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Monitoring of early humoral immunity to identify lung recipients at risk for development of serious infections: A multicenter prospective study

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KEYWORDS:
lung transplantation;
infection;
hypogammag lobulinemia;
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risk factors

BACKGROUND: Infection is still a leading cause of death during the first year after lung transplantation. We performed a multicenter study among teaching hospitals to assess monitoring of early humoral immunity as a means of identifying lung recipients at risk of serious infections.

METHODS: We prospectively analyzed 82 adult lung recipients at 5 centers in Spain. Data were collected before transplantation and at 7 and 30 days after transplantation. Biomarkers included IgG, IgM, IgA, complement factors C3 and C4, titers of antibodies to pneumococcal polysaccharide antigens (IgG, IgA, IgM) and antibodies to cytomegalovirus (IgG), and serum B-cell activating factor (BAFF) levels. The clinical follow-up period lasted 6 months. Clinical outcomes were bacterial infections requiring intravenous antimicrobial agents, cytomegalovirus (CMV) disease, and fungal infections requiring therapy.

RESULTS: We found that 33 patients (40.2%) developed at least 1 serious bacterial infection, 8 patients (9.8%) had CMV disease, and 10 patients (12.2%) had fungal infections. Lower IgM antibody levels against pneumococcal polysaccharide antigens at Day 7 (defined as <5 mg/dl) were a risk factor for serious bacterial infection (adjusted odds ratio [OR] 3.96; 95% confidence interval [CI] 1.39 to 11.26; $p = 0.0099$). At Day 7 after transplantation, IgG hypogammaglobulinemia (defined as IgG <600 mg/dl) was associated with a higher risk of CMV disease (after adjustment for CMV mismatch: OR 8.15; 95% CI 1.27 to 52.55; $p = 0.028$) and fungal infection (adjusted OR 8.03, 95% CI 1.51 to 42.72; $p = 0.015$). Higher BAFF levels before transplantation were associated with a higher rate of development of serious bacterial infection and acute cellular rejection.

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CONCLUSION: Early monitoring of specific humoral immunity parameters proved useful for the identification of lung recipients who are at risk of serious infections.
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Infections are a leading cause of death in lung recipients. According to a 2017 report of the Registry of the International Society for Heart and Lung Transplantation, non-cytomegalovirus (non-CMV) infection was the second cause of death during the first month after transplantation (19.1%) and the leading cause of death between the first month and 1 year after transplantation (34.8%).[1] Bacterial infection was the most frequent etiology and CMV infection was the second most frequent.[1] New early biomarkers are urgently needed to improve assessment of the risk of developing infections after lung transplantation. Biomarkers with potential reconstitution are of interest, because detection and modulation of the biomarker could lead to a change in clinical practice and, therefore, a decrease in the incidence of infection.

Our group has reported on the prevalence, characteristics, and impact of secondary antibody deficiency and other secondary immunodeficiency factors after specific types of solid-organ transplantation.[2] Our focus is on identifying biomarkers with real potential for introduction into clinical practice. For example, if immunoglobulin G (IgG) hypogammaglobulinemia is shown to be a risk factor for serious infections, then the potential role of IgG replacement can be evaluated. Proving the efficacy and safety of IgG replacement in secondary antibody deficiency after lung transplantation could lead to a change in clinical practice.

IgG hypogammaglobulinemia has been evaluated extensively in heart and lung transplantation. Previous single-center studies have analyzed the role of monitoring IgG concentrations in various immunosuppressive settings in lung recipients.[3–9] IgG hypogammaglobulinemia (based on various cut-offs) has been associated with development of infection, including bacterial, CMV, and invasive fungal infections, in single-center studies.[3–9] However, other studies have not described such an association.[10,11]

We recently reported the results of the first multicenter study of humoral immunity profiles for identification of heart recipients at risk of serious infections and confirmed that IgG hypogammaglobulinemia is a risk factor for bacterial and CMV infection.[2] Moreover, a recent meta-analysis suggested that serious IgG hypogammaglobulinemia is a risk factor for respiratory, CMV, and fungal infections during the first year in solid-organ recipients.[12]

Herein we present the results of the first multicenter, prospective, observational study of biomarkers of humoral immunity in adult lung recipients. The specific aims of this multicenter study were to: (1) evaluate whether the kinetics of the biomarkers varied between centers; (2) evaluate the reproducibility of IgG testing results in different lung transplant centers; (3) determine whether IgG hypogammaglobulinemia and other humoral immunity biomarkers were associated with higher rates of bacterial, CMV, and fungal infection; and (4) evaluate the potential role of serum B-cell activating factor (BAFF) as a marker for infection.

Methods

Study design

We prospectively studied 123 adult patients who had been evaluated to determine their suitability for lung transplantation. Of these, 82 patients received a transplant during the study period at one of the 5 teaching hospitals throughout Spain as follows: Santander (Hospital Universitario Marques de Valdecilla [$n = 24$]); Barcelona (Hospital Universitario Vall d'Hebron [$n = 22$]); Madrid (Hospital Universitario Puerta de Hierro [$n = 15$] and Hospital Universitario Doce de Octubre [$n = 8$]); and Valencia (Hospital Universitario La Fe [$n = 13$]). Biomarker testing was centralized at a coordinating center in Madrid (Hospital General Universitario Gregorio Marañon).

The main indications for transplantation were: chronic obstructive pulmonary disease (COPD, 37.8%); idiopathic pulmonary fibrosis (26.8%); cystic fibrosis (13.4%); and α_1-anti-trypsin deficiency (6.1%). The clinical characteristics of the patients are presented in Table S1 (refer to Supplementary Material online at www.jhltonline.org/). Induction therapy was used at 3 centers (anti-CD25 monoclonal antibodies, basiliximab) in a total of 69.5% of patients. As for maintenance immunosuppressive therapy, all patients used triple immunosuppressive therapy based on cyclo sporine (9.8%), tacrolimus (90.2%), mycophenolate mofetil (85.4%), and prednisone. During the 6 months of follow-up, none of the patients used proliferation signal inhibitors (everolimus or rapamycin).

Anti-microbial prophylaxis in the post-transplant period included trimethoprim-sulfamethoxazole and nebulized amphotericin B. Anti-CMV prophylaxis was with valganciclovir, ganciclovir, or both. All patients received a dose of 23-serotype polysaccharide pneumococcal vaccine before transplantation.

The follow-up period was the 6 months after transplantation. Serious infections were defined according to the definitions of the US Centers for Disease Control and Prevention. The only infections included were serious infections, that is, those requiring intravenous anti-microbial therapy in hospital. Non-serious infections, superficial surgical-site infections, and catheter-associated infections were not included. Standardized definitions of bacterial infections in cardiothoracic transplant recipients were used.[13] CMV infection included definitions of CMV end-organ disease (pneumonia, gastrointestinal disease, hepatitis, and other) and CMV syndrome according to Ljungman et al.[14] CMV syndrome was defined as the documented presence of fever (temperature $>38°C$) for at least 2 days within a 4-day period, the presence of neutropenia or thrombocytopenia, and detection of CMV in blood. Invasive fungal disease (IFD) was included as an outcome. IFD was defined according to the European Organization for the Research and Treatment of Cancer and the Mycoses Study Group[15] and ISHLT definitions for cardiothoracic transplant recipients[13] via laboratory and clinical assessments as the presence of fungus in respiratory secretions (sputum or bronchoalveolar lavage [BAL])