Cell mediated immunity and the prediction of CMV disease in solid organ transplant recipients

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON33378

Source
ToetsingOnline

Brief title
CMI and CMV in organ transplantation

Condition

- Viral infectious disorders

Synonym
Cytomegalovirus infection, viral infection

Research involving
Human

Sponsors and support

Primary sponsor: University of Alberta
Source(s) of monetary or material Support: Grant van de Canadese overheid

Intervention

Keyword: Cellular Immunity, CMV, Organ transplant, Quantiferon

Outcome measures

Primary outcome

The primary study endpoint is value of the assay result at the end of prophylaxis for the prediction of CMV disease within the 6 months after stopping prophylaxis. Follow-up will be at 12 months for all patients. The definition of CMV disease will be based on the criteria recommended by the AST for use in clinical trials.

Secondary outcome

The secondary endpoint is prediction of CMV viremia and the value of measurement of CMI at other times points.

Study description

Background summary

CMV is the most common viral infection after solid organ transplantation (SOT) and is associated with significant morbidity. Without prophylaxis, most CMV disease occurs in the first 3 months post-transplant during the period of intense of immunosuppresion. SOT recipients at the greatest risk are those that are seronegative recipients of organs from seropositive donors (CMV D+/R-). Antiviral agents have proven to be useful in the prevention of CMV infection and disease in SOT recipients, including the high-risk D+/R- patients. Upon completion of prophylaxis however, CMV infection and disease occurs in about 50% and 25-30% respectively of D+/R- SOT recipients within the first year after transplant. The incidence of CMV infection following prophylaxis in D+/R- lung transplant recipients may be as high as 80%. As CMV disease occurring after prophylaxis will continue to impact morbidity and mortality in SOT recipients, it would be desirable to be able to predict which patient will develop this complication. Currently, there are no reliable methods that are routinely available to predict the risk of CMV infection or disease in an individual patient. CMV viral load testing after prophylaxis in D+/R- patients has been

shown to have poor predictive value for subsequent CMV disease. CMV serology (a measure of humoral immunity) was also shown to be only of marginal use in predicting the risk of late onset disease. Cell mediated immunity (CMI) is known to be more important than humoral immunity in controlling CMV infection. CMV infection elicits a strong virus specific CD4+ and CD8+ T-cell response. CD8+ T-cell responses to the virus often contain multiple antigen-specific reactivities including to viral pp65 or IE-1 antigens as well as pp50, glycoprotein B, and IE-2 and other antigens. CD4+ T cells also play a part in CMV control via promotion of priming, expansion and maintenance of CD8+ CMV-specific CTLs. Measuring an individual*s CMI response to CMV may be a useful predictor of the risk of CMV infection or disease after prophylaxis. Patients with a poor CMI response (especially a poor CD8+ T-cell response) could then be targeted with longer courses of antiviral prophylaxis.

Cell mediated immunity testing
Most of the previous studies have focused on CTL responses to the CMV phosphoprotein pp65. However, since CD8+ T-cell responses to CMV often contain multiple antigen-specific reactivities, measurement of CMI using epitopes restricted to a single protein may not yield adequate results. In conjunction with Dr. Rajiv Khanna (Queensland Institute of Medical Research, Australia), and Cellestis Ltd (Sydney, Australia), we have done preliminary validation and assessment of a CMI (Quantiferon-CMV) assay in which we measure the IFN-γ responses to a range of T-cell epitopes of CMV viral proteins including pp65, pp50, the glycoprotein gB, and the immediate early IE-1 antigen that are specific for a wide range of HLA class I specificities. The assay employs a peptide pool for stimulation of whole blood and is suitable for routine clinical use and evaluation in multicenter studies
The Quantiferon-CMV assay has been compared to an ELISPOT assay in a study involving 37 healthy volunteers and 25 SOT recipients. In this study, the Quantiferon-CMV assay was at least as sensitive as the ELISPOT for some CMV epitopes, and more sensitive for other CMV epitopes. In addition, the Quantiferon-CMV results highly correlated with the CMV serostatus, in both healthy volunteers and transplant recipients. In another study, the Quantiferon-CMV assay was used in HIV-infected individuals with and without a history of CMV disease. The CMV specific immune response measured by the Quantiferon-CMV assay was higher in patients without a history of CMV disease, suggesting that a positive result of the Quantiferon-CMV may predict the likelihood for developing a protective immune response against CMV.

