INVITED COMMENTARY

Donor-specific antibodies' C1q binding: improvement in kidney graft management?

Sylvie Ferrari-Lacraz

Transplantation Immunology Unit and National Reference Laboratory for Histocompatibility, Division of Nephrology, Department of Genetic and Laboratory Medicine, Geneva University Hospitals, Geneva, Switzerland

Correspondence
Sylvie Ferrari-Lacraz, Transplantation Immunology Unit and National Reference Laboratory for Histocompatibility, Division of Nephrology, Department of Genetic and Laboratory Medicine, Geneva University Hospitals, 4 rue Gabrielle Perret-Gentil, 1211, Geneva, Switzerland.
Tel.: +41223729404; fax: +41223729390; e-mail: sylvie.ferrari@hcuge.ch

Transplant International 2017; 30: 344–346

Received: 30 January 2017; Accepted: 31 January 2017

The diagnosis of acute antibody-mediated rejection (ABMR) after kidney transplantation is based on three parameters: (i) decreased renal function, (ii) histopathological signs of rejection, (iii) presence of donor-specific antibody (DSA) [1]. Patient survival and graft survival have improved from 5 to 10 years [2], thanks to several factors, including better management of patients, better immunosuppressive regimens, detection and avoidance of donor-specific antibody (DSA). Although anti-HLA antibody follow-up has improved ABMR management, its treatment remains challenging, and outcome may be worsened because of a delay in the diagnosis.

Donor specific antibody is associated with ABMR and is directly involved in the mechanisms of renal lesions [1,3]. It is important to determine the repertoire of specific anti-HLA antibodies: (i) Before transplantation, the presence DSA has a direct impact on the patient's management for the allocation of the organ [4,5]; (ii) after transplantation, the development of DSA could lead to a modification of the immunosuppressive treatment [6,7].

To accurately follow patients, various techniques of detection of anti-HLA antibodies have been developed over time. Nowadays, methods used to detect anti-HLA antibodies are very sensitive, questioning the clinical relevance of anti-HLA antibodies with low, intermediate, or high MFI (mean fluorescence intensity). The role of DSA at low or intermediate MFI remains a matter of intense debate in the transplantation community [8]. The presence of DSA before transplantation could result in denying a kidney offer to a patient or, after transplantation, in overtreating a recipient having developed DSA [9]. To take advantage of the Luminex® assay with specific anti-HLA antibody detection (SAB) and the capacity to bind complement and being cytotoxic determined by the classical CDC cross-match, the Luminex® C1q-binding assay was recently developed. C1q is one of the first components of the classical activation pathway of the complement cascade. This technique is supposed to differentiate complement binding anti-HLA antibodies from noncomplement binding anti-HLA antibodies, the former being the effective and detrimental ones. According to recent publications, DSA-binding C1q are associated with a worse graft survival when compared with nonbinding DSA C1q [10–12]. Although this technology is promising after transplantation, current data failed to demonstrate that DSA-binding C1q can predict AMR and worse graft survival in the pretransplant situation [4,10,13]. Therefore, it remains to be demonstrated that DSA-binding C1q is a useful additional tool that can be introduced in allocation algorithm to increase the clinical relevance of DSA and predict short- and-long term outcome.

In this issue of Transplant International, the publication of the work of Malheiro *et al.* [14] and of Kauke *et al.* [15] reflects the concern and debates in the transplantation community.

doi:10.1111/tri.12933

Malheiro *et al.* [14] retrospectively studied the impact of preformed DSA, their intensity, and their ability to bind C1q as predictor of AMR. They also aim to help clinicians to distinguish deleterious DSA from irrelevant ones for pretransplantation risk stratification [14]. In their study, they demonstrate that 30% of patients with preformed DSA will present AMR and that graft survival at 6 years is significantly decreased in patients with DSA strength, $C1q^+$ DSA^+ compared to $C1q^-$ DSA^+ patients. But they also notice that $C1q^-$ DSA^+ is a risk factor for chronic active AMR. Therefore, C1q-binding test could help physicians in choosing the best HLA-incompatible kidney donor for a sensitized recipient keeping in mind that DSA binding or not C1q remain important risk factors for AMR.

Kauke *et al.* [15] studied, retrospectively, the role of de novo DSA binding or not C1q at 2 and 5 years postkidney graft transplantation. They also compared their cohort with patients developing non-donor-specific DSA (nDSA). They observed that 60% of patients with de novo DSA will suffer AMR episode (34% for nDSA patients) and will have a significant decrease in graft survival (65% vs. 86% for nDSA patients). Interestingly, they demonstrated that $C1q^+$ DSA^+ and $C1q^-$ DSA^+ patients present the same risk of AMR episode and a similar decrease in graft survival at 5 years. Therefore, they conclude that 'de novo DSAs independent of their C1q-binding capacity are at significant risk of kidney graft loss' [15]. Moreover, they also suggest that nDSAs should also be carefully followed as these nDSA may decrease kidney graft function if they bind C1q!

