells won*t infiltrate the blood vessel, and therefore most PMR patients don*t have vasculitis. Using an animal model, the same authors further confirmed this idea by showing that T cells of GCA could indeed readily infiltrate the artery samples of PMR patients, but not that of controls persons. So T cells seem to determine whether a patient has PMR only, or GCA as well. But how T cells of PMR patients differ from T cells in GCA patients remains unknown.

GCA and PMR patients in the long run go into remission. We would like to know what the characteristics are of peripheral CD4 + T-cells, B-cells and monocytes, in patients in remission. It is also unclear which genes are involved in the pathogenesis of GCA and PMR. From the genetic profiles we hope to get more insight in the pathways important in the development of GCA and/

or PMR.

Study objective

Primary Objective: to study the differences in CD4+ T cell subsets (Th1/Th2/Th17/Tregulatory/Tsenescent) between GCA patients and healthy controls at diagnosis and during follow up and in remission.

Secondary Objective(s):
- To characterize the cell subsets that migrate into the arterial wall in GCA
- To identify a biomarker (CD4+ T cell diversity, the IRP, cytokines) predicting relapse in GCA
- To study the relation between the IRP and frailty (as assessed by the GFI)
- To identify a biomarker (CD4+ T cell diversity, the IRP, cytokines) distinguishing PMR from GCA or the combination of both diseases.
- To characterize the T cell subsets that migrate into the joints of PMR patients
- To characterize the genes involved in the pathogenesis of GCA and PMR

Study design

Observational study with assessment of CD4+ T cell subsets and cytokines in the blood, and in PMR patients also synovial fluid and tissue.

Study burden and risks

The burden for patients is the filling in of questionaires and the extra blood withdrawal during regular visits. Healthy and infectious controls will have to pay a visit to the outpatient clinic, fill in questionnaires and give blood.
The risks associated with the questionnaires and venapunction in this study we consider as 'nihil'. Although a common procedure in rheumatology, arthrocentesis (joint puncture) may lead to infection in rare cases (<0,1%).

Patients and controls will gain no direct benefit from the study. This study is directed to unravel pathogenetic mechanisms involved in GCA and PMR. We hope that it will lead to new targets for therapy (for example CD161). But the most important benefit foreseen will be the identification of biomarkers (IRP/CD4+ T cell diversity/CD161 expression) that predict which patients are at risk for relapse after withdrawal of corticosteroid therapy and should continue therapy to prevent morbidity like blindness, and which patients are likely to remain disease free and can be safely withdrawn from therapy limiting high cumulative doses of corticosteroids. Furthermore we hope to find markers that will allow a better discrimination between PMR and GCA patients, and especially biomarkers that predict which PMR patients develop GCA. In addition we will study T cell subsets in the joints of PMR patients, which may guide future specific

therapeutic studies in PMR.
Finally we hope to link aging of the immune system with frailty in elderly. In times of rising age expectancies and demographic shifts towards older populations, we believe that more insights in the role of the immune system in the ageing process, will be useful to develop healthy ageing strategies in the future.

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

GCA patients
1. Fulfilling ACR criteria for GCA
2. Not yet treated with corticosteroids
3. Age >= 50 years

4. Being able to give informed consent

GCA patients in remission
1. Fulfilling ACR criteria for GCA
2. Age >= 50 years
3. Being able to give informed consent ;PMR patients
1. Fulfilling Healey criteria for PMR
2. Not yet treated with corticosteroids
3. Age >= 50 years
4. Being able to give informed consent

;PMR patients in remission
1. Fulfilling Healey criteria for PMR
2. Age >= 50 years
3. Being able to give informed consent ;Healthy controls
1. Having no chronic disease
2. Age >= 50 years
3. Being healthy according to SENIEUR protocol
4. Being able to give informed consent;Infectious controls
1. Having no chronic disease
2. Age >= 50 years
3. Being healthy according to SENIEUR protocol, exept for an urinary tract or upper airway infection
4. Being able to give informed consent

Exclusion criteria

GCA patients
1. Not fulfilling the ACR criteria for GCA
2. Concomitant chronic diseases that may affect immune system (such as prior or current malignant disease, active infectious disease, other rheumatological disease, kidney disease, active allergy etc.) ;PMR patients
1. Not fulfilling Healey criteria for PMR
2. Concomitant chronic diseases that may affect immune system (such as prior or current malignant disease, active infectious disease, other rheumatological disease, kidney disease, active allergy etc.) ;Healthy controls
1. Having chronic diseases
2. Not being healthy according to SENIEUR protocol;Infectious controls
1. Having chronic diseases
2. Not being healthy according to SENIEUR protocol, except for an urinary or upper airway infection.;GCA patients, PMR patients, healthy and infectious controls
1. No informed consent
2. Severe anaemia defined as a Hb of less than 6,0 g/dL

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:	Recruiting
Start date (anticipated):	01-10-2010
Enrollment:	1500
Type:	Actual

Ethics review

Approved WMO Date:	13-09-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-09-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	20-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-01-2014
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-04-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-11-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	18-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL31734.042.10