Influenza vaccination during the first 6 months after solid organ transplantation is efficacious and safe

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Abstract

Preventing influenza infection early after transplantation is essential, given the disease's high mortality. A multicentre prospective cohort study in adult solid organ transplant recipients (SOTR) receiving the influenza vaccine during four consecutive influenza seasons (2009–2013) was performed to assess the immunogenicity and safety of influenza vaccination in SOTR before and 6 months after transplantation. A total of 798 SOTR, 130 of them vaccinated within 6 months of transplantation and 668 of them vaccinated more than 6 months since transplantation. Seroprotection was similar in both groups: 73.1% vs. 76.5% for A/(H1N1)pdm (p 0.49), 67.5% vs. 74.1% for A/H3N2 (p 0.17) and 84.2% vs. 85.2% for influenza B (p 0.80), respectively. Geometric mean titres after vaccination did not differ among groups: 117.32 (95% confidence interval (CI) 81.52, 168.83) vs. 87.43 (95% CI 72.87, 104.91) for A/(H1N1)pdm, 120.45 (95% CI 82.17, 176.57) vs. 97.86 (95% CI 81.34, 117.44) for A/H3N2 and 143.32 (95% CI 103.46, 198.53) vs. 145.54 (95% CI 122.35, 174.24) for influenza B, respectively. After adjusting for confounding factors, time since transplantation was not associated with response to vaccination. No cases of rejection or severe adverse events were detected in patients vaccinated within the first 6 months after transplantation. In conclusion, influenza vaccination within the first 6 months after transplantation is as safe and immunogenic as vaccination thereafter. Thus, administration of the influenza vaccine can be recommended as soon as 1 month after transplantation.

Keywords: Early vaccination, immune response, influenza vaccine, seroprotection, solid organ transplantation
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Introduction

After the 2009 influenza pandemic, substantial morbidity and mortality due to influenza infection was described in solid organ transplant recipients (SOTR) [1]. Given the risk of severe disease in this population, recommendations for diagnosis, prevention and therapy of influenza infection were given by several scientific societies [2–4].

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Time since transplantation has been associated with a higher risk of complications due to influenza infection in transplant recipients. Patients diagnosed with influenza infection within the first 3 months after receiving a transplant have a five times greater risk of developing severe disease compared to those infected after the first 3 months after transplantation [5]. Current recommendations, mostly based on expert opinion, support influenza vaccination after 3 months after transplantation [6,7]. More recent recommendations state that not vaccinating may leave a transplant recipient vulnerable to influenza infection for an entire influenza season. However, results of immunologic response to influenza vaccination during the first 6 months after transplantation are controversial [2,8]. While some authors reported a lower response [6,9], others found a similar response independent of the time since transplantation [10]. In addition, most of the studies with patients vaccinated within the first 6 months after transplantation are small series.

Although no solid evidence exists indicating that vaccination can cause acute rejection, there has been worry that nonspecific immune activation caused by vaccination could result in transplant rejection. In this context, safety should be the primary consideration when administering the influenza vaccine early after transplantation. Despite the need for preventing influenza infection in the first 6 months after transplantation, solid evidence regarding the efficacy and safety of influenza vaccination is lacking. Further, adequately sized studies are needed to clarify and firmly establish recommendations regarding the optimal timing of influenza vaccination in the transplant setting.

We hypothesized that early vaccination of SOTR had similar immunologic responses to SOTR vaccinated 6 months after transplantation. Thus, the aim of the study was to assess the immunogenicity, efficacy and safety of influenza vaccination in SOTR before and after 6 months since transplantation.

Material and Methods

Subjects and study design

We performed a multicentre prospective cohort study of influenza vaccinated SOTR during four consecutive influenza seasons. Kidney, heart and liver recipients older than 15 years of age who received one dose of the influenza vaccine between November 2009 and January 2013 were enrolled in 12 Spanish university hospitals belonging to the Spanish Network for Research in Infectious Diseases (REIPI). Patients were excluded if they received the transplant less than 1 month before immunization, if they had an allergy to any of the vaccine components or if they were pregnant. Serum samples were collected from each patient at the time of vaccination (baseline) and 5 weeks after vaccination. Patients were followed up during 90 days and up to 10 months if influenza infection or adverse effects were detected to evaluate the clinical efficacy of the vaccine. The study procedures were approved by the University Hospital Ethic Committee for Clinical Research according with the Helsinki Declaration of the World Medical Association. All patients provided written informed consent.

Clinical parameters and definitions

Baseline characteristics, immunologic and clinical response and adverse effects, including graft rejection and mortality, were recorded using a standardized questionnaire. Biopsies and histologic evaluation of graft rejection were only performed in cases of suspicion if signs of biochemical, echocardiographic or spirometry testing disorders were detected. Comorbidities were assessed by the Charlson comorbidity index [11].

Rejection was defined by the Banff and International Society for Heart and Lung Transplantation criteria [12]. Chronic renal insufficiency was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 for more than 3 months (modified criteria of the Kidney Disease Improving Global Outcomes) [13]. The definition of chronic liver disease was that of the Charlson comorbidity index [11]. Induction therapy was considered when administered within the 6 months before vaccination. Hypogammaglobulinemia was defined as IgG levels lower than 700 mg/dL. The general immunosuppressive regimens consisted of mycophenolate mofetil, calcineurin inhibitor and prednisone. Heart and kidney transplant recipients with medium-high immunologic risk for graft rejection or delayed introduction of tacrolimus received induction therapy with anti–interleukin 2 receptor monoclonal antibodies or polyclonal anti-thymocyte globulin. For liver transplant patients where induction therapy was indicated, anti–interleukin 2 receptor monoclonal antibody therapy was used.

Vaccines

Patients from the 2009–2010 influenza season received the pandemic H1N1-2009 (A/California/7/2009-H1N1) monovalent MF59-adjuvanted vaccine (Focetria, Novartis, Siena, Italy). Patients from the 2010–2011 and 2011–2012 influenza seasons received the trivalent nonadjuvant inactivated vaccine (Gripavac, Sanofi-Pasteur MSD, Madrid, Spain) containing the following strains: A/California/7/2009-H1N1, A/Perth/16/2009-H3N2 and B/Brisbane/60/2008. Patients from the 2012–2013 influenza season received one dose of the trivalent nonadjuvant inactivated vaccine (Mutagrip, Sanofi-Pasteur MSD) with the following strains: A/California/7/2009-H1N1, A/Victoria/361/2011-H3N2 and B/Wisconsin/1/2010. Adverse events were assessed according to established criteria [14].

