Complement-binding anti-HLA antibodies are independent predictors of response to treatment in kidney recipients with antibody-mediated rejection

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A major hurdle to improving clinical care in the field of kidney transplantation is the lack of biomarkers of the response to antibody-mediated rejection (ABMR) treatment. To discover these we investigated the value of complement-binding donor-specific anti-HLA antibodies (DSAs) for evaluating the response to treatment. The study encompassed a prospective cohort of 139 kidney recipients with ABMR receiving the standard of care treatment, including plasma exchange, intravenous immunoglobulin and rituximab. Patients were systematically assessed at the time of diagnosis and three months after treatment initiation for clinical and allograft histological characteristics and anti-HLA DSAs, including their C1q-binding ability. After adjusting for clinical and histological parameters, post-treatment C1q-binding anti-HLA DSA was an independent and significant determinant of allograft loss (adjusted hazard ratio 2.57 (95% confidence interval 1.29-5.12). In 101 patients without post-treatment C1q-binding anti-HLA DSA there was a significantly improved glomerular filtration rate with significantly reduced glomerulitis, peritubular capillaritis, interstitial inflammation, tubulitis, C4d deposition, and endarteritis compared with 38 patients with posttreatment C1q-binding anti-HLA DSA. A conditional inference tree model identified five prognostic groups at the time of post-treatment evaluation based on glomerular filtration rate, presence of cg lesion and C1q-binding anti-HLA DSA (cross-validated accuracy: 0.77). Thus, circulating complement-binding anti-HLA DSAs are strong and independent predictors of allograft outcome after standard of care treatment in kidney recipients with ABMR.

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Antibody-mediated rejection (ABMR) has been identified as the leading cause of kidney allograft failure[1,2] and is considered an outcome of paramount importance for all stakeholders, including patients, caregivers, and physicians.[3] Despite the use of intensive therapeutic strategies, allograft failure occurs in 25% to 55% of patients within the first 5 years after ABMR diagnosis.[4–8]

The current standard of care (SOC) and most frequently used therapeutic intervention for treating ABMR relies on antibody-targeting therapies, including plasma exchange and i.v. immune globulin, following the recommendations of an expert consensus led by the US Food and Drug Administration (FDA).[9–11] This therapeutic combination is also part of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for the care of kidney transplant recipients.[12] However, the level of evidence *per se* for this SOC management of kidney recipients with ABMR is low. One of the major issues for clinical trials addressing ABMR therapies is the lack of early and reliable markers of the response to ABMR therapies that surrogate long-term outcomes,[10] which would allow acceptable duration for trials and reduce sample sizes and costs. This has important consequences for drug registration in the treatment of ABMR patients through accelerated regulatory approval, as highlighted by the FDA (Arlington meeting in 2015).[9] Early surrogate markers of

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long-term outcomes have been identified as the cornerstones of pivotal trials in other medical fields.[13] Furthermore, the early assessment of response to treatment in patients with ABMR should help the decision-making process for transplant clinicians by accurately identifying responders and nonresponders to the SOC.

Accumulating clinical and experimental evidence embodied by the humoral theory of transplantation[14] has placed circulating donor-specific anti-HLA antibodies (DSAs) to human leukocyte antigen (HLA) in the causal pathway of ABMR, making anti-HLA DSA one of the most promising surrogate biomarkers to evaluate the response to ABMR treatment, with a clear biological rationale, among clinical, histological, and immunological parameters in the context of ABMR.[15] Moreover, the capacity of anti-HLA DSAs to activate complement, a critical pathway in ABMR, has been associated with increased incidences of allograft rejection and loss.[16–24] Whereas prior studies have reported different magnitudes of effect for these antibodies, ranging from strong effects to the absence of associations with allograft outcomes, a recent systematic review and meta-analysis based on 21 studies highlighted a deleterious effect of complement-activating anti-HLA DSAs on allograft outcomes.[25] To date, the clinical value of complement-activating anti-HLA DSAs in patients with ABMR is not defined. Recent studies have shown that C1q-binding anti-HLA DSAs detected at the time of ABMR were not relevant for predicting subsequent allograft survival,[26–28] while the presence of C1q-binding anti-HLA DSAs after ABMR treatment may be associated with allograft loss, as suggested by 2 small studies including 30 and 25 kidney transplant recipients, respectively.[27,28]

