T cell-mediated immunity targeting polyomavirus BK

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Clarifying the qualitative and quantitative aspects of the T cell response targeting and controlling polyomavirus BKV.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immunodeficiency syndromes
Study type	Observational invasive

Summary

ID

NL-OMON37893

Source
ToetsingOnline

Brief title
Not applicable

Condition

- Immunodeficiency syndromes
- Viral infectious disorders
- Nephropathies

Synonym
BK virus-associated nephropathy / BK virus-associated renal disease

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Nierstichting Nederland

Intervention

Keyword: BKV, polyomavirus BK, T cells

Outcome measures

Primary outcome

Numbers of BKV-specific T cells

Phenotype of BKV-specific T cells

Functional characteristics of BKV-specific T cells

Identification of new epitopes on and in the BKV virion

cytokines, chemokines and chemokine receptors in urine

Secondary outcome

the development of new tetramers through the identification of novel BKV

epitopes.

Study description

Background summary

Transplant recipients are treated with immunosuppressive agents to prevent rejection of the allograft, a process mediated by the host*s immune system. The ensuing impairment of the different compartments of the immune system, among which most prominently the T cell compartment then leads to inadequate defence against invading microorganisms among which viruses.

Polyomavirus BK (BKV) is a double-stranded DNA virus that resides in a latent state in the urogenital tract in 70-90% of the general population and is not associated with disease in immunocompetent individuals. However, in immunocompromised patients, especially in transplant recipients and to a lesser degree also in HIV patients, BKV currently is a prominent troublemaker. In renal transplant recipients it is the leading cause of graft failure, causing nephritis in up to 7% of cases. In haematopoietic stem cell recipients, BKV causes severe haemorrhagic cystitis in up to 30% of patients, a clinical entity leading to significantly prolonged hospitalisation and increased mortality. Apart from the clinical aspects, also a significant amount of resources is

currently being directed towards the monitoring of BKV replication in urine and blood in order to pre-emptively identify patients at risk of nephropathy or haemorrhagic cystitis.

Currently, the only mode of therapy with established efficacy is tapering of immunosuppressive agents so that the host*s immune system can mount a response against the virus. However, in transplant recipients this is a double-edged sword since the reconstituted immune responses not only target BKV, but also the allograft, therewith causing rejection. As such, it is of paramount importance that new modes of therapy targeting BKV are identified.

T cells, and more specifically CD8+ T cells, play an important role in the protection against viral infections, and have been shown to be important in keeping BKV infection at bay in transplant recipients. Currently, little is known about the T cell responses directed against BKV in healthy or immunocompromised patients. As such, in-depth knowledge of the qualitative and quantitative aspects of the T cell response targeting BKV, will aid in the search for new future modes of therapy such as for example vaccination or the infusion of ex-vivo generated BKV-specific T cells as been done previously in the case of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) associated disease.

Study objective

Clarifying the qualitative and quantitative aspects of the T cell response targeting and controlling polyomavirus BKV.

Study design

The study will involve one group of study subjects comprising 400 renal transplant recipients with or without BKV reactivation. The clinical management of these renal transplant recipients included is not to be influenced on any level by this study.

Blood samples will be obtained at several specific time points, in order for us to be able to identify changes in T cell numbers and phenotype in the context of the course of the disease. Sampling moments comprise: once pre-transplantation, and then consecutively at 3, 6, 9 and 12 months in the first year after transplantation. After the first year, the sampling frequency will be reduced to once every two years. If the patient shows BKV reactivation, the sampling frequency will be increased to once every month during the first year after transplantation and once every 3 months after the first year post-transplantation.
Blood samples will comprise 45 ml blood for the isolation of peripheral blood mononuclear cells (among which lymphocytes), 4.5 ml for serum measurements, 4.5 for plasma measurements and 4.5 for virologic measurements.

As such, patients will not have to come to the hospital more often than would be required of them normally. Also, patients do not have to undergo more peripheral venous punctions than that they would otherwise.

In order to identify BKV reactivation, real-time quantitative polymerase chain reaction (rt-QPCR) is used on plasma samples in all patients to measure the viral load. During the pre-transplantation work-up, and after having given written informed consent, the patient will be included, and will subsequently undergo the sampling protocol as described above.

For the identification of numbers of T cells, we will utilise fluorescent antibodies targeting a variety of different cell markers measured by flowcytometry. To identify MHCI and MHCII-restricted BKV-specific T cell responses, we will respectively utilize fluorescent HLAI-BKV-peptide tetramers and BKV-antigen pulsed APCs. Further phenotypic analysis will occur through the use of fluorescent antibodies and flowcytometry. Functionality of BKV-specific T cells will be assessed by measurement of the various cytokines, chemokines and effector molecules. Lastly, new T cell epitopes will be identified using an epitope discovery assay.

Using these laboratory techniques, we will be able to compare T cell numbers, phenotypes and T cell epitopes over the different time points, therewith revealing what kind of T cells, T cell functions and T cell epitopes are important in controlling BKV infection.

At the same time points, urine samples will be collected and frozen. At a later time point they will be analysed for the presence of pro-and anti-inflammatory cytokines and chemokines.

Study burden and risks

Patients will be burdened with the donation of extra blood samples and urine samples in addition to the samples needed for clinical practice. The sampling moments for patients will be done once pre-transplantation, followed by respectively 3, 6, 9 and 12 months during the first year post-transplantation. Thereafter, sampling moments are reduced to a 2 yearly basis. The sampling comprises 58.5 ml per sampling moment, including 45 ml for the isolation of peripheral blood mononuclear cells (among which lymphocytes) plus 4.5 ml for plasma measurements, 4.5 ml for serum measurements and 4.5 for virologic measurements. When the virologic measurements reveal viral (re)activation, sampling moments will be increased to a monthly basis in the first year post-transplantation and to a 3 monthly basis in the period after the first year post-transplantation, up until viral clearance. On the same time points, urine samples will also be obtained. As such, patients will not have to come to the hospital more often than would be required of them normally. Also, patients do not have to undergo more peripheral venous punctions than that they would otherwise. The individual patient will not directly benefit from these

extra samples taken. We regard the risk and the burden to be minimal.

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

- Being a kidney transplant recipient treated according to the standard treatment protocols applying to kidney transplant recipients treated in the Academic medical Centre Amsterdam.
- Age equal- to or older than eighteen years.

Exclusion criteria

Age under eighteen years.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-09-2012
Enrollment:	400
Type:	Actual

Ethics review

Approved WMO

Date:	15-05-2012
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	NL39356.018.12