Vaccine 31 (2013) 770–776

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety and immunogenicity of a quadrivalent inactivated influenza vaccine compared to licensed trivalent inactivated influenza vaccines in adults☆,☆☆

David P. Greenberg[a,*], Corwin A. Robertson[a], Michael J. Noss[b], Mark M. Blatter[c], Rex Biedenbender[d], Michael D. Decker[a]

[a] Sanofi Pasteur, Discovery Drive, Swiftwater, PA 18370, USA
[b] Radiant Research, 11500 Northlake Drive, Cincinnati, OH 45249, USA
[c] Primary Physicians Research, 1580 McLaughlin Run Road, Pittsburgh, PA 15241, USA
[d] Eastern Virginia Medical School, 825 Fairfax Avenue, Hafheimer Hall Suite 201, Norfolk, VA 23507, USA

ARTICLE INFO

Article history:
Received 25 June 2012
Accepted 27 November 2012
Available online 8 December 2012

Keywords:
Influenza vaccine
Quadrivalent
Immunogenicity
Safety
Adults
United States

ABSTRACT

Purpose: To evaluate the safety and immunogenicity of a prototype quadrivalent inactivated influenza vaccine (QIV) containing two influenza B strains, one of each lineage, compared with licensed trivalent inactivated influenza vaccines (TIVs) containing either a Victoria B-lineage strain (2009–2010 TIV) or a Yamagata B-lineage strain (2008–2009 TIV).
Methods: Healthy adults ≥18 years of age were eligible to participate in this phase II, open-label, randomized, controlled, multicenter study conducted in the US. Participants received a single dose of 2009–2010 TIV, 2008–2009 TIV, or QIV. Sera were collected before and 21 days after vaccine administration to test for hemagglutination inhibition (HAI) antibodies to each of the four influenza strains. Immunogenicity endpoints included geometric mean HAI antibody titers (GMTs) and rates of seroprotection (titer ≥1:40) and seroconversion (4-fold rise pre- to post-vaccination). Safety endpoints included frequency of solicited injection-site and systemic reactions occurring within 3 days of vaccination, and unsolicited non-serious adverse events (AEs) and serious AEs (SAEs) within 21 days of vaccination.
Results: One hundred and ninety participants were enrolled to each vaccine group. QIV induced GMTs to each A and B strain that were noninferior to those induced by the 2009–2010 and 2008–2009 TIVs (i.e., lower limit of the two-sided 95% confidence interval of the ratio of $GMT_{QIV}/GMT_{TIV} > 0.66$ for each strain). Rates of seroprotection and seroconversion were similar in all groups. Incidence and severity of solicited injection-site and systemic reactions, AEs, and SAEs were similar among groups.
Conclusion: QIV, containing two B strains (one from each B lineage), was as safe and immunogenic as licensed TIV. QIV has the potential to be a useful alternative to TIV and offer protection against both B lineages.

1. Introduction

Beginning with the 2010–2011 influenza season, the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) expanded their annual influenza vaccine recommendations to include all persons ≥6 months of age [1]. Most vaccinated children and healthy adults develop high post-vaccination titers of hemagglutination inhibition (HAI) antibodies. With a good match between vaccine and circulating strains, influenza vaccine has been shown to prevent illness in 70–90% of healthy persons <65 years of age and to be 30–70% effective in preventing hospitalization among community-based elderly [1]. Persons who are ≥65 years of age generally develop lower post-vaccination antibody titers than healthy young adults and thus may be more susceptible to influenza infection [2–4]. Nevertheless, influenza vaccine has been shown to be 50–60% effective in preventing hospitalization, pneumonia, and other secondary complications, and 80% effective in preventing death in this population [1,2,5–7]. New influenza vaccines have been licensed or are under development to induce higher immune responses and offer improved protection among older adults [8,9].

☆ NCT ID: NCT00988143.
☆☆ *Prior presentations*: Presented in part at the 48th Annual Meeting of the Infectious Diseases Society of America (IDSA), Abstract 870, Vancouver, Canada, October 21–24, 2010, and IDSA's Seasonal and Pandemic Influenza 2011, Abstract 13, Arlington, VA, January 27–28, 2011.

* Corresponding author at: Sanofi Pasteur, Discovery Drive, Swiftwater, PA 18370, USA. Tel.: +1 570 957 3289; fax: +1 570 957 2038.
E-mail addresses: David.Greenberg@sanofipasteur.com (D.P. Greenberg), corey.robertson@sanofipasteur.com (C.A. Robertson), michaelnoss@radiantresearch.com (M.J. Noss), mmbppr@gmail.com (M.M. Blatter), rexbiedenbender@aol.com (R. Biedenbender), michael.decker@sanofipasteur.com (M.D. Decker).

0264-410X/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2012.11.074

Vaccine effectiveness also depends on the similarity between the virus strains present in the vaccine and those circulating in the community. Trivalent influenza vaccines (TIVs) are traditionally composed of one A/H1N1 strain, one A/H3N2 strain, and one B strain, each chosen to provide protection against the strains anticipated to circulate during the upcoming influenza season. For over a decade, two distinct lineages of influenza B (the Victoria and Yamagata lineages) have circulated worldwide, neither providing good cross-protection against the other [10]. Unfortunately, the ability to predict with acceptable accuracy which B lineage will be dominant in an upcoming season has been unsatisfactory, with frequent mismatches. Consequently, the possibility of including both B lineages in seasonal influenza vaccines has been discussed by the Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee and others for some years [11].

