International Journal of Cardiology 290 (2019) 33

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

From microvascular impairment to cardiac allograft vasculopathy: A disease continuum

Carmine Morisco, Emanuele Barbato *

Department of Advanced Biomedical Sciences, University of Naples Federico II, Italy

ARTICLE INFO

Article history:
Received 4 May 2019
Accepted 7 May 2019
Available online 11 May 2019

Acute allograft rejection (AAR) is a complex and multifactorial phenomenon that strongly predicts poor prognosis following heart transplantation [1]. Early diagnosis of AAR plays a key role in the management of post-transplant patients, enabling to promptly tailor a more intensive follow-up, and a more gradual weaning from immunesuppressants [2]. Dr. Fearon and collegues in this issue of the *Journal* [3] investigated the association between AAR with several clinical parameters and invasive diagnostic assessments in order to identify reliable predictors of incident AAR. Within 8 weeks from the heart transplant, 88 patients underwent thorough clinical and laboratory examination, as well as invasive diagnostic evaluation with coronary angiography, intravascular ultrasound and invasive functional assessment. At 1-year clinical follow-up, AAR was found in nearly one fourth of the patients in line with previous evidences [1]. Patients developing AAR presented higher mortality rate up to 12 years follow-up. The only parameter, assessed early after transplantation, significantly associated with incident AAR was an Index of Microvascular Resistance (IMR) value >16, suggesting a role of microvascular impairment in future development of AAR.

Along with a significant IMR increase, initial cardiac allograft vasculopathy (CAV) was disclosed by greater intimal growth at IVUS and a reduction in FFR (a proxy of increased epicardial atheroma burden). Interestingly, CAV that was traditionally considered a feature of chronic rejection [4] now appears to be rather a disease continuum that starts early after heart transplantation at the microvascular level followed thereafter by an involvement of the epicardial coronaries. CAV is characterized, in fact, by vascular cell proliferation (smooth muscle and endothelial cells), infiltration of inflammatory cells, resulting in vascular dysfunction and thickening. These abnormalities might contribute to the onset of both microvascular dysfunction and epicardial lesions.

Importantly, mortality rate was found elevated when IMR was higher at baseline and further increased at the follow-up as compared with patients with an IMR unchanged or even decreased over time. This association between changes in the microcirculatory status and clinical outcomes further corroborates the importance of serial microvascular assessments as potential diagnostic tool to monitor effective response to therapy. At this regard, AAR occurred despite these patients were taking more frequently sirolimus, a mTOR inhibitor which has proven to counteract development and progression of CAV [4]. On the other side, tacrolimus use was significantly lower in patients developing AAR. Tacrolimus is a macrolide antibiotic with immunosuppressive properties mainly acting as calcineurin phosphatase inhibitor. Intracoronary administration of tacrolimus, in experimental model of myocardial infarction, attenuates myocardial inflammation, limits infarct extension, and preserves LV function [5]. Whether tacrolimus exerts its beneficial effect by preventing or reducing microvascular impairment is a hypothesis deserving further investigation.

Dr. Fearon and collegues should be commended for having proposed a novel diagnostic and therapeutic approach for patients early after heart transplantation. We are eager to see whether focusing on the microvascular impairment might potentially impact the clinical outcomes of these patients.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

References

[1] L.H. Lund, L.B. Edwards, A.Y. Kucheryavaya, C. Benden, A.I. Dipchand, S. Goldfarb, The registry of the International Society for Heart and Lung Transplantation: thirty-third adult heart transplantation Report-2016; focus theme: primary diagnostic indications for transplant, J. Heart Lung Transplant. 35 (2016) 1158–1169.
[2] B.N. Weber, J.A. Kobashigawa, M.M. Givertz, Evolving areas in heart transplantation, JACC Heart Fail. 5 (2017) 869–878.
[3] Fearon et al. (current paper).
[4] S. Chih, A.Y. Chong, L.M. Mielniczuk, D.L. Bhatt, R.S.B. Beanlands, Allograft vasculopathy: the Achilles' heel of heart transplantation, J. Am. Coll. Cardiol. 68 (2016) 80–91.
[5] C.H. Yang, J.J. Sheu, T.H. Tsai, S. Chua, L.T. Chang, H.W. Chang, et al., Effect of tacrolimus on myocardial infarction is associated with inflammation, ROS, MAP kinase and Akt pathways in mini-pigs, J. Atheroscler. Thromb. 20 (2013) 9–22.

DOI of original article: https://doi.org/10.1016/j.ijcard.2019.04.018.
* Corresponding author at: Department of Advanced Biomedical Sciences, University of Naples Federico II, Via Pansini n. 5, 80131 Napoli, Italy.
E-mail address: emanuele.barbato@unina.it (E. Barbato).

https://doi.org/10.1016/j.ijcard.2019.05.022