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Non-inferiority of mammalian cell-derived quadrivalent subunit influenza virus vaccines compared to trivalent subunit influenza virus vaccines in healthy children: a phase III randomized, multicenter, double-blind clinical trial

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SUMMARY

Objectives: The safety and immunogenicity of mammalian cell-derived quadrivalent influenza vaccine (QIVc) as compared with trivalent influenza vaccines (TIV1c/TIV2c) was evaluated in children aged ≥4 to <18 years.

Methods: Two thousand three hundred and thirty-three subjects were randomized 2:1:1 to receive either one or two doses of study vaccine depending on previous vaccination status. Hemagglutination inhibition antibody responses for all four influenza strains were performed 3 weeks after the last dose. Reactogenicity and safety were also assessed (ClinicalTrials.gov: NCT01992107).

Results: QIVc met the non-inferiority criteria against all four vaccine strains and demonstrated superiority for both influenza B strains over the unmatched B lineage included in the comparator vaccines, when geometric mean titers and seroconversion rates were compared at 3 weeks after the last vaccination. Similar percentages of subjects experienced solicited and unsolicited adverse events (AEs) across all subgroups. Unsolicited AEs, serious AEs, medically attended AEs, and new onset chronic disease were reported in comparable percentages of subjects in all study groups. No vaccine-related serious AEs or deaths occurred.

Conclusions: QIVc demonstrated a similar safety profile and immunogenicity responses against all four vaccine strains without signs of immune interference on addition of an alternate lineage B strain compared with TIV1c/TIV2c and may provide broader protection against both influenza B lineages in children.

1. Introduction

Influenza virus infection is a worldwide and major public health burden causing up to 500 000 deaths each year.[1] Globally, there is an estimated annual attack rate of 5–10% in adults and 20–30% in children, causing illness, hospitalization, and death.[1] When compared with the general population, children are at a high risk of infection, particularly during epidemics, with the rate of infection being >40% in pre-school children and 30% in school-age children. These children are more likely to spread the influenza infection into households and communities.[2–5]

The majority of influenza cases since 1977 have been caused by the circulating influenza strains A/H1N1, A/H3N2, and B/Victoria and B/Yamagata lineage.[6] The current challenge in protecting individuals against influenza is to provide a vaccine with an antigenic match against the circulating strains in a given influenza

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season.[7] Moreover, in five of the 10 influenza seasons (2001–2002 through 2010–2011), the most common circulating influenza B lineage was not that selected for the vaccine.[8,9] Therefore, there was very limited effectiveness in relation to the influenza vaccination campaigns, as a large percentage of the disease was caused by the influenza B strains during the epidemics. Including one strain from each B lineage in addition to A/H1N1 and A/H3N2 strains in the seasonal influenza vaccines may increase the efficacy of the influenza vaccine.[10] It is therefore warranted to include one strain from each B lineage in addition to A/H1N1 and A/H3N2 strains in order to increase the efficiency of the seasonal influenza vaccines.

Since 1985, two antigenically distinct lineages of influenza B viruses have disseminated worldwide and there is no cross-protection between the lineages.[7] Also, there is a risk of mismatch for the influenza B strain as only one lineage is selected for inclusion in the currently available trivalent influenza vaccines (TIVs).[11,12] The use of quadrivalent influenza vaccines (QIVs) might eliminate the risk of B lineage mismatch, and some QIVs have recently been approved in the USA.[13] Therefore, the use of a QIV may lead to a decrease in the influenza burden.[14]

The Madin Darby canine kidney (MDCK) cell line is optimized for influenza replication and is regarded as a well characterized and safe cell line that adheres to Good Manufacturing Practices.[15] The cell line is compliant with the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and World Health Organization (WHO) guidelines for purity, identity, and for the absence of adventitial viruses.[15] In addition, the cell line offers advantages of 'on-demand' production and lack of antibiotic use.[15] Because the mammalian cell lineage is closer to human cell lines, replication of influenza viral strains in the MDCK cell line may reduce the degree of antigen change that occurs in influenza strains replicated in eggs. It is expected that this may produce a better antigenic match against circulating viral strains isolated from humans.[3,16–18]

The present study was designed to evaluate the safety and immunogenicity in children aged ≥4 to <18 years of each of the four influenza strains contained in the cell-derived QIV (QIVc) vaccine as compared with the influenza strains contained in two trivalent inactivated influenza vaccines: TIV1c and TIV2c. All three influenza vaccines are based on the same manufacturing process and contain the same A/H3N2 and A/H1N1 strains, but TIVc1 and TIVc2 contain B strains of the opposite lineage: B/Yamagata and B/Victoria, respectively; QIV contains both B strains.

