A 24-month, multi-center, open-label, randomized, controlled trial to investigate efficacy, safety and evolution of cardiovascular parameters in de novo renal transplant recipients after early calcineurin inhibitor to everolimus conversion (CRAD001A2429, ELEVATE study)

Published: 21-06-2010
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Primary objective: To demonstrate superior renal allograft function in de novo renal transplant recipients after early CNI to everolimus conversion assessed by Glomerular Filtration Rate (eGFR) estimated by the Modification of Diet in Renal Disease...

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

Summary

ID

NL-OMON34407

Source
ToetsingOnline

Brief title
ELEVATE

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym
renal transplantation

Health condition

niertransplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: calcineurin inhibitors, conversion, Everolimus, renal transplantation

Outcome measures

Primary outcome

eGFR after 12 months.

Secondary outcome

BPAR, graft loss, death, LV mass index (LVMi), other renal function parameters,

side effects, cardiovascular events, PK, blood pressure during 24 h, arterial

stiffness.

Study description

Background summary

The introduction of the immunosuppressive agent Sandimmun Neoral (cyclosporine A, CsA) significantly improved the outcome of clinical renal transplantation in the eighties by reducing acute rejection rates and increasing patient and graft survival. CsA and the later introduced
drug tacrolimus, both known as calcineurin inhibitors (CNIs), are at present the cornerstones in most of the immunosuppressive protocols used worldwide. Although CNIs have a well documented prophylactic effect against severe acute

rejections, they do not prevent the development of chronic allograft nephropathy (CAN)/interstitial fibrosis and tubular atrophy (IF/TA) leading to a substantial graft loss in the long term . In addition an increased risk for cardiovascular morbidity and of malignancies was reported as two major other long term threads for transplanted patients, which also might be aggravated by CNIs . The ultimate goal of immunosuppressive therapy after organ transplantation is to provide an efficacious regimen while minimizing side effects. By the combination of synergistic immunosuppressants it may be possible to reduce the exposure to individual drug and therefore avoid adverse events whilst maintaining favorable clinical outcomes. For that reason there has been an increasing interest to explore combination of treatments that allow for reduction in CNI exposure, as this may potentially enhance long term outcomes. The introduction of new immunosuppressive agents may offer the opportunity to reduce renal toxicity and cardiovascular risk factors, without impairment of efficacy. Such recent advances in immunosuppression, especially the introduction of mycophenolic acid (MPA) and proliferation signal inhibitors (PSI), also called mTOR inhibitors, have led to the evaluation of new immunosuppressive strategies with CNI minimization or elimination early post transplantation in stable patients.

Mycophenolate mofetil (MMF) may also allow withdrawal of CNIs in maintenance recipients . However, the addition of MMF does not permit early withdrawal or completely CNIs-free regimens, without a significant increase in acute rejections. In contrast, results of cyclosporine reduction in combination with a proliferation signal inhibitor, i.e. everolimus or sirolimus based therapy after early cyclosporine withdrawal, are particularly encouraging.

Everolimus (RAD, [40-O-[2-hydroxyethyl]-rapamycin], SDZ RAD, RAD001) is a proliferation signal inhibitor that has been developed for use in combination with Neoral® (cyclosporine for micro-emulsion) for the prophylaxis of acute rejection and the prevention of chronic rejection in patients receiving allogeneic kidney and heart transplants. There are experimental and clinical data indicating that PSIs reduce the development of CAN/IFTA, by their antiproliferative qualities, making CNI-reduction feasible. In heart transplanted recipients PSIs have been shown to reduce cardiac allograft vasculopathy. There is also evidence of anti-tumour properties of these drugs, demonstrated in experimental as well as in clinical studies.

On the other hand PSIs have a known interaction in combination with CNIs as they amplify the CNI-nephrotoxicity and thus requiring a thorough dosing and monitoring of both drugs. Other side effects reported for PSIs are hyperlipidemia and wound healing problems. There are still few number of reports of completely CNI-free regimens, using PSIs as the initial immunosuppression in de novo renal recipients. So it is evident that, although CNI-free immunosuppression now is a realistic opportunity by the use of PSIs, the optimal design of such a protocol remains to be investigated.

