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Randomized Double-Blind Study of the Safety and Immunogenicity of Standard-Dose Trivalent Inactivated Influenza Vaccine versus High-Dose Trivalent Inactivated Influenza Vaccine in Adult Hematopoietic Stem Cell Transplantation Patients

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Hematopoietic stem cell transplantation (HCT) survivors are less likely than matched healthy controls to mount a strong immune response to trivalent inactivated influenza vaccine (TIV). High-dose (HD) or standard-dose (SD) TIV were given to adult HCT subjects 18 years or older at least 6 months after transplantation. Subjects were randomized 2:1 to receive either the HD (60 μg hemagglutinin [HA]/strain/dose) or the SD (15 μg HA/strain/dose) TIV. Injection-site and systemic reactions were documented after each vaccination and immune responses were measured before and after each vaccination. A total of 44 subjects were enrolled (25 in year 1 and 19 in year 2), with 15 in the SD group and 29 in the HD group. The median time to vaccination after transplantation was 7.9 months (range, 6 to 106 months), the median age was 50 years (range, 19.6 to 73 years), and 61% were male. No differences in demographic or lab data were noted between groups; however, the HD group had higher median baseline total IgG level (676 versus 469 mg/dL, $P = .025$). No differences in individual injection-site or systemic reactions were noted between groups; however, more events of any injection-site symptom combined were reported in the HD group. No serious adverse events were attributed to vaccination. After vaccination, the HD group had a higher percentage of individuals with titers $\geq$1:40 and a higher geometric mean titer (GMT) against the H3N2 strain compared with that of the SD group. HD and SD TIV were found to be safe and well tolerated in adult HCT recipients. However, the HD group had higher frequency of injection-site reactions but the majority of the reactions were mild and resolved. The HD group had a higher percentage of individuals with post-vaccination titer $\geq$ 1:40 and GMT for H3N2 antigen, indicating better immunogenicity. These data support the need for a phase II immunogenicity trial in HCT recipients.

INTRODUCTION

Infections account for 8% to 17% of deaths among allogeneic hematopoietic cell transplantation (HCT) patients who died within 100 days after transplantation [1]. Moreover, infections, particularly due to respiratory viruses, continue to be an important cause of morbidity and mortality beyond 100 days after transplantation [2]. Because of the expanding indications for HCT and improvements in supportive care [3,4], the use of HCT for treating various malignant and nonmalignant diseases is continually increasing [5]. Currently, more than 60,000 HCTs are performed annually worldwide and numbers are continuing to rise [6,7]. Influenza is an important cause of morbidity and mortality in high-risk individuals, including HCT recipients [8]. In a

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prospective viral surveillance study involving 37 European transplantation centers, 23% of the patients with confirmed influenza died, with 15% having direct influenza-associated mortality [9]. Other studies demonstrated a similar estimated mortality rate of 15% in untreated HCT patients infected with influenza [9,10]. Patients with influenza pneumonia, which includes 9.5% to 75% of HCT recipients with influenza, have higher mortality rates [8-13]. In the community, an influenza epidemic can be associated with attack rates of 10% to 20% in the general population; however, attack rates are higher in individuals with cancer [14-17]. Moreover, significant morbidity and mortality were noted in HCT patients during the recent H1N1 pandemic, with several reports of pneumonia, lower respiratory tract infections, rhabdomyolysis, and death, including many individuals who were affected more than 6 months after their HCT [18-24].

Influenza vaccination is the primary mode for prevention of influenza infection and is the only approved vaccine formulation to prevent respiratory viral infections. Protection is primarily mediated by virus-specific antibodies that depend on an intact humoral response, which is impaired in HCT recipients. Influenza vaccine trials have been conducted in mostly adult HCT recipients and the majority of these studies demonstrate lower antibody titers, especially when compared with those of healthy controls [25-39]. Therefore, strategies to optimize their responses to influenza vaccines are necessary. A promising method and practical alternative to overcome the poor immunogenicity of influenza vaccination may be to increase the antigen dose in the vaccine. This strategy has been successful in individuals ≥65 years, a group with a historically poor response to influenza vaccines [40-43]. Thus, a similar rationale of administrating high-dose trivalent inactivated vaccine (TIV) in this HCT population could improve their immune response to influenza vaccines. Therefore, we sought to determine the safety and immunogenicity of high-dose (HD) TIV compared with those of the standard-dose (SD) TIV in an adult HCT population.

METHODS

Study Design

This was a prospective, randomized, double-blind, phase I safety and immunogenicity study comparing HD to SD TIV in adult allogeneic HCT recipients (ClinicalTrials.gov: NCT01215734). Subjects were randomized in a 2:1 fashion to receive either .5 mL of the HD (60 μg hemagglutinin [HA]/strain/dose) or SD (15 μg HA/strain/dose) TIV intramuscularly. The study was approved by the Vanderbilt University institutional review board and was conducted during the 2010 to 2011 and 2011 to 2012 influenza seasons. Participants and research staff who performed clinical evaluations remained blinded to the subjects' assigned dosage, whereas designated unblinded nurses administered the requisite vaccine.

