Desensitization of highly pre-sensitized dialysis patients waiting for kidney transplantation by Rituximab, IVIG-L and rescue Plasmapheresis
THE DRIP STUDY

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1. Primary end point is achievement of a negative cross-match test with the donor kidney and transplantability.2. Secondary objectives are patient and graft survival, graft function as assessed by calculated creatinine clearance, proteinuria, the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON30466

Source
ToetsingOnline

Brief title
THE DRIP STUDY

Condition

- Other condition

Synonym
Transplantation

Health condition

niertransplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Roche Nederland BV voor MabThera verstrekking,Sanquin voor IVIG verstrekking,Sanquin voor IVIG verstrekking en Roche Nederland BV voor MabThera verstrekking

Intervention

Keyword: anti-CD20 monoclonal antibodies, desensitization, donor specific allo-antibodies, humoral rejection

Outcome measures

Primary outcome

Primary end point is achievement of a negative cross-match test with the donor

kidney and transplantability.

Secondary outcome

Secondary objectives are patient and graft survival, graft function as assessed

by calculated creatinine clearance, proteinuria, the number and severity of

acute (antibody mediated) rejections, blood pressure (antihypertensive

treatment), monitoring of infections and the occurrence of malignancies.

Study description

Background summary

A substantial part of dialysis patients awaiting transplantation possesses anti HLA antibodies. In the Netherlands 14% of the renal transplant candidates are pre-sensitized with a varying range of 5 to 85% panel reactivity. Sensitization occurs after blood transfusion, pregnancy or following previous transplantation. These allo-antibodies are a substantial obstacle to the transplantability with subsequent deleterious socioeconomic consequences. In addition, after transplantation these allo-antibodies have a negative effect on

both short- and long-term graft survival.
Highly pre-sensitized recipients have a prolonged waiting time for transplantation, due to difficulties in finding a crossmatch negative donor organ. For some, the chances of finding such an organ are almost nihil. Increased waiting time for renal transplantation is associated with increased morbidity. Several strategies are employed to find a matching organ for sensitized candidates. Two modes of desensitization therapy have been applied which are discussed in detail further (Modes of desensitization). These include the plasmapheresis (PP)/low dose IVIG protocol (Johns Hopkins and Mayo Clinic Protocol) and the high-dose IVIG protocol (Cedars-Sinai Protocol). Other approaches involve the The Acceptable Mismatch Program and The Cross Over Exchange Program. Strategies based on identification of acceptable HLA-mismatches (AM) result in available kidneys for approximately 60% of these patients. Currently, the Dutch AM waiting list contains 99 broadly allo-immunized patients waiting more than 2 years for a crossmatch negative cadaveric kidney. Among these patients are approximately 20 with current PRA values of >=80%. For these patients the chance of transplantation within another 2 years is negligible.
Here, we present the Dutch desensitization protocol, involving candidates for a cadaveric kidney with a current PRA >=80 % who are on the list of AM Program for longer than 2 years. Only heart beating donors will be accepted. Highly sensitized candidates for a living donor will be excluded considering the operating Cross-Over Transplant Program which can offer these candidates a higher chance to find a crossmatch negative donor organ.
Modes of desensitization
Intravenous immunoglobulins (IVIG):
In theory, administration of IVIG can both remove and diminish the synthesis of allo-antibodies. IVIG contains polyclonal, mostly IgG antibodies, prepared from plasma of human blood donors. These preparations contain antibodies against a whole array of antigens amongst others antibody idiotypes, CD40, HLA-class I and II antigens, interleukin 1α and β and interferon-γ. The workingmechanisms on immune modulation are complex and various and affect both T and B cell function. Several studies have been published in which IVIG are used to desensitise highly immunized recipients. These studies were all open and non-randomized. They varied greatly in timing of the IVIG infusion, the administered dose, and the additional immunosuppressive therapy. Currently, two protocols have emerged. These include the plasmapheresis/low dose IVIG protocol (Johns Hopkins and Mayo Clinic Protocol) and the high-dose IVIG protocol (Cedars-Sinai Protocol). Briefly, Johns Hopkins and Mayo Clinic Protocol consists of daily 1-plasma volume exchange using 5% albumin followed by administration of IVIG (100 mg/kg) in order to achieve a negative Cross Match Test (CMX). Therefore the number of pre-transplant PP in this protocol can vary greatly. In addition, patients undergo several PP/IVIG courses on post-operative days. Cedars-Sinai Protocol utilizes four monthly high dose IVIG (2g/kg, maximal dose of 140 g) administrations in order to achieve a negative CDC CMX. Patients continue with one additional high dose IVIG one month after transplantation. To be enrolled, patients should show some degree of inhibition

in their so-called *in vitro IVIG inhibition CMX test* . Using this protocol Jordan et al evaluated 77 highly sensitized patients who had positive CMX tests with their potential donors in the IVIG-PRA test system. Desensitization was in 97% of the patients successful and 87% could be transplanted.
B-cell targeted therapy (Rituximab):
In order to prevent de novo allo-antibody synthesis and circumvent the production of newly formed (long lived) plasma cells, CD20 positive (naive and memory) B-cells can be targeted by rituximab (RTX); the up to now most specific B-cell targeting drug. Rituximab (MabThera; Roche) is a chimeric IgG1 kappa monoclonal antibody that causes B lymphocyte depletion by means of complement dependent cytotoxicity, antibody dependent cellular cytotoxicity and direct induction of apoptosis. RTX has been widely used in the treatment of human B cell malignancies and autoimmune diseases. B-cell depletion, induced by RTX is typically followed by a B-cell recovery after 6-9 months. Preliminary studies indicate that RTX decreases the concentration of pre-existing and post-transplantation antibodies. Vieira et al described encouraging results from a phase I clinical trial of RTX in pre-sensitized recipients who are awaiting a renal transplant. The study showed that RTX could be safely administered to recipients with dialysis dependent end stage renal disease. It showed some efficacy in the inhibition of presumed pre-existing memory B cells and long-lived plasma cells. RTX is also successfully used in the preconditioning regimen in AB0 incompatible renal allograft recipients.

