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Immunogenicity and safety of Fluzone® intradermal and high-dose influenza vaccines in older adults ≥65 years of age: A randomized, controlled, phase II trial☆

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ABSTRACT

We conducted a randomized, controlled, multicenter, phase II study to evaluate the immunogenicity and safety of an investigational intradermal (ID) trivalent influenza vaccine (TIV) and a high-dose (HD) intramuscular (IM) TIV in older adults (≥65 years of age). Older adult subjects were immunized with ID vaccine containing either 15 μg hemagglutinin (HA)/strain (n = 636) or 21 μg HA/strain (n = 634), with HD IM vaccine containing 60 μg HA/strain (n = 320), or with standard-dose (SD) IM vaccine (Fluzone®; 15 μg HA/strain; n = 319). For comparison, younger adults (18–49 years of age) were immunized with SD IM vaccine. In older adults, post-vaccination geometric mean titers induced by the ID vaccines were superior to those induced by the SD IM vaccine for the A/H1N1 and A/H3N2 strains and non-inferior for the B strain. Seroconversion rates induced by the ID vaccines were superior to those induced by the SD IM vaccine in older adults for the A/H1N1 and B strains and non-inferior for the A/H3N2 strain. Results did not differ significantly for the two ID vaccine dosages. Post-vaccination geometric mean titers, seroconversion rates, and most seroprotection rates were significantly higher in HD vaccine recipients than in older adult recipients of the SD IM or ID vaccines and, for most measures, were comparable to those of younger adult SD IM vaccine recipients. Injection-site reactions, but not systemic reactions or unsolicited adverse events, were more common with the ID vaccines than with the IM vaccines. No treatment-related serious adverse events were reported. This study demonstrated that: (1) the ID and HD vaccines were well-tolerated and more immunogenic than the SD IM vaccine in older adults; (2) the HD vaccine was more immunogenic than the ID vaccines in older adults; and (3) the HD vaccine in older adults and the SD IM vaccine in younger adults elicited comparable antibody responses (ClinicalTrials.gov identifier no.: NCT00551031).

1. Introduction

Despite progressive increases in seasonal influenza vaccine coverage, influenza-related morbidity, mortality, and hospitalization rates remain high and have continued to increase in older adults (≥65 years of age) [1]. Up to 90% of all annual influenza-related deaths occur in the older adults [2], whose aging immune systems respond weakly to vaccines and are less able to combat infection [1,3–5]. Consequently, more effective vaccines are needed to prevent influenza in older adults.

Intradermal (ID) vaccines are an alternative to intramuscular (IM) vaccines that may offer improved immunogenicity in older adults [6]. ID vaccination exploits the numerous

Abbreviations: AE, adverse event; CI, confidence interval; GMT, geometric mean titer; HA, hemagglutinin; HI, hemagglutination inhibition; HD, high-dose inactivated trivalent influenza vaccine (60 μg HA/strain) for the intramuscular route; ID, intradermal; IM, intramuscular; SD, standard-dose inactivated trivalent influenza vaccine (15 μg HA/strain) for the intramuscular route.

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antigen-presenting dendritic cells, macrophages, and T-cells present in the skin as well as its dense network of lymphatic and blood vessels [7–9]. These features enable strong innate and adaptive immune responses to be generated following ID exposure to vaccine antigens [10,11]. In addition, new microinjection systems have made routine ID vaccine administration feasible [7,12]. Fluzone® Intradermal (Sanofi Pasteur, Swiftwater, PA) is an inactivated split-virion trivalent influenza vaccine (TIV) that is delivered with the BD Soluvia™ microinjection system (BD, Franklin Lakes, NJ) and licensed in the US for use in adults 18–64 years of age. A phase II study in this age group showed that the 9 μg formulation (9 μg hemagglutinin [HA]/strain) of this vaccine induced non-inferior immune responses compared to the standard 15 μg formulation of Fluzone TIV delivered by the IM route [13]. The immunogenicity and safety of ID influenza vaccine in older adults (≥65 years old) in the US has not been previously established. However, in Europe, phase II and III studies with Intanza®/IDflu® (Sanofi Pasteur, Lyon, France), a similar ID TIV licensed in Europe and also administered with the BD Soluvia microinjection system, indicated superior immunogenicity of the 15 and 21 μg formulations compared to the standard 15 μg formulation of TIV (Vaxigrip®) delivered by the IM route in adults ≥60 years of age [14,15].

Increasing the HA dose in IM vaccines is another approach to improve vaccine-induced immune responses. In the US, standard-dose TIV for the IM route (SD) contains 15 μg HA per strain for all persons at least 36 months of age [16]. In 2009, the US Food & Drug Administration approved a high-dose TIV for the IM route (HD) that contains 60 μg HA per strain (Fluzone® High-Dose, Sanofi Pasteur, Swiftwater, PA) [17]. This HD vaccine was licensed in older adults based on the results of a phase III clinical trial in which it induced geometric mean antibody titers (GMTs) and seroconversion rates superior to those of the SD vaccine [18]. However, whether the HD vaccine in older adults can elicit responses similar to those induced by the SD vaccine in younger adults has not been determined.

Here, we report the results of a phase II study conducted in the US during the 2007/2008 influenza season to assess the safety, immunogenicity, and acceptability of 15 and 21 μg formulations of ID vaccine and of HD IM vaccine in older adults compared to SD IM vaccine in older and younger adults.

2. Materials and methods

2.1. Study design

This study was a phase II, multicenter, five-arm, randomized, controlled trial examining the safety, immunogenicity, and acceptability of two investigational ID vaccines (15 and 21 μg HA/dose), HD vaccine (60 μg HA/dose), and SD vaccine (15 μg HA/dose) in older adults (≥65 years of age) compared to SD vaccine in younger adults (18–49 years of age) (ClinicalTrials.gov ID: NCT00551031). The four study arms in older adult subjects were double-blinded for dose but open-label for vaccination route, whereas the fifth arm in younger adults was open-label. The primary objectives of the study were to demonstrate that the GMTs and seroconversion rates of each ID vaccine in older adults were: (i) non-inferior to those of the SD vaccine in older adults for each immunizing strain and (ii) superior to those of the SD vaccine for at least two of the three strains once non-inferiority was demonstrated. The secondary objectives of the study were to describe: (i) the post-vaccination seroconversion rates and GMTs of older adult HD vaccine recipients compared to those of younger adult SD vaccine recipients; (ii) the seroprotection rates of all groups; and (iii) the safety profiles of the vaccines in all groups.

The study was performed at 31 centers in the US between October 24, 2007 and June 2, 2008. The study was approved by a central institutional review board and five local institutional review boards and was conducted in accordance with the Edinburgh revision of the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice and Good Laboratory Practice guidelines. All subjects provided written informed consent before being enrolled in the trial.

2.2. Subjects

Subjects were medically stable, ambulatory, older adults (≥65 years of age) or younger adults (18–49 years of age). Women could not be pregnant or breastfeeding and if of child-bearing potential had to be using an effective method of contraception within 4 weeks before and after vaccination. Subjects were excluded if they had any of the following: known sensitivity to any of the vaccine components or to influenza vaccine; vaccinated against influenza within 6 months or any other vaccination within 4 weeks; history of Guillain-Barré syndrome; known or suspected immunodeficiency; immunosuppressive therapy within 6 months or long-term systemic corticosteroid therapy for more than 2 consecutive weeks within 3 months; bleeding disorder or received anticoagulants within 3 weeks; seropositive for human immunodeficiency virus, hepatitis B, or hepatitis C; received blood or blood-derived products within 3 months; or any other disease, condition, or treatment that might, in the opinion of the investigator, interfere with the assessment of immune responses or blood sample collection.

Target enrollment in older adult subjects was 600 for each of the ID vaccine groups, 300 for the SD vaccine group, and 300 for the HD vaccine group. Target enrollment for the younger adult SD group was 150. Assuming a drop-out rate of 5% and based on data from similar studies comparing ID and IM TIVs [14,15], at $\alpha = 0.05$, the power to meet the primary objectives for the 15 μg ID vaccine was 95.2% for the H1N1 strain, 98.6% for the H3N2 strain, and 71.6% for the B strain, and for the 21 μg ID vaccine, was >99.9% for each of the three strains. With these enrollment targets, safety events that occurred in 2% of 150 subjects, 1% of 300 subjects, and in 0.5% of 600 subjects were detectable with a probability of 0.95.

2.3. Vaccines

All vaccines were formulated as recommended by the US Food and Drug Administration for the 2007/2008 influenza season and contained the A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 strains. The investigational ID vaccines were manufactured by Sanofi Pasteur (Swiftwater, PA) and contained either 15 μg (batch UD09995) or 21 μg (batch UD09996) of HA per strain in 0.1 mL in a prefilled BD Soluvia microinjection device bearing a staked 30-gauge, 1.5 mm intradermal needle. The HD vaccine (Sanofi Pasteur, Swiftwater, PA; batch UD09997) contained 60 μg of HA per strain and the SD vaccine (Fluzone®, Sanofi Pasteur, Swiftwater, PA; older adults, batch UD10002; adults, batch UD09999) contained 15 μg of HA per strain in ready-to-use 0.5-mL syringes and were delivered by the IM route.

2.4. Treatments

Older adult subjects (≥65 years of age) were randomized 2:2:1:1 using an interactive computer system to receive a single dose of the 15 μg ID vaccine, the 21 μg ID vaccine, HD vaccine, or SD vaccine. All younger adult subjects were assigned to receive the SD vaccine. All vaccines were administered into the deltoid area of the upper arm.

2.5. Immunogenicity

Blood samples were collected before vaccination (day 0) and 28 days after vaccination. Hemagglutination inhibition (HI) titers

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