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High-dose influenza vaccine favors acute plasmablast responses rather than long-term cellular responses

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ABSTRACT

High-dose (HD) influenza vaccine shows improved relative efficacy against influenza disease compared to standard-dose (SD) vaccine in individuals ⩾65 years. This has been partially credited to superior serological responses, but a comprehensive understanding of cell-mediated immunity (CMI) of HD vaccine remains lacking. In the current study, a total of 105 participants were randomly administered HD or SD vaccine and were evaluated for serological responses. Subsets of the group (n = 12–26 per group) were evaluated for B and T cell responses at days 0, 7, 14 and 28 post-vaccination by flow cytometry or ELISPOT assay. HD vaccine elicited significantly higher hemagglutination inhibition (HI) titers than SD vaccine at d28, but comparable titers at d365 post-vaccination. HD vaccine also elicited higher vaccine-specific plasmablast responses at d7 post-vaccination than SD vaccine. However, long-lived memory B cell induction, cytokine-secreting T cell responses and persistence of serological memory were comparable regardless of vaccine dose. More strategies other than increased Ag amount may be needed to improve CMI in older adults.

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1. Introduction

Adults ⩾65 years of age suffer the most from seasonal influenza-related hospitalizations and death [1,2]. Although influenza vaccination is recommended to reduce disease burden in this population, a steady and systemic degeneration of the immune system with increasing age, termed 'immunosenescence' [3], reduces vaccine effectiveness (VE) [4]. As a strategy to increase immunogenicity of influenza vaccines, FDA approved high-dose (HD) influenza vaccine that contained 4-times (60 μg HA/strain) more hemagglutinin (HA) than the standard-dose (SD) vaccine (15 μg HA/strain) for people aged ⩾65 years in 2009 [5]. This was based on a study in 2006, demonstrating significantly higher antibody (Ab) responses (seroconversion and seroprotection rates) by HD vaccine without an increase in clinically relevant adverse reactions [6]. Subsequently, a large randomized-control trial demonstrated a clinical benefit of HD vaccine in reducing laboratory-confirmed influenza illness by 24.2% [95% confidence interval (CI) 9.7–36.5] as compared to SD vaccine during the 2011–2013 influenza seasons [7]. In addition, a retrospective cohort analysis with US Medicare beneficiary records showed the relative effectiveness of HD vaccine in reducing influenza infections, defined by receipt of rapid influenza test followed by dispensing oseltamivir, and influenza-related hospital care [8]. HD vaccine also significantly reduced cardio-respiratory adverse events associated with influenza-related hospitalization [9]. Therefore, HD influenza vaccine is a more effective alternative to SD vaccines in individuals aged ⩾65 years.

Neutralizing Abs remain the primary target of vaccine development and the standard assessment of immunogenicity for licensure of inactivated influenza vaccines [10]. However, clinical contribution of cell-mediated immunity (CMI) in reducing influenza disease symptoms has been recently demonstrated in healthy adults [11,12]. For individuals aged ⩾65 years in particular, the frequency of IFNγ-secreting T cells, rather than HI titers, correlates better with clinical protection following vaccination [13,14]. Many studies have shown that HD vaccine elicits superior HI titers [6,7,15], but whether HD vaccine elicits superior CMI is unknown. Therefore, a comprehensive understanding of the scope of

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immunogenicity conferred by HD vaccines, encompassing humoral and cellular immunity, is important for the evaluation of the clinical benefits of existing HD vaccines and the development of better influenza vaccines for older adults. This study represents the first comprehensive evaluation of the induction of vaccine-specific, cytokine-secreting CD4 or CD8 T cell responses as well as B cell responses of healthy volunteers aged ⩾65 years receiving HD or SD influenza vaccines.

2. Material and methods

2.1. Study design, participants and specimens

A total of 105 community-dwelling adults (SD, $n = 52$ and HD, $n = 53$) ⩾65 years were enrolled, prior to the 2010–11 influenza season in Nashville, TN. Participants were not excluded due to any medical conditions except for prior allergic reaction to influenza vaccine or a history of Guillain-Barré syndrome. Written informed consent was received from study participants, who were then randomized to receive either SD or HD vaccine by intramuscular injection. Vaccine allocation was blinded to participants and researchers except for a designated un-blinded nurse who performed vaccination. All further steps including sample preparation, data analyses and evaluation were performed by blinded staff members and researchers. Peripheral blood mononuclear cells (PBMCs) were collected at days 0, 7, 14 and 28 post-vaccination and stored at −80 °C until shipment to CDC for CMI analysis. Serum samples were collected at days 0, 28 and 365 post-vaccination and stored at −80 °C until shipment to Battelle (Columbus, OH) for HI assay. Procedures, informed consent documents and data collection forms were reviewed and approved by the Institutional Review Boards at Vanderbilt University and Centers for Disease Control and Prevention.

