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Evaluation of humoral immunity profiles to identify heart recipients at risk for development of severe infections: A multicenter prospective study

Elizabeth Sarmiento, MD, PhD,[a] Maria Jaramillo, LB,[a] Leticia Calahorra, LB,[a] Juan Fernandez-Yañez, MD,[b] Miguel Gomez-Sanchez, MD, PhD,[c] Maria G. Crespo-Leiro, MD, PhD,[d] Maria Paniagua, MD, PhD,[d] Luis Almenar, MD, PhD,[e] Monica Cebrian, MS, PhD,[e] Gregorio Rabago, MD, PhD,[f] Beltran Levy, MD, PhD,[f] Javier Segovia, MD, PhD,[g] Manuel Gomez-Bueno, MD, PhD,[g] Javier Lopez, MD, PhD,[h] Sonia Mirabet, MD, PhD,[i] Joaquin Navarro, LB, PhD,[a] Juan Jose Rodriguez-Molina, LB,[a] Eduardo Fernandez-Cruz, MD, PhD,[a] and Javier Carbone, MD, PhD[a]

From the [a]Clinical Immunology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain; [b]Cardiology Department, Hospital General Universitario Gregorio Marañon, Madrid, Spain; [c]Cardiology Department, Hospital Universitario Doce de Octubre, Madrid, Spain; [d]Cardiology Department, Complexo Hospitalario Universitario de A Coruña, A Coruña, Spain; [e]Heart Failure and Heart Transplant Unit, Cardiology Department, Hospital Universitario La Fe, Valencia, Spain; [f]Heart Surgery Department, Clínica Universidad de Navarra, Pamplona, Spain; [g]Heart Failure and Cardiomyopathy Unit, Heart Failure and Heart Transplant Section, Department of Cardiology, Hospital Universitario Puerta de Hierro, Madrid, Spain; [h]Heart Failure and Heart Transplant Unit, Hospital Clínico Universitario, Valladolid, Spain; and the [i]Cardiology Department, Sant Pau Hospital, Barcelona, Spain.

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BACKGROUND: New biomarkers are necessary to improve detection of the risk of infection in heart transplantation. We performed a multicenter study to evaluate humoral immunity profiles that could better enable us to identify heart recipients at risk of severe infections.

METHODS: We prospectively analyzed 170 adult heart recipients at 8 centers in Spain. Study points were before transplantation and 7 and 30 days after transplantation. Immune parameters included IgG, IgM, IgA and complement factors C3 and C4, and titers of specific antibody to pneumococcal polysaccharide antigens (anti-PPS) and to cytomegalovirus (CMV). To evaluate potential immunologic mechanisms leading to IgG hypogammaglobulinemia, before heart transplantation we assessed serum B-cell activating factor (BAFF) levels using enzyme-linked immunoassay. The clinical follow-up period lasted 6 months. Clinical outcome was need for intravenous anti-microbials for therapy of infection.

RESULTS: During follow-up, 53 patients (31.2%) developed at least 1 severe infection. We confirmed that IgG hypogammaglobulinemia at Day 7 (defined as IgG <600 mg/dl) is a risk factor for infection in general, bacterial infections in particular, and CMV disease. At Day 7 after transplantation, the combination of IgG <600 mg/dl + C3 <80 mg/dl was more strongly associated with the outcome (adjusted odds ratio 7.40; 95% confidence interval 1.48 to 37.03; $p = 0.014$). We found that

Reprint requests: Javier Carbone, MD, PhD, Clinical Immunology Department, Hospital General Universitario Gregorio Marañón, Dr. Esquerdo 46, 28007 Madrid, Spain. Telephone: 34-91-4265180. Fax: 34-91-5866698.
E-mail address: javier.carbone@salud.madrid.org

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quantification of anti-CMV antibody titers and lower anti-PPS antibody concentrations were independent predictors of CMV disease and bacterial infections, respectively. Higher pre-transplant BAFF levels were a risk factor of acute cellular rejection.

CONCLUSION: Early immunologic monitoring of humoral immunity profiles proved useful for the identification of heart recipients who are at risk of severe infection.

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Infections continue to be a barrier to long-term survival in heart recipients. According to the 2014 report of the Registry of the International Society for Heart and Lung Transplantation, infection is the leading cause of death between 1 month and 1 year after transplantation.[1] New early biomarkers are needed to improve assessment of the risk of developing infection after heart transplantation.[2]

Immunoglobulin G (IgG) hypogammaglobulinemia has been evaluated extensively in heart transplantation. Previous studies have analyzed the role of monitoring IgG concentrations in various immunosuppressive settings.[3–6] A recently published meta-analysis suggested that IgG hypogammaglobulinemia is a risk factor for infection in solid-organ recipients.[7] However, previous studies are limited by the fact that data were gathered from a single institution. Multicenter studies are necessary to validate biomarkers for use in clinical practice.

In this study we present the results of a multicenter, prospective, observational study of humoral immunity biomarkers in adult heart recipients. The specific aims of this multicenter study were as follows: (1) to confirm whether IgG hypogammaglobulinemia is an independent risk factor of severe infection; (2) to identify humoral immunity profiles that could better enable us to identify the risk of infection; (3) to evaluate the reproducibility of IgG and complement factor 3 (C3) testing results in different centers; and (4) to evaluate potential immune factors of hypogammaglobulinemia before heart transplantation.

Methods

Study design

We prospectively evaluated 170 adult patients undergoing heart transplantation in 8 geographically dispersed teaching hospitals in Spain. The centers were distributed as follows: Madrid (Hospital General Universitario Gregorio Marañon [coordinating center, $n = 59$], Hospital Universitario Doce de Octubre [$n = 27$], Hospital Universitario Puerta de Hierro [$n = 8$]); La Coruña (Complexo Hospitalario Universitario A Coruña [$n = 26$]); Navarra (Clinica Universitaria de Navarra [$n = 19$]); Valladolid (Hospital Clínico Universitario [$n = 9$]); Valencia (Hospital Universitario La Fe [$n = 20$]); and Barcelona (Hospital de la Santa Creu i Sant Pau [$n = 2$]). Data were collected later at some centers than at others. Twenty-five patients from the coordinating center overlapped with the population studied in a previous publication.[8]

The clinical characteristics of the patients are presented in Supplementary Table S1 (available online www.jhltonline.org). Induction therapy was taken by 147 patients (86.5%; anti-CD25 monoclonal antibodies, $n = 146$; anti-thymocyte globulin, $n = 1$). The frequency of induction therapy was similar between institutions and ranged from 86% to 100%. With respect to maintenance immunosuppression therapy, 54 patients (31.8%) received cyclosporine and 107 received tacrolimus (62.9%). Differences were observed between the centers. The frequency of administration of cyclosporine varied from 15% to 100%, and that of tacrolimus from 25% to 100%. Mycophenolate mofetil was taken by 164 patients (96.5%), with few differences in frequency (range 86% to 100%). During the 6 months of follow-up, none of the patients used proliferation signal inhibitors (everolimus or rapamycin).

Anti-microbial prophylaxis included peri-transplant cephalosporins in 133 patients (78.2%), quinolones during the first month in 75 (44.1%), and trimethoprim–sulfamethoxazole during the 6-month follow-up period in 123 patients (72.4%). As for anti-cytomegalovirus (anti-CMV) prophylaxis, 69 patients (40.6%) received valganciclovir, 30 (17.6%) received ganciclovir, and 47 (27.6%) did not receive CMV prophylaxis. Differences were detected between the centers. The frequency of administration of valganciclovir varied from 4.2% to 100%, and that of ganciclovir from 0% to 100%. As for anti-fungal prophylaxis, nystatin was indicated in 147 patients (86.5%). None of the patients received intravenous immunoglobulin (IVIg) before the immunologic tests performed at Day 7 after transplantation. One patient received IVIg after diagnosis of thrombocytopenic purpura at Day 14 after transplantation. No patients received IVIg before development of a severe infection.

The follow-up period was the 6 months after transplantation. Severe infections were defined according to the definitions of the U.S. Centers for Disease Control and Prevention. The only infections included were severe infections, that is, those requiring intravenous anti-microbial therapy in hospital. Superficial surgical-site infections and catheter-associated infections were not included. CMV disease was defined as positive results in CMV antigenemia or polymerase chain reaction (PCR) assay and clinical symptoms.

Clinical and epidemiologic data on all patients enrolled in the study were collected by local investigators during the follow-up period. Rejection episodes were diagnosed based on endomyocardial biopsy findings. We included only treated rejection episodes in the analysis.

Immunologic studies

Immunologic tests were performed in serum samples obtained at inclusion on the waiting list and at Days 7 and 30 after transplantation. Levels of immunoglobulins (IgG, IgA, IgM) and complement factors (C3 and C4) were determined using nephelometry (Beckman-Coulter-Izasa, Brea, CA). Variations in the kinetics and values of selected immunologic parameters (IgG and C3) among patients in heart transplant units at the various institutions were observed to assess the reproducibility of biomarkers.