TNFR2 Agonism and the Ex Vivo Expansion of Regulatory T Cells of Patients with Autoimmune or Inflammatory Disease

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In the current *proof of principle* study, it is hypothesized that ex vivo expansion of Tregs originating from patients with the prototypic examples from the spectrum of autoimmune or inflammatory diseases (SLE, AAV, MS or CD) can be accomplished by…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON50055

Source
ToetsingOnline

Brief title
TNFR2 Agonism and Ex Vivo Expansion of Regulatory T Cells

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders
- Demyelinating disorders

Synonym
'AAV'; 'Crohn's disease', 'CD', 'MS'; 'Systemic lupus erythematosus', 'Multiple sclerosis', 'SLE'; 'ANCA-associated vasculitides'

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Autoimmune disease, Ex vivo expansion, Regulatory T-lymphocyte, TNFR2 agonism

Outcome measures

Primary outcome

The primary outcomes of the current study are the following: First, we would like to assess the degree of in vitro proliferation of MACS-isolated regulatory T cells, obtained from patients with autoimmune or inflammatory disease as specified in the hypothesis, in response to the currently applied ex vivo expansion protocol, i.e. interleukin (IL)-2, monoclonal antibodies anti-CD3 and anti-CD28, rapamycin, and the monoclonal anti-TNFR2 antibody MR2-1. The degree of proliferation of Tregs from healthy blood donors will serve as the standard to which the proliferation of Tregs from patients with autoimmune disease will be compared. Second, the suppressive capacity of the expanded Tregs will be analyzed by means of a suppression assay, in which different ratios of Tregs and responder T cells are incubated together and the degree of proliferation of the responder cells is measured. The suppressive capacity of the Tregs can then be expressed as a function dependent on the ratio of Tregs to responder cells (dose-response curve). This function will facilitate the identification of the effective dose (ED) necessary to inhibit 50% of the responder cells from proliferating (ED50). Furthermore, the supernatant of the suppression assay

will be screened for the presence of cytokines.

Secondary outcome

The secondary outcomes of the current study are the following: The phenotype (intra-/extracellular) of the Tregs will be analyzed in order to describe the Treg population obtained from the diseased individual and to determine the degree of homogeneity before and after expansion. In order to do so, several characteristic surface and intracellular markers will be investigated. Furthermore, the stability of the expanded Tregs will be assessed by (i) exposing the expanded cells to an artificial pro-inflammatory environment and tracking the cytokine secretion, (ii) analyzing the degree of demethylation of the DNA region *T-Cell Specific Demethylated Region* (TSDR), and (iii) evaluation of expression of characteristic, effector T-cell-associated transcription factors in response to exposure to a pro-inflammatory environment.

Study description

Background summary

In autoimmune and inflammatory disease, current immunosuppressive interventions focus mainly on the inhibition of the pro-inflammatory response. Unfortunately, this highly effective approach also entails potentially severe side effects. The ex vivo expansion and subsequent re-administration of autologous regulatory T lymphocytes (Tregs) seems promising in the search for an alternative, less toxic, and more specific therapeutic approach. However, the current ex vivo expansion protocol has been shown to lead to expanded Tregs that lack sufficient stability and homogeneity, therefore hindering the transition of this therapeutic approach to the clinic. Recently, the agonistic monoclonal anti-TNFR2 antibody MR2-1 has been identified to be an important addition to the ex vivo expansion protocol due to its capability to enhance ex vivo proliferation, suppressive capacity, homogeneity, and stability. So far, the

advantageous effects of MR2-1 have only been shown in Tregs from healthy individuals. Therefore, its full potential needs to be verified in Tregs from diseased individuals. In the current *proof of principle* study, it is hypothesized that ex vivo expansion of Tregs originating from patients with autoimmune or inflammatory disease (systemic lupus erythematosus (SLE), ANCA-associated vasculitides (AAV), multiple sclerosis (MS) or Crohn*s disease (CD)) by means of the TNFR2 agonist MR2-1 can be accomplished to the same extent as seen in Tregs from healthy individuals and will lead to improved proliferation, highly suppressive capacity, high stability and increased homogeneity.

Study objective

In the current *proof of principle* study, it is hypothesized that ex vivo expansion of Tregs originating from patients with the prototypic examples from the spectrum of autoimmune or inflammatory diseases (SLE, AAV, MS or CD) can be accomplished by means of the monoclonal TNFR2 agonist MR2-1 to the same extent as seen in Tregs from healthy individuals. Furthermore, it is expected that the addition of MR2-1 to the ex vivo expansion protocol will lead to a highly suppressive capacity, increased stability, and increased homogeneity, independent of the underlying disease.

Study design

A *proof of principle* study will be performed, in which four prototypic autoimmune-diseased or immune-dysfunctional study groups will be investigated, i.e. SLE, AAV, MS, and CD, each consisting of 12 participants (Ntotal = 48 patients). A fifth study group will consist of 12 individuals as healthy controls. Of each participant, venous blood will be sampled once (100 mL): the blood sample will serve as the source for (i) regulatory T cells (CD4+CD25+CD127low) for the ex vivo expansion (duration 7 days) and (ii) responder T cells required for the suppression assay (duration 4 days) following the expansion of Tregs. In this suppression assay, the responder T cells will be co-incubated with the expanded regulatory T cells by which the suppressive capacity of the expanded regulatory T cells is assessed. Furthermore, the regulatory T cells will be analyzed according to the secondary outcomes. Other outcomes will consist of analysis of blood values (CRP, ESR, WBC, vitamin D status) and description of disease activity status (SLEDAI, BVAS, EDSS, Montreal classification/SES-CD).
The study duration will approximately be 24 months, considering that (i) processing and analyzing the regulatory T cells will take 11 days per participant and (ii) blood from a maximum of 3-4 participants can be processed simultaneously.

Study burden and risks

Burden: Single time venipuncture for blood sampling (phlebotomy), performed at the MUMC+/ZMC.
Risks: Venipuncture is associated with a low risk of bruising and pain.

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:
- Patient of the Maastricht University Medical Center (MUMC+) in Maastricht, The Netherlands, or of the Zuyderland Medical Center in Sittard-Geleen, The Netherlands
- Diagnosis of respective disease (MS, SLE, AAV, or IBD)
- Disease duration <5 years
- Ethnicity: Caucasian
- Untreated at the time of blood sampling or prednisone treatment of <10 mg/day

- Age: 18 * 65 years;Healthy Controls:
- Untreated at the time of blood sampling
- Ethnicity: Caucasian
- Age: 18 * 65 years

Exclusion criteria

Patients:
- Proven infections two weeks prior to blood sampling
- Strong immunomodulation and/or immunosuppression in the last 3 months
- Other diseases: cancer (malignancies)
- Pregnancy;Healthy Controls:
- Proven infection two weeks prior to blood sampling
- Immune-related diseases
- Other diseases: cancer (malignancies)
- Pregnancy

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):	25-02-2019
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	01-03-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-10-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL59692.068.16