Immune monitoring to characterize T-cell responses of kidney transplant patients during co-stimulation blockade by belatacept

Published: 23-08-2012
Last updated: 26-04-2024

Here, we postulate that the balance between the effect of belatacept on regulatory T-cell function and the relative insensitivity of memory T-cells for belatacept leads to donor-specific alloreactivity. We plan to study the peripheral CD28-dependent...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON41595

Source
ToetsingOnline

Brief title
Characterizing T-cell responses during belatacept treatment

Condition

- Immune disorders NEC
- Nephropathies
- Renal and urinary tract therapeutic procedures

Synonym
acute rejection, Kidney transplantation

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Astellas Pharma Europe Ltd.,Bristol-Myers Squibb,Bristol-Myers Squibb;de fabrikant van belatacept en Astellas Pharma Europe Ltd.;fabrikant van Tacrolimus.

Intervention

Keyword: Belatacept, Co-stimulation blockade, Kidney transplantation, T-cell response

Outcome measures

Primary outcome

Primary Objectives: Lab endpoints

1) To determine the presence, frequency, and characteristics of effector CD4+

and CD8+ T-cells

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

3) To assess belatacept concentrations and neutralizing anti-belatacept

antibodies (pharmacokinetic [PK] study), saturation and functional consequences

of CD80/CD86 receptor blockade of peripheral blood cells (pharmacodynamic [PD]

study)

Lab end points

We will use the following methods (all of which are established in our

laboratory) to analyze peripheral blood samples of the study (belatacept) and

the control group.

Objective 1)

- Mixed lymphocyte reaction (MLR) during 16-24 hr of anti-donor stimulated peripheral blood cells followed by flowcytometry to measure cell surface expression of CD137 and CD154 on CD4+ and CD8+ T-cells, respectively. Anti-CD3/anti-CD28 stimulated T-cells will serve as a positive control.
- Co-culture experiments of isolated Tregs with CD154+ CD4+ T-cells and CD137+ CD8+ T-cells to define the suppressive activities of Tregs on donor-antigen driven proliferation and cytokine production by the CD4+ and CD8+ T-cells.
- Flowcytometry and DNA-based techniques to determine the frequency and nature of Tregs (Helios positivity, demethylation of the FOXP3 gene).
- Flowcytometry to study the efficacy of belatacept to block cytokine production (IFN-gamma and granzyme B) of polyclonally activated CD28+ and CD28- CD4+ and CD8+ T-cells.

Objective 2)

- Flowcytometry to measure the number and frequency of Tfh cells (CXCR5+ CD4+) and CD19+ CD20- CD27+ CD38++ circulating plasma cells.
- Co-culture experiments of sorted Tfh cells with B-cells. The T-cell-dependent B-cell Elispot will be used to analyze the B-cell help function of Tfh.
- Donor-specific antibodies in patient plasma by Luminex® technology.

Objective 3)

- By ELISA we aim to measure belatacept serum concentrations and concentrations of neutralizing anti-belatacept antibodies.
- Belatacept CD80/CD86 saturation efficacy on peripheral blood cells by

flowcytometry

Objective 4)

In the extension phase all patients will receive Tacrolimus and lab parameters will be measured as mentioned above on timepoints month 18 and 24.

Secondary outcome

This study, as indicated above, focuses on the immunologic mechanisms behind the drug belatacept and therefore has a number of immunological endpoints. Clinical endpoints, such as the incidence and severity of acute rejection, renal function (as determined by the estimated glomerular filtration rate [eGFR]), and the incidence of serious adverse events will be collected as part of routine clinical care. The described immunological, pharmacokinetic and pharmacodynamic measurements will then be correlated to the occurrence of these clinical endpoints in a secondary analysis.

Study description

Background summary

Belatacept represents a potential new treatment option for renal transplant recipients which addresses the current unmet need for an immunosuppressive treatment that provides short-term outcomes comparable to calcineurin inhibitor (CNI)-based immunosuppressive regimens with the potential to avoid the renal, cardiovascular, and metabolic toxicities of CNIs. In the two phase III studies in renal transplant recipients of kidneys from standard or extended criteria donors (the so-called BENEFIT and BENEFIT-EXT trials), belatacept was comparable to ciclosporin (CsA) with regard to kidney allograft and patient survival. In addition, belatacept treatment resulted in clinically meaningful reductions in the proportions of patients with advanced renal dysfunction, defined as chronic kidney disease (CKD) stage 4 or 5. While rates of acute rejection (AR) were higher with belatacept than CsA (approximately 3-10%

higher), the rates of rejection that led to severe renal dysfunction or graftloss were low.

