Multicentric, randomized trial to evaluate the efficacy of baseline Immune-risk stratification based on selective Biomarkers (HLA Eplet mismatching and donor-specific IFN-γ ELISPOT) to optimize Immunosuppressive therapy in Living-kidney transplant patients

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49228

Source
ToetsingOnline

Brief title
BIOIMMUN

Condition

- Other condition
- Renal and urinary tract therapeutic procedures

Synonym

immunosuppression after kidney transplant, preventing rejection kidney after transplant

Health condition

nier transplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Chiesi Farmaceutici

Intervention

Keyword: Biomarker stratification, Individualizing immunosuppressive therapy, Kidney transplant from living donor

Outcome measures

Primary outcome

Composite end-point evaluated at 2 years of follow-up as a proportion of

patients that meet any of the following criteria: loss of renal function,

incidence of acute clinical rejection confirmed by biopsy (BPAR) and

development of dnDSA.

Secondary outcome

• Death at 24 months.

• Graft loss at 24 months.

• Incidence and severity of subclinical and chronic rejection (according to

protocol biopsies at 3 and 24 months).

• Incidence of opportunistic infections at 24 months.

• Incidence of metabolic disorders derived from treatment (diabetes mellitus,

dyslipidemia and HBP) at 24 months.

• Incidence of cardiovascular events at 24 months.

• Incidence of malignancy (cutaneous and non-cutaneous cancer) at 24 months.

• Proportion of patients who maintain the treatment according to the protocol

at the end of the follow-up.

• Changes in the immune response at 24 months according to biomarkers:

o Allogenic response (dn-DSA, d-sp IFN-γ ELISPOT , Memory B cell Elispot,

urine cytokines CXCL9 and CXCL10)

o Rejection risk of blood transcriptional profile, according to the KSORT test

o Antiviral cellular response against CMV, VEB, VBK, NKG2

• Proportion of patients with Serious adverse events related to study drugs.

Study description

Background summary

Kidney transplantation is the election treatment for patients with chronic end-stage kidney disease (CKD), since it offers a greater benefit in patient survival, a better quality of life and an economic saving compared to the rest of renal replacement therapies. Despite the fact that the improvement in the patient's clinical care, surgical capabilities, the appearance of powerful immunosuppressants and the better knowledge of the biology of alloimmunity have allowed the improvement of graft survival during the first year after transplantation, mainly due to a reduction of acute rejection rates, long-term allograft survival remains suboptimal. The process of progressive loss of the renal graft is multi-causal, but the activation of the donor-specific alloimmune response (d-sp), as well as the direct renal toxicity of the immunosuppressants, play a fundamental role.

Currently, immunosuppressive strategies are based on high dose with maximum effectiveness without taking into account the individual susceptibility of each patient to reject or accept the graft (*one size fits all*).
At this moment the immune risk stratification of transplant patient candidates is done via the assessment of primary alloimmune activation. The differences between donor and recipient in the HLA system and preformed donor-specific alloantibodies (DSA are examined.. However, the post-transplant monitoring of

the pharmacodynamic effect of immunosuppressive treatment is carried out exclusively by indirect data, such as the plasma levels of immunosuppressive drugs, the presence of lymphopenia, opportunistic infections or by the appearance of graft dysfunction suggestive of rejection. Following this paradigm, a large fraction of transplant patients have a high probability of receiving excessive or insufficient immunosuppression, thus being exposed to a high risk of infections and drug toxicity or, conversely, to transplant rejection, respectively. For this reason there is a need for biomarkers that can make a stratification before transplantation between patients with a high and patients with a low risk of rejection. In this way, immunosuppression can be dosed to size. This can be crucial to improve the current results of kidney transplantation.

In summary, in order to minimize immunosuppression safely in the post-transplant period, sensitive non-invasive biomarkers are needed to stratify the risk of graft rejection beforehand and which could be used iteratively after transplantation in a non-invasive manner. Thus, the evaluation of preformed immune memory, both humoral through pre-transplant DSA, and and the assessment of the risk of primary alloimmune activation using a better donor/recipient HLA mismatching a the Eplet level could significantly help transplant physicians regarding decision-making of the type and burden of immunosuppression.

