Tacrolimus monotherapy in immunologically low-risk kidney transplant recipients: a pilot randomized-controlled study.

Published: 08-07-2014
Last updated: 20-04-2024

The primary objective of the main non-inferiority study is to determine the safety of TACmono starting nine months after kidney transplantation in immunologically low-risk patients in terms of BPAR-rate 15 months after transplantation compared to...

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

Summary

ID

NL-OMON46987

Source
ToetsingOnline

Brief title
Tacrolimus monotherapy.

Condition

- Viral infectious disorders
- Miscellaneous and site unspecified neoplasms benign
- Renal disorders (excl nephropathies)

Synonym
rejection kidney transplant

Research involving
Human

Sponsors and support

Primary sponsor: nefrologie
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: immunological risk, kidney transplantation, monotherapy, tacrolimus

Outcome measures

Primary outcome

This pilot study is an exploratory, randomized-controlled trial. The primary endpoint of this study is a number of immunological measurements and not clinical efficacy nor safety. These immunological measurments are:

I. Number of cytokine-producing alloreactive CD137+ T-cells

II. Total number of infectious episodes

III. Vaccination response score.

The feasibility outcomes will be:

- estimation of the risk on BPAR in the control group

- recruitment rates.

Secondary outcome

The secondary study parameters will be:

- BPAR rate 15 months after kidney transplantation

- presence of complement-fixating alloantibodies.

- renal allograft function (eGFR with CKD-EPI formula and proteinuria expressed in urine protein/creatinine ratio).

- number of donor-specific CD137+ T cells

- composition of leucocyte subsets

- blood pressure levels and number of antihypertensive drugs after

discontinuation of MMF versus controls

- gastrointestinal side effects and quality of life outcomes

Study description

Background summary

Kidney transplantation is the treatment of choice for patients with end-stage kidney disease. Current immunosuppressive drugs have allowed for 5-year patient survival of approximately 90% [2, 3]. Malignancy and infectious diseases are feared and well-known side effects of the immunosuppressive burden after transplantation [4-8]. Attempts to address these issues by lowering the total immunosuppressive load must be weighed against the risk of rejection. This risk differs substantially among patients according to HLA matching [9, 10] and level of panel reactive antibodies (PRA) [11].
Allograft survival diminishes with each extra mismatch on HLA loci of A, B and DR [12]. A higher PRA correlates with poorer allograft survival [13]. Therefore lowering of immunosuppressive drugs to improve long-term malignancy and infection related outcomes should be carried out according to HLA mismatches and PRA levels.

Calcineurin inhibitors (CNI) have shown superior renal allograft survival over azathioprine [14, 15], mTOR-inhibitors [16, 17] and MMF [18]. Therefore CNIs continue to be the cornerstone of immunosuppressive drugs used after solid organ transplantation. The once daily formulation Advagraf has proven similar efficacy [19, 20] and better compliance than twice daily formulation [21].

Attempts to minimize TAC based regimens have mainly been carried out after induction therapy with alemtuzumab irrespective of the immunological status of the recipient [22-27]. TACmono after this T-cell depleting agent seems safe [25, 27], although some studies lack a control group [22-24]. Vitko et al. conducted a large study comparing steroid-free regimens including basiliximab/ TAC (n=153) to triple steroids/ TAC/ MMF (n=147) in the first six months after transplantation. TACmono patients revealed more BPAR than triple therapy in this early postoperative period (26.1 vs. 8.2%, $p < 0.001$).

Therefore a window of opportunity should be determined when to lower the immunosuppressive regimen, weighing incidence of rejection against cumulative immunosuppressive load. The risk for acute rejection is highest in the first

six months after transplantation and substantially decreases after 3-6 months [9, 28, 29].

