

“Complement-Binding Anti-HLA Antibodies and Kidney-Allograft Survival”

Alexandre Loupy, Carmen Lefaucheur, Dewi Vernerey, Christof Prugge, Jean-Paul Duong van Huyen, Nuala Mooney, Caroline Suberbielle, Véronique Frémeaux-Bacchi, Arnaud Méjean, François Desgrandchamps, Dany Anglicheau, Dominique Nochy, Dominique Charron, Jean-Philippe Empana, Michel Delahousse, Christophe Legendre, Denis Glotz, Gary S. Hill, Adriana Zeevi, Xavier Jouven
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Susana Sampaio

Nephrology Department, Hospital São João. Porto, Portugal.

The advances in the area of transplantation have allowed the reduction of acute rejection and increased survival of renal allografts in the first year after transplantation with excellent results. Patel *et al.* reported that the anti-HLA antibodies are lymphocytotoxic¹ and, nowadays, we know that alloimmune response mediated by donor-specific antibodies (DSA) is the cornerstone in antibody-mediated rejection (ABMR) and may lead to graft loss².

However, the expression of this type of injury is very varied and can range from a subclinical way to a severe rejection^{3,4}.

Recognizing this high variability, it seems mandatory to perform an early detailed characterization of anti-HLA DSA, in order to diagnose not only the patients at risk, but also those with subclinical or clinical presentation of these events, thus improving graft survival.

The activation of the complement cascade is one of the components in the ABMR. Deposition of C4d in peritubular capillary of renal graft biopsies was considered a marker of ABMR⁵. The ability of anti-HLA antibodies to bind to C1q complement fraction, which is the first step in activation of the classical complement pathway, seems crucial to the cytotoxic potential of these antibodies. The evaluation of the ability of DSA for complement binding can be useful in the diagnosis and risk stratification of ABMR.

This can be the first article demonstrating that DSA with the ability to bind complement, mainly if detected after transplantation, are involved in the failure of the allograft being a risk and prognostic factor in graft survival.

This work has nothing to point out in terms of methodology considering its high quality. The large number of patients enrolled is very relevant and the groups are perfectly homogeneous with no significant differences in demographic characteristics and in the therapy schemes (the protocols of immunosuppression and treatment of rejection were identical in the involved centers). The fact that it is a prospective study with a mean follow-up time after transplantation of 3.9 years is another important factor in the quality of the results.

The results are presented in detail in the Supplementary Appendix including the findings in the per-protocol biopsies or biopsies performed by rejection. The paper also presents the results of an external validation cohort of patients with a third center, which confirmed the results presented in the study.

Freitas *et al.* showed that the presence of persistent complement-binding DQ DSA negatively impacts kidney allograft outcomes⁶.

In this paper, the authors, demonstrated similar results showing that the receptors with DSA had lower graft survival compared with those without DSA (83 vs 94%, $p < 0.0001$). When the group of patients with DSA were stratified according to the capacity of binding complement, patients with DSA that bind C1q had worse graft survival at 5 years (54%).

This study demonstrated that in a group of patients who were carefully evaluated, in terms of the presence of DSA and in their ability to bind the complement, the detection of these antibodies in the first year of transplant are a predictor of graft loss factor

even 5 years after transplantation. This may be a significant improvement in the individual risk stratification for graft loss.

Compared with the usual strategy of risk assessment of graft loss in the presence of DSA, these data, comprising the capacity of complement binding, identifies an additional group of patients with a greater risk of graft loss. Whereas mean immunofluorescence intensity (MFI) is widely used in risk stratification for graft loss, this study showed that DSA that bind C1q maintains a very strong risk ratio for graft loss independent of MFI.

These authors consider that C1q test can help identify patients at risk, despite C4d negativity. In previous studies, it was shown that despite C4d specificity the test lacked sensibility, as an indicator for humoral rejection⁷.

Identifying the pathways responsible for graft loss might have future therapeutic implications since there are agents acting on the complement that has been used in transplant patients (as an inhibitor of C5, eculizumab). This study, as stated by the authors, can be a basis for clinical trials.

As referred by Freitas *et al.*, “post-transplant early detection, monitoring, and removal of complement binding might be critical for improving long-term kidney transplantation outcomes”⁶.

From my point of view, this study demonstrated that DSA binding C1q will be an important tool in

our clinical activity, as well as a valuable predictor factor of graft loss highlighting the relevance of risk stratifying to improve long-term graft survival.

References

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Correspondence to:

Dr^a Susana Sampaio
Nephrology Department, Hospital de São João
Alameda Prof. Hernâni Monteiro
4200 – 319 Porto
Portugal
E-mail: susana.sampaio@sapo.pt