LETTER TO THE EDITORS

## Further evidence on HLA-DR matching in determining heart transplantation outcomes

Francesco Cacciatore<sup>1,2</sup>, Vittorio Palmieri<sup>1</sup>, Cristiano Amarelli<sup>1</sup> , Ciro Maiello<sup>1</sup> & Claudio Napoli<sup>3</sup>

- 1 Cardiac Transplantation Unit, Department of Cardiac Surgery and Transplantation, Ospedali dei Colli, Naples, Italy
- 2 Department of Translational Medical Sciences, Federico II University of Naples, Naples, Italy
- 3 Clinical Department of Internal Medicine, Specialistic Units and Regional Referring Centre for Clinical Immunology of Organ Transplantation (LIT), University Department of Advanced Medical and Surgical Sciences (DAMSS), University of Campania "Luigi Vanvitelli", Naples, Italy

E-mail: claudio.napoli@unicampania.it

We read the recent retrospective study of Osorio-Jaramillo et al. [1] conducted on 1167 cardiac transplant recipients between 1984 and 2016 among which typing at serological split antigen level was available in 312 recipients. The authors reported that patients with a higher HLA-DR amino acid mismatch-load (AAMM) had inferior 1-year graft survival (hazard ratio [HR], 1.14; 95% confidence interval [CI], 1.01-1.28) [1]. No impact on the development of cardiac allograft vasculopathy (CAV) was found, and they concluded that molecular-level HLA mismatch analysis could be used as a tool for risk stratification after heart transplantation [1]. When we read their paper we noted that relevant studies that gave similar results were omitted in the list of references. Although they analyzed the role of mismatch at level of epitopes [1], the original idea that HLA-DR mismatching would correlate with early cardiac allograft rejection and graft survival was hypothesized in the early 90' [2]. Besides, our group published in 2013 [3] the evidence that HLA-DR mismatch was associated with increased in-hospital mortality after a heart transplant in 158 consecutive patients who had undergone a heart transplant between 2000 and 2008. More recently, we [4] and another group [5] have published the long-term effects of HLA-DR Matching on outcomes after heart transplantation. Preliminary data from these findings were presented annually both at the European Society of Organ Transplantation (ESOT) and the European Society of Cardiology (ESC) between 2012 and 2018. None of these studies [2-5] were quoted by Osorio-Jaramillo et al. [1]. Overall, the "take-home" message of these papers is similar; in fact, all studies declared that HLA-DR mismatch is associated with worse prognosis in heart transplant. One major concern of the Reviewers of our first paper [3] was the long window of our observation (i.e., 2000-2008) which may affect outcomes due to diverse immunosuppressive regimens. In this regard, the above study [1] was conducted in a very long window of observation time (i.e., 1984-2016) and, thus, with an evident difference in immunosuppressive drug regimens and potential bias of the study results. However, since our multidisciplinary group has more than 35 years of experience in heart trasplantation [3,4,6–9], we retain the scientific conclusions of the study [1] convincing and in line with published studies [2–5] but we believe that the topic should be addressed by large registries analyses to gain more granular differences taking account of the role of induction therapy, different pri-(CYA Tac) immunosuppressant, antiproliferative drugs. We should keep in mind the HLA-DR mismatch during allocation in a clinical environment in which, implementing new technologies of graft preservation (ex situ organ perfusion), mechanisms of organ exchange (also transborder) - similar to the kidney exchange programs used for the living donations could permit to allocate the right graft aiming to save the life of the recipient during the short term, but also aiming to lower the immunosuppressive burden and the best long-term organ preservation. Finally, the clinical application of precision medicine in the real world of transplant centres is quite difficult; however, the International Group on Network Medicine [10] is working on new algorithms that can be useful at the bedside to personalize treatments and novel drug strategies of complex diseases and, possibly, in the clinical setting of transplantation.

## RFFFRFNCFS

- 1. Osorio-Jaramillo E, Haasnoot GW, Kaider A, *et al.* Molecular-level HLA mismatch is associated with rejection and worsened graft survival in heart transplant recipients. *Transpl Int* 2020 May 22. https://doi.org/10.1111/tri. 13657
- De Mattos AM, Head MA, Everett J, et al. HLA-DR mismatching correlates with early cardiac allograft rejection, incidence, and graft survival when highconfidence-level serological DR typing is used. Transplantation 1994; 57: 626.
- 3. Crudele V, Cacciatore F, Grimaldi V, et al. Human leukocyte antigen-DR mismatch is associated with increased in-hospital mortality after a heart transplant. Exp Clin Transplant 2013; 11: 346.

- 4. Cacciatore F, Amarelli C, Sabia C, *et al.* Effect on long-term mortality of HLA-DR matching in heart transplantation. *J Card Fail* 2019; **25**: 409.
- 5. Ansari D, Bućin D, Höglund P, Ohlsson M, Andersson B, Nilsson J. Analysis of the influence of HLA-A matching relative to HLA-B and -DR matching on heart transplant outcomes. *Transplant Direct* 2015; 1: e38.
- 6. De Santo LS, Amarelli C, Romano G, et al. Evolving practice patterns in heart transplantation: a single-center experience over 15 years. *Transplant Proc* 2004; **36**: 627.
- Amarelli C, De Santo LS, Marra C, et al. Early graft failure after heart transplant: risk factors and implications for improved donor-

- recipient matching. *Interact Cardiovasc Thorac Surg* 2012; **15**: 57.
- 8. Cacciatore F, Amarelli C, Maiello C, et al. Sacubitril/valsartan in patients listed for heart transplantation: effect on physical frailty. ESC Heart Fail 2020; 7: 757.
- 9. Marfella R, Amarelli C, Cacciatore F, et al. Lipid accumulation in hearts transplanted from nondiabetic donors to diabetic recipients. *J Am Coll Cardiol* 2020; 75: 1249.
- Silverman EK, Schmidt HHHW, Anastasiadou E, et al. Molecular networks in Network Medicine: development and applications. Wiley Interdiscip Rev Syst Biol Med. 2020; e1489.