Study objective

1. Primary end point is achievement of a negative cross-match test with the donor kidney and transplantability.
2. Secondary objectives are patient and graft survival, graft function as assessed by calculated creatinine clearance, proteinuria, the number and severity of acute (antibody mediated) rejections, blood pressure (antihypertensive treatment), monitoring of infections and the occurrence of malignancies.

Study design

Prospective clinical observational trial

Intervention

Description of the treatment protocol:

-Administration of Rituximab (two doses)
The first dose of rituximab (MabThera, Roche) 375 mg/m2 intravenously will be administered five months prior to transplantation. The second and last dose will be administered before transplantation and after the completion of a successful treatment course with 4 doses of monthly IVIG administrations (see

below) and at the time-point at which the patient can indeed be transplanted. We expect that the patient can indeed be transplanted up to 6 weeks after completion of desentizisation therapy.
Initial infusion: Start rate of 50 mg/hour; if there are no adverse side effects; increase the rate 50 mg/hour every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions: Start at 100 mg/hour; if it is safe; increase the rate 100 mg/hour every 30 minutes, to a maximum of 400 mg/hour. All recipients will be given acetaminophen (1000 mg) and Di-adresoneF (25 mg), tavegil (2 mg), 30 min before the infusion.
-Administration of IVIG-L
Four monthly doses of IVIG-L will be administered prior to the transplantation in a dose of 2 g/kg with a maximum of 140 gram per treatmentsession, in a dilute low-osmolaric solution, which can be repeated monthly in case of prolonged waiting time for a matched donor kidney. IVIG-L administration will be started at a speed of 30 ml/hr during the first 15 minutes. IVIG-L can be infused with infusion rates up to 8 ml/min (7 ml/kg/hr) without occurrence of severe side effects (Sanquin Clinical Study Report KB 97003B). In case of minor side effects, infusion will be withhold and after full clinical recovery of symptoms restarted at 50% of the original speed. To avoid the risk of overhydration in haemodialysis patients, IVIG-L has to be given during dialysis in a 4-hr period and if necessary continued thereafter (dependent on the total dose which has to be infused), or otherwise IVIG-L infusion can be started on a not-dialysis day (dependent on the cardiovascular status of the patient and under clinical surveillance) followed by dialysis thereafter.
Briefly, IVIG-L (2 g/kg; maximum dose: 140 g) will be administered, on dialysis or the day after, monthly maximally for 4 months with the last course one month before transplantation. If the patient who has completed the full desensitizing treatment course has to wait longer than 4 weeks in order to find a cross match negative organ , then another IVIG-L dose should be administered.
Plasmapheresis (PP)
If treatment consisting of the first dose of rituximab and the full IVIG-L course of four monthly doses fail to achieve an acceptable low PRA (lower than or equal with 5%) and a negative CMX against the primarily unacceptable antigens, the patients can not be considered for transplantation. In this case we will institute a *rescue plasmapheresis* protocol encompassing maximal 7 courses of daily large volume pheresis (40 ml/kg body weight) substituting plasma with saline/albumin solution in order to remove the antibodies as it is known that a part of these patients can still respond to PP. If this occurs, the second dose of rituximab will be administered according to the protocol before tarnsplantation. After each third pheresis, plasma will be substituted with fresh frozen plasma (FFPs) in order to prevent and minimize the risk of bleeding.
-Transplantation
Whenever a substantial decrease of HLA-alloantibodies (PRA,lower than or equal with 5%) is reached with this regimen and a negative crossmatch against a (selected) cell panel is obtained, transplantation has to be carried out as soon as possible. The kidney allograft will be allocated according to the

already known acceptable antigen profile for each individual patient and avoiding DR mismatches. Modification of the AM-status means that only acceptable HLA-antigen profile which is achieved after rituximab/IVIG-L/PP are taken into account before allocation takes place. Transplantation will be performed only in the case of a negative current cross-match test with the selected donor. Only heart beating donors will be accepted.

Study burden and risks

Nature and extent of the burden and risks:

Side effects are that of the study medication. Both IVIG-L and Rituximab are registered drugs in Europe and USA. In USA these medication are used for the same objectives as discussed in this study (see references in protocol and in section " additional remarks"). These drugs seemed to be safe and effective in our target group; namely the dialysis patients. The spectrum of their side effects comprises undesired evens ranged from allergic reactions to increased risk of overhydration. The patients will be admitted during these therapeutic interventions and dialysed extra if necessary.

Benefit is of course the possibility of kidney transplantation. The chances for this group of patients; waiting longer than two years for a kidney transplant with a PRA level >=80% is nihil. Each kind of dialysis is accompanied by increased risk of morbidity and mortality. Moreover, transplantation is the most cost effective kind of renal function replacement therapy.

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

-Patients older than 18 years with end stage renal failure and a current Panel Reactive Antibody level >= 80 % who are for more than two years on the waiting list for a cadaveric donor kidney, and included in the Acceptable Mismatch program of Eurotransplant.
-Written informed consent

Exclusion criteria

Complete IgA deficiency
Overhydration
History of anaphylaxis against blood/plasma products
Significant cardiac or pulmonary disease, hepatitis C or HIV infection, or malignancy within the last 5 years

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2007
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	MabThera
Generic name:	Rituximab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nanogam
Generic name:	Human normal immunoglobulin for intravenous use
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	01-02-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2006-006248-72-NL
CCMO	NL15304.018.07