Interpretation of anti-HLA antibody profiles is subject of debate and should be carefully analyzed as they often lead to taking clinical decisions that could be appropriate or not. Anti-HLA antibody by the luminex technology is mainly a qualitative test, but the MFI or the titer (by dilution) is considered to be also quantitative by most centers. The C1q binding has been shown to correlate with the MFI level [12,16]. The problem of relevance of DSA MFI, C1q and the lack of correlation with the clinical observation in many situations, has certainly several explanations. From a technical point of view, SAB assays, and even more C1q-binding assays, are not always (never?) standardized between centers, leading to important variations in MFI levels of HLA specificities detected. Analyses are not always performed at the best time, which should be before the diagnosis of ABMR, and the profile or characteristic of DSA could change over time (MFI, C1q, isotype, affinity...). Other factors such as concomitant event (infection, even subclinical) or persisting local inflammation are often not taken into account. According to the publication of Wiebe *et al.* [12], 'these tests are not robust independent predictors but should be analyzed and compared all together. However, at present, the additional cost and time associated with these approaches are barely justified in routine practice [12]'. We are still in the learning phase, and the presence or development of the de novo DSA- and non-DSA-binding or not C1q is an important parameter in the workup of patient before and after transplantation. Each transplant center should validate and standardize the methods selected by participating in quality control program. The most suitable DSA cutoff levels with or without C1q could be determined according to clinical outcomes. With specific test selected and results expected, risk stratification can be drawn and selected for each center-specific transplant program.

Funding

The author has declared no funding.

Conflict of interest

The author has declared no conflicts of interest.

REFERENCES

1. Mengel M, Campbell P, Gebel H, *et al.* Precision diagnostics in transplantation: from bench to bedside. *Am J Transplant* 2013; **13**: 562.
2. Opelz G, Dohler B, Ruhenstroth A, *et al.* The collaborative transplant study registry. *Transplant Rev (Orlando)* 2013; **27**: 43.
3. Haa M, Sis B, Racusen LC, *et al.* Banff 2013 meeting report: inclusion of C4d-negative antibody-mediated rejection and antibody-associated arterial lesions. *Am J Transplant* 2014; **14**: 272.
4. Crespo M, Torio A, Mas V, *et al.* Clinical relevance of pretransplant anti-HLA donor-specific antibodies: does C1q-fixation matter? *Transpl Immunol* 2013; **29**: 28.
5. Mihaylova A, Baltadjieva D, Boneva P, *et al.* Clinical relevance of anti-HLA antibodies detected by flow-cytometry bead-based assays – single-center experience. *Hum Immunol* 2006; **67**: 787.
6. Montgomery RA, Lonze BE, King KE, *et al.* Desensitization in HLA-incompatible kidney recipients and survival. *N Engl J Med* 2011; **365**: 318.
7. Orandi BJ, Garonzik-Wang JM, Massie AB, *et al.* Quantifying the risk of incompatible kidney transplantation: a multicenter study. *Am J Transplant* 2014; **14**: 1573.

8. Tait BD, Hudson F, Brewin G, Cantwell L, Holdsworth R. Solid phase HLA antibody detection technology – challenges in interpretation. *Tissue Antigens* 2010; **76**: 87.
9. Baxter-Lowe LA, Cecka M, Kamoun M, Sinacore J, Melcher ML. Center-defined unacceptable HLA antigens facilitate transplants for sensitized patients in a multi-center kidney exchange program. *Am J Transplant* 2014; **14**: 1592.
10. Loupy A, Lefaucheur C, Vernerey D, Complement-binding anti-HLA antibodies and kidney-allograft survival. *N Engl J Med* 2013; **369**: 1215.
11. Wiebe C, Gibson IW, Blydt-Hansen TD, *et al.* Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant* 2012; **12**: 1157.
12. Wiebe C, Gareau AJ, Pochinco D, *et al.* Evaluation of C1q status and titer of de novo donor-specific antibodies as predictors of allograft survival. *Am J Transplant* 2016; doi: 10.1111/ajt.14015. [Epub ahead of print].
13. Guidicelli G, Guerville F, Lepreux S, *et al.* Non-complement-binding de novo donor-specific anti-HLA antibodies and kidney allograft survival. *J Am Soc Nephrol* 2016; **27**: 615.
14. Malheiro J, Tafulo S, Dias L, *et al.* Determining donor-specific antibody C1q-binding ability improves the prediction of antibody-mediated rejection in human leucocyte antigen-incompatible kidney transplantation. *Transpl Int* 2016; **30**: 347.
15. Kauke T, Oberhauser C, Lin V, *et al.* De novo donorspecific anti-HLA antibodies after kidney transplantation are associated with impaired graft outcome independently of their C1q-binding ability. *Transpl Int* 2016; **30**: 360.
16. Schaub S, Honger G, Koller MT, Liwski R, Amico P. Determinants of C1q binding in the single antigen bead assay. *Transplantation* 2014; **98**: 387.