



Comparable humoral response after two doses of adjuvanted influenza A/H1N1pdm2009 vaccine or natural infection in allogeneic stem cell transplant recipients



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ABSTRACT

Background: The present study evaluated immunogenicity and tolerance of two-dose influenza A/H1N1pdm09 vaccination in allogeneic hematopoietic stem cell transplantation (HSCT) recipients, and compared the vaccine-induced humoral response to that triggered by natural infection in another group of HSCT patients.

Methods: Adult allogeneic HSCT recipients vaccinated with two doses of influenza A/H1N1pdm09 vaccine, separated by 3 weeks, and patients with proven influenza A/H1N1pdm09 infection were included. Antibody responses were measured by hemagglutination-inhibition assay 1) on days 0, 21, 42 and 6 months after the first vaccine injection in vaccinated patients and 2) before pandemic and after influenza A/H1N1pdm09 infection, in patients presented natural infection.

Results: At baseline, 3% of 59 recipients of adjuvanted vaccine and 0% of 20 infected patients were seroprotected (antibody titer $\geq 1/40$). Seroprotection rate observed 42 days after vaccination was not different from that observed after natural infection (66% and 60% respectively, $p = 0.78$). In vaccinated patients, seroprotection rate increased significantly from 54% to 66% between day 21 and 42 ($p = 0.015$). Moreover, after 6 months, seroprotection rate in 21 vaccinated patients was similar to that observed in 10 infected patients evaluated at least 76 days after infection (D76–217) (60% and 81% respectively, $p = 0.2$). In multivariate analysis, no immunosuppressive treatment or chronic graft-versus-host disease (GVHD) and longer time between transplantation and vaccination/infection were associated with a stronger humoral response. The adjuvanted vaccine was safe with low rate of GVHD worsening.

Conclusion: In HSCT recipients, two doses of influenza A/H1N1pdm09 adjuvanted vaccine were safe and induced a humoral response comparable to that triggered by natural infection in these patients.

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1. Introduction

Influenza is a potentially serious infection in hematopoietic stem cell transplant (HSCT) recipients [1–5]. A mortality rate around 15% was reported in untreated patients, but recent data suggest an improvement of outcome for patients treated with neuraminidase inhibitors [3,5]. In a large prospective study of allogeneic HSCT recipients with influenza A/H1N1pdm2009 infection, 11% of patients with low respiratory tract disease required mechanical ventilation and 6% died from influenza infection or its complications [6].

Vaccination by an inactivated vaccine is the main prophylactic approach for influenza infection, but appears to be less effective in immunocompromised patients such as HSCT recipients, particularly during the first months after transplantation, or in patients with graft-versus-host disease (GVHD) receiving immunosuppressive treatments [7–12]. In this population, alternative modalities of vaccination have been evaluated such as the use of a second dose of vaccine, which allows an enhanced humoral response in some studies [7,13–15], and only marginal effect in others [16]. Moreover, in 2009, the emergence of a pandemic influenza virus has prompted the use of oil-in-water-emulsion adjuvant to enhance influenza vaccine immunogenicity [17]. Therefore, the French Health Authorities recommended the use of two doses of the adjuvanted pandemic influenza A/H1N1pdm09 vaccine in allogeneic HSCT recipients [18].

In this prospective study, we evaluated in allogeneic HSCT the immunogenicity and the safety of two doses of influenza A/H1N1pdm09 vaccine. The safety assessment was particularly focused on the potential risk of GVHD worsening with the adjuvanted vaccine which potentially could trigger an immune reaction against the recipient. To further evaluate the effect of these vaccination modalities, we compared the humoral response observed after adjuvanted vaccination to that observed after influenza A/H1N1pdm09 virus infection in HSCT patients included retrospectively. The primary objective was to compare humoral response observed after vaccination by 2 doses of influenza A/H1N1pdm09 adjuvanted vaccine and natural infection in allogeneic HSCT recipients.

2. Patients and methods

2.1. Study design

This observational study was conducted in 8 centers of the “Société Française de Greffe de Moëlle et Thérapie Cellulaire.

