Lymphnodes with and without Alemtuzumab to Measure Broad Alloreactivity against Donor Antigens

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Primary objective of the study:- The primary objective for this study is to determine the prognostic characteristics for BPAR in the first 3 months after transplantation, as assessed in the lymphocyte composition of the lymph node in immunologically…

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

Summary

ID

NL-OMON42749

Source
ToetsingOnline

Brief title
LAMBADA

Condition

- Other condition
- Renal disorders (excl nephropathies)

Synonym
rejection of kidney allograft

Health condition

niertransplantatie

Research involving
Human

Sponsors and support

Primary sponsor: Interne Geneeskunde, sector Nefrologie en Niertransplantatie
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: alloreactivity, kidney transplantation, lymphnode, rejection

Outcome measures

Primary outcome

The primary objective for this study is to determine the prognostic characteristics for BPAR in the first 3 months after transplantation, as assessed in the lymphocyte composition of the lymph node in immunologically high-risk kidney transplantation.

Secondary outcome

Secondary objectives of the study are:

- to capture global composition of lymph node and blood leukocyte subsets [20].

- to compare the immunological ageing profile of T cells in the peripheral blood to the T cells derived from the lymph node.

- to assess whether pre-transplant frequencies of lymph node derived TFH, T and B cells predict BPAR.

- to assess differences in lymphocyte composition of lymph nodes in alemtuzumab treated versus untreated patients both in single cell suspension and within the tissue. (ABO-incompatible kidney transplant recipients receive alemtuzumab induction therapy three weeks before transplantation).

Study description

Background summary

Allograft rejection after kidney transplantation is a major determinant of allograft survival [1-3]. Different cells of the adaptive and innate immune response infiltrating the graft contribute to the allo-antigen specific organ injury. Traditionally T-cells have been the main focus of transplantation immunology research, while in recent years B-cells have been recognized to be important not only in antibody production by plasma cells, but also as regulators of immune responses and in providing T-cell help [4]. New detection techniques for donor-specific antibodies for example contribute to the understanding of antibody-mediated allograft injury [5]. Despite these new laboratory techniques, the results of sampling the peripheral blood to study specific cell populations and functions that can predict the risk for allograft rejection are disappointing. The composition and function of lymphocyte subsets in the peripheral blood poorly correlate with clinical outcomes like BPAR (biopsy-proven acute rejection) [6].
Lymph nodes differ in lymphocyte composition and contain for example more follicular T-helper cells and less cytotoxic CD4+ T cells than peripheral blood [7]. It is known that the migration of antigen presenting cells from the allograft to the draining lymph nodes is essential for the initiation of the alloreactive T-cell response and subsequent rejection [8]. Therefore, the lymph nodes may be a better site than the peripheral blood compartment to study cells involved in allograft rejection.
Different phenotypic and functional characteristics of lymph node derived versus peripheral blood derived lymphocytes in kidney transplantation have mainly been studied following the administration of lymphocyte-depleting agents. After T-cell depleting induction therapy, profound T-cell depletion is found in bone marrow, spleen and peripheral blood, but not in lymph nodes [9]. It has been demonstrated that while B cells were completely depleted in the peripheral blood after treatment with the B-cell depleting agent rituximab, B cells in the kidney allograft could still produce donor-specific antibodies and B-cell survival factors [10]. After rituximab administration, lymph node derived B-cells shifted from a naïve to a memory phenotype [11]. In a similar fashion the T- and B-cell depleting antibody against CD52 (alemtuzumab) is highly effective for total and long lasting depletion of peripheral blood lymphocytes but not of the central lymphoid compartment [12]. This observation most likely explains why after induction therapy with alemtuzumab, the risk for AR is only reduced by approximately 50% [13, 14].
Given these data, we would like to investigate whether the phenotypical features and functions of lymph node derived lymphocytes are associated with BPAR. Differences in lymph node derived versus peripheral blood derived lymphocytes have not been studied so far in patients with renal failure before the start of immunosuppressive medication.
To study lymphocellular composition and risk of BPAR, a patient cohort with a

relative high risk of BPAR is warranted. Patients with a high percentage of panel reactive antibodies (PRA) of more than six per cent [15], and/ or more than 3 HLA mismatches with the donor kidney are both at increased risk for acute rejection.

