Vaccine 31 (2013) 5572–5578

Contents lists available at ScienceDirect

Vaccine

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

Safety and immunogenicity of a quadrivalent inactivated influenza vaccine in adults

Stéphanie Pépin[a,*], Yves Donazzolo[b], Alen Jambrecina[c], Camille Salamand[a], Melanie Saville[a]

[a] Sanofi Pasteur, Lyon, France
[b] Eurofins Optimed, Gières, France
[c] Clinical Trial Center North, MediGate GmbH, Hamburg, Germany

ARTICLE INFO

Article history:
Received 27 May 2013
Received in revised form 7 August 2013
Accepted 19 August 2013
Available online 7 September 2013

Keywords:
Influenza
Vaccine
Quadrivalent
Trivalent
Immunogenicity
Safety

ABSTRACT

Background and aims: Although two antigenically distinct B strain lineages of influenza have co-circulated globally since the mid-1980s, trivalent influenza vaccines (TIVs) contain only one, resulting in frequent mismatches. This study examined the safety and immunogenicity of an inactivated quadrivalent influenza vaccine (QIV) candidate.
Methods: This was a phase III, randomized, active-controlled, multicenter trial in adults during the 2011/2012 influenza season. Enrollment was stratified to include equal numbers of subjects 18–60 and >60 years of age. Subjects were randomized 5:1:1 to be vaccinated with the QIV, the licensed TIV, or an investigational TIV containing the alternate B strain lineage. Hemagglutinin inhibition antibody titers were assessed pre-vaccination and 21 days post-vaccination.
Results: 1116 subjects were vaccinated with QIV, 226 with the licensed TIV, and 223 with the investigational TIV. For all four vaccine strains, antibody responses to the QIV were non-inferior to the response to the TIV for the matched strains. For both B strains, post-vaccination antibody responses to the QIV were superior to the responses to the TIVs lacking the corresponding B strain. The QIV met all European Medicines Agency criteria for all four vaccine strains. Solicited reactions, unsolicited adverse events, and serious adverse events were similar for the QIV and pooled TIV groups. The most commonly reported solicited reactions were injection-site pain, headache, and myalgia, and most solicited reactions were mild or moderate and appeared and resolved within 3 days of vaccination. No treatment-related serious adverse events or deaths were reported.
Conclusions: The inactivated QIV was well tolerated without any safety concerns. For all four vaccine strains, antibody responses to the QIV were superior to the responses to TIV for the unmatched strains and non-inferior for the matched strains. QIV could therefore help address an unmet need due to mismatched B strains in previous influenza vaccines.
Clinical trial registry number: EudraCT: 2011-001976-21.

1. Introduction

Since the 1970s, influenza vaccines have been trivalent and have included two A strains (H1N1 and H3N2) and one B strain lineage, even though since the mid-1980s, two antigenically distinct B strain lineages, Yamagata and Victoria, have co-circulated globally [1,2]. The result has been mismatches between the circulating and vaccine B strains in about half of the years over the last decade [3] and therefore missed opportunities for prevention [4]. In fact, a systematic analysis of clinical trials of live attenuated influenza vaccines found that efficacy in children was 86% against closely matched B strains but only 31% against opposite B lineage strains [5]. Due to increases in vaccine production capacity [6], quadrivalent influenza vaccines (QIVs)[1] including A/H1N1, A/H3N2, B Yamagata, and B Victoria strains are now becoming available [7]. These vaccines are

* Corresponding author at: Sanofi Pasteur, 1541 avenue Marcel Merieux, 69280 Marcy l'Etoile, France. Tel.: +33 (0)4 37 37 58 50; fax: +33 (0)4 37 37 78 88.
E-mail address: stephanie.pepin@sanofipasteur.com (S. Pépin).

[1] AE, adverse event; CI, confidence interval; EMA, European Medicines Agency; GMT, geometric mean titer; HAI, hemagglutination inhibition; LAIV, live attenuated influenza vaccine; QIV, quadrivalent influenza vaccine; Q/LAIV, quadrivalent live attenuated influenza vaccine; SAE, serious adverse event; TIV, trivalent influenza vaccine.

0264-410X/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2013.08.069

expected to substantially reduce illness and hospitalizations due to seasonal influenza [8,9].

An open-label phase II trial showed that a prototype inactivated QIV was safe and as immunogenic as a licensed inactivated trivalent influenza vaccine (TIV) in adults [10]. Here, we describe the results of a phase III trial during the 2011/2012 influenza season assessing this candidate inactivated QIV in healthy adults. The primary objective of this study was to show that, for all vaccine strains, antibody responses to an inactivated intramuscular QIV are non-inferior to those obtained with the TIVs containing the matched B strains. The study also examined whether B-strain immune responses to QIV are superior to those obtained with TIVs lacking the matched B strain.