2. Materials and methods

2.1. Study design and objectives

This phase III, double-blind, stratified, randomized study was conducted at 90 sites in the USA between November 2013 and August 2014. The study had two primary objectives: to demonstrate non-inferiority of antibody responses post-vaccination as measured by the ratio of geometric mean titers (GMTs) and differences in seroconversion (SC) rates of QIVc in comparison with TIVc against all four vaccine strains, i.e., A/H1N1, A/H3N2 and B strain to TIV1c and the alternate B strain response to TIV2c. Secondary objectives were to evaluate the antibody responses against all four strains according to the Center for Biologics Evaluation, Research and Review (CBER) criteria, to evaluate antibody responses according to the Committee for Medicinal Products for Human Use (CHMP) criteria against the four strains, to demonstrate superiority of QIVc for the unmatched influenza B strain in TIVc as assessed by GMT ratios and SC rates, and to determine the reactogenicity and safety of all four vaccine strains. The study was approved by institutional review boards (central institutional review board and in a few cases at individual study sites) and the study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent was obtained from the parents/legal guardians of all children before enrollment; assent was also obtained from the subjects, if applicable. The study was registered at ClinicalTrials.gov (NCT01992107).

2.2. Study subjects

Subjects were excluded for the following reasons: a recent body temperature ≥38 °C (within 3 days prior to vaccination); a history of any significant ongoing chronic/acute illness that would interfere with their ability to comply with study-related procedures and or interfere in the evaluation of the study vaccine; females of child-bearing potential who had not used any of the acceptable contraceptive methods for at least 2 months prior to study entry and/or were not willing to do so through day 60; females who were pregnant or breast-feeding; those of child-bearing potential with a positive or indeterminate pregnancy test; history of any bleeding disorder; history of anaphylaxis to previous influenza vaccination, serious vaccine reactions, or hypersensitivity to any of the vaccine components, or on exposure to latex; received any influenza vaccination or had documented influenza disease within the prior 6 months; history of known or suspected congenital or acquired immunodeficiency or receipt of immunosuppressive therapy; history of known Guillain–Barré syndrome.

2.3. Vaccines

Each 0.5-ml dose of the investigational QIVc contained purified viral hemagglutinin (HA) antigens, approx. 15 μg of HA for each of the four influenza strains recommended by the WHO for the 2013/14 influenza vaccine composition for the Northern Hemisphere season: A/Brisbane/10/2010 (H1N1), A/Texas/50/2012 (H3N2), B/Massachusetts/2/2012, and B/Brisbane/60/2008.

The comparator TIVc vaccines administered (TIV1c and TIV2c) consisted of approximately 0.5 ml, which included purified viral HA from each of the three influenza strains A/Brisbane/10/2010 (H1N1), A/Texas/50/2012 NYMC X-223A (H3N2), and B/Massachusetts/02/2012 (B1) in TIV1c, recommended by the WHO for inclusion in the trivalent vaccine composition for the 2013/2014 influenza season, and A/Brisbane/10/2010 (H1N1), A/Texas/50/2012 NYMC X-223A (H3N2), and B/Brisbane/60/2008 (B2) in TIV2c. The vaccines were administered in the deltoid muscle, preferably of the non-dominant arm.

2.4. Study procedures

Subjects were stratified into two age cohorts: ≥4 to <9 years and ≥9 to <18 years. Within the ≥4 to <9 years cohort, subjects were further stratified as previously vaccinated and not previously vaccinated. Within each age cohort, subjects were randomized by an interactive response technology system at a pre-specified ratio of 2:1:1 to receive QIVc or TIV1c or TIV2c. Previously vaccinated subjects aged ≥4 to <9 years and ≥9 to <18 years received one vaccine dose on day 1; not previously vaccinated ≥4 to <9-year-old subjects received two vaccine doses, one dose each on days 1 and 29.

Safety data were collected using diary cards provided to the subjects and/or their parents through day 29 in previously vaccinated subjects and through day 50 for not previously vaccinated subjects. Additional safety data were collected through day 180 based on interviews and records provided at follow-up visits performed in the follow-up period. Blood samples were taken from all subjects for hemagglutination inhibition (HI) assay: