Intravenous immunoglobulin as an intervention strategy of risk factor modification for prevention of severe infection in heart transplantation

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Despite advances in anti-microbial prophylaxis, infection continues to be one of the most important barriers for long-term survival in solid organ transplantation. According to the 2013 report of the International Society for Heart and Lung Transplantation Registry, infections were the main cause of death in heart recipients between 1 month and 1 year after transplantation [1]. Heart recipients who develop an infection before post-transplantation discharge have a higher risk of death at 5 years even if they survive the first year [1]. Methods to identify heart recipients at risk of infection could allow physicians to make targeted adjustments to immunosuppressive strategy and prophylaxis aimed at decreasing patient morbidity [2].

Biomarkers for the identification of transplant recipients at risk of infection must be validated clinically in large prospective multi-centre studies using standardized measurement techniques and evaluation methods. Immunoglobulin (Ig)G hypogammaglobulinaemia was investigated as a risk factor for infection in heart recipients by Avery and collaborators at the Cleveland Clinic in retrospective single-centre studies [3]. We have confirmed these findings in prospective single-centre studies evaluating the role of IgG hypogammaglobulinaemia as a risk factor of severe infection in heart recipients who received non-cytolytic induction therapy with anti-CD25 monoclonal antibodies [4,5]. In a recent prospective multi-centre national study, we assessed the usefulness of a panel of humoral immunity biomarkers in 267 heart recipients in Spain [6]. Our study confirmed that monitoring IgG and distinct humoral immunity profiles (for example, combining IgG and C3 determinations) after transplantation can help to identify a subgroup of patients at greater risk of infection. Transplant recipients with moderate IgG hypogammaglobulinaemia and C3 hypocomplementaemia 1 month after transplantation were at greater risk of infection. In this study, most infections occurred during the first 3 months post-transplantation [6], suggesting that identification and management of risk factors would be most effective early after transplantation. The role of IgG hypogammaglobulinaemia as a risk factor for infection has also been confirmed in a recently published meta-analysis by Florescu and collaborators [7]. In this study, severe IgG hypogammaglobulinaemia (defined as IgG < 400 mg/dl) was a risk factor for infection in solid organ transplantation. The odds of respiratory infection, cytomegalovirus (CMV), Aspergillus and other fungal infections for patients with severe IgG hypogammaglobulinaemia were higher than the odds for patients with IgG > 400 mg/dl.

Opportunities for designing prevention trials that target the management of risk factors for infection in solid organ transplantation should be explored fully. In clinical trials, the use of biomarkers may allow close monitoring of response to treatment and also enable the selection of patients most likely to respond to specific therapies. An important aspect of IgG hypogammaglobulinaemia is that it is a risk factor that can be managed by replacing infusions of intravenous immunoglobulin (IVIg). The Cleveland Clinic group observed that prophylactic administration of specific anti-CMV IVIg in heart recipients with moderate hypogammaglobulinaemia (IgG < 500 mg/dl) was associated with a decrease in the incidence of CMV infection [8]. We have also demonstrated the impact of humoral

immunity restoration in heart recipients with IgG hypogammaglobulinaemia at the time of diagnosis of a severe infectious episode [9].

We are currently evaluating the potential role of IVIg replacement therapy for prevention of severe infections in heart recipients with moderate post-transplant IgG hypogammaglobulinaemia in a Phase II, open-label pilot study (EudraCT 2009–011165-85). A preliminary analysis included nine adult heart recipients who developed moderate hypogammaglobulinaemia (serum IgG concentration < 500 mg/dl). An interesting aspect of our trial is that this risk factor for infection was detected during the screening phase that was included as part of the trial protocol. IgG testing was performed prospectively at fixed study points (days 7, 14, 30, 60 and 90 after transplantation). Eligible patients received two doses of 200 mg/kg (days 0 and 14 of the trial) of a 5% non-specific IVIg product (Flebogamma, Barcelona, Spain), followed by up to five additional doses of 300 mg/kg (days 30, 60, 90, 120 and 150 of the clinical trial) if IgG was below 750 mg/dl in samples obtained in previous visits. The objective of this design was to maintain normal IgG levels (>750 mg/dl) during the study period. The primary end-point was defined as the development of severe infections during the first 6 months after transplantation. The severe infections considered in this trial were defined as those requiring intravenous (i.v.) antimicrobial therapy in hospital. Superficial surgical site infections and catheter-related infections were not included. Outcomes observed in these patients were matched with those observed in nine control patients with IgG hypogammaglobulinaemia who were not included in the clinical trial during the same study period. These control patients accepted IgG monitoring and clinical follow-up in the same way as IVIg-treated recipients.

The baseline clinical characteristics of both groups were similar and included age, sex, pre-transplant diabetes, urgent transplantation, type of immunosuppressive therapy and use of ventricular assisting devices. Patients received induction therapy with interleukin 2 receptor antagonist basiliximab combined with mycophenolate mofetil and methylprednisolone. Maintenance immunosuppression included mycophenolate mofetil, prednisone and either cyclosporin or tacrolimus. Universal CMV prophylaxis with i.v. ganciclovir or oral valganciclovir was administered to all seropositive recipients for 14 days after surgery. CMV antigenaemia testing was performed weekly from 2 to 4 weeks and every other week from 1 month to 3 months.

We observed that introducing non-specific IVIg prophylaxis in heart recipients with IgG hypogammaglobulinaemia was associated with an increase of IgG levels and with a decrease in the incidence of severe infection compared with recipients who did not receive replacement IVIg therapy. Severe infection was detected in two of nine patients who were receiving IVIg and in eight of nine patients who were not receiving IVIg ($P = 0.015$). When specific types of infec-tions were analysed, CMV infection that required anti-viral treatment developed in only one patient receiving IVIg compared with six patients who were not receiving IVIg ($P = 0.05$). We also observed a trend towards reduction in the incidence of severe bacterial infections (22·2% with IVIg *versus* 66·6% without IVIg, $P = 0.15$). Readmission or prolonged hospitalization due to infection was observed more frequently in untreated heart recipients. The survival rate during the first 6 months after transplantation did not differ between the groups.

With regard to safety, no moderate or severe IVIg-related side effects were recorded during the follow-up period. There were no thrombotic or hypersensitivity events. Urea, creatinine, C3, C4, alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT) and bilirubin at 1, 3 and 6 months after transplantation were similar in patients who had received IVIg and controls. During follow-up none of the IVIg-treated patients developed acute cellular or humoral rejection.

In conclusion, a valid biomarker must be correlated with the clinical end-point, capture a reliable and sufficiently large portion of the treatment effect on the clinical end-point and should allow prediction of the treatment effect on the clinical end-point. IgG hypogammaglobulinaemia has been correlated with the development of severe infection in heart recipients. Preliminary data of the clinical trial demonstrate that IVIg is associated with reconstitution of IgG and improvement of specific antibody titres despite intensive immunosuppression [9]. More importantly, the preliminary results showed that a strategy for detection and management of moderate IgG hypogammaglobulinaemia can decrease the incidence of severe infections in heart recipients. IVIg administration is well tolerated and safe in heart recipients early after transplantation.

IVIg has been proposed as adjuvant therapy for infection in other solid organ transplantations and in distinct clinical settings, even though the clinical studies demonstrating its efficacy and safety are relatively small [10,11]. Further evidence from large, randomized controlled trials is required.

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Disclosure

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