Response to Letter to the Editor From Bouwmeester RN et al.: "Eculizumab in Postransplant TMA: Unproven Benefit."

The Author Replies: We would like to thank Dr. Bouwmeester and colleagues for their critical analysis of our article titled *"Eculizumab first" in the Management of Posttransplant Thrombotic Microangiopathy*.[1] In their letter, authors affirm that eculizumab does not appear instrumental in the improvement of graft function in the context of posttransplant thrombotic microangiopathy (TMA) due to the nature of the study (uncontrolled) and the incidence of graft failure, which is within the range previously reported from other eculizumab-naïve posttransplant TMA cohorts.

It is difficult to make comparison between our study cohort and the patients included in previous studies, which were performed before eculizumab era. The article from Schwimmer *et al*.[2] includes a cohort of patients who underwent kidney transplant before 2000. This cohort was not well-characterized in terms of transplant characteristics and calcineurin inhibitor (CNI) levels. However, the difference of graft survival among patients experiencing systemic TMA and patients without TMA is impressive (as shown from Kaplan Meier curves) and the incidence of graft loss (38%) is higher than ours (22%). The paper from Le Quintrec *et al*.[3] also reported a higher incidence of graft loss within 1 year from posttransplant TMA diagnosis (33%) than ours. Again, it is difficult to compare study results with ours because the article from Le Quintrec *et al*.[3] includes younger patients and kidney transplant characteristics were not well-specified. The study from Bren *et al*.[4] includes patients who underwent kidney transplant from 1986 to 2004 with a cyclosporine-related TMA. In this series, graft prognosis was good but it should be considered that donor characteristics were different from ours (no extended criteria donors were included) and TMA diagnosis was not well-defined. Finally, in their review, Avila *et al*.[5] report an incidence of graft loss of 33% to 40% in the first 2 years after posttransplant TMA. Interestingly, they stress the role of complement activation in disease pathogenesis and propose the early use of eculizumab as a valid therapeutic option in the management of these patients, by anticipating the findings from our study.

We are aware that CNI may trigger TMA, especially in case of kidney transplant from extended criteria donors. However, even if many case reports showed the potential effectiveness of CNI discontinuation in the treatment of this condition, no controlled studies have prospectively evaluated this finding. In our cohort, tacrolimus trough levels at the diagnosis of TMA were on target and no signs of CNI toxicity were found in biopsies. We decided to reduce CNI dose (and not to discontinue) due to the increased rejection risk and we immediately associated eculizumab. This approach resulted, in our retrospective analysis, in a good graft outcome. Even if belatacept is reported as effective in CNI-related delay graft function, its use is not provided by the Italian National Health System. In addition, data about belatacept in the treatment of posttransplant TMA are scarce.

Therefore, we agree with the authors that controlled prospective studies are certainly needed to better clarify the role of complement inhibition in the treatment of posttransplant TMA. However, the close temporal association which we found between the use of eculizumab and TMA remission both in terms of hematologic parameters and graft function, in our opinion, demonstrates that the interruption of a complement-mediated endothelial damage is a step in the right direction for the management of this tricky condition.

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