Immunomonitoring of stable renal transplantation patients receiving triple immunosuppressive therapy

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1. To monitor the level of immunosuppression in individual renal transplantation patients, based on cell-based ex vivo PD readout measures over a short time window (one day);2. To evaluate the relationship between the pre-dose in vitro PD effect and...

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

Summary

ID

NL-OMON55264

Source
ToetsingOnline

Brief title
Immunomonitoring of stable renal transplantation patients

Condition

- Other condition

Synonym
Immunosuppression

Health condition

Prophylaxis of the rejection of an allogeneic organ

Research involving
Human

Sponsors and support

Primary sponsor: Centre for Human Drug Research
Source(s) of monetary or material Support: CHDR funded study

Intervention

Keyword: Immunosuppressive therapy, Kidney transplantation, PD-based Drug monitoring

Outcome measures

Primary outcome

Pharmacokinetic endpoints

* Tacrolimus whole blood concentrations

* MPA plasma concentrations

* Prednisolone plasma concentration

Pharmacodynamic endpoints

* Proliferation of T cells in PHA-stimulated whole blood

* Cytokine production in PHA-stimulated whole blood

* T cell activation marker expression in PHA-stimulated whole blood

* Circulating regulatory T and B cell subsets

Safety and tolerability endpoints

* Treatment-emergent (serious) adverse events ((S)AEs).

* Concomitant medication

* Clinical laboratory tests

Secondary outcome

N.A.

Study description

Background summary

Kidney transplantation is a successful treatment option for patients with end-stage renal disease. To prevent allograft rejection, renal transplant patients need long-term immunosuppressive therapy with tacrolimus, mycophenolate mofetil (MMF) and prednisolone. The disadvantages of this maintenance treatment regimen, however, is the large intra- and interpatient variability in clinical outcome, especially for tacrolimus. Too little exposure leads to a risk of acute rejection and formation of donor-specific antibodies, while too much exposure leads to an increased risk of infection and nephrotoxicity.

To minimize adverse effects and improve effectiveness of the current treatment regimen, therapeutic drug monitoring (TDM) is routinely performed. For tacrolimus, the most common method of TDM is measuring pre-dose trough concentration (C0) in whole blood. These trough concentrations, however, are highly variable and the correlation with clinical outcome is still debatable. TDM is not standardly performed for MMF and prednisolone treatment, and therapy is usually not individualized. To improve dosing strategies and minimize adverse effects, the current TDM should be optimized. We advocate that PD-based instead of PK-based therapeutic drug monitoring, by using clinically relevant immune tests to quantify the immunosuppressive state of the individual patient, may improve the clinical outcome.

For that reason, we have developed several whole blood-based PD readout measures for the quantification of immunosuppression. These readout measures (PHA-induced cytokine production, T cell proliferation and T cell activation marker expression) were previously tested in healthy volunteers and have shown to be suitable for quantification of the immunosuppressive effect of a single dose of tacrolimus, cyclosporine A and mycophenolic acid. In the current clinical study we aim to evaluate if the selected PD readout measures are also suitable for immunomonitoring of renal transplantation patients receiving long-term triple immunosuppressive therapy. We will evaluate the relationship between drug concentrations and cellular PD measures, and between the PD measures in vitro and ex vivo.

Besides the high variability and small therapeutic window of tacrolimus, the patient*s age also affects clinical outcome. Elderly transplantation patients are generally prescribed lower doses of tacrolimus, while the dose-normalized C0 concentrations are higher than in the younger patients. Moreover, aging causes the number of effector lymphocytes to decrease, which result in a reduced immune response to the transplanted organ. These age-related changes are one of the reasons that elderly transplant recipients are more likely to

suffer from side effects of over-immunosuppression, such as diabetes and de novo malignancies. To investigate if the relationship between drug concentration and cellular PD measures changes with age, we aim to include kidney transplantation patients with a wide range in age (>18 years).

Study objective

1. To monitor the level of immunosuppression in individual renal transplantation patients, based on cell-based ex vivo PD readout measures over a short time window (one day);
2. To evaluate the relationship between the pre-dose in vitro PD effect and the post-dose ex vivo PD effect in renal transplantation patients;
3. To evaluate the relationship between the different PD readout measures (T cell activation, proliferation, cytokine production) in renal transplantation patients;
4. To evaluate the variability in PD readout measures between stable renal transplantation patients;
5. To evaluate the effect of age on the PK and PD profiles of renal transplantation patients;
6. To evaluate circulating regulatory T and B cell subsets in renal transplantation patients;
7. To evaluate the relationship between drug concentrations (tacrolimus, MPA and prednisolone) and PD readout measures in renal transplantation patients, based on a semi-mechanistic modelling approach.

Study design

Observational study in young and elderly renal transplantation patients on a combination of tacrolimus, MMF and corticosteroid treatment.
Patients will be in-house for a single visit to take PK and PD blood samples before and after their medication intake.

Study burden and risks

This study does not involve the use of investigational medical products. Renal transplantation patients enrolled in this study will be on triple immunosuppressive therapy (tacrolimus, MMF and prednisolone), which is the standard treatment for these patients and is prescribed by their treating nephrologist. The dose and regimen of these drugs will not be adjusted for their participation to this study. The main intervention that the study participants will undergo is blood withdrawal for PD measures. There is no benefit for the patients participating in this study. The only risk associated with participation is bruising from the blood sampling.

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

- Signed informed consent prior to any study-mandated procedure
- Male or female kidney transplantation patients >18 years of age (inclusive)
- Patients that have undergone a kidney transplantation > 2 years before study start
- Patients on maintenance immunosuppression with low-dose prednisolone, MMF and tacrolimus adjusted to target trough levels.
- Patients that have the ability to communicate well with the Investigator in the Dutch language and willing to comply with the study restrictions

Exclusion criteria

- The use of any medication other than the patient*s standard treatment within less than 5 half-lives prior to study participation, if the investigator judges that it may interfere with the study objectives;
- The use of immunosuppressive or immunomodulatory medication, other than the patient*s standard treatment, within 3 months before study participation, if the investigator judges that it may interfere with the study objectives;
- Any known factor, condition, or disease that might interfere with study conduct or interpretation of the results, in the opinion of the investigator.
- Unwillingness or inability to comply with the study protocol for any other reason.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-11-2021
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	09-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	01-09-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 29204
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL73304.056.20
OMON	NL-OMON29204