Other transplantation centers (UMC Maastricht) use CNI monotherapy in selected patients with a low immunological risk, however randomized controlled trials are lacking. In addition, there are no data on the immunological consequences both in vivo and ex vivo of CNI monotherapy. A study powered for superiority in malignancy and infectious diseases would take a period too long to conduct a randomized trial. It is not expected that lowering the immunosuppressive load would lead to superiority in BPAR-free survival, however TACmono is expected to be better at secondary endpoints (malignancy and infection) and is a more patient-friendly regimen with once daily administration of an immunosuppressant. Before a non-inferiority study is to be carried out in hundreds of kidney transplant recipients, a pilot study could provide for information on BPAR rate in the control group and allow termination of the study when a discrepant high rate of BPAR is observed in the TACmono intervention group.

Therefore we have designed a pilot study in which patients are randomized six months after kidney transplantation to either minimize their immunosuppressive regimen to TACmono or to continue standard TAC/ MMF. By studying general and donor-specific immune responses the rationale behind minimization can be further explored. The impact of reducing the total immune suppressive burden in study participants can be assessed in vivo after vaccination [30, 31]. Staining of the cell surface marker CD137, a member of the tumor necrosis factor-family, is a novel flow cytometry assay to identify the total pool of circulating alloreactive T cells [32]. The intervention of discontinuing MMF offers an opportunity to study the effect of MMF on blood pressure in humans. Animal models reveal a relationship between T cell infiltration and hypertension, and a protective effect on blood pressure while on MMF treatment [33-36]. Monotherapy with Advagraf offers patients theoretically a more patient-friendly regime: MMF is known for its gastrointestinal side effects [37-39] and monotherapy Advagraf is a truly once-daily immunosuppressive regimen. The complement-fixating Luminex assay is a promising assay to predict rejection rates [40-42]. Therefore the presence of DSA (donor specific antibodies) as detected by Luminex will be analysed in both treatment arms.

14. REFERENCES

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Study objective

The primary objective of the main non-inferiority study is to determine the safety of TACmono starting nine months after kidney transplantation in immunologically low-risk patients in terms of BPAR-rate 15 months after transplantation compared to dual therapy with TAC and MMF.

First a pilot or feasibility study is needed to investigate the feasibility objectives:
1. Methodology: Outcome in the control group: what is the BPAR-rate in the control group?
2. Process: Recruitment rates. How many patients can be included, what is the rate of consent, determining centre willingness and capacity?
3. Scientific (biological plausibility):
Estimate of the treatment effect using surrogate endpoints is the primary objective of the pilot study:
Does TACmono provides for better general immune responses than dual therapy as measured by:
I. Number of cytokine-producing alloreactive CD137+ T-cells
II. Total number of infectious episodes
III. Vaccination response score.

The secondary objectives of the pilot study are:
1. BPAR rate 15 months after kidney transplantation.
2. Assessment of de novo (complement-fixating) alloantibody formation as detected by Luminex.

3. Kidney allograft function (eGFR with CKD-EPI formula and proteinuria expressed in urine protein/creatinine ratio).
4. Detection of donor-specific CD137+ T cells.
5. Composition of leucocyte subsets.
6. Blood pressure levels and number of antihypertensive drugs after discontinuation of MMF as compared to continuation with dual TAC/MMF therapy.
7. Gastrointestinal symptoms and quality of life outcomes.

Criteria for success of pilot study:
1. A minimum of 40 patients is recruited per group.
2. Consent is given in 70% of eligible patients.
3. The descriptive outcomes in general immune responses provide for a biological plausible benefit of TACmono over dual therapy.
*