Study objective

Main objective of the trial is to determine the effect of individualizing the immunosuppressive therapy based on baseline immune-risk stratification according to 2 new biomarkers (d-sp ELISPOT IFN-γ and donor/recipient HLA Eplet Mismatch), in a composite end-point made by the loss of renal function, incidence of acute rejection and development of dnDSA at 2 years of follow-up in LDKT patients as compared to patients who are managed according to standard immunosuppression.

Secundary objectives:
• To assess whether the individualized stratification of immunological risk and therapeutic optimization reduces patient:
o Mortality;
o Renal graft loss;
o Development of subclinical acute and chronic rejection assessed in protocol biopsies at 3 and 24 months;
o Opportunistic infections;
o Metabolic diseases derived from treatment (diabetes mellitus, dyslipidemia and hypertension) and malignancy (cutaneous and non-cutaneous cancer) after 2 years of follow-up;
• Economical savings derived of treatment decision-making according to refined immune-risk stratification;
• Changes in the allogenic d-sp alloresponse throughout the 2 years of

follow-up using ancillary biomarkers such as dnDSA, d-sp IFN-γ and memory B-cell ELISPOT, urinary cytokines (CXCL9/CXCL10), and the transcriptional profile risk of rejection evaluated with the kidney solid-organ rejection test (kSORT) as well as the evaluation of cellular antiviral responses against CMV, EBV and VBK viruses.

Study design

This is a randomized, open-label study, with parallel groups, stratified according to donor age. This is a prospective interventional study in which two strategies for the determination of immunosuppressive treatment in kidney transplant patients from a live donor with low immunological risk according to solid phase antibody detection assays (cPRA up to 50% but absence of actual or historical DSAs) and negative Flow-cytometry crossmatch (FCXM) are compared. Patients are randomized in a 1: 1 ratio to receive one of two immunosuppressive treatment strategies:
a) Experimental group (groups A), in which the immunosuppressive treatment of the patients is determined according to the result of 2 immunological risk biomarkers (d-sp IFN-γ ELISPOT assay and number of HLA Eplet mismatch at the DRB1 and DQB1 loci),
b) Control group (group B), in which all patients receive the usual triple immunosuppressive treatment, without taking into account the results of the two biomarkers.

After signing the informed consent the screeningperiod starts, lasting up to 28 days. In this period the donor will also consent for blood draw for biomarker testing. The transplanted patients will be followed in the study for 24 months after transplantation. In this 24 months period the patient will have 8 study visits.

Intervention

The following combinations of immunosuppressive medication will be provided in this study:
• thymoglobulin, tacrolimus, mycophenolate mofetil and prednisone (arm A1);
• basixilimab, tacrolimus, mycophenolate mofetil and prednisone (arm A2);
• tacrolimus, mycophenolate mofetil and prednisone, in which prednisone is discontinued after 3 months (arm A3);
• basixilimab, tacrolimus, mycophenolate mofetil and prednisone (arm B)

There are two treatment arms, arm A and arm B, in which arm A is subdivided in three different combinations of immunosuppressive medications. When randomized in arm A the results of the biomarker test will be guiding which treatment the patient will receive (arm A1, A2 or A3). When randomized to arm B the results of the biomarker test will be blinded. Arm B is the standard treatment patients would normally receive after a kidney transplant.

In the study a biopsy will be performed at month 3 and month 24 to determine the incidence and severity of subclinical and chronic rejection.

Study burden and risks

Kidney transplantation is the election treatment for patients with chronic end-stage kidney disease (CKD). A large fraction of transplant patients have a high probability of receiving excessive or insufficient immunosuppression, thus being exposed to a high risk of infections and drug toxicity or, conversely, to transplant rejection, respectively. Therefore, the need to individually adjust the type and amount of immunosuppression to kidney transplant patients according to biomarkers that allow a more accurate immune-risk assessment is key to overcome current kidney transplant outcomes.

The immune suppressive medication used in this study is registered for transplants. Based on 2 biomarker tests, it is possible to give patients a more individually targeted immune suppressive regime. Patients are well monitored for adverse reactions / rejection reactions during the study. Where necessary, action is taken for the benefit of the patient.