In the present study, performed in a prospective population of kidney transplant recipients with ABMR receiving SOC treatment, we evaluated the capacity of complement-binding anti-HLA DSAs, systematically assessed at the time of diagnosis and after treatment, to predict allograft loss and their value for reflecting the response to ABMR treatment. We assessed the relationships between the kinetics of anti-HLA DSA complement-binding status under ABMR treatment and the evolution of allograft function and histologic injury.

RESULTS

Patient characteristics

Among 1196 people who received kidney transplants between January 2008 and December 2011, we identified 139 recipients with a first episode of biopsy-proven active ABMR according to the most recent international Banff classification criteria, diagnosed at a median time of 15.5 months (interquartile range: 5.8–26.8) since transplantation. All patients received standardized treatment comprising plasma exchanges, high-dose i.v. immune globulins, methylprednisolone pulses, and rituximab, together with maintenance immunosuppression therapy, including mycophenolate mofetil, tacrolimus, and prednisone from the time of ABMR diagnosis (see Methods section for ABMR treatment protocol). These patients underwent a systematic post-treatment evaluation 3 months after the diagnosis of ABMR, including clinical parameters, anti-HLA DSAs, and allograft histology. The flow diagram of the study population is provided in Figure 1. The baseline recipient, donor, and transplant characteristics are summarized in Table 1.

Characteristics at the time of ABMR diagnosis. At the time of ABMR diagnosis, patients showed an estimated glomerular filtration rate (eGFR) of 32.4 (15.9) ml/min per 1.73 m^2 and a proteinuria level of 0.72 (0.80) g/g. The mean number

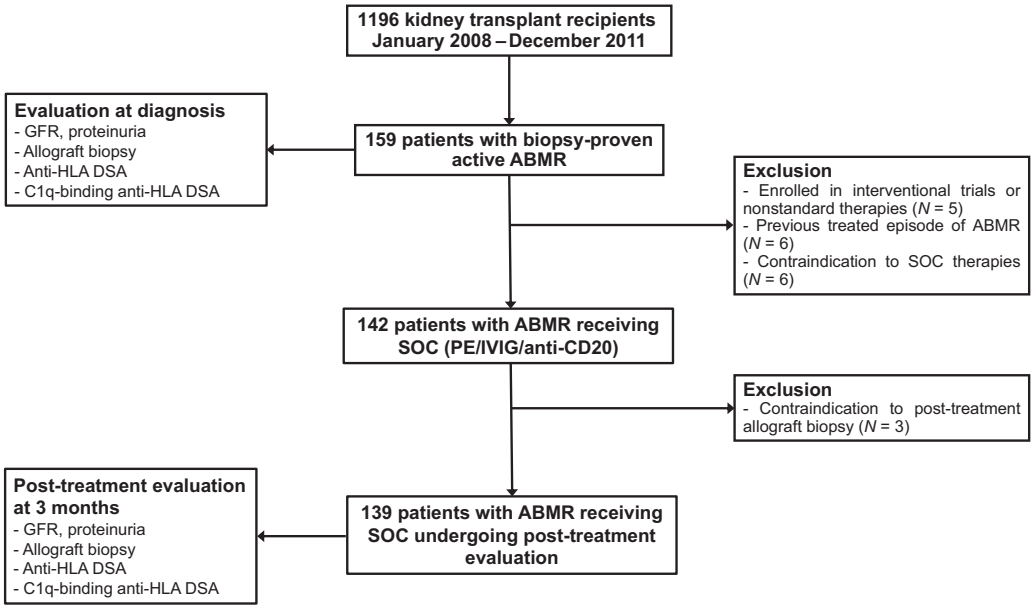

Figure 1 | Flow diagram of the study population. ABMR, antibody-mediated rejection; DSA, donor-specific antibody; GFR, glomerular filtration rate; HLA, human leucocyte antigen; IVIG, intravenous immune globulin; PE, plasma exchange; SOC, standard of care.