The effect of blockade of the CD40-CD40L pathway on T and B cell mediated alloreactivity after kidney transplantation

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Does blockade of the CD40-CD40L pathway reduce T and B cell mediated alloreactivity after kidney transplantation?

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

Summary

ID

NL-OMON42873

Source
ToetsingOnline

Brief title
Effect of blockade of CD40 on alloreactivity after kidney transplantation

Condition

- Other condition

Synonym
kidney transplantation, organ transplantation

Health condition

orgaantransplantatie

Research involving
Human

Sponsors and support

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

Intervention

Keyword: anti-CD40 monoclonal antibody, immunosuppression, kidney transplantation

Outcome measures

Primary outcome

Peripheral Blood

1. The number and characteristics of peripheral effector and regulatory T-, and

B- cells and dendritic cells (DC) of CFZ533-treated patients

a. Multicolor flow cytometry to determine the number and characteristics of

circulating T and B cells using the One study protocol in combination with

intracellular cytokine measurements to determine the frequency of IFN-γ, IL-21

and IL-10 producing T and B cells.

2. To analyze T-B cell interaction during co-stimulation blockade

a. Pure cell populations will be sorted with FACS Aria Cell SorterTM:

CD4+CXCR5+ T-cells (Tfh cells)and CD19+CD27+ B cells (memory B cells). These

memory B cells will be co-cultured with Tfh in the presence of donor antigen

for 7 days to study the maximal Tfh-B cell interaction. Differentiation of B

cells into plasmablasts (CD19+IgD-CD27+CD38++ cells) will be determined with

flow cytometry. IgM and IgG production will be measured with a sandwich ELISA

on the supernatant of the co-cultures. Donor-specific antibodies in culture

supernatant by Luminex technology.

b. Differentiation of patient derived CD43neg B cells into plasma cells will be studied after stimulation with an agonist CD40, anti-IgM and IL-21 (mimicking T cell stimulation). This assay will determine the functional blockade by the test compound.

c. Elispot will be used to determine the frequency of donor-antigen specific Tfh-IL-21 producing cells. The frequency of donor specific IgG producing plasma cells will be counted using Elispot.

3. To study the efficacy of CFZ533 on CD40 receptor expression by peripheral blood cells

a. CD40 saturation efficacy on peripheral B cells and DC by flow cytometry

Biopsy

4) Characterization and quantification of the cellular infiltrate by immunohistochemistry

a. CD3, CD4, CD8, CD79a, CD20, CD19, CD38, granzyme B, TIA1, C4d, C3d, CD40, CD40L, PD1, PD1L, BCL6, FoxP3

b. T and B cell mRNA expression profile by Q-PCR

Secondary outcome

not applicable

Study description

Background summary

Blocking the CD40-CD154 pathway has been shown to effectively prolong renal allograft survival in non-human primates. CFZ533 is a novel, fully human, Fc-silent, anti-CD40 monoclonal antibody being developed for use in transplantation. In non-clinical studies, CFZ533 prolonged allograft survival and inhibited T-dependent antibody response (TDAR). CFZ533 has minimal agonistic effects.

Study objective

Does blockade of the CD40-CD40L pathway reduce T and B cell mediated alloreactivity after kidney transplantation?

Study design

Patients participating in the main study (MEC 2015-730) will be randomized to treatment with CFZ533 or tacrolimus. At given timepoint bloodsamples will be taken for extensive immunological assesments.

Study burden and risks

No risk, and no benefit.
This study is a lab study, for which blood will be taken from participating patients.
If a renal biopsy is performed, additional immunological test will be performed on the biopsy.

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

All patients participating in the main trail (MEC 2015-730)

Exclusion criteria

None

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-08-2016

Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	05-08-2016
Application type:	First submission
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
CCMO	NL58077.078.16