Role of NTproBNP and donor-derived cell-free DNA in the diagnosis of acute rejection in heart transplant recipients: a prospective study


1University Hospital Ramon y Cajal, Madrid, Spain
2CHUAC, Cardiology, A Coruna, Spain
3University Hospital 12 de Octubre, Cardiology, Madrid, Spain
4University Hospital Puerta de Hierro Majadahonda, Cardiology, Madrid, Spain
5University Hospital La Fe, Cardiology, Valencia, Spain
6University Hospital Gregorio Maranon, Cardiology, Madrid, Spain
7Hospital Clinic de Barcelona, Cardiology, Barcelona, Spain
8Hospital de la Santa Creu i Sant Pau, Cardiology, Barcelona, Spain
9University Hospital Central de Asturias, Cardiology, Oviedo, Spain
10University Hospital Bellvitge, Cardiology, Barcelona, Spain
11Complex Public Hospital Virgen del Rocio Regional, Cardiology, Sevilla, Spain, Spain
12University Clinic of Navarra, Cardiology, Navarra, Spain
13Virgen de la Arrixaca University Clinical Hospital, Cardiology, Murcia, Spain

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Background: Donor-derived cell-free DNA (dd-cfDNA) has shown a good ability to rule out rejection in heart transplant (HT) recipients, but there is scarce information on the utility of NTproBNP (and the combination of both biomarkers) in this setting.

Methods: We prospectively obtained levels of both biomarkers in all patients included in the FreeDNA-CAR study (NCT 04973943), just before performing surveillance endomyocardial biopsies (EMB) at 0.5, 1, 2, 3, 4, 6 and 12 months post-HT. Primary end-point was the correlation between dd-cfDNA and NTproBNP levels.

Results: A total of 206 HT patients from 12 different centers were included (mean age 54±12 years, 74% male), with a median of 5.6 EBM per patient. After excluding visits with missing data, 883 pairs of EMB-both biomarkers were available for analysis.

ACR, defined as grade ≥2R, was present in 37 EMB (4.2%), and AMR ≥1 in 16 EMB (1.8%). Median (IQR) NTproBNP values for each ACR group were: 0R 1067 pg/ml (454-2563), 1R 1300 pg/ml (562-3298) and 2R-3R 1780 pg/ml (943-4880) and median dd-cfDNA values: 0R 0.08% (0.038-0.178), 1R 0.105% (0.04-0.34), 2R-3R 0.22% (0.058-0.7). Regarding AMR, median NTproBNP in pAMR0 was 1200 pg/ml (504-2840) and in pAMR 1 2230 pg/ml (806-4256) (Figures 1A and 1B).

Using a GEE (generalized estimating equation) approach to account for repeated measures in each individual, a statistically significant correlation between both biomarkers was found, with a coefficient of 0.001 (CI95% 0.0006-0.002), meaning that for every increase of 100 units of NTproBNP, %dd-cfDNA increased in 0.001, p <0.001 (Figure 2).

Moreover, in a multivariable analysis, both biomarkers were associated with the risk of acute rejection, with an OR 1.48 (CI95% 1.04-2.11), p=0.03 for dd-cfDNA, and OR 1.007 (IC95% 1.001-1.013) p=0.017 for each additional 100 pg/ml of NTproBNP.

Conclusion: In a cohort of HT patients in their first post-transplant year, dd-cfDNA and NT-proBNP levels were associated with acute rejection and showed a good correlation between them. Further studies are needed in order to determine if the combination of both biomarkers could improve individual performance and increase the number of EMB that could be safely eliminated.
Linear prediction of dd-cfDNA