lek. Michał Gniewkiewicz

Ocena przydatności monitorowania przeciwciał przeciwko antygenom zgodności tkankowej dawcy u pacjentów po transplantacji nerki w stratyfikacji ryzyka immunologicznego utraty przeszczepu

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

Promotor: prof. dr hab. n. med. Magdalena Durlik

Klinika Medycyny Transplantacyjnej, Nefrologii i Chorób Wewnętrznych
Warszawskiego Uniwersytetu Medycznego

Obrona rozprawy doktorskiej przed Radą Dyscypliny Nauk Medycznych

Warszawskiego Uniwersytetu Medycznego

Warszawa 2023r.

Streszczenie w języku angielskim

Value of donor-specific anti-human leukocyte antigen antibodies monitoring in kidney transplant recipients for immunological risk stratification of graft loss

Immune monitoring is currently one of the important aspects of post-transplant care of kidney transplant recipients. The presence of donor-specific antibodies (DSAs) directed against human leukocyte antigen (HLA), is a proven risk factor for the development of antibody-mediated rejection (ABMR) and kidney allograft loss. Antibodies can damage renal graft through different mechanisms: activation of the complement cascade, direct interactions with the vascular endothelium, and antibody-dependent cellular cytotoxicity. The pathogenicity of anti-HLA DSAs is determined by antibody classes, specificity, mean fluorescent intensity (MFI), C1q-binding capacity, and IgG subclasses. There are three identified clinical patterns of anti-HLA DSAs post-transplant evolution: persistent preformed DSAs, resolved preformed DSAs, and *de novo* DSAs.

The doctoral dissertation consists of two articles that are the result of the "Diamond Grant" program research project regarding the value of anti-HLA DSAs monitoring in kidney transplant recipients. The aims of the conducted studies were: 1) to investigate the association of circulating DSAs and their characteristics, including antibody class, specificity, mean fluorescent intensity (MFI), C1q-binding capacity, and IgG subclasses, with renal allograft function and long-term outcomes; 2) to analyze the impact of resolved preformed, persistent preformed, and *de novo* anti-HLA DSAs on long-term renal allograft outcomes and to identify factors affecting the post-transplant evolution of anti-HLA DSAs.

The study included 108 consecutive patients from our transplant center who underwent kidney allograft biopsy 3 to 24 months after kidney transplantation from brain-dead deceased donors. From all the patients at the time of the biopsy, sera were collected for analysis of circulating anti-HLA DSAs and their characteristics. The primary endpoint was the composite of sustained 30% reduction from the estimated glomerular filtration rate at biopsy or death-censored graft failure. Patients were followed for a median time of 39 months.

Nineteen patients were identified with circulating anti-HLA DSAs at the time of the biopsy (17.6%). The immunodominant anti-HLA DSAs (antibody with the highest MFI) were class I in 8 patients (42.1%) and class II in 11 patients (57.9%). Ten patients (52.6%)

had immunodominant anti-HLA DSAs with C1q-banding capacity. The most frequent IgG subclass was IgG1 (73.7%), followed by IgG3 (36.8%), IgG4 (21.1%), and IgG2 (10.5%). The detection of anti-HLA DSAs at the time of biopsy (HR = 5.133, 95% CI 2.150–12.253, $p = 0.0002$) and their C1q-binding capacity (HR = 14.639, 95% CI 5.320–40.283, $p \leq 0.0001$) were independent predictors of the primary endpoint.

Based on the DSA status at the time of the biopsy, there were identified 9 patients (8.3%) with resolved preformed anti-HLA DSAs, 9 patients (8.3%) with persistent preformed anti-HLA DSAs and 10 patients (9.3%) with *de novo* anti-HLA DSAs. The identification of persistent preformed DSAs at the time of biopsy was the most significant predictor of the primary endpoint of the study (HR = 5.96, 95% CI 2.041–17.431, $p = 0.0011$), followed by the occurrence of *de novo* DSAs (HR = 4.48, 95% CI 1.483–13.520, $p = 0.0079$). No increased risk was observed in patients with resolved preformed DSAs (HR = 1.10, 95% CI 0.139–8.676, $p = 0.9305$). The use of anti-thymocyte globulin as an induction of immunosuppression was a risk factor for resolved preformed anti-HLA DSAs. The persistence of preformed anti-HLA DSAs was associated with previous transplantation and the increased age of the donor. Moreover, a prior transplant was identified to be a risk factor for the development of *de novo* anti-HLA DSAs.

To summarize, identification of circulating anti-HLA DSAs and their C1q-binding capacity are independent predictors for inferior renal allograft function and graft failure after kidney transplantation from a brain-dead deceased donor. Currently, analysis of C1q is limited by its cost, but it is noninvasive, easily accessible, and might be considered in routine clinical practice in post-transplant management. Detection of circulating DSA (in particular those binding C1q) should result in a thorough analysis of immunosuppressive treatment and careful patient monitoring.

Patients with resolved preformed anti-HLA DSAs have similar graft prognoses as patients without DSAs. The persistence of preformed anti-HLA DSAs after kidney transplantation and the occurrence of *de novo* anti-HLA DSAs are independent predictors of inferior kidney graft function and graft failure. Post-transplant evolution of anti-HLA DSAs is associated with anti-thymocyte globulin therapy, prior transplantation, and the donor's age. Candidates for renal transplantation (particularly for retransplantation) should undergo a cautious immunological risk assessment. These findings are valuable in light of the development of new desensitization protocols.

Transplant immunology evolves rapidly, but there are many gaps in the current knowledge, and therefore further studies are needed to answer clinical questions.