Prospective donor-specific Cellular alloresponse assessment for Immunosuppression Minimization in de novo renal transplantation

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Observational invasive

Summary

ID

NL-OMON45147

Source
ToetsingOnline

Brief title
CELLIMIN

Condition

- Renal disorders (excl nephropathies)

Synonym
immuneresponse, renal transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Charite Universiteitskliniek Berlijn

Source(s) of monetary or material Support: EuFP7

Intervention

Keyword: alloresponse, kidney, minimalization of medication, transplantation

Outcome measures

Primary outcome

The main objective of the study is to demonstrate the utility and safety of the IFN-γ ELISPOT marker for the stratification of kidney transplant recipients into low and high IS regimens. The enrichment study will test non-inferiority of low IS regimen compared to high IS regimen, assuming 10% of BPAR at 6-months in the control group, and allowing a non-inferiority limit of maximum 15%.

Secondary outcome

To investigate differences across treatment arms in the following secondary outcomes:

- eGFR (ml/min) assessed by the CKD-EPI formula at 6 and 12 months

- Prevalence of biomarkers* of tolerance/hyporesponsiveness at 3 and 12 months.

- Incidence, type, severity, treatment, and outcome of BPAR by 6 and 12 months after transplantation.

- Prevalence, type, severity, treatment, and outcome of subclinical rejection by 6 and 12 months after transplantation.

- Prevalence of death, and graft loss by 6 and 12 months.

- Prevalence of metabolic and cardiovascular co-morbidity (new onset diabetes mellitus (NODAT), dyslipidemias, hypertension) by 12 months.

- Prevalence of subjects that remain MMF and steroid-free at 6 and 12

months after transplantation

- Prevalence of Acute and chronic histologic lesions assessed by the

Bannf'11 score in protocol biopsies at months 3 and 12 posttransplantation.

- Prevalence of patients that remain on Therapy at 12 months after

transplantation.

- Distribution of patients in distinct chronic kidney diseases (CKD) stages

by 12 months.

- Health economics, H-R QoL and treatment cost (cost/benefit) at 1, 3, 6,

12 and 24 months.

E.5.2.1

Study description

Background summary

The current immunosuppressive therapy consists mainly from combination of three to four immunosuppressant agents. This therapy is not only costly, but leads also to many undesirable side effects, which not only limit its efficacy (impossibility to titrate to the required dose) but decrease also the patients adherence to therapy. Intensive research is currently ongoing to improve the treatment complexity and thus improve the adherence of patients, reduce the burden of side effects and decrease the cost of therapy. Minimizing immunosuppression (IS), e.g. monotherapy, as early as possible without losing control of acute/chronic rejections would be of great benefit and could reduce adverse effects and costs. However, this is only possible in a minority of patients yet. Therefore, a precise evaluation of the anti-donor alloimmune response in order to identify patients likely to accept the graft with no or very low IS would be of great value. One of possible approaches is the tacrolimus (TAC) monotherapy avoiding corticosteroids and antiproliferative agents (mycophenolate mofetil - MMF), which may lead to substantial reduction of the immunosuppressive load and improve the cardiovascular risk profile. Several papers about TAC monotherapy were already published in the area of kidney transplantation. Although most of them reported relatively positive

results with monotherapy, BPAR rates were significantly higher as compared to standard of care IS, despite using relatively high TAC trough levels which also negatively impacted to the 6-month allograft function. Other attempts for TAC monotherapy have been done in non-randomized, single centre pilot studies, especially using T-cell depleting agents such as Alemtuzumab with rather contradictory and inconclusive results.
In humans, the assessment of the immunologic risk is exclusively based on the detection of preformed circulating alloantibodies, with the assumption that humoral allosensitization also illustrates the allospecific T-cell effector/memory immune response. This is of great importance, as it is well known that cellular memory may occur without humoral activation and that alloreactive cellular responses are key players in initiating and mediating allograft rejection. In fact, with the current accurate screening of humoral sensitization, rates of antibody-mediated rejection (ABMR) have significantly been reduced but T-cell mediated acute and chronic rejection (TCMR) is still observed after renal transplantation, especially among patients not receiving CNI-based IS. This fact is in line with in vitro studies showing that alloreactive T-cell responses are particularly sensitive to CNI drugs as compared to other immunosuppressants. Noteworthy, in the last years, attempts trying to immune-monitor the T-cell alloimmune response using novel immune assays have been done in kidney transplantation. Among the most robust functional assays measuring T-cell alloreactivity the IFN-γ enzyme-linked immunosorbent spot (ELISPOT) assay has been shown in multiple reports to be capable of accurately assess the presence of highly alloreactive circulating memory/effector T-cells with donor-antigen specificity, both before and after transplantation, discriminating patients with increased risk for TCMR and worse graft function evolution, even in absence of humoral allosensitization. Furthermore, 2 recent reports performed in the context of the European RISET consortium, showed on the one hand, the cross-validation among different laboratories of the IFN-γ ELISPOT assay to accurately assess anti-donor alloreactive T-cell frequencies in the context of kidney transplantation, and on the other, that prospectively monitoring donor and non donor-specific T-cell alloreactivity using the IFN-γ ELISPOT before and after transplantation may allow safe individualization for induction and maintenance of CNI-free IS in renal transplant recipients, discriminating patients with the better 1-year graft function as well as individuals with preserved graft parenchyma at 6-month protocol biopsies.
Therefore, pre-transplant assessment of anti-donor T-cell alloresponses using the IFN-γ ELISPOT may help to accurately discriminate patients that may safely benefit from receiving low IS based on induction therapy with basiliximab and low doses TAC monotherapy, from others that should stay on higher IS such as the current standard

Study objective

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recipients into low and high IS regimens. The enrichment study will test non-inferiority of low IS regimen compared to high IS regimen, assuming 10% of BPAR at 6-months in the control group, and allowing a non-inferiority limit of maximum 15%.

Study design

This is a biomarker strategy design randomized trial, whereby only pre-TX ELISPOT negative patients will be enrolled into the study and randomized 1:1 to either low or high IS regimen. The study will test non-inferiority of low IS regimen compared to high IS regimen, assuming 10% of BPAR at 6-months in the control group, and allowing a non-inferiority limit of maximum 10%. First kidney transplant recipients that provide consent to participate in the study will be evaluated for their anti-donor T-cell alloresponse using the IFN-γ ELISPOT assay before kidney transplantation (TX). Patients with a positive anti-donor IFN-γ ELISPOT assay result (>25 spots/300.000 PBMC) will be ruled out of the study and patients with negative anti-donor IFN-γ ELISPOT test (<25 spots/300.000 PBMC) will be randomized in 2 different groups (1:1): GROUP A: STANDARD OF CARE: Standard of care immunosuppressive regimen based on TAC (achieving 4-8ng/ml trough levels), MMF (1gr bid) and steroids (according to KDIGO guidelines). GROUP B: *Low* Immunosuppression regimen (based on TAC monotherapy to achieve 8-10 ng/ml trough levels during the first 4 weeks after transplantation and 6-8 ng/ml thereafter, MMF (1g bid) during the first 7 days post-transplant and stopped thereafter) and steroids (tapering until discontinuation on month 2 post-transplant). All patients will homogenously receive 2 doses of Basiliximab (day 0 and day 4 after transplantation). In addition to the decision-making ELISPOT, several other biomarkers* will be analyzed during follow-up in all randomized kidney transplant patients. The trial will need to recruit 301 patients allowing for 10% drop-out rate, having 271 patients with complete follow up for primary outcome. Considering that approximately 45% of patients are ELISPOT negative, 669 patients will need to be screened. Patients will be followed up for a total of 12 months for secondary outcome measures.

Study burden and risks

Most visits will be intertwined with the regular follow-up visits. Extra is a renal transplant biopsy performed at three months after transplantation. The patient will have to be admitted to the hospital for half a day. This biopsy is < 5% complicated by a small hematoma around or in the kidney.

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

1) Men and women, age >=18 years.
2) Subject must be a recipient of a first renal transplant from a deceased or living donor.
3) Subject must have a current documented PRA <20% and no detectable anti-class I and II HLA antibodies by solid phase assay (Luminex®).
4) Subject is willing to provide signed written informed consent.

Exclusion criteria

1) Subjects undergoing renal transplant with a current documented PRA >20% and/or detectable anti-class I and II HLA antibodies by solid phase assay (Luminex®).
2) CDC positive cross match.
3) Subjects receiving an allograft from a donor older than 65 years with elevated creatinine levels and/or treated diabetes.
4) Cold ischemia time (CIT) higher than 24h.
5) Subjects with a prior solid organ transplant (SOT), including renal re-transplantation, or

receiving a concurrent SOT.

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-01-2016
Enrollment:	200
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cellcept
Generic name:	Mycophenolate Mofetyl
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisolon
Generic name:	Prednisolon
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prograf
Generic name:	Tacrolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-09-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-02-2019
Application type:	Amendment
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	EUCTR2014-001325-33-NL
CCMO	NL49056.018.15