Central to our understanding of the immune responses after transplantation is the emerging role played by specific cell subsets, such as T-effector (Teff) cells, T-regulatory cells (Tregs), B-cells, and dendritic cells. These cells determine the occurrence of allograft rejection and tolerance by their ability to migrate towards immunological hot-spots where they interact with each other and orchestrate immune reactions. It is now possible to prevent allograft rejection by inhibiting activation of Teff cells via costimulation blockade. Inhibition of the T-cell costimulatory pathway CD28-B7 blocks T-cell activation and promotes anergy or apoptosis. The modified cytotoxic T-lymphocyte antigen-4 (CTLA-4)-Ig belatacept (Nulojix®) indirectly blocks CD28 signaling and is approved for the prevention of rejection after kidney transplantation. Two recently completed phase III trials of belatacept have shown that it is a safe and effective immunosuppressant that leads to a significantly better renal function (GFR, glomerular filtration rate) as compared to a CsA-based regimen in kidney transplant recipients. Acute rejection occurred at a higher frequency among belatacept-treated patients, but at rates generally thought to be clinically acceptable (17-22% at 12 months in the belatacept groups versus 7-14% in the CsA-groups). Moreover graft and patient survival where comparable between belatacept and CsA-treated patients.

These clinical findings may be explained by laboratory observations. Cells that down-regulate inflammatory immune activity, the FoxP3+CD25+ Tregs, are dependent on costimulation for their homeostasis and function. Blockade of costimulatory pathways not only suppresses Teff cells, but may also impair activation of Tregs. This is possibly a dose-related phenomenon, with higher concentrations of belatacept inhibiting both proinflammatory costimulation as well as the negative signal imparted by CD86 in the CD28-B7 interaction. Furthermore, any beneficial immunoregulatory response may have been compromised by propensity of anti-CD25 induction therapy (utilized in the trial) to temporarily reduce the number FoxP3+CD25+ Tregs in the circulation which appear to develop more easily in patients receiving CNI-free immunosuppressive regimens. Another explanation for the clinical finding of a higher incidence of acute rejection in belatacept-treated patients may relate to memory T-cells. Upon restimulation, memory T-cells express a rapid and robust response to the transplanted organ and therefore represent a significant barrier to successful transplantation. Unlike naïve T-cells, memory T-cells are activated relatively independently of CD28-mediated costimulation, and are therefore less susceptible to belatacept-based immunosuppression.

A unique feature of CD28 pathway is the activation of the NF-*B and NF-*B-regulated genes, e.g. those of the pro-inflammatory cytokines IFN-γ, TNF-alpha, and IL-2. Furthermore, CD28-mediated signals lead to the enhancement of several T-cell functions, including survival and regulation of both cytotoxic and humoral T-cell responses. In the presence of T-cell help, B-cells react to

protein antigens and differentiate into plasma cells. This T-B-cell contact depends on the interaction with the co-stimulatory molecules CD28, CD154 (CD40Ligand), inducible costimulator (ICOS), and programmed death (PD)-1, and the cytokine IL-21. Particularly, the follicular helper T-cell (Tfh cell) subset of CD4+ T-cells is specialized in the provision of help to B-cells. However, activated memory T-cells express other co-stimulatory molecules: CD137 (4-1BB) and CD154. Both are members of the TNF superfamily of molecules and enhances after binding, T-cell proliferation, IL-2 secretion, survival, cytolytic activity and B-cell activity. Recently, it has been shown that antigen-specific T-cells are present in CD154-expressing CD4+ T-cells and CD137 CD8+ T-cells. A strong association between acute cellular rejection and the frequency of peripheral allospecific CD154 memory T-cells was reported. Alloactivated T-cells can be measured after an activation step, followed by a brief incubation period (16-24h) with alloantigen, and subsequent staining for CD137 and CD154.