Vaccinated patients were prospectively included if they were older than 18 years of age, and between 3 months and 5 years after allogeneic hematopoietic stem cell transplantation. Main exclusion criteria were: relapse of hematological disease, immunoglobulin infusion in the last 3 months, seasonal influenza vaccination within 3 weeks before first vaccine dose, on-going fever or infectious disease, allergy to egg or other components of the vaccine. Patients received two intramuscular injection (in deltoid muscle) of monovalent influenza A/H1N1pdm09 vaccine administered 21 days apart. The day of inclusion in the study was the day of the first vaccine administration.

Influenza-infected patients older than 18 years followed in our centers were eligible for the study if a pre-epidemic frozen serum sample was available. Post-infection sera were sampled at least 21 days after infection, whenever the patients came for a follow-up post-transplant visit. The day of sampling with positive PCR for diagnosis was considered as day 0.

Patients gave their oral consent to participate in the study as required for observational study. The protocol followed the Declaration of Helsinki and French law.

2.2. Vaccines

Fifty nine patients received an inactivated split-virion preparation of the influenza A/California/07/2009 (H1N1) strain containing 3.75 µg of hemagglutinin and AS03 adjuvant (Pandemrix®, GSK, UK). However, 11 patients received a non-adjuvanted vaccine (Panenza® [15 µg of hemagglutinin], Sanofi-Pasteur, Lyon, France) according to the choice of the physician, particularly in patients with active GVHD.

2.3. Safety assessment

Vaccinated patients recorded occurrence and severity of local or general reactions and any unsolicited adverse events during 21 days after each injection. Clinical or biological data about potential onset or worsening of GVHD were also collected.

2.4. Laboratory assays

2.4.1. Quantitative detection of influenza A/H1N1pdm09 antibodies

Humoral response to influenza A/H1N1pdm09 was evaluated on frozen sera using an hemagglutination-inhibition (HI) assay modified from Kendal et al. [19]. Briefly, after treatment with receptor destroying enzyme, two-fold dilutions of serum beginning 1/10, were tested against 4 hemagglutinin units of antigen (Panenza®, Sanofi-Pasteur, Lyon, France) on human O rhesus negative red blood cells. The titer of hemagglutination-inhibiting (HI) antibodies was defined as the reciprocal of the highest serum dilution that completely inhibited hemagglutination.

In all vaccinated patients, sera were obtained and tested prior to vaccination (D0) and 21 days after each vaccine injection (D21, and D42); in 21 of these patients, sera could be obtained and tested at 6 months post-immunization (M6). In infected patients, available frozen sera sampled before the onset of symptoms and at least 21 days after the diagnosis of infection were tested.

Immunogenicity was evaluated at each time point using the standard HI requirements used by European regulatory authorities for evaluation of influenza vaccines (EMA) [20–22]. Seroprotection was defined as antibody titer $\geq 1/40$ and seroconversion as a pre-vaccination/infection titer $< 1/10$ and a post-vaccination/infection antibody titer $\geq 1/40$ or a pre-vaccination/infection titer $\geq 1/10$ and at least a four-fold increase after vaccination/infection. Geometric mean of antibody titers (GMT) was also calculated. The 3 endpoints (with 95% confidence intervals) were (1) seroprotection rate (percentage of patients with antibody titer $\geq 1/40$ before and after vaccination/infection) (2) seroconversion rate (percentage of patients who seroconverted after vaccination/infection) and (3) GMT ratio (GMT post-vaccination or infection/GMT at D0).

2.4.2. Molecular detection of influenza A/H1N1pdm09 virus

H1N1pdm09 infection was diagnosed from nasopharyngeal secretions by real-time reverse transcription-PCR assay according to the National Influenza Center Northern-France protocol (Institut Pasteur, Paris, France) [23] or to the Centers for Disease Control protocol (CDC) [24].

2.4.3. Definitions

Myeloablative conditioning regimens included either high dose busulfan (dose > 8 mg/kg orally or intravenous equivalent) or high dose total body irradiation (≥ 8 Gy fractionated dose), both associated

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