LETTER TO THE EDITORS

HLA-EMMA, a tool for molecular-level HLA matching after heart transplantation

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Dear Editors,

We thank Cacciatore and colleagues for their valuable comments [1]. Our study was the first in cardiac transplantation to investigate, in an exploratory manner, whether the Epitope MisMatch Algorithm (HLA-EMMA) could serve for post-transplant risk stratification [2].

Numerous studies have previously shown that a higher HLA allele mismatch is associated with inferior clinical outcomes, as has been correctly pointed out. We are sorry that out of this myriad for reasons of space we were only able to cite a selection: One of the first was Norman Shumway in 1987 [3]. We also aimed to cover more recent patients and therefore referred to the largest collective, the ISHLT registry data [4].

Thanks to rigorous work in the field of histocompatibility, the whole amino acid sequence of all HLA antigens is now known. This has enabled HLA matching to evolve to the next level, and several groups have investigated the clinical effect of HLA eplet or epitope matching. The principle behind it is that matching of donor and recipient is restricted to the actual targets of antibody reactivity on the antigen's surface [5]. This enables to discriminate between very and less immunogenic HLA allele mismatches on the basis of the number of eplets present on the donor HLA, which are not shared by the recipient. It represents a major advancement as compared to conventional HLA allele matching, because recipients showing the same quantity of antigen mismatches can have very different amounts of mismatches on a molecular level [6]. This method is being used successfully within the *Eurotransplant Acceptable Mismatch Program* [7]. Further progress has been made through the identification of antibody-verified eplets [8], because not every eplet is able to cause an immunologic response. For this reason, we have used the validated HLA-EMMA algorithm [9] in order to match only antibody-verified amino acids. There has been another recently published study by Sapir-Pichhadze et al.[10] conducted in kidney transplant recipients providing additional evidence for the usefulness of such an approach.

We agree that our study was conducted in a very long window of observation time. We tried to overcome this potential bias by multivariable adjustment including the era of transplantation for all endpoints and by accounting for the immunosuppression regimen (cyclosporin A vs tacrolimus) for the secondary endpoint, that is, rejection. This can obviously not represent full bias correction since it is still a retrospective study, with all its associated weaknesses.

We thank Cacciatore et al. for retaining our scientific conclusions as convincing. We absolutely agree that further evidence and prospective data will be needed. A key issue that needs to be addressed is that some mismatch combinations seem to be more immunogenic than others. Therefore, a collaborative effort is currently underway (as part of the 17th International Histocompatibility and Immunogenetics Workshop) in order to grade the varying immunogenicity of individual epitopes in kidney transplantation. These studies will also focus on the nature of the amino acid mismatches considering differences in size and charge. Questions for future research will include whether the above findings generated in kidney transplantation apply to heart transplant recipients.

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