Here, we postulate that the balance between the effect of belatacept on regulatory T-cell function and the relative insensitivity of memory T-cells for belatacept leads to donor-specific alloreactivity. We plan to study the peripheral CD28-dependent intracellular signalling pathway, regulatory T-cell, memory T-cell and Tfh functions. The proposed study will identify patients at risk for rejection and will at the same time unravel the complex network of cellular interactions during belatacept treatment.

Study objective

Here, we postulate that the balance between the effect of belatacept on regulatory T-cell function and the relative insensitivity of memory T-cells for belatacept leads to donor-specific alloreactivity. We plan to study the peripheral CD28-dependent intracellular signalling pathway, regulatory T-cell, memory T-cell and Tfh functions. The proposed study will identify patients at risk for rejection and will at the same time unravel the complex network of cellular interactions during belatacept treatment. The primary aim of this study, therefore is to characterize the function and phenotype of peripheral T-cells that determine rejection and graft acceptance during belatacept therapy.

In addition, throughout the clinical study in all patients both immunologic, pharmacokinetic and pharmacodynamic data will be collected. Pharmacokinetic analyses will include the belatacept serum concentrations, as well as the concentrations of neutralizing anti-belatacept antibodies. Based on the PK data, the time-varying exposure to belatacept will be described. Belatacept exposure-pharmacodynamic effect relationships will be established, and the influence of covariates including bodyweight, age, and albumin concentration will be studied. Of main interest will be the influence of belatacept serum concentrations on saturation of CD80 and CD86 on lymphocytes (flowcytometry) and on immunological tests (see description of PD and immunologic parameters).

The primary objectives of this study are:

1) To determine the presence, frequency, characteristics of effector CD4+ and CD8+ T cells
2) To analyze T-B cell interaction during co-stimulation blockade
3) To assess belatacept concentrations and neutralizing anti-belatacept antibodies (PK study), as well as the saturation and functional consequences of CD80/CD86 receptor blockade by peripheral blood cells (PD study).

Study design

This will be an exploratory, hypothesis-generating, open-label, active-controlled, randomized-controlled, clinical trial in which a total of n = 40 consecutive, kidney transplant recipients (meeting the inclusion criteria) will be treated with either a belatacept-based immunosuppressive regimen (intervention group; protocol A) or our standard, Tac-based immunosuppressive regimen (control group; protocol B) after providing written informed consent. Patients will receive the routine clinical care and will be admitted to hospital at the designated time points to receive their belatacept intravenously in a day care setting. In addition, blood will be drawn to study the above-described immunological parameters at day 4, and month 1, 3, 6 and 12 after transplantation. Patients randomized to the control arm will receive our standard immunosuppressive regimen consisting of Tac in combination with MMF, prednisolone, and basiliximab. Blood will be drawn at the same time points as in the belatacept-treated patients to study the immunological endpoints of interest. Follow-up will be 12 months (the first posttransplant year). Treatment with belatacept will be continued after the first posttransplant year provided that patients are willing and the drug is reimbursed. It is an investigator-initiated study made possible by a grant from the manufacturer of belatacept.

Patients in the Belatacept group (group A; experimental groep) will be treated as follows:
Belatacept: 10 mg/kg intravenously on days 0, 4, 15, 30, 60, and 90 and 5 mg/kg intravenously on month 4, 5, 6, 7, 8, 9, 10, 11, and 12.

In addition, all patients will receive Basiliximab (20 mg intravenously on days 0 and 4), mycophenolate mofetil (MMF; Cellcept®; starting dose of 1000 mg b.i.d. aiming for predose concentrations of 1.5 - 3.0 mg/L), and prednisolone (50 mg intravenously b.i.d. on days 0, 1, and 2, followed by 20 mg orally once daily, which will be tapered subsequently to 5 mg per day at month 3 after transplantation. Patients will continue to receive a low dose of prednisolone throughout the first posttransplant year (minimum 2.5 mg per day).

