BRIEF ARTICLES

Enhanced Immune Response after a Second Dose of an AS03-Adjuvanted H1N1 Influenza A Vaccine in Patients after Hematopoietic Stem Cell Transplantation

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Seroconversion rates following influenza vaccination in patients with hematologic malignancies after hematopoietic stem cell transplantation (HSCT) are known to be lower compared to healthy adults. The aim of our diagnostic study was to determine the rate of seroconversion after 1 or 2 doses of a novel split virion, inactivated, AS03-adjuvanted pandemic H1N1 influenza vaccine (A/California/7/2009) in HSCT recipients (ClinicalTrials.gov Identifier: NCT01017172). Blood samples were taken before and 21 days after a first dose and 21 days after a second dose of the vaccine. Antibody (AB) titers were determined by hemagglutination inhibition assay. Seroconversion was defined by either an AB titer of ≤1:10 before and ≥1:40 after or ≥1:10 before and ≥4-fold increase in AB titer 21 days after vaccination. Seventeen patients (14 allogeneic, 3 autologous HSCT) received 1 dose and 11 of these patients 2 doses of the vaccine. The rate of seroconversion was 41.2% (95% confidence interval [CI] 18.4-67.1) after the first and 81.8% (95% CI 48.2-97.7) after the second dose. Patients who failed to seroconvert after 1 dose of the vaccine were more likely to receive any immunosuppressive agent ($P = .003$), but time elapsed after or type of HSCT, age, sex, or chronic graft-versus-host disease was not different when compared to patients with seroconversion. In patients with hematologic malignancies after HSCT the rate of seroconversion after a first dose of an adjuvanted H1N1 influenza A vaccine was poor, but increased after a second dose.

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INTRODUCTION

A novel split virion, inactivated, adjuvanted pandemic H1N1 influenza A vaccine (A/California/7/2009 NYMC X-179A; Pandemrix) was licensed in most European countries in 2009. The Centers for Disease Control (CDC) [1] recommended H1N1 influenza A vaccination for adult individuals, especially for immunocompromised or patients with chronic medical conditions. Patients with hematologic malignancies after hematopoietic stem cell transplantation (HSCT) seem to be at a higher risk of seasonal and H1N1 influenza A–related complications with a reported case fatality of up to 25% for seasonal [2-7] and up to 33% for H1N1 influenza A [8-11]. Protection against influenza is primarily mediated by virus-specific antibodies (AB) and depends on the humoral immune response [12,13], which is impaired in these individuals. Based on data from seasonal influenza, it is assumed that a H1N1 virus-specific antibody titer of ≥1:40 is associated with an approximately 50% lower risk of developing H1N1 influenza A and is therefore referred to as a seroprotective titer [14]. The immunogenicity of seasonal influenza vaccines in patients after HSCT seems lower compared to the general population, especially when vaccinated <6 months after HSCT (reviewed in [7] and [15]). First reports are also indicating weak response rates to vaccination against the 2009 H1N1 influenza A [16].

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Whether a second dose of an influenza vaccine results in a higher rate of seroconversion is still under debate. Thus, the aim of the present study was to investigate the rate of seroconversion after 1 and 2 doses of a novel H1N1 influenza A vaccine (ClinicalTrials.gov Identifier: NCT01017172).

METHODS

Patients

Adult patients with hematologic malignancies after HSCT from the Medical Department of the Johann Wolfgang Goethe University, who were routinely scheduled to receive a H1N1 influenza A vaccine, were asked to participate in this diagnostic study. The study protocol was approved by the local ethics committee and complied with the ICH-GCP guideline on the conduct of clinical trials and the Declaration of Helsinki. All patients gave written informed consent.

A 10-mL blood sample was taken immediately before (day 0) and 3 weeks after the first dose of the vaccine (day 21). On day 21, a second dose of the vaccine was given, and subsequently, a third blood sample was taken 21 days after the second vaccination on day 42. All blood samples were centrifuged (10 minutes at 1500 r.p.m.), and the sera were frozen (−20°C) for further analysis. Clinical data were retrieved from the medical records.

Vaccine

Split influenza virus, inactivated, containing 3.75-μg antigen equivalent to A/California/7/2009 (H1N1) v-like strain (X-179A) hemagglutinin with AS03 adjuvant composed of squalene (10.69 mg), DL-α-tocopherol (11.86 mg), and polysorbate 80 (4.86 mg) (Pandemrix, GlaxoSmithKline Biologicals, Dresden, Germany) was used for an intramuscular vaccination into the deltoid muscle of the nondominant arm. The second dose was given into the opposite arm.

Hemagglutination Inhibition Test

Hemagglutination inhibition assay (HAI) was done after removing naturally occurring, nonspecific inhibitors from the sera, according to the World Health Organization guidance on influenza diagnosis and surveillance and as previously described [17,18]. Reagents used for testing were standardized fresh red blood cells (RBC) of turkeys in Alsever's solution (Bundesinstitut für Risikobewertung, Alt-Marienfelde, Berlin, Germany) and H1N1-Virus split antigen (A/California/7/2009 NYMC X-179A; Pandemrix; GlaxoSmithKline Biologicals). Titers below the detection limit of 1:10 were assigned a value of 1:5 for the purpose of calculating the geometric mean titer. In accordance with the European and international guidance, seroconversion after vaccination was defined by either an AB titer of ≤1:10 before and ≥1:40 after or ≥1:10 before and ≥4-fold increase in AB titer 21 days after vaccination [14,17], respectively.

Statistical Analysis

To compare antibody titers, the geometric mean with the corresponding 95% confidence interval (CI) was calculated. Other values are shown as mean values ± standard deviation if not indicated otherwise. Continuous variables were compared using the Wilcoxon matched pairs test, nominal values were compared using Fisher's exact test. All tests were 2-tailed for a significance level of .05. Statistical analyses were done using SPSS for Windows, release 16 (SPSS Inc., Chicago, IL).

RESULTS

The study was started on November 11, 2009, and the last blood sample was taken on February 1, 2010. Seventeen patients (5 females) were included in the study and received 1 dose of the AS03-adjuvanted H1N1 influenza vaccine. All 17 patients were offered a second dose of the vaccine 21 days after the first dose. Eleven of these 17 patients received a second dose 3 weeks after the first dose and had serum samples taken on days 0, 21, and 42 available for analysis. The other 6 patients decided against a second dose, because local and federal health authorities publicized a single dose. None of the patients refused the second dose because of adverse events.

Before vaccination (day 0), 3 of 17 patients (17.6%) had a seroprotective HAI titer of 1:40 or more. Three weeks (day 21) after the first dose of the H1N1 influenza A vaccine, 9 of 17 patients (52.9%) and 3 weeks after the second dose (day 42), 10 of 11 patients (90.9%) had a seroprotective HAI titer of 1:40 or more. Seroconversion was detected in 41.2% (7 of 17 patients) at day 21 after the first and in 81.8% (9 of 11 patients) at day 42 following the second dose of the H1N1 influenza A vaccine (Table 1). When focusing on the subgroup of 11 patients who received 2 doses, 6 patients failed to seroconvert after the first dose, but 4 of these 6 seroconverted after the second dose. Accordingly, the geometric mean HAI titer increased significantly after the second dose when compared to the HAI titer developed after the first dose ($P = .002$).

The geometric mean HAI titer for patients with seroconversion after 1 dose was 182 (95% CI, 119-280) compared to 13.8 (95% CI, 5.2-36.9) for those who failed to seroconvert ($P = .003$).

The mean time between vaccination and HSCT was 19.7 (range: 4.7-49.3) months. Two patients