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Safety and immunogenicity of high-dose trivalent inactivated influenza vaccine in adults 50–64 years of age

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ABSTRACT

Background: Individuals 50–64 years of age have reduced immune responses to influenza vaccines. The current study examined whether a high-dose inactivated trivalent influenza vaccine (IIV3-HD) might improve immune responses over a standard-dose inactivated influenza vaccine (IIV3-SD) in this age group.

Methods: This was a multicenter, observer-blinded, randomized, active-controlled phase II trial. Adults 50–64 years of age were randomized 1:1 to receive IIV3-HD or IIV3-SD. Hemagglutination inhibition titers were measured before and 28 days after vaccination. Reactogenicity was recorded for 7 days after vaccination and adverse events for 28 days.

Results: 148 participants received IIV3-HD and 152 received IIV3-SD. For all vaccine strains, day 28 geometric mean hemagglutination inhibition titers were significantly higher in the IIV3-HD group than in the IIV3-SD group (geometric mean titer ratio [95% confidence interval (CI)] = 1.43 [1.04–1.97] for A/H1N1, 1.65 [1.21–2.25] for A/H3N2, and 1.60 [1.23–2.08] for B). Seroconversion rates were significantly higher in the IIV3-HD group than in the IIV3-SD group for strains A/H3N2 and B but not A/H1N1 (difference [95% CI] = 13.5% [4.76–22.0] for A/H3N2, 23.1% [11.7–33.6] for B, and −0.2% [−9.66 to 9.18] for A/H1N1). The post-vaccination seroprotection rate was significantly higher in the IIV3-HD group than in the IIV3-SD group for strain B but not for strains A/H1N1 or A/H3N2 (difference = 9.1% [2.95–15.7] for B, 2.0% [−0.907 to 5.68] for A/H1N1, and 0.6% [−3.14 to 4.43] for A/H3N2). Reactogenicity was higher in the IIV3-HD group than in the IIV3-SD group, but reactions were mostly of low intensity, transient, and self-limited. Rates of unsolicited adverse events were similar between groups. No serious AEs, AEs leading to early withdrawal, or deaths were reported.

Conclusions: The study suggests that in adults 50–64 years of age, IIV3-HD may improve immunogenicity compared to IIV3-SD while maintaining an acceptable safety profile.

Abbreviations: AE, adverse event; CI, confidence interval; GMT, geometric mean titer; HA, hemagglutinin; HAI, hemagglutination inhibition; IIV3, trivalent inactivated influenza vaccine; IIV3-HD, high-dose trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; SAE, serious adverse event.

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1. Introduction

Persons ≥50 years of age are at increased risk for serious complications of influenza, such as pneumonia, exacerbation of chronic heart or lung disease, and death [1,2]. However, vaccine efficacy and antibody responses are substantially reduced in older adults due to immunosenescence [3]. This loss in immune response is well established for adults ≥65 years of age, but immune responses to influenza vaccination are also weaker in adults 50–64 years [4–6].

Increasing the dose of hemagglutinin (HA)[3] per vaccine strain is one approach for improving the immune response in older adults [3]. A high-dose trivalent inactivated influenza vaccine (IIV3-HD) has been licensed in the US for persons aged ≥65 years based on its ability to induce a stronger immune response than a standard-dose trivalent inactivated influenza vaccine (IIV3-SD) in this population [7–10]. IIV3-HD contains 60 μg HA per viral strain, a 4-fold increase over IIV3-SD. A recent phase IIIb/IV study in more than 30,000 participants confirmed that in persons ≥65 years, IIV3-HD induced superior antibody responses and provided better protection against laboratory-confirmed influenza illness than IIV3-SD [11]. However, whether the IIV3-HD might also provide improved protection in persons 50–64 years of age has not been established. In this article, we describe the results of a phase II study investigating the safety and immunogenicity of the IIV3-HD compared to IIV3-SD in adults 50–64 years of age.

2. Methods

2.1. Study design and ethics

This was a multicenter, modified double-blind (observer blinded), randomized, active-controlled phase II trial in adults 50–64 years of age (ClinicalTrials.gov no. NCT01258595). The study was conducted at four centers in the United States between November 15, 2010 and January 14, 2011. The objective of the study was to describe the immunogenicity and safety of IIV3-HD compared to IIV3-SD. The study was approved by a central institutional review board (Quorum Review) and was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines for Good Clinical Practice, and local and national laws. All participants provided written informed consent.

