T cells and innate lymphoid cells (ILCs) in cutaneous graft-versus-host disease

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Haematological disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON46564

Source
ToetsingOnline

Brief title
TIC Study

Condition

- Haematological disorders NEC
- Immune disorders NEC
- Skin and subcutaneous tissue disorders NEC

Synonym
Graft-versus-host disease, Graft-versus-host reaction

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Graft-versus-host disease, Innate lymphoid cells, Skin disease, T cells

Outcome measures

Primary outcome

Hypothesis: Pathogenic alloreactive clones in GvHD expand in skin during rejection and may be present in blood at low levels, capable of being detected by the newly developed High-throughput TCR deep sequencing. Moreover these pathogenic clones may differ in their function during times of rejection versus tolerance.

To evaluate this hypothesis, we will carry out experimentswith the following specific aims:

Aim 1: to identify pathogenic T cell and ILC clones expanded in GvHD skin lesions.

Aim 2: to study the function and possible pathogenicity of T cell and ILC clones identified in Aim 1.

Aim 3: to track the pathogenic T cell and ILC clones identified in Aim 1 in the blood of the same GvHD patients in times of tolerance versus GvHD, and study their function and phenotypic plasticity.

Secondary outcome

N/A

Study description

Background summary

Allogeneic hematopoietic stem cell transplantation (HSCT) is an important modality in the treatment of hematologic malignancies and bone marrow failure syndromes. While curative in many, allogeneic HSCT is often complicated by graft versus host disease (GvHD), an alloimmune response of donor immune cells against healthy recipient*s tissues including skin, liver, lungs and gut with high morbidity and mortality.

GvHD continues to be the main cause of non-relapse mortality and morbidity developing in more than 50% of patients after HSCT. GvHD is primarily a donor T cell-mediated syndrome whereby T cells derived from the stem cell graft elicit an immune response, resulting in host tissue damage. Despite its high prevalence and its considerable morbidity and mortality, the biology of GvHD remains incompletely understood.

At the AMC, two groups are studying GvHD immunology. Drs Tiago R. Matos (Dermatology department) is an immunologist interested in T cell biology. He has set up the T cell receptor (TCR) CDR3-specific deep-sequencing technique, to study the dynamics and function of T cell clones in health and disease, in particular in GvHD. The group of Dr Mette Hazenberg (Hematology department) has an interest in innate lymphoid cells (ILCs), a recently identified group of cells that are important in inflammatory diseases. They were the first to demonstrate the importance of ILC in GvHD of the gut.

With their joined interest in GvHD immunology of the skin Drs Matos and Hazenberg decided to join forces. They will study the immune pathophysiology of cutaneous GvHD longitudinally, using blood and skin biopsies from patients with active GvHD and after treatment, when symptoms have resolved.

Study objective

The overall aim of the study is to improve our understanding of the role of T cells and ILCs in cutaneous GvHD, to lay the foundation for the development of better therapies to treat cutaneous GvHD.

1. T cells in GvHD
The dominant cell population in tissues affected by GvHD is the T cell population, in particular CD4 and CD8 T cells that produce interferon (IFN) gamma, interleukin (IL)-17 and IL-22. In addition, the lack of immuneregulatory T cells (Tregs), that have a dampening effect on the immune response, is important in GvHD pathophysiology. To make things more complicated, it has been demonstrated that T cells are plastic: Tregs can become effector T cells, and activated T cells can become Tregs. Recently, it has become possible to study

the plasticity of T cells by tracking the fate of T cell clones, using the TCR CDR3-specific deep-sequencing technique. With this technology, we will track the fate of T cell clones that are present in the skin and blood of GvHD patients during active disease and after resolution of symptoms.

2. ILCs in GvHD of the skin
ILCs are the innate equivalents of T cells. In the past years we have presented data suggesting that IL-22 producing ILCs are important in protecting the gut from GvHD. However, IL-22 producing ILC can also have detrimental effects, as we have shown in the setting of the autoimmune skin disease psoriasis. In the present study we aim to study the contribution of ILCs in GvHD pathophysiology, by analyzing the phenotype and function of ILCs in skin and blood of patients during activate GvHD and after resolution of symptoms.

As T cells and ILCs produce the same cytokines (IFNg, IL-17 and IL-22), results will be combined and compared to study the interaction of both immune populations.

Study design

This is a single center, single arm, observational trial.

Study burden and risks

Risks associated with skin biopsy are bleeding and infection, both of which neglectable because of the small size of the biopsy. At both time points blood will be drawn. Vena puncture can result in a hematoma at the site of puncture. We hope that this research unveils the specific pathogenic subsets of T cells and ILCs that promote GvHD. Such knowledge is essential for future studies, which then can monitor those cell subsets in patients that received allogenic stem cell transplantation as a potential early biomarker of GvHD, and allow the development of better therapies to treat cutaneous GvHD.

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 with Graft-versus-host disease
- Male and female
- * 18 years of age
- Patient is willing and able to give written informed consent

Exclusion criteria

- Patients taking anticoagulant medication

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Ethics review

Approved WMO Date:	15-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL62235.018.17