TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

INVITED COMMENTARY

Rejection despite C5 blockade: a distinct role of IgM?

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Conflicts of interest
The authors have declared no conflicts of interest.

Received: 6 July 2014
Accepted: 20 July 2014

doi:10.1111/tri.12407

The establishment of safe and efficient protocols for recipient desensitization to enable kidney transplantation across major immunological barriers, in particular alloantibodies against donor HLAs, remains a big challenge. A main caveat is that, despite intense antihumoral treatment at multiple levels, cross-match-incompatible transplants are frequently complicated by the early occurrence of antibody-mediated rejection (AMR) and in the long-term, irreversible chronic allograft injury. Indeed, for such transplants, recent studies have documented adverse long-term survival rates [1,2]. Accordingly, there will be a need for the design of new treatment strategies to more efficiently and specifically counteract humoral rejection processes. Of similar importance will be a further refinement of diagnostic procedures to reliably assess individual immunological risks and better guide targeted treatment.

A promising new approach for preventing antibody-mediated tissue damage is the targeted blockade of terminal complement. A seminal study conducted by Stegall and colleagues [3] has suggested effective prevention of early AMR in cross-match-positive live donor transplant recipients by the anti-C5 monoclonal antibody eculizumab. A remarkable finding was that, despite rebound of alloantibodies and capillary C4d deposition, the majority of treated patients did not reject their grafts, at least in the early post-transplant period. Nevertheless, there were still a few recipients who experienced early AMR, despite effective complement inhibition [3].

These patients were the focus of a study published in the current issue of Transplant International. In search for plausible explanations for AMR occurrence under C5 blockade, Bentall *et al.* [4] have retrospectively analyzed their cohort of 26 patients applying modified Luminex-based HLA antibody detection assays. They made the interesting observation that early AMR occurrence was associated with a rise in IgM donor-specific antibodies (DSA). Rejection could be reversed by plasmapheresis, presumably as a result of rapid IgM depletion. In contrast, post-transplant levels of IgG or IgG3 DSA well as *in vitro* C1q fixation did not relate to immunological outcomes. Among recipients without morphologic injury on early protocol biopsies only one showed detectable IgM DSA. This patient developed transplant glomerulopathy leading to subsequent graft failure.

The study by Bentall *et al.* [4] is suggestive of a role of IgM as a trigger of eculizumab-resistant AMR. Of course,

the reader should be aware of inherent study limitations, particularly the small sample size. Nevertheless, this is the largest reported cohort of patients subjected to C5 blockade for prevention of AMR, a unique opportunity to better understand the clinical effects of terminal complement inhibition in this specific context.

There is a controversial discussion on the role of IgM in HLA- or ABO-incompatible transplantation. In recent years, the establishment of supersensitive and highly specific diagnostic tools, in particular bead array technologies, has heralded a new era in HLA serology and substantially increased our understanding of the important role of IgG alloreactivity as an effector of transplant rejection. Nevertheless, as shown in many studies, there are still unpredictable discrepancies, such as preformed or *de novo* IgG DSA that do not associate with AMR occurrence, and vice versa [5]. What is the place of alloreactive IgM in this context? From a theoretical point of view, one may expect a causative contribution to rejection, as IgM, a polyvalent pentamer, has high avidity to targeted antigen and is known to have excellent agglutinating and complement activating properties. Indeed, the present study, as well as a very recent longitudinal cohort study [6], may be suggestive of a distinct pathogenetic role of IgM, at least under certain circumstances. Clearly, as also pointed out by the authors, such data do not question a critical role of IgG, but reinforce the need for a careful analysis of individual antibody patterns to assess immunological risks and guide targeted treatment. Maybe it is the concomitant presence of different Ig types, for example, IgM and IgG3 that culminates in severe rejection [6].

Of course, the mechanisms by which HLA-specific IgM causes injury to the graft cannot be deduced from associative observations. Considering the high C3 binding potency of IgM, the authors discuss a role of injury mediated by C3 and its split products, a key component that is not targeted by eculizumab. However, such candidate mechanisms, or even the assumption that detected IgM DSA could be a direct trigger of injury, will remain a matter of speculation. Indeed, without any experimental evidence for a causative inter-relationship between circulating IgM DSA, IgM binding to the endothelial surface, and AMR development, one may also argue that IgM formation could reflect a particular quality of an alloresponse, including a role of concomitant cellular immunity.

In summary, the findings of Bentall *et al.* [4] suggest a potential role of IgM as a trigger of rejection refractory to complement inhibition. Inclusion of IgM detection in our diagnostic armamentarium may help categorize risk groups and provide a valuable basis for the use of new options for recipient desensitization targeting complement and/or circulating IgM [3,7].

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