Subjects

The study population consisted of allogeneic HCT recipients who were at least 6 months after transplantation, ≥18 years old, and available for the duration of the study. Additionally, if patients were on immunosuppressive therapy for treatment of graft-versus-host disease (GVHD), those on stable doses for at least 4 weeks or on tapering doses were also eligible. Patients were screened and recruited from the outpatient adult transplantation clinics at Vanderbilt.

Subjects were excluded from the study for the following reasons: hypersensitivity to influenza vaccination, egg, egg protein, or latex; history of Guillain-Barre syndrome; evidence of hematologic malignancy or disease relapse after transplantation (mixed chimerism and molecular evidence of disease were permitted); platelet count less than 50,000 cells/μL; pregnancy; prior receipt of influenza vaccine or documented influenza infection in the current influenza season; or known hepatitis B, hepatitis C, or human immunodeficiency virus infection. In addition, the criteria for temporarily delaying vaccine administration included a fever (≥100.4°F/38.0°C) or acute illness within 48 hours of enrollment, receipt of any live vaccines within 4 weeks, or receipt of any inactivated vaccines within 2 weeks of study vaccination.

Vaccine

All patients received either the SD TIV (Fluzone, Sanofi Pasteur, Swiftwater, PA) or the HD TIV (Fluzone High-Dose, Sanofi Pasteur). The 2010–2011 and 2011–2012 influenza vaccines were used for their respective influenza seasons. The .5-mL doses of SD TIV (15 μg HA/strain/dose) and HD TIV (60 μg HA/strain/dose) for both influenza seasons contained the same strains: A/California/7/09 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus. Each subject received the vaccination intramuscularly in the right or left deltoid and was observed closely for at least 20 minutes after vaccination.

Study Procedures

Subjects were asked to record solicited reactogenicity events, which included injection-site reactions (pain, tenderness, redness, swelling, and induration at the injection site) and systemic reactions (fevers, fatigue/malaise, headache, nausea, body ache/myalgia, general activity level, and vomiting) for 7 days after vaccination. Solicited injection-site and systemic reactions were graded on a scale from 0 to 3 (none, mild, moderate, or severe) (Supplement Table I). Study personnel contacted the subjects by telephone 1 to 3 days and again 8 to 10 days after TIV to review any adverse events (AEs) and serious adverse events (SAEs). Unsolicited AEs were collected for 28 days after each vaccination. SAEs and new-onset chronic medical conditions were collected through 180 days after final vaccination via phone call and medical chart review.

All unsolicited AEs and SAEs were assessed by a study investigator and classified as being either associated with or not associated with TIV administration. Concomitant medication use was also documented 28 days after TIV.

Assessment of Immunogenicity and HA Inhibition Testing

Serum samples were obtained on all subjects before administration of TIV and 28 to 42 days after administration of TIV for HA inhibition (HAI) testing. Clinical specimens were sent to the laboratory at Vanderbilt University for a complete blood count, serum quantitative immunoglobulin (IgG) levels, and quantitative $CD4^+$, $CD8^+$ and $CD19^+$ before administration of TIV and 28 to 42 days after vaccination. Sera were centrifuged and frozen until shipment to Sanofi Pasteur Global Clinical Immunology, Swiftwater, PA for HAI testing per standard protocols [44].

Outcome Measurements

The primary objective was to determine the safety of HD influenza vaccine compared with that of the SD influenza vaccine. The primary outcome measures were the frequency of (1) solicited injection-site and systemic reactogenicity within the first 7 days after each vaccination event; (2) unsolicited AEs within 28 days after vaccination; and (3) SAEs up to 180 days after final vaccination. The secondary objective was to compare the immunogenicity of the HD versus that of the SD influenza vaccine. The secondary outcome measures were (1) geometric mean titers (GMT) of HAI titers, (2) percentage of subjects who developed HAI antibody titers ≥1:40 (presumed protective titers), and (3) percentage of subjects who developed seroconversion (4-fold or greater rise in HAI antibody titer to each antigen of TIV) 28 to 42 days after either SD or HD TIV administration.

Statistical Analysis

Descriptive statistics were calculated to determine the median with interquartile range or percentages (frequencies) when appropriate. The HD group was compared with the SD group using the Wilcoxon rank sum test or Pearson chi-square test. For immunogenicity, both years were combined for analysis. GMTs at each study visit were presented with 95% bootstrap confidence intervals. We used logistic regression models to assess the treatment effect on seroconversion and seroprotection with adjustment for IgG and CD19 levels. All tests were 2-tailed with a significance level of .05. Statistical analyses were performed using open source R statistical software (version 3.1.2, Vienna, Austria).

RESULTS

During the 2 influenza study seasons, 44 subjects were enrolled (25 in year 1 and 19 in year 2), with 15 in the SD group and 29 in the HD group. The median time after transplantation was 7.9 months (range, 5.7 to 105.6 months). The median age was 50.1 years (19.6 to 72.8 years), 61.4% were male, and 100% were white. Demographic and clinical characteristics are shown in Table 1. The 2 groups were