Open label multicentre randomized trial comparing standard immunosuppression with tacrolimus and mycophenolate mofetil with a low exposure tacrolimus regimen in combination with everolimus in the novo renal transplantation in elderly patients.

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This study has been transitioned to CTIS with ID 2024-516509-22-00 check the CTIS register for the current data. 1. To test the hypothesis that an age adapted immunosuppressive regimen targeted at reduced immunosuppression with low calcineurin…

Ethical review	Approved WMO
Status	Completed
Health condition type	Nephropathies
Study type	Interventional

Summary

ID

NL-OMON48113

Source
ToetsingOnline

Brief title
Optimize

Condition

- Nephropathies

Synonym
immunosuppression, Renal transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: ZonMW ,Chiesi Farmaceutici,Novartis

Intervention

Keyword: elderly, immunosuppression, quality improvement, Renal transplantation

Outcome measures

Primary outcome

Primay outcome is succesfull transplantation. As outcome is expected to be markedly different in stratum A and stratum B, different primary outcome criteria will be used. We have defined successful transplantation as our primary outcome variable combining patient and graft survival with a minimum level of renal function. In our opinion this endpoint combines the most relevant outcomes for the patient. Stratum A: Primary endpoint: successful transplantation at 1 year after transplantation defined as: absence of graft or patient loss in the presence of an eGFR above 30 ml/min/1.73m2. Stratum B: Primary endpoint: successful transplantation at 1 year after transplantation defined as absence of graft or patient loss in the presence of an eGFR above 45 ml/min/ 1.73m2. Both strata are pooled for analysis.

Secondary outcome

Secondary outcomes both strata: • Incidence of individual endpoints of death, graft loss, rejection eGFR below 30 or 45 ml/min/ 1.73m2 rejection at Months 12 and 24. • Rejection treatment and type of rejection treatment • The evolution of renal function (eGFR) over time by slope analysis. • The incidence of

adverse events, serious adverse events and adverse reactions • The incidence of clinically relevant infections, new onset diabetes mellitus and malignancies • Presence of frailty at 3, 12 and 24 months after transplantation and change in frailty from baseline •Presence of markers for immunosenescence at 12 and 24 months and changes from baseline •hrQOL at 3, 12 and 24 months and changes from baseline. •Development of donor specific antibodies.

Study description

Background summary

Elderly patients increasingly contribute to both the dialysis and transplant population. In 2015 more than 30% of the transplant patients in the Netherlands were above 65 years of age while more than 50% of the dialysis population is older than 65 years. Kidney transplantation has some important age-dependent characteristics. Older patients with increased frailty and co-morbidity clearly have different risk profiles when compared with younger patients. While graft loss in younger patients is largely due to loss of the kidney with the recipient needing an alternative form of renal function replacement (e.g. dialysis and/or re-transplantation), death censored graft loss is a relatively rare phenomenon in older patients. Increased rates of malignancy and infection-related mortality have been reported in older transplant recipients. On the other hand, it has become clear that the aging immune system renders elderly recipients less prone to rejection. Kidneys from elderly donors are preferentially allocated to older recipients. A recent analysis of the results of deceased donor kidney transplantation in the elderly showed that in these patients graft loss is dominated by patient loss. Poor renal function in these patients may be both related to chronic damage of the kidney prior to transplantation (due to older donor age), and to an increased susceptibility to the toxicity of the immune suppressant tacrolimus. Especially in elderly recipients receiving marginal grafts it is essential to shift the focus from prevention of rejection to a stronger focus on preservation of graft function and preventing over-immunosuppression. In this study two immunosuppressive regimes will be tested; the standard therapy consisting of prednisolone, mycophenolate acid and tacrolimus once daily (Envarsus®), or the comparator in which mycophenolate acid will be replaced by everolimus combined with strongly reduced levels of tacrolimus once daily (Envarsus®). The hypothesis is that reduced CNI exposure will lead to improved allograft function, a reduced incidence of complications and improved quality of life. This study will

consist of two strata: Stratum A: Elderly recipients (>=65 years) of kidneys from elderly deceased donors (>=65 years) within the Eurotransplant Senior Program Stratum B: Elderly recipients (>=65 years) of kidneys from living donors (all ages) or deceased donors (<65 years). The primary endpoint will be successful transplantation defined as survival with a functioning allograft with a minimum estimated GFR of 30 ml/min in stratum A and 45 ml/min in stratum B, after 2 years. The study will be performed by almost all Dutch transplant centers,1 Belgian centre and the Dutch Kidney Patient Organization (NVN) will participate. This study will form a starting point for future collaboration between the renal transplant groups of the university medical centers in The Netherlands, who never before have participated together in a prospective clinical trial. Furthermore, this study will provide important guidance for the treatment of the elderly renal transplant population.

Study objective

This study has been transitioned to CTIS with ID 2024-516509-22-00 check the CTIS register for the current data.

1. To test the hypothesis that an age adapted immunosuppressive regimen targeted at reduced immunosuppression with low calcineurin inhibitor exposure will result in improved outcome in elderly recipients of A: kidneys from older deceased donors (>64 years) and B: Kidneys from living donors (all ages) and younger deceased donors (<65 years). 2. To evaluate the impact of transplantation and adapted immunosuppression on frailty and quality of life in older Dutch transplant recipients 3. To monitor the function of the aged immune system after transplantation and the effect of everolimus based immunosuppression on parameters of immunosenescence compared to standard tacrolimus based immunosuppression. 4. To establish a national platform for trials in kidney transplantation as a basis for future high impact clinical trials. 5. To identify immunologic parameters that may serve as biomarkers of immunosenescence for future clinical application.

Study design

Open label randomized national multicentre intervention trial comparing standard immunosuppression with tacrolimus and mycophenolate mofetil with a low exposure tacrolimus regimen in combination with everolimus. The trial will consist of two strata: Stratum A: Elderly recipients (>=65 years) of kidneys from elderly deceased donors (>=65 years) within the Eurotransplant Senior Program Stratum B: Elderly recipients (>=65 years) of kidneys from living donors (all ages) or deceased donors (<65 years).

Intervention

Study patients will be randomized to the following regime in both stratum A and

stratum B in a 1:1ratio. Arm 1: Basiliximab (B) induction (20 mg iv on days 0 and 4), prednisolone taper to 5 mg at 3 months after transplantation, tacrolimus once daily (Envarsus®) with an initial target trough level of 8-12 tapered to 5-8ug/l at 6 months after transplantation, mycophenolate mofetil at dose of 500 mg bd throughout the trial. Arm 2: Basiliximab (B) induction (20 mg iv on days 0 and 4), prednisolone taper to 5 mg at 3 months after transplantation, tacrolimus once daily (Envarsus®) with initial target trough level of 5-7 tapered to 2-4 ug/l from 3 months, and 1.5-4 ug/l from 6 months after transplantation, everolimus (EVL) will be initiated at a starting dose of 1.5 mg bid with target trough level of 3-6 ug/l throughout the trial.

Study burden and risks

Benefit: The combination of everolimus and tacrolimus in a lower dose can provide better renal function and a lower mortality rate. Burden: Completing forms can take some extra time Everolimus has, as all immunnosuppresive agents, its own side effects Taking bloodsamples might be painfull and can cause bruises (in the study 162.5 ml extra

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Elderly (65 years and older)

Inclusion criteria

nclusion criteria 1. Written informed consent must be obtained before any assessment is performed 2. Male or female subject >= 65 years old 3. Subject randomized within 24 hours of completion of transplant surgery 4. Stratum A: Recipient of a primary (or secondary, if first graft is not lost due to immunological reasons) renal transplant from a deceased donor aged 65 years or older 5. Stratum B: Recipient of a primary (or secondary, if first graft is not lost due to immunological reasons) renal transplant from a deceased donor aged below 65 years or a living donor of any age

Exclusion criteria

Exclusion criteria for both stratum A and B 1. Subject is a multi-organ transplant recipient 2. Recipient of ABO incompatible allograft or CDC cross-match positive transplant 3. Subject at high immunological risk for rejection as determined by local practice for assessment of anti-donor reactivity 4. Recipient of a kidney with a CIT > 24 hr 5. Recipients of a kidney from an HLA identical related living donor 6. Known intolerability for one or more of the study drugs 7. Subject who is HIV positive 8. HBsAg and/or a HCV positive subject with evidence of elevated LFTs (ALT/AST levels >= 2.5 times ULN). Viral serology results obtained within 6 months prior to randomization are acceptable * 9. Recipient of a kidney from a donor who tests positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV) 10. Subject with a BMI greater than 35 11. Subject with severe systemic infections, current or within the two weeks prior to randomization 12. Subject requiring systemic anticoagulation that cannot be temporarily interrupted and which would preclude renal biopsy 13. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases 14. Subject with severe restrictive or obstructive pulmonary disorders 15. Subject with severe hypercholesterolemia or hypertriglyceridemia that cannot be controlled 16. Subject with white blood cell (WBC) count <= 2,000 /mm3 or with platelet count <= 50,000 /mm3

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:	Completed
Start date (anticipated):	22-07-2019
Enrollment:	351
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cellcept
Generic name:	Mycophenolate mofetil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Certican
Generic name:	everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Ciclosporine
Generic name:	Neoral
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Envarsus

Generic name:	tacrolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prednisolone
Generic name:	Prednisolone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-09-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-03-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-07-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-02-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EU-CTR	CTIS2024-516509-22-00
EudraCT	EUCTR2018-003194-10-NL
ClinicalTrials.gov	NCT03797196
CCMO	NL68661.042.18