Risks/burden associated with procedures:
- Blood draws: The risks of blood draws may include fainting, pain and/or bruising. Rarely there may be an infection at the site of the needle puncture.
- Kidney biopsy: Risks of biopsy include pain, discomfort and bleeding.
- ECG: redness or itching caused by sticky pads.

The following procedures are performed:
- Physical examination at all visit;
- Measurement vital signs at all visit:
- ECG at screening and visit 1;
- Blood draws at all visits (local lab 9 x, biomarkers 6 x);
- Kidney biopsy at month 3 and month 24 visit.

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

• Male or female patients >= 18 years old.
• Recipients of a primary kidney transplant from a living non-HLA identical donor (at least 1 HLA missmatch).
• Compatible ABO transplant.
• Patients with a calculated PRA (cPRA) <= 75% by solid-phase assays and absence of donor-specific anti-HLA antibodies (DSA) against class I and class II in an actual or historical screened sera.
• Written informed consent must be obtained before any assessment is performed.
• Women of child-bearing potential must use highly reliable contraceptive methods (Pearl-Index <1) in order to avoid pregnancy during the entire duration of the study and up to 6 weeks after the end of their treatment with Mycophenolate Mofetil (MMF). Women of child-bearing potential include any woman who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or who is not post-menopausal (defined as amenorrhea >= 12 consecutive months, or women who are receiving hormone replacement therapy with a documented level of follicle stimulating hormone (FSH)> 35 mIU / ml). Women of child-bearing potential must have a pregnancy test with a negative result in the 72 hours prior to the start of the trial.
• Sexually active males (also vasectomized men) receiving MMF must use a condom during MMF treatment and the following 90 days. Fertile partners must use an effective method of contraception.
• Patients must agree not to donate blood during MMF treatment and for 6 weeks thereafter. Males should not donate sperm during MMF treatment and up to 90

days after completion.

Exclusion criteria

• Patients with a calculated PRA (cPRA) > 75% by solid-phase assays and/or presence of donor-specific anti-HLA antibodies (DSA) against class I and class II in an actual or historical screened sera.
• Positive pre-transplant Cross Match test (either CDC or FCXM).
• Recipients of a deceased donors.
• HLA identical subjects
• Multi-organ transplant recipients or prior kidney transplant.
• Patients with one of the following diseases:
o Primary focal and segmental glomerulosclerosis
o Atypical Uremic Hemolytic Syndrome (aHUS) / Thrombotic Thrombocytopenic Purpura.
• Patients with active infection with Hepatitis B virus (HBV) and / or active infection with Hepatitis C virus (positive PCR result) at the time of transplant.
• Patients with known HIV disease.
• Patients with active systemic infection that requires continuing antibiotic treatment.
• Patients with malignancy of any organ system, with the exception of localized excised skin cancer.
• Patients with severe anemia (hemoglobin <6g/dl), leukopenia (WBC <2500/mm3) and/or thrombocitopenia (platelet count <80.000/mm3).
• Hemodynamically unstable patients, even if they have hemoglobin levels> 6g / dl.
• Patients with intestinal pathology or severe diarrhea that may decrease absorption according to medical criteria.
• Patients with known hypersensitivity to any of the drugs used in this study.
• Patients who have received any investigational drug in the 30 days prior to their inclusion in this study.
• Women of child-bearing potential who do not agree to use reliable contraceptive measures during the trial, who are pregnant, breast-feeding or presents a positive pregnancy test at the time of inclusion in the study.
• Patients who are legally detained in an official institution.

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2020
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	CellCept
Generic name:	Mycophenolate mofetil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisone
Generic name:	Prednisone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prograft
Generic name:	Tacrolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Simulect
Generic name:	Basiliximab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Thymoglobuline
Generic name:	ANTI-HUMAN T-LYMPHOCYTE IMMUNOGLOBULIN FROM RABBITS

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-04-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2020
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
EudraCT	EUCTR2017-002293-39-NL
ClinicalTrials.gov	NCT03465397
CCMO	NL71246.018.20