The purpose of this study was to evaluate the safety and immunogenicity in adults of a prototype quadrivalent influenza vaccine (QIV) containing two influenza B strains, one from each lineage. The TIV formulations recommended for 2008–2009 and 2009–2010 seasons were identical with respect to their influenza A/H1N1 and A/H3N2 strains, but differed in their B-strain lineages, offering an ideal opportunity to evaluate a QIV that incorporated both lineages of influenza B compared to the respective licensed 2008–2009 and 2009–2010 TIVs.

2. Participants and methods

This was a phase II, open-label, randomized, controlled, multicenter study conducted in the United States (NCT ID: NCT00988143) from October 2009 through December 2009, in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol and informed consent forms were reviewed and approved by the appropriate Institutional Review Board for each study site. Written informed consent was obtained from each participant prior to initiation of any study-specific procedures. The manuscript was prepared following guidelines established by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

2.1. Participants

At study entry, participants were ≥18 years of age and judged to be in good health. Key exclusion criteria included history of allergy to egg, chicken proteins, or other vaccine components; history of serious adverse reaction to any influenza vaccine; confirmed influenza infection or vaccination against influenza in the 6 months preceding enrollment; history of Guillain-Barré syndrome; immunocompromising condition or immunosuppressive therapy within 6 months preceding enrollment; pregnancy or breast feeding; acute illness with or without fever in the 72 h preceding enrollment; receipt of any vaccine within the preceding 14 days; or receipt of blood or blood products within the 3 months preceding enrollment.

2.2. Vaccines

Each study vaccine was manufactured by Sanofi Pasteur (Swiftwater, PA, USA), provided in liquid form, and contained no preservative.

All study vaccines contained 15 μg hemagglutinin (HA) each of the same two A strains per 0.5-mL dose: A/Brisbane/59/2007 (H1N1) and A/Uruguay/716/2007 (H3N2; an A/Brisbane/10/2007-like virus). However, their composition differed with respect to the B strains: investigational QIV (lot# UD12581) contained 15 μg HA each of B/Brisbane/60/2008 (Victoria lineage) and B/Florida/04/2006 (Yamagata lineage), the 2009–2010 TIV (lot# U3190AA) contained 15 μg HA B/Brisbane/60/2008 (Victoria lineage), and the 2008–2009 TIV (lot# U2853AB) contained 15 μg HA of B/Florida/04/2006 (Yamagata lineage) per 0.5-mL dose.

2.3. Study design

Eligible participants were randomly assigned to vaccination with 2009–2010 TIV (group 1), 2008–2009 TIV (group 2), or QIV (group 3). Randomization was performed using an interactive voice response system. Each participant received a single 0.5-mL dose of assigned vaccine administered intramuscularly into the deltoid at Visit 1 using a needle length appropriate (as determined by the investigator) for the size and weight of the participant. Sera for immunogenicity testing were obtained immediately prior to vaccine administration and at 21 (window, 21 to 28) days post-vaccination. (An additional study group of pediatric subjects received 2009–2010 TIV and is not further reported herein.)

2.4. Endpoints

The primary immunogenicity endpoints were the post-vaccination HAI antibody titers to each influenza strain expressed as pre- and post-vaccination geometric mean antibody titers (GMTs), individual post- to pre-vaccination GMT ratios (GMTRs), and rates of seroprotection and seroconversion post-vaccination across treatment groups. Seroprotection was defined as an HAI titer ≥1:40. Seroconversion was defined as either a pre-vaccination titer <1:10 and a post-vaccination titer ≥1:40, or a pre-vaccination titer ≥1:10 and a ≥4-fold increase in post-vaccination titer.

Safety endpoints included the frequency of solicited injection-site and systemic reactions occurring within 3 days after vaccination. Unsolicited adverse events (AEs), including serious AEs (SAEs), were collected for 21 (window, 21 to 28) days post-vaccination.

2.5. Serologic evaluations

A validated HAI assay was used to quantify antibody titers against study vaccine antigens. The assay utilized turkey red blood cells (RBCs) and a serum-virus incubation temperature of 37 °C to provide optimal sensitivity and specificity for the vaccine antigens. Assays were performed by Sanofi Pasteur personnel who were blinded to vaccine assignment.

Control and participant sera were incubated with type III neuraminidase to eliminate non-specific inhibitors. Spontaneous anti-species agglutinins were adsorbed by incubating the sera with a suspension of turkey RBCs. Ten two-fold dilutions (starting at 1:10) of the treated sera were incubated with a previously titrated influenza virus solution at a concentration of 4 hemagglutination units/25 μL. Following incubation, the results of the assay were read, with the endpoint being the highest serum dilution in which complete inhibition of hemagglutination occurred. Each serum sample was tested in duplicate.

2.6. Statistical analysis

The sample size was chosen to provide adequate power to test the primary hypotheses based on the criteria for the primary endpoints, the expected responses, and a possible attrition rate of up to 11%. The goal was to enroll 570 participants (190 per vaccine group) with approximately half of the enrollees 18 through 60 years of age and half ≥61 years of age. With an evaluable sample size of 504 participants (168 per vaccine group), the overall power to achieve the primary hypotheses was estimated to be 80.2%.

The primary hypotheses tested were that the post-vaccination HAI GMT for strain B/Brisbane/60/2008 (Victoria lineage;