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Treatment of antibody-mediated rejection including immunoadsorption during first year after renal transplantation – Clinical results and regulation of endothelial progenitor cells

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Abstract

Objective: Antibody-mediated rejection (AMR) is associated with poor allograft survival. Therefore, effective treatment strategies are required. Extracorporeal strategies are increasingly included in treatment of antibody-mediated rejection to eliminate the detrimental alloantibodies. Yet, other mechanisms contributing to the beneficial effect of apheresis besides the removal of antibodies are under consideration.

Methods: We retrospectively analyzed data of 427 transplant patients from 2006 to 2013 with special focus on occurrence, treatment – always including immunoadsorption – and 12-months outcome of antibody-mediated rejection.

Besides, we prospectively monitored how the number and phenotype of endothelial progenitor cells in four patients experiencing antibody-mediated rejection changed during the treatment course of 6–20 sessions of immunoadsorption in comparison to seven patients subjected to immunoadsorption because of preparation for ABO-incompatible transplantation.

Results: 24 patients were diagnosed with acute AMR and treated with immunoadsorption resulting in patient and allograft survival of 100% and 87.5%, respectively. In patients with antibody-mediated rejection, the endothelial progenitor cell number after successful immunoadsorption therapy was always transiently decreased and the adhesive and migratory ability improved. This regulation of circulating endothelial precursor cells was not seen in patients undergoing repetitive immunoadsorptions before ABO-incompatible transplantation.

Conclusion: Combined therapy with immunoadsorption allows a successful treatment of AMR. Treatment seems to be associated with a transient regulation of circulating endothelial precursor cells.

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Keywords: Immunoadsorption; Renal transplantation; Antibody-mediated rejection; Endothelial progenitor cells

1. Introduction

Acute humoral rejection is a rare but serious complication after renal transplantation (RT) that has been associated with rates of graft loss up to 50% within the first year [1].

No standard treatment regimen for acute humoral rejection is defined but in most transplant centers treatment includes an intensification of the basal immunosuppressive therapy via introduction of a steroid pulse therapy, tacrolimus switch, and T-cell and/or B-cell depletion combined with removal of the harming antibodies via therapeutic apheresis. While the clinical effectiveness of immunoadsorption therapy has only been demonstrated in one randomized, prospective trial with a total of 10 renal transplant recipients [2], even less is known regarding the mechanisms of the beneficial impact of immunoadsorption

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therapies besides a temporarily and quantitatively restricted reduction of anti-graft antibodies.

Acute antibody-mediated rejection (AMR) is frequently associated with severe vascular or both vascular and interstitial injury and inflammation. Several studies demonstrated that circulating endothelial as well as endothelial precursor cells (EPC) may be involved in the repair process of vascular allograft rejection [3]. Hereby, recipient EPC are apparently recruited to and incorporated into injured grafts reconstituting a chimeric graft endothelium particularly of the renal microvascular compartment [3].

This study therefore evaluates the clinical outcome of renal allograft recipients with acute humoral rejection under current state of the art therapy including immunoadsorption. In addition, we investigated whether the number or phenotypic characteristics of circulating EPC are influenced by the apheresis procedure itself as evaluated during preparation for ABO-incompatible transplantation or in the context of a combined treatment of acute antibody-mediated vascular rejection of kidney allografts.

2. Methods

In this study, we retrospectively analyzed demographic, histologic and outcome data of 427 patients undergoing kidney transplantation from 2006 to 2013 at the transplant center at the University Hospital Erlangen (2006–2009) and at the transplant center at the University Hospital of Dresden (2010–2013) with special focus on occurrence, treatment and outcome of AMR.

All patients were followed for the first year after kidney transplantation. Demographic data included age, sex, duration of renal replacement therapy, kind of transplantation (living versus deceased donation), kind of immunosuppressive therapy as well as immunologic risk at the time of transplantation (defined by HLA mismatch and panel reactive antibodies).

Transplant kidney biopsies were performed in all patients with non-functioning renal allografts as well as decreasing renal function (i.e. rise in creatinine above 20% of the baseline value) and were assessed according to the Banff criteria.

Outcome data included patient and allograft survival as well as kidney function (creatinine) at 12 months after transplantation. Graft failure was defined as permanent requirement for renal replacement therapy at the time point of 12 months. The following safety parameters were also assessed during the first year after renal transplantation: hospitalization due to infectious complications as well as overall incidence of CMV, BKV, or malignancies.

2.1. Definition of AMR

AMR was defined by kidney-non-function or an increase in creatinine of at least 20% above baseline with histologic evidence of AMR defined by Banff criteria, update 2007 [4] such as acute tubular necrosis, inflammatory cells in the lumen of peritubular capillaries and fibrinoid necrosis in vessel walls as well as positive staining for C4d in peritubular capillaries. Furthermore, all patients with histologic features of AMR were screened for donor specific antibodies (DSA) via luminex assay. These DSA data were only completely available for the Dresden patient group.

2.2. Treatment of AMR

All patients with AMR received steroid pulse (3 × 250 mg prednisolone) as well as T-cell depleting therapy with thymoglobulin (total of 6–8 mg/kg body weight). All patients on cyclosporine were switched to tacrolimus therapy (tacrolimus switch). Nine patients also received one dose of rituximab (375 mg/m^2), five patients also IVIG (1 g/kg), one patient was additionally treated with eculizumab (first 900 mg weekly, then 1200 mg every other week).

Besides, apheresis was started in all patients with AMR the day after the diagnosis of AMR to eliminate circulating (anti-HLA) antibodies. 14 patients had one session of plasmapheresis using FFP (exchange 50 ml/kg) after which immunoadsorption (IA) was started (2.5 plasma volumes per patient being processed). In 10 patients, IA was started from the beginning. In the first three days, apheresis was performed daily, then every other day for a total of at least 6 treatments (6–20). IA was carried out using Globaffin columns (Fresenius Medical Care, Bad Homburg, Germany).

2.3. Statistical analysis

Demographic data is shown as frequency or mean ± standard deviation.

Comparison between the two groups was performed using Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables.

2.4. Measuring and analyzing of EPC

In four patients, experiencing AMR blood samples for measurement of EPC were taken.

First measurement was performed on the day AMR was diagnosed and before apheresis was started. Second measurement was carried out after the last session of IA and the last measurement 6 months after the rejection. EPC counts as well as migratory and adhesive capacity of EPC in patients with AMR were compared to data of seven patients undergoing IA in the preparation of ABO-incompatible living transplantation at comparable time points before and after IA therapy as well as 6 months after transplantation.

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