Two research lines in our transplantation laboratory can be further explored when studying lymph node derived lymphocytes. First, in an ongoing study we are investigating the relation between a prematurely aged immune system in patients receiving a kidney allograft, and the risk for acute rejection [16, 17]. Recent results indicate that the numbers of cytotoxic T cells which circulate through the lymphoid compartments (called central-memory CD8+ T cells) are in particular associated with acute allograft rejection [Meijer and Betjes, manuscript in preparation]. Therefore we would like to extend the research on the ageing immune system to the composition of lymph nodes in patients undergoing kidney transplantation. Second, the T-helper CD4+ subset named follicular T-helper (Tfh) cells are of importance for the differentiation of B-cells into immunoglobulin-producing plasmablasts [18]. In addition, higher frequencies of Tfh cells were measured in the peripheral blood of patients with antibody-mediated allo-reactivity; a poorly characterized immune response often refractory to treatment with conventional immunosuppression. Tfh-cells are mainly active in secondary lymphoid organs where these CD4+ T cells support activated B cells via IL-21 after binding to the IL-21Receptor expressed by these B cells. By studying the phenotypical characteristics and functions of lymph node T, Tfh and B cells we aim to better understand their interaction in the setting of allo-immunity. We hope to provide novel insights into recruitment, compartment and function of the T, Tfh - B cell network.

Another group of patients is at particular risk for acute rejection: blood group ABO-incompatible (ABOi) kidney transplant recipients have a high risk of BPAR of approximately 40 per cent based on our own data (antibody-mediated component 20% [19]). Therefore lymphocyte-depleting induction therapy is given preoperatively (alemtuzumab). In contrast to rituximab, only non-human data are available on the effect of alemtuzumab administration on lymphocyte composition [12]. In a substudy the composition of lymph nodes after alemtuzumab induction therapy administered three weeks before transplantation and its effect on BPAR will be studied.

References:

1. Naesens, M., et al., The Histology of Kidney Transplant Failure: A Long-Term Follow-Up Study. Transplantation, 2014. 98(4): p. 427-435.
2. El-Zoghby, Z.M., et al., Identifying Specific Causes of Kidney Allograft Loss. American Journal of Transplantation, 2009. 9(3): p. 527-535.
3. Matignon, M., et al., Concurrent Acute Cellular Rejection Is an Independent Risk Factor for Renal Allograft Failure in Patients With C4d-Positive Antibody-Mediated Rejection. Transplantation, 2012. 94(6): p. 603-611.
4. Coelho, V., et al., Rethinking the multiple roles of B cells in organ transplantation. Current Opinion in Organ Transplantation, 2013. 18(1): p. 13-21.
5. Lawrence, C., et al., Preformed Complement-Activating Low-Level Donor-Specific Antibody Predicts Early Antibody-Mediated Rejection in Renal

Allografts. Transplantation, 2013. 95(2): p. 341-346.
6. van de Berg, P.J.E.J., et al., Circulating lymphocyte subsets in different clinical situations after renal transplantation. Immunology, 2012. 136(2): p. 198-207.
7. Havenith, S.H.C., et al., CXCR5CD4 follicular helper T cells accumulate in resting human lymph nodes and have superior B cell helper activity. International Immunology, 2014. 26(3): p. 183-192.
8. Herrera, O.B., et al., A novel pathway of alloantigen presentation by dendritic cells. J Immunol, 2004. 173(8): p. 4828-37.
9. Page, E.K., et al., Enhanced De Novo Alloantibody and Antibody-Mediated Injury in Rhesus Macaques. American Journal of Transplantation, 2012. 12(9): p. 2395-2405.
10. Thaunat, O., et al., B cell survival in intragraft tertiary lymphoid organs after rituximab therapy. Transplantation, 2008. 85(11): p. 1648-1653.
11. Kamburova, E.G., et al., A Single Dose of Rituximab Does Not Deplete B Cells in Secondary Lymphoid Organs but Alters Phenotype and Function. American Journal of Transplantation, 2013. 13(6): p. 1503-1511.
12. Marco, M.R., et al., Post-transplant repopulation of naive and memory T cells in blood and lymphoid tissue after alemtuzumab-mediated depletion in heart-transplanted cynomolgus monkeys. Transpl Immunol, 2013. 29(1-4): p. 88-98.
13. Group, C.S.C., et al., Alemtuzumab-based induction treatment versus basiliximab-based induction treatment in kidney transplantation (the 3C Study): a randomised trial. Lancet, 2014. 384(9955): p. 1684-90.
14. Hanaway, M.J., et al., Alemtuzumab induction in renal transplantation. N Engl J Med, 2011. 364(20): p. 1909-19.
15. van den Hoogen, M.W., et al., Rituximab as induction therapy after renal transplantation: a randomized, double-blind, placebo-controlled study of efficacy and safety. Am J Transplant, 2015. 15(2): p. 407-16.
16. Betjes, M.G., et al., Premature aging of circulating T cells in patients with end-stage renal disease. Kidney Int, 2011. 80(2): p. 208-17.
17. Betjes, M.G., et al., Terminally differentiated CD8+ Temra cells are associated with the risk for acute kidney allograft rejection. Transplantation, 2012. 94(1): p. 63-9.
18. de Graav, G.N., et al., Follicular T-helper cells and humoral reactivity in kidney-transplant patients. Clin Exp Immunol, 2014.
19. van Agteren, M., et al., The First Fifty ABO Blood Group Incompatible Kidney Transplantations: The Rotterdam Experience. Journal of Transplantation, 2014. 2014: p. 6.

Study objective

Primary objective of the study:
- The primary objective for this study is to determine the prognostic characteristics for BPAR in the first 3 months after transplantation, as assessed in the lymphocyte composition of the lymph node in immunologically high-risk kidney transplantation.
Secondary objectives of the study are:

- to capture global composition of lymph node and blood leukocyte subsets [20].
- to compare the immunological ageing profile of T cells in the peripheral blood to the T cells derived from the lymph node.
- to assess whether pre-transplant frequencies of lymph node derived Tfh, T and B cells predict BPAR.
- to assess differences in lymphocyte composition of lymph nodes in alemtuzumab treated versus untreated patients both in single cell suspension and within the tissue. (ABO-incompatible kidney transplant recipients receive alemtuzumab induction therapy three weeks before transplantation).
This study will result in a set of defined markers that will identify patients at risk to develop rejection.

Study design

This is an investigator-driven, prospective, observational study to explore immunological processes. Kidney transplant recipients will be asked for their consent during admission before kidney transplantation. This consent relates to extra blood sampling at one time point when blood is already drawn, and to harvest a local lymph node during transplantation. During surgery, the surgeon will harvest a lymph node from the inguinal area before revascularization (open procedure). This harvesting of a local lymphnode is often necessary to have good access for anastomosis and these extirpated lymphnodes are discarded as residual material. Peripheral blood will be sampled before transplantation (and thus before immunosuppressive therapy). Kidney transplant recipients will be treated by current standard immunosuppressive protocol. 'For cause' kidney transplant biopsies will be performed according to local protocol: in case of deteriorating kidney transplant function in the absence of an obvious alternative diagnosis, the radiologist will perform an ultrasound-guided kidney transplant biopsy.

Study burden and risks

The risk of the venapuncture is small, as extra blood tubes are taken at a time point when blood is already drawn. The risk of a venapuncture is the occurrence of a bruise after puncture and possible pain-symptoms at the site of puncture. The risk of harvesting a regional lymph node during transplantation by the surgeon is negligible, since it is an open procedure. During transplantation, the surgeon needs to harvest lymph nodes to have good access to the artery and vein for anastomosis in approximately half of all standard kidney transplantation procedures. These lymph nodes are then discarded and can be regarded as *residual material*. In previous trials performed in the Erasmus Medical Center, lymph nodes were harvested during kidney transplantation: [27, 28, 29]. There are no benefits for individual patients when participating in this study.

References:

27. Tanis, W., et al., Human hepatic lymph nodes contain normal numbers of mature myeloid dendritic cells but few plasmacytoid dendritic cells. Clin Immunol, 2004. 110(1): p. 81-8.
28. Peters, J.H., et al., Human secondary lymphoid organs typically contain polyclonally-activated proliferating regulatory T cells. Blood, 2013. 122(13): p. 2213-23.
29. Eissens, D.N., et al., Defining early human NK cell developmental stages in primary and secondary lymphoid tissues. PLoS One, 2012. 7(2): p. e30930.

Contacts

Public
Selecteer

's Gravendijkwal 230
Rotterdam 3015 CE
NL
Scientific
Selecteer

's Gravendijkwal 230
Rotterdam 3015 CE
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adult patients receiving a deceased or living kidney transplant in the Erasmus Medical Center Rotterdam, The Netherlands and:

- Group 1:
o Historical PRA (panel reactive antibodies) > 6% and/ or:
o HLA MM (human leucocyte antigen mismatches) >=4 on A, B and DR loci
- Group 2:
o Recipients of an ABO-incompatible kidney graft.
Patients have to give written informed consent to participate in the study.

Exclusion criteria

- ABO-compatible HLA identical living-related transplant recipients.
- Patients unable to give written informed consent.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-08-2015
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	23-07-2015
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	NL53179.078.15