Study design

This is a randomized, investigator-driven, open-label, single centre pilot study. The pilot is conducted to assess the feasibility of a larger non-inferiority study. The follow-up will be 15 months for the primary and secondary outcomes. Kidney transplant recipients will be asked for consent in the first week after kidney transplantation. At day 7, the tacrolimus twice daily formulation Prograft® is converted to the slow release formulation Advagraf® with once daily administration.
Six months after transplantation participants are randomized to either continue dual therapy with TAC and MMF or gradually decrease the MMF to TACmono therapy at 9 months. TAC trough levels are aimed for 6-8 ng/ml in both groups.
Both groups have received the same *standard of care* regimen till 6 months:
- induction therapy with basiliximab (IL-2 receptor blocker) 20 mg day 0 and 4
- prednisone
o day 0, 1 and 2: 50 mg twice daily intravenously.
o day 3-14: 20 mg once daily
o day 15-28: 15 mg once daily
o month 2: 10 mg once daily
o month 3: 7.5 mg once daily
o month 4-5: tapering from 5 mg once daily to discontinuation month 5.
- tacrolimus targeted trough levels:
o day 0-14: 10-15 microg/l
o day 15-28: 8-12 microg/l
o week 5-12: 6-10 microg/l
o from month 4 onwards: 6-8 microg/l
- mycophenolate mofetil acid: targeted trough levels 1.5-3 mg/l, according to common practice (not exceeding 1000 mg twice daily).
Patients will be vaccinated against pneumococcus and tetanus at month 12. Three weeks after vaccination extra blood will be drawn to compare IgG titers after vaccination with baseline. Influenza vaccination is offered in seasonal

clusters between month 12-15 after transplantation. During regular outpatient clinic visits, extra blood samples are drawn to study ex vivo immune responses. Blood pressure levels are monitored with *Datascope* measurements according to local practice. At months 6, 12 and month 15 patients are asked to fill in questionnaires about gastrointestinal symptoms and quality of life issues.
To study ex vivo immunological responses against donor cells, donor cells are either harvested from the spleen after postmortal donation or from blood samples of living donation donors. Donors are asked for their consent (see donor PIF) to donate blood (total maximum of 105 ml) during admission or during the regular outpatient clinic visit.

Intervention

Six months after kidney transplantation participants are randomised to decrease MMF and discontinue this drug at nine months, continuing with TACmono thereafter. The control group receives standard therapy with TAC and MMF.

Study burden and risks

The risk of the venapunctures is small, as extra blood tubes are taken at time points when blood is already drawn, except for the blood drawn to measure vaccination responses. The risk of a venapuncture is the occurrence of a bruise after puncture and possible pain-symptoms at the site of puncture. Vaccination can give local reactions the first day(s): pain, redness and swelling. Fever, malaise, fatigue and headaches are also reported in the first week after vaccination. Known history of anaphylactic reactions or Guillain-Barré syndrome in 6 weeks after vaccination is a contra-indication to vaccination. By participating in this study, patients will have easy access to national and international recommended vaccinations after transplantation.
Treatment by TACmono has theoretically a greater risk of BPAR. Therefore a time window for discontinuation at nine months has been chosen. The investigators and the DSMB will closely monitor BPAR rates. The potential/ theoretical benefit of treatment by TACmono consists of less infections and less malignancies. In the intervention group participants have a more patient-friendly medication regime with only once daily a immunosuppressive tablet, enhancing compliance.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:;- Adult patients receiving a deceased or living kidney transplant in the Erasmus Medical Center Rotterdam, The Netherlands and:;- Historical PRA <5 and;- HLA MM <4.;Re-transplantation are allowed when meeting the before mentioned criteria.;Patients have to give written informed consent to participate in the study.;Before randomization at 6 months, renal function should be stable with eGFR (CKD-EPI formula) >30 in mL/min with proteinuria *0.5 gram per 10 mmol creatinin in spot urine.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:;- HLA identical living-related transplant recipients.;- Patients with an indication to continue MMF or other immunosuppressive drugs, e.g. vasculitis, SLE etc. (according to judgement of treating physician).;- Recipient of an ABO-incompatible allograft or with a positive crossmatch (complement-dependent cytotoxicity or flow cytometry).;- Biopsy proven rejection three months and later after transplantation.;- Recipient of multiple organ transplants.;- Females of childbearing potential who are planning to become pregnant, who are pregnant and/or lactating or who are unwilling to use effective means of contraception.;- T-cell depleting therapy (anti-thymocyte globulin and alemtuzumab) after transplantation.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-09-2014
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Advagraf
Generic name:	tacrolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	CellCept
Generic name:	mycophenolate mophetil acid
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	PNEUMO-23
Product type:	Medicine
Brand name:	Revaxis

Ethics review

Approved WMO Date:	08-07-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-11-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	01-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-001372-66-NL
CCMO	NL48634.078.14