Response to Letter to the Editor From Ville S. et al. About: "Eculizumab First" in the Management of Posttransplant Thrombotic Microangiopathy

The Author Replies: We would like to thank Ville *et al*. for showing interest in our article[1] titled "Eculizumab First" in the management of posttransplant thrombotic microangiopathy (TMA), by allowing us to better clarify more findings from our experience.

Indeed, the incidence of posttransplant TMA reported in the literature ranges from 3% to 14% depending on many transplant characteristics.[2] The incidence we reported in this study is widely included in this range and may be related to a high number of marginal donors or to a cold ischemia duration longer than 12 hours, which are reported as trigger factors for posttransplant TMA. Even if the diagnosis is performed at a very early stage and it is difficult to distinguish from other causes such as the use of antilymphocyte serum or bleeding, we are very confident in diagnostic accuracy. In fact, all laboratory TMA characteristics (not only anemia and low platelets count, but also haptoglobin, lactate dehydrogenase and schistocytes values) had to be satisfied for study inclusion. In addition, 91% of graft biopsies showed TMA lesions. We are aware that the histopathologic diagnosis of posttransplant TMA relies on the subjective interpretation of a multitude of histopathologic findings, that vary in extent and frequency, and depends on its acute or chronic character. Recently, the Banff TMA working group reported the first phase of a consensus study aiming to better define the minimum diagnostic criteria for posttransplant TMA; the 2 subsequent phases of this study are still ongoing.[3] Thus, we have to wait for major details eventually to redefine histology changes from our patients.

In our study, 77.8% of patients received a kidney transplant from a marginal donor or from a donor after a circulatory death. In these cases, a pretransplant biopsy was performed to evaluate Karpinski-Remuzzi score and any signs of donor-related TMA. Thus, this last condition is histologically excluded in the majority of patients. In the other patients, pretransplant biopsy was not performed; however, we can affirm that any clinical and laboratory findings of the donors associated with TMA and often related to sepsis or neoplastic diseases, such a disseminated intravascular coagulation, are always carefully evaluated and often the reasons for exclusion from donation. Thus, overall, we think that this point cannot be considered in the evaluation of study results.

We agree with the authors that the MCPggaac haplotype is rather common and when isolated, it is unlikely to be pathogenic in normal conditions. Le Clech *et al*.[4] found that only the homozygous MCPggaac haplotype was associated with secondary hemolytic uremic syndrome; however, the paper did not include kidney transplant patients and only 8% of the cohort were patients with extrarenal organ transplantation. Transplant patients are exposed to multiple strong insults, including ischemia-reperfusion injury, immunosuppressive drugs, and the immune response against the donor graft. In these exceptional conditions, we can hypothesize that even the small effect of the MCPggaac haplotype may become manifest. In addition, MCP is ubiquitously expressed and its functions have expanded dramatically beyond its initial discovery as a regulator of complement activation. Specifically, it regulates T cell activation via providing costimulatory signals during T cell receptor engagement[S1]; and small changes in MCP expression depending on the MCPggaac haplotype could impact on host immune response to the kidney graft and predispose to TMA.

Finally, it is well known among nephrologists that it is difficult to perform a case-control study in the context of TMA, both due to the rarity of this condition and to ethical issues. It is a fact that eculizumab approval for atypical hemolytic uremic syndrome is based on 3 nonrandomized and noncontrolled studies, including very few numbers of patients in which clinical history drastically changed due to the significant improving of renal function.[S2,S3] Therefore, considering the high risk of graft failure and the potential benefit from this drug, we believe that, once recognized, posttransplant TMA deserves the same management of atypical hemolytic uremic syndrome. More prospective and cost-effectiveness studies are needed to confirm our opinion.

SUPPLEMENTARY MATERIALS

Supplementary File (PDF)

Supplementary References.

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2. Abbas F, Abbas SF. Abbas SF de novo and recurrent thrombotic microangiopathy after renal transplantation: current concepts in management. *Exp Clin Transplant*. 2022;20:549–557. https://doi.org/10.6002/ect.2021.0069
3. Afrouzian M, Kozakowski N, Liapis H, et al. Thrombotic microangiopathy in the renal allograft: results of the TMA Banff working group consensus on pathologic diagnostic criteria. *Transpl Int*. 2023;36:11590. https://doi.org/10.3389/ti.2023.11590
4. Le Clech A, Simon-Tillaux N, Provôt F, et al. Atypical and secondary hemolytic uremic syndromes have a distinct presentation and no common genetic risk factors. *Kidney Int*. 2019;95:1443–1452. https://doi.org/10.1016/j.kint.2019.01.023

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