Safety and Efficacy of MCA-derived Mesenchymal Stromal Cell Therapy in Renal Transplant Recipients: The Nereid Study*

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To study whether MCA-derived MSC therapy is safe and effective in allowing tacrolimus reduction after kidney transplantation.Secondary Objective(s): To assess the effect of MCA-derived MSC therapy and subsequent tacrolimus reduction on renal...

Ethical review	Approved WMO
Status	Pending
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON53310

Source
ToetsingOnline

Brief title
MCA-derived MSC therapy in renal transplant recipients

Condition

- Renal disorders (excl nephropathies)

Synonym
BPAR, rejection transplanted kidney

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: Immune modulation, Mesenchymal stromal Cells, Pluripotent Stem Cells, Renal transplantation

Outcome measures

Primary outcome

The primary end point is the incidence of BPAR/graft loss after MCA-derived MSC

treatment

Secondary outcome

- Renal function by calculated GFR , eGFR (CKD-EPI formula) and iohexol

clearance

- CMV and BK infection (viremia, disease and syndrome and subtype of BK).

- Donor specific HLA sensitization by luminex before and after MSC infusions

- Immune monitoring before and after MSC treatment

- Incidence and severity of reported SAEs and AEs at 12 months

Study description

Background summary

Kidney transplantation has improved survival and quality of life for patients with end-stage renal disease. However, despite advances in immunosuppressive therapy, long- term allograft survival outcomes have not improved over the last decade. There is a clear need for therapeutic alternatives because 1) patients may not respond to existing therapeutic choices, 2) they do not show an improvement of the fibrosis reaction 3) they do not show an effect on long term survival, 4) they may develop immunosuppression induced serious (sometimes fatal) side effects and toxicities. LUMC has conducted 3 trials using bone-marrow derived mesenchymal stromal cells (BM-MSC) showing both safety and efficacy of their use in the setting of kidney transplantation.
MSC isolation and culture from both autologous and allogeneic sources is being

hampered by cellular heterogeneity and replicative senescence. Generation of MSC from induced pluripotent stem cells (iPSC) so called MCA-derived MSC may circumvent these limitations. MCA-derived MSC have recently been tested in clinical trials and found to be safe and more cost effective than traditional MSC. Given the benefits of MCA-derived MSC we propose to test whether MCA-derived MSC are safe in the setting of kidney transplantation in a clinical study. The TRITON study in which MSC therapy was shown to allow withdrawal of the nephrotoxic calcineurin inhibitor tacrolimus, will form the backbone for this clinical trial in which 16 patients will receive MCA-derived MSC combined with tacrolimus reduction to study safety and immunological efficacy of MCA-derived MSC therapy.

Study objective

To study whether MCA-derived MSC therapy is safe and effective in allowing tacrolimus reduction after kidney transplantation.

Secondary Objective(s):
To assess the effect of MCA-derived MSC therapy and subsequent tacrolimus reduction on renal function, the occurrence of opportunistic infections, the development of de novo donor specific antibodies

Study design

A non-randomized, open-label, non-blinded, prospective, single-center clinical phase I/IIb study to investigate whether MCA-derived MSC are safe by assessing the incidence of adverse events and BPAR/graft loss after MCA-derived MSC treatment.

Intervention

All patients will receive steroids according to the LUMC protocol and induction treatment with basiliximab at day 0 and 4 (20 mg intravenously). Patients will receive either 1 or 2 doses of 2x10^6 (+/- 10%) MCA-derived MSC/kg - the first at week 6 and the second at week 7 after transplantation.

Study burden and risks

Visits to the hospital: 14 visits of which 4 are extra above standard visits (including 1 or 2 MSC infusions); during 2 visits an Iohexol clearance will be done, which consists of 4 extra blood samples, during 2 hours, which will be done by using a peripheral venous catheter. All other blood samples will be combined with the routine blood samples. In total an extra 576 ml of blood will be taken during the course of 12 months; risks MSC infusion are considered low (possibly infections and sensitization).
Different from the previous MSC studies, we will not perform potentially

harmful protocol kidney biopsies, as our previous trials did not show reduction in quantitative fibrosis scoring during the study period (fibrosis was overall low at these timepoints).

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. Female or male, aged between 18 and 75 years.
2. Subject is willing to participate in the study, must be able to give informed consent
and the consent must be obtained prior to any study procedure.
3. Recipients of a first kidney graft from a living-unrelated or non-HLA identical living related donor.
If a donor is > 50 years of age, recipient must be >25 years of age.

4. Panel Reactive Antibodies (PRA) <= 10%.
5. No HLA repeated mismatch between MCA-derived MSC and the HLA mismatch between kidney graft and recipient.
6. Patients must be able to adhere to the study visit schedule and protocol requirements.
7. If female and of child-bearing age, subject must be non-pregnant, non-breastfeeding,
and use adequate contraception.

Exclusion criteria

1. Double organ transplant recipient.
2. Biopsy proven acute rejection (according to the Banff criteria) in the first 6 weeks after
transplantation.
3. Patients with evidence of active infection or abscesses (with the exception of an
uncomplicated urinary tract infection) before MSC infusion.
4. Patients suffering from hepatic failure.
5. Patients suffering from an active autoimmune disease.
6. Patients who have had a previous BM transplant.
7. A psychiatric, addictive or any disorder that compromises ability to give truly informed
consent for participation in this study.
8. Use of any investigational drug after transplantation.
9. Documented HIV infection, active hepatitis B, hepatitis C or TB according to current transplantation inclusion criteria.
10. Subjects who currently have an active opportunistic infection at the time of MCA-derived MSC infusion (e.g., herpes zoster [shingles], cytomegalovirus (CMV), Pneumocystis carinii (PCP), aspergillosis, histoplasmosis, or mycobacteria other than TB, BK) after transplantation.
11. Malignancy (including lymphoproliferative disease) within the past 2-5 years (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence) according to current transplantation inclusion criteria.
12. Known recent substance abuse (drug or alcohol).
13. Patients who are recipients of ABO incompatible transplants.
14. Cold ischemia time >30 hrs.
15.Patients with severe total hypercholesterolemia (>7.5 mmol/L) or total hypertriglyceridemia (>5.6 mmol/L) (patients on lipid lowering treatment with controlled hyperlipidemia are acceptable).
16. Repeated HLA mismatch present between the MCA-derived MSC and the mismatches between donor and kidney graft

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-07-2023
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	26-01-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-08-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-05-2024
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2022-004168-11-NL
CCMO	NL83484.000.22