Preliminary Data in Solid Organ Transplantation
In our validation study in 40 healthy volunteers, IFN-γ detection had an excellent correlation with CMV serostatus. In a single-center study done by our group, the CMV- CMI assay was evaluated in 108 transplant recipients including 38 D+/R- patients. Detection of CMI at 3-months post-transplant had good predictive value for protection against CMV disease (unpublished data). Based on this study, the optimal cut-off for the test in D+/R- patients was

determined to be 0.1 IU of IFN-γ/ml.

Study objective

The primary aim of this study is to determine the utility of measurement of CMV specific cell mediated immunity using the Quantiferon-CMV assay for predicting the risks of CMV infection and disease in D+/R- SOT recipients after the completion of antiviral prophylaxis. It is hypothesized that those with a strong CMI response to CMV are at low risk of subsequent CMV disease, while those with absent or weak CMI are at high risk. Theoretically the latter group could then be targeted for more prolonged antiviral prophylaxis.

Study design

Patients at high risk (based on pre-transplant serology D+/R-) will be followed longitudinally to assess the development of CMV specific CMI.
CMV cell mediated immunity will be assessed at 3 time points in each patient.
1. At the time of prophylaxis discontinuation (3 or 6 months post-transplant)
2. 1-month post-prophylaxis discontinuation
3. 2-months post-prophylaxis discontinuation

In patients who develop CMV disease, a further assessment will be done at the time of CMV disease.
The number of assessments of CMI has been kept to a minimum because 1) this will facilitate the performance of a multi-center study, 2) this will decrease costs, and 3) if ever used in a clinical setting, simple regimens for evaluation of CMI will have the most direct clinical applicability.
In patients receiving 6-months of prophylaxis, testing will be performed at 6 months, 7 months and 8 months. Immunosuppression protocols will be as per the center specific standard. Data on immunosuppression medications will be gathered to allow for analysis of this as a potential confounder.
Laboratory methods:
Cell mediated immunity will be assessed using the Quantiferon-CMV assay. CMV epitopes restricted through various HLA class I alleles (HLA-A1, HLA-A2, HLA-A23, HLA-A24, HLA-B8, HLA-B35, HLA-B41, and HLA-B57) will be used in this study. The assay is conducted in 2 parts: initially, there is an overnight incubation of patient*s blood with the CMV synthetic peptide epitopes. The next day, supernatant is harvested and quantification of IFN-γ production is performed using a standard ELISA [the latter half of the assay can be performed on frozen samples and is suitable for batch testing at a central laboratory].
All testing is performed in conjunction with a negative control (sterile PBS/no-antigen) and a positive control (PHA, positive mitogen control). A positive cut-point of 0.1 IU of γ-interferon will be used [this cut-point is based on previous data from our lab studying D+/R- patients].

Study burden and risks

Possible Benefits:
It is not known whether there will be direct benefit from being in the study. However, the information learned in this study may help other patients with similar conditions in the future.

Possible Risks:
Taking blood is briefly uncomfortable, but not dangerous. When having blood drawn, participant may have some bruising where it is taken. This may take several days to go away. Every effort will be made so that blood will be collected for the study at times when subjects are having other routine blood tests.

Contacts

Public
University of Alberta

8308-114 Street, Edonton
T6G 2E1, Alberta
Canada
Scientific
University of Alberta

8308-114 Street, Edonton
T6G 2E1, Alberta
Canada

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Adult CMV D+/R- liver transplant recipients
AND
2. All eligible patients must be scheduled to receive 3 months of either valganciclovir, oral ganciclovir, or intravenous ganciclovir prophylaxis

Exclusion criteria

1. Scheduled to receive longer or shorter than 3-6 months of prophylaxis
OR
2. Unable to provide informed consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-03-2010
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO

Date:	11-09-2009
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL28140.058.09