An alternative strategy is to delay the introduction of PSIs, until the risk of initial wound healing problems has subsided. By then making an early and rapid switch from CNIs to PSIs, the duration of nephrotoxic exposure would be reduced. Such a switch has safely been made in maintenance patients, but no

controlled studies of early conversions from CNIs to PSIs are yet available. One might assume that an early switch could cause a higher risk of acute rejections, since this was found in studies of early CsA withdrawal in combined treatments. However, in these withdrawal studies, MMF and anti-IL-2 induction were not used. By adding these drugs together with steroids as in the former CNI-free protocols, one would expect that an early and rapid switch 10-14 weeks after renal transplantation from CNIs to PSIs would be possible, without an unacceptable increase in rejection. The risk of increased rejection rates after early elimination of CNI could be further reduced, if sensitized patients or patients that were already treated for severe acute rejections would be excluded from the switch.
To summarize, although PSIs may have a potential to improve the long term condition for renal allograft recipients, by reducing CAN/IFTA, malignancies and cardiovascular morbidity, the optimal way to use everolimus in routine protocols for de novo transplantations still remains to be clarified. Thus, the use of a protocol with an early conversion from CNIs to everolimus would be an option of great potential.
Therefore, this controlled study was designed in order to test an immunosuppressive protocol based on steroids, enteric coated Mycophenolic Sodium and basiliximab, and an early switch from CNI to everolimus, with the primary objective to improve the long-term function of renal allograft.

Study objective

Primary objective: To demonstrate superior renal allograft function in de novo renal transplant recipients after early CNI to everolimus conversion assessed by Glomerular Filtration Rate (eGFR) estimated by the Modification of Diet in Renal Disease formula 4 (MDRD4) at month 12 versus the active control.
Secundary objectives: Major: 1. To demonstrate non-inferior efficacy (defined by a composite efficacy endpoint of treated Biopsy Proven Acute Rejection (BPAR) * IB, graft loss or death) at month 12. 2. To demonstrate improvement of Left Ventricular Hypertrophy as assessed by
LV mass index (LVMi) using echocardiogram at month 12. Others: after 12 and 24 months: individual components of composite endppoint, acute rejection, graft function (various parameters), side effects, cardiovascular events.
Substudies (to be performed in all NL centres): arterial stiffness, 24 hour blood pressure measurement, PK sodium mycophenolate.

Study design

Multicenter randomized open phase IIIB parallel group study.
Run-in period of 10-14 weeks after transplantation with standard treatment (induction with basiliximab 20 mg infuxion on day 0 and 4, tacrolimus C0: 6-12 ng/mL, sodium mycophenolate1.08 - 1.44 g/day, steroids according to local protocol, but at least 5 mg/day).
After 10-14 weeks randomization (1:1) to:

1. Continuation run-in treatment (however, tacrolimus C0: 5-10 ng/mL).
2. Conversion from tacrolimus to everolimus (C0 through level 6-10 ng/mL).
Overnight replacement or stepwise within 1 week.
Total study duration 2 years.
Approx. 670 patients.
Independent data safety monitoring board.

Intervention

Conversion from CNI to everolimus or continuation of CNI.

Study burden and risks

Risk: side effects of study medication, renal biopsy.
Burden: 14 visits in 2 years. Physical exam and blood test during each visit (approx. 10-30 (2x 45-50) mL/visit, approx. 400 mL in total). Screening for HIV and hepatitis B-C.
In addition: renal biopsy 2x (plus 1 during transplantation), echocardiogram 3x, pregnancy test 2x, arterial stiffness 3x, 24 hour blood pressure measurement (ambulatory) 3x.
2 visits with extended measurments (5-9 h) related to PK.

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

At baseline:
* 18 years and above.
* 1st or 2nd renal transplantation from a cadaveric or living unrelated-/related donor.
* Negative pregnancy test (if relevant).
At randomization:
* Use of a CNI (tacrolimus or cyclosporin) plus sodium mycophenolate plus steroids.
* Serum creatinin less than 250 *mol/l and actual eGFR (MDRD4) at least 25 mL/min/1.73 m2

Exclusion criteria

At baseline:
* Recipient of multiple organ transplants.
* Recipient of ABO incompatible allograft or a positive cross-match.
* Patient with current Panel Reactive Antibodies (PRA) level * 30 %.
* HIV, hepatitis B or C (AST/ALT *2,5 x ULN) positive.
* Organ from a HIV or hepatitis B or C positive donor.
* Severe restrictive or obstructive pulmonary disease.
* Severe hypercholesterolaemia of hypertriglyceridaemia.
At randomization:
* Graft loss.
* Renal replacement therapy.
* Serious humoral and/or cellulare rejection.
* 2 or more episodes of acute rejection or an episode that needed antibody treatment.
* Ongoing- or currently treated acute rejection (2 weeks prior to randomization).
* Proteïnuria more than 1 g/day.
* Severe hypercholesterolaemia of hypertriglyceridaemia.
* Impaired would healing.
* Serious immunosuppressive complications or side effects.
* Anticoagulants as contraindication for a renal biopsy.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-09-2010
Enrollment:	90
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Certican
Generic name:	everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Myfortic
Generic name:	sodium mycofenolate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prograft
Generic name:	tacrolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	21-06-2010

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-06-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-07-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-03-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-06-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-09-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-04-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-04-2012
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-06-2013
Application type:	Amendment
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
Other	clinicaltrials.gov; registratienummer nog niet bekend
EudraCT	EUCTR2009-015918-22-NL
CCMO	NL32120.058.10