2. Materials and methods

2.1. Study design

This was a phase III, randomized, active-controlled, multicenter trial in adults (EudraCT: 2011-001976-21). The study was performed at 14 sites in France and 4 sites in Germany. The primary objective of the study was to demonstrate non-inferiority of antibody responses induced by QIV compared with the licensed 2011–2012 TIV (containing the B/Brisbane strain) and an investigational TIV containing the alternate B strain lineage (B/Florida). Secondary safety objectives were to describe the safety profile (injection site reactions and systemic events) of each vaccine during the 21 days following vaccination, and the serious adverse events (SAEs) throughout the study in all subjects. Secondary immunogenicity objectives were to demonstrate, in adults 18–60 and >60 years of age, that the antibody response to each B strain in the QIV group was superior to the antibody response to the corresponding B strain induced in the control group immunized with the TIV lacking this strain. The study was approved by all institutional review boards and was carried out in accordance with International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Written informed consent was obtained from all subjects included in the trial.

2.2. Study population

Adults who had not previously received the 2011/2012 northern hemisphere seasonal influenza vaccine were considered for inclusion in this study. They were excluded if they had received another vaccination within 4 weeks before inclusion, were hypersensitive to any of the vaccine components, had a history of serious adverse reactions to any influenza vaccine, had a known or suspected congenital or acquired immunodeficiency, had received immunosuppressive therapy within the preceding 6 months, had received long-term systemic corticosteroid therapy for more than 2 consecutive weeks within the past 3 months, had received immune globulins, blood, or blood-derived products in the past 3 months, or had moderate or severe acute illness/infection in the opinion of the investigator or a temperature ≥38.0 °C. Women were excluded if they were pregnant, lactating, or of childbearing potential and not using adequate birth control. Enrollment was stratified by age at each site into adults 18–60 and >60 years of age.

2.3. Treatments

Subjects were randomized 5:1:1 to be immunized with a single injection of QIV, licensed TIV, or investigational TIV. All vaccines were administered by intramuscular injection with a 16-mm, 25-gauge needle. The subjects were randomized using a list generated with the permuted block method with stratification by site and age group and were assigned to treatment via an interactive voice or web response system. The study was double-blind for all subjects included in the QIV and in the licensed groups and open-label for subjects included in the investigational TIV group. Blood samples were collected before vaccination (day 0) and 21 days after vaccination.

2.4. Vaccines

All vaccines were inactivated, split-virion preparations containing 15 μg hemagglutinin per strain in a total volume of 0.5 mL. The QIV (batch S4361) contained the A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), B/Brisbane/60/2008 (Victoria lineage), and B/Florida/04/2006 (Yamagata lineage) strains. The B/Florida strain was selected for inclusion in QIV as it was the Yamagata lineage strain most recently included in TIV (2008/2009 formulation) prior to this study. The licensed TIV (batch H0229) was the 2010/2011 formulation of Vaxigrip® (Sanofi Pasteur), which contained A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Brisbane/60/2008 (Victoria lineage) strains. The investigational TIV (batch S4366) contained the A/California/07/2009 (H1N1), A/Victoria/210/2009 (H3N2), and B/Florida/04/2006 (Yamagata lineage) strains.

2.5. Hemagglutination inhibition (HAI) assay

The HAI assay was performed as previously described [10]. The highest serum dilution resulting in complete inhibition of hemagglutination was determined for duplicates of each sample. The titer for each sample was calculated as the geometric mean of the reciprocal of the duplicate values. The lower limit of quantification was a titer of 10, which is the reciprocal of the lowest dilution used in the assay. Samples with HAI antibody titers below 10 were assigned a titer of 5. The seroprotection rate for each group was the percent of subjects with a titer ≥40. The seroconversion rate for each group was the percent of subjects with either a pre-vaccination titer <10 and a post-vaccination titer ≥40 or a pre-vaccination titer ≥10 and a ≥4-fold increase in titer at day 21.

2.6. Safety

Solicited injection-site reactions (pain, erythema, swelling, induration, ecchymosis) and systemic reactions (fever, headache, malaise, myalgia, shivering) were recorded for 7 days after each vaccination. Unsolicited adverse events (AEs) and SAEs were collected according to the International Committee for Harmonization Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. Unsolicited AEs were collected up to 21 days after vaccination. Immediate unsolicited AEs were those occurring within 30 min of vaccination. SAEs and AEs of special interest were collected up to 6 months after vaccination. AEs of special interest included anaphylaxis, Guillain-Barré syndrome, encephalitis, myelitis, neuritis, convulsions, and vasculitis. AEs and SAEs were classified by the investigator as related or unrelated to the treatment. Erythema, swelling, induration, and ecchymosis were considered grade 1 for ≥25 to ≤50 mm, grade 2 for ≥51 to ≤100 mm, and grade 3 for >100 mm. Fever was considered grade 1 for ≥38.0 °C to ≤38.4 °C, grade 2 for ≥38.5 °C to ≤38.9 °C, and grade 3 for ≥39.0 °C. All other reactions and AEs were considered grade 1 for not interfering with activity, grade 2 for some interference with activity, and grade 3 for significant, preventing daily activity.