Patients in the control group (protocol B) will receive our standard immunosuppressive regimen consisting of tacrolimus (Prograf®) with a starting dose of 0.2 mg/kg per day in two equally-divided doses aiming for predose

concentrations (C0) of 10-15 ng/mL (week 1-2), 8-12 ng/mL (week 3-4), and 5-10 ng/mL, thereafter. In addition, all patients will be treated with basiliximab, MMF and prednisolone in the same dose as that of patients in the belatacept group (see above).

In the second year of this study we want to investigate whether there are any changes in the immune system caused by treatment with Belatacept. In the second year of this study, after discontinuing belatacept and the conversion to tacrolimus we want to investigate whether there are any changes in the immune system. To monitor this, extra blood samples will be drawn at month 18 and month 24 and whenever rejection is suspected.

Intervention

Patients will receive belatacept (Nulojix®) or tacrolimus (Prograf®). In addition, all patients -both in the experimental and control groups- will be treated with mycophenolic acid, prednisolone and basiliximab

The firm Bristol Myers Squibb supplied Belatacept for one year. As the health insurance does not reimburse this treatment in the Netherlands at this moment, all patients in this study will be converted to once-daily, modified-release Tacrolimus at time point month 12.

Study burden and risks

Clinical trials investigating belatacept have demonstrated that the incidence of acute rejection is higher compared to classical, CNI-containing immunosuppressive regimens (about 3-10% higher). This adverse effect has to be balanced against the better renal function and more favourable cardio-vascular profile that was obtained during belatacept therapy. The rejection episodes occuring during belatacept treatment responded, in general, well to anti-rejection therapy.

Second, the incidence of posttransplant lymphoproliferative disorder (PTLD) was higher in the two phase III clinical trials among patients who received belatacept as compared to the control group who received a CsA-based immunosuppressive regimen. However, the higher incidence of PTLD occured mainly in patients who were EBV-seronegative prior to transplantation. In the current study, EBV-naïve patients will not be included, as mandated by the package insert of belatacept.

In addition and unlike patients receiving the standard, tacrolimus-based therapy, patients that will receive belatacept will be admitted to hospital for intravenous administration of the drug. This will be done in daycare setting and will in the early phase after transplantation coincide with the hospitalization for the transplantation itself. These admissions will be short

(3 hrs) and coincide with scheduled visits to the outpatient clinic for routine follow-up after transplantation. Apart from the admission for administration of the drug, the insertion of an i.v. cannula, and the drawing of additional blood for immunological monitoring purposes (explained above), the patients will experience no other burdens.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

's Gravendijkwal 230
Rotterdam 3000 CA
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

's Gravendijkwal 230
Rotterdam 3000 CA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

a) Male or female kidney transplant recipients.
b) Age >= 18 years.
c) Patients to be transplanted with a first or second kidney allograft.
d) Patients receiving a kidney allograft from a living donor.
e) Patients receiving a bloodgroup AB0-compatible kidney transplant.

f) Patients receiving a non-HLA identical kidney transplant.
g) Panel reactive antibodies (PRA) <30%.
h) Patients must have known EBV serostatus, and that status must be positive.
i) Patients receiving a non-HLA-DR mismatched kidney transplant.

Exclusion criteria

a) Recipients of a third (or higher) allograft.
b) Recipients of a non-renal organ transplant.
c) Recipients of a kidney transplant from a deceased donor.
d) Recipients under the age of 18 years.
e) Sensitized transplant recipients (defined as a PRA of >=30%).
f) Recipients of a HLA-identical kidney allograft.
g) Recipients of a bloodgroup AB0-incompatible kidney allograft.
h) Recipients with a historically positive cross-match.
i) Patients with a history of lymphoma.
j) Seronegative or unknown EBV serostatus.
k) Patients with tuberculosis who have not been treated for (latent) infection.
l) Patients at high risk for polyoma virus-associated nephropathy.
m) Patients receiving an HLA-DR mismatched kidney transplant.

Study design

Design

Study phase:	4
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):	01-10-2013
Enrollment:	40

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nulojix
Generic name:	Belatacept
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Prograf
Generic name:	Tacrolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-08-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-05-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-10-2015
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	EUCTR2012-003169-16-NL
CCMO	NL41402.078.12

Study results

Date completed:	21-02-2017
Actual enrolment:	41