Vaccine 36 (2018) 4663–4671

Contents lists available at ScienceDirect

Vaccine

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

Randomized trial comparing the safety and antibody responses to live attenuated versus inactivated influenza vaccine when administered to breastfeeding women

Rebecca C. Brady [a,*], Lisa A. Jackson [b], Sharon E. Frey [c], Andi L. Shane [d], Emmanuel B. Walter [e], Geeta K. Swamy [e], Elizabeth P. Schlaudecker [a], Elena Szefer [f], Mark Wolff [f], Monica Malone McNeal [a], David I. Bernstein [a], Mark C. Steinhoff [a]

[a] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
[b] Group Health Research Institute, Seattle, WA, USA
[c] Saint Louis University, St. Louis, MO, USA
[d] Emory Children's Center, Atlanta, GA, USA
[e] Duke University, Durham, NC, USA
[f] The EMMES Corporation, Rockville, MD, USA

ARTICLE INFO

Article history:
Received 22 December 2017
Received in revised form 15 June 2018
Accepted 16 June 2018
Available online 28 June 2018

Keywords:
Live attenuated influenza vaccine
Inactivated influenza vaccine
Breastfeeding
Infants
Safety
Immunogenicity

ABSTRACT

Background: Live attenuated influenza vaccine (LAIV) and inactivated influenza vaccine (IIV) are both licensed for administration to nursing mothers. Little is known about the potential for transmission of LAIV viruses from the mother to the infant and the comparative breast milk antibody responses to LAIV and IIV.

Methods: We performed a randomized, double-blind study comparing the immunogenicity of LAIV to IIV when administered to nursing mothers. The safety of LAIV to IIV in women and their infants was also compared. Women received LAIV + intramuscular placebo, or IIV + intranasal placebo on Day 0. Breast milk and nasal swabs (from women and infants) were collected on Days 0, 2, and 8 for detection of LAIV. Breast milk and serum antibody responses were measured at Days 0 and 28. The primary hypothesis was that LAIV would provide superior induction of breast milk IgA responses to influenza as compared to IIV when administered to nursing mothers.

Results: Breast milk IgG, breast milk IgA (H1N1 only), serum hemagglutination inhibition (HAI), and serum IgG responses were significantly higher following administration of IIV compared to LAIV. Receipt of either LAIV or IIV was safe in women and their infants. One (1%) LAIV recipient transmitted vaccine virus to her infant who remained well. No influenza virus was detected in breast milk.

Conclusions: Breast milk and serum antibody responses were higher for IIV compared to LAIV. LAIV and IIV were safe for nursing women but there was one (1%) possible transmission of LAIV to an infant. This study suggests that IIV may be the preferred vaccine for nursing mothers.

1. Introduction

Influenza is an important cause of respiratory illness among young infants. Among infants < 3 months old in the United States, influenza has been associated with an annual average of 3000 hospitalizations [1]. A recent prospective surveillance study reported average annual rates of hospitalization attributable to influenza to be 0.27% for those <6 months of age [2]. Influenza vaccines are not licensed for administration to infants <6 months [3]. Maternal influenza vaccination has the potential to protect the young infant from influenza by placental transport of maternal antibodies and by preventing serious influenza in the mother [4]. Therefore, pregnant women are recommended to receive inactivated influenza vaccine (IIV) during any trimester of pregnancy.

Either IIV or live attenuated influenza vaccine (LAIV) is licensed to be administered postpartum to breastfeeding women [5,6]. Little information is available to guide decisions regarding this immunization choice [7]. In addition to maternal serum antibody transferred through the umbilical cord, there may be a potential

* Corresponding author at: Cincinnati Children's Hospital Medical Center, Division of Infectious Diseases, 3333 Burnet Avenue, MLC 6014, Cincinnati, OH 45229-3039, USA.
E-mail address: rebecca.brady@cchmc.org (R.C. Brady).

https://doi.org/10.1016/j.vaccine.2018.06.036
0264-410X/

protective effect from the oral transfer of maternal antibodies through breast milk when women are vaccinated during pregnancy and their infants consume milk from immunized women [8,9]. However, the amount of vaccine-specific antibodies present in breast milk when women are immunized postpartum with LAIV versus IIV is not known [7], nor is the amount of maternal nasal shedding and the potential for transmission of vaccine virus to the infant [10,11]. Further, it is not known if vaccine virus is excreted in breast milk after LAIV administration. Experience with other live virus vaccines with respect to virus excretion in human milk is variable. While there are no data on excretion of either varicella [12] or measles vaccine viruses [10], rubella vaccine virus [13–15] may be excreted in human milk and cause infection without clinical disease in the infant. It is assumed that if infection with a live vaccine occurs, it will be well-tolerated because the vaccine virus is attenuated [16]. On the other hand, both yellow fever virus [17–19] and smallpox vaccines [16] should be avoided during breastfeeding because of the risks for transmission from mother to infant and the potential for vaccine-associated complications in the infant. To address these questions, we conducted a randomized, double-blind clinical trial comparing LAIV versus IIV administration in breastfeeding women. The primary hypothesis was that LAIV would provide superior induction of breast milk IgA antibody responses to influenza as compared to IIV when administered to nursing women.

2. Materials and methods

2.1. Subjects

Healthy lactating women 18–49 years who had not previously received current season influenza vaccine, and who delivered a healthy infant at ≥36 weeks gestation, within 28–120 days before enrollment were recruited at 5 US sites before the 2011–12 or 2012–13 influenza season. No women were enrolled in both seasons. Women were excluded if they were not eligible to receive seasonal influenza immunization, had any chronic medical conditions, or had any known immunocompromised family member/household contact. Women must also have successfully provided breast milk for at least the two days prior to enrollment. Infants were excluded if they had any chronic medical conditions or were not receiving at least half of their feeding from breast milk.

The protocol and consent forms were approved by the institutional review board at each participating site. Women provided written, informed consent for themselves and their infants.

2.2. Study design

We conducted a randomized, double-blind clinical trial. Women were randomized 1:1 to receive either LAIV + intramuscular placebo, or IIV + intranasal placebo. On the day of immunization, women were given memory aids to record solicited and unsolicited adverse events (AEs) for themselves and their infants.

Women recorded the maximum intensity of solicited and unsolicited AEs for themselves and their infants and scored the AEs on a scale of 0–3 (0 = absent, 1 = easily tolerated, 2 = interferes with normal activity, and 3 = prevents normal activity).

Women recorded injection site symptoms [pain, tenderness, erythema, and induration], and the presence of nasal congestion, runny nose, cough, sore throat, and nasal bleeding for 7 days post-immunization. Erythema and induration were scored on a scale of 0–3 (0 = absent, 1