2.2. Influenza virus and vaccines

Influenza viruses, A/California/08/2009 (H1N1) and A/Perth/16/2009 (H3N2), were propagated for 2 days in the allantoic cavity of 10–11 days old embryonated chicken eggs (Hy-line, Mansfield, GA) and clarified by centrifugation. Pooled allantoic fluid was used for stimulation of PBMCs, as previously described [16]. Influenza vaccines (Sanofi Pasteur) contained 2010–11 trivalent inactivated influenza viruses; A/California/7/2009 (H1N1), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008.

2.3. Hemagglutinin inhibition (HI) assay

HI assay was performed in duplicate against the influenza vaccine strains in the 2010–11 Northern Hemisphere influenza vaccine components according to the standardized protocol by the world health organization [17]. Seroprotection was defined as an HI titer of ⩾40; seroconversion was defined as a four-fold rise in HI titers at post-influenza vaccination compared to pre-vaccination, or ⩾40 if pre-vaccination titer was <10.

2.4. Assessment of CMI

CMI was assessed using PBMCs collected at days 0, 7, 14 and 28 days post-vaccination as previously described [16]. Level of activated, cytokine-expressing T cells was expressed as %cytokine/total $CD4^+CD69^+$ or $CD8^+CD69^+$ T cells. The limit of detection was 0.05%.

2.5. Assessment of B cell responses

Frequencies of plasmablasts ($CD3^-CD20^-CD38^{hi}CD27^{hi}$) and memory B cell subsets (class switched memory B cells: $CD20^+IgD^-CD27^+$ and IgM memory B cells:$CD20^+IgD^+CD27^+$) were measured by flow cytometry using paired d0 and d7 PBMCs. Activation status of memory B cells was simultaneously evaluated by flow cytometry and shown as mean fluorescence intensity (MFI) of cell surface markers CD69, CD86 or cells expressing $CD69^{hi}$ or $CD86^{hi}$. Vaccine-specific plasmablasts (antibody-secreting cells) were measured *ex vivo* by ELISPOT as described [16] without *in vitro* stimulation. Induction of long-lived memory B cells were measured by ELISPOT as described [16].

2.6. Statistical analysis

Calculation of $\log_2$-transformed HI titers for geometric mean titers (GMT), $\log_{10}$-transformed percentages (B and T cell responses), and antigen-specific B cells (ELISPOT) for geometric mean percentage (GMP) have been described [16]. Cell-surface activation markers were calculated as geometric mean value (GMV). Means and differences in means were estimated using repeated measures linear mixed models [18,19]. Back-transforming model-estimated means yielded GMT/GMP/GMV and back-transforming differences between days at post-vaccination and day 0 means yielded GMT/GMP/GMV fold-rises. Fold-rise >1 indicates significant induction of vaccine responses. HD/SD ratios were calculated from estimated GMT/GMP/GMV of HD or SD vaccine at each time point to determine if the HD vaccine induced greater responses than SD vaccine. HD/SD >1 indicates that HD vaccine induces significantly higher responses than SD vaccine. Chi-square tests or Wilcoxon rank-sum tests were performed appropriately for comparisons between treatment groups and categorical or continuous variables respectively. Serological responses at d28 post-vaccination were evaluated using logistic regression models. Multiple linear regression models were conducted using post-vaccination CMI as outcome and age, vaccine dose, and pre-existing CMI level as covariates. Comparison between stimulated (A/Cal(H1) or A/Perth(H3)) vs. unstimulated cells shown in Table 2 was analyzed by paired *t*-test. All analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC) and R version 3.1.3 (www.cran.r-project.org).

3. Results

3.1. Study participants characteristics

A total of 105 participants were randomly grouped into SD ($n = 52$) and HD ($n = 53$) groups (Supplemental Fig. 1). Demographic information was comparable between the two groups (Supplemental Table 1). Subjects selected for CMI assessment (26 HD and 22 SD) were also similar in age with a mean age (± standard deviation) of 72.9 years ± 6.4 (HD) and 72.7 years ± 6.6 (SD), high-risk medical conditions and body mass index. The HD group had 13 samples from females (50%) and SD had 8 (36%) ($p = 0.34$).

3.2. Summary of serological responses

Both vaccine groups induced geometric mean titer (GMT) fold-rise >1 at days 28 and 365 post-vaccination for all vaccine components (Fig. 1A, Supplemental Fig. 2A). HD vaccine elicited significantly higher Ab responses than SD vaccine at d28 post-vaccination, as shown by seroconversion and seroprotection rates (Supplemental Table 2) and the HD/SD ratio > 1 for all vaccine components (Fig. 1B). At d365 post-vaccination, Ab responses were comparable between the two groups (Fig. 1B). Significant cross-reactive responses against H3 and B strains of the prior (2009–10) influenza vaccine were also induced in both vaccine

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