2.2. Participants

Medically stable adults 50–64 years of age were considered for enrollment. Participants were excluded if they had received a seasonal or pandemic influenza vaccine in the past 6 months; received blood or blood-derived products in the previous 3 months; received or planned to receive any vaccine before or after 4 weeks of trial vaccination; participated in another clinical trial investigating a vaccine, drug, medical device, or medical procedure in the 4 weeks preceding the trial vaccination; a known or suspected congenital or acquired immunodeficiency; received immunosuppressive therapy within the previous 6 months; a neoplastic disease or any hematologic malignancy; a bleeding disorder or receipt of anticoagulants in the previous 3 weeks; a history of Guillain-Barré syndrome; a systemic hypersensitivity to eggs, chicken proteins, or any of the vaccine components; a history of a life-threatening reaction to the IIV3-SD or to a vaccine containing any of the same substances; or were seropositive for human immunodeficiency virus, hepatitis B, or hepatitis C. Women could not be pregnant or breastfeeding.

2.3. Study conduct

Participants were randomized 1:1 to receive a single intramuscular injection of the 2010–2011 Northern Hemisphere formulation of IIV3-HD (Fluzone® High-Dose) or IIV3-SD (Fluzone) into the deltoid area. Both vaccines were manufactured by Sanofi Pasteur (Swiftwater, PA, USA) and contained the A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (B) strains. To insure adequate representation of the older age group, recruitment was stratified to enroll participants 50–59 and 60–64 years of age in a 2:1 ratio. Randomization and allocation were concealed via an interactive voice response system, which supplied a centralized, stratified, randomization code. The participants, investigators, study site personnel, and clinical team members involved in the trial were blinded to the vaccines administered, with the exception of unblinded qualified study staff members who administered the vaccines and the corresponding site monitors. The unblinded qualified study staff did not participate in the collection of safety data. Blood was collected at randomization and at the second visit (day 28, allowed range, days 28–35).

2.4. Study endpoints

Immunogenicity endpoints included the geometric mean hemagglutination inhibition (HAI) titer (GMT) on day 0 and 28; day 28/day 0 GMT ratio; and seroconversion and seroprotection rates for each treatment group. Seroprotection was defined as an HAI titer ≥40 and seroconversion was defined as either (i) a pre-vaccination HAI titer <10 and a post-vaccination HAI titer ≥40 or (ii) a pre-vaccination HAI titer ≥10 and a ≥4-fold increase in HAI titer at day 28. HAI assays were performed as previously described [12] by personnel blinded to vaccine assignment. The HAI titer was the reciprocal of the highest dilution resulting in complete inhibition of hemagglutination. The lower limit of quantitation for the assay was a titer of 10. Samples with titers below the lower limit of quantitation were assigned a titer of 5, and samples with titers above the upper limit of quantitation (10,240) were assigned a titer of 10,240.

Safety endpoints included the occurrence, nature, duration, intensity, action taken, and relationship to vaccination of any immediate unsolicited systemic adverse event (AE), solicited reaction, unsolicited AE, or serious adverse events (SAE). AEs and SAEs were recorded according to International Conference on Harmonisation Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting and were coded using MedDRA version 13.0 (MedDRA MSSO, McLean, VA, USA). Solicited systemic reactions (fever, headache, malaise, myalgia, and shivering) and solicited injection-site reactions (pain, erythema, swelling, induration, and ecchymosis) were recorded by participants on diary cards for 7 days following vaccination. Other non-serious unsolicited AEs were recorded by patients for 28 days after vaccination. SAEs were recorded by investigators for 28 days after vaccination. AEs of special interest were reported and analyzed as SAEs and included new onset of Guillain-Barré syndrome, Bell's palsy, encephalitis/myelitis, optic neuritis, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Immediate AEs were defined as AEs occurring within 30 min after vaccination.

2.5. Statistical analysis

All calculations were performed using SAS version 9.1 (SAS Institute, Cary, NC). Missing data were not replaced. As this was a pilot study, sample size was not based on power calculations but rather was arbitrarily selected to provide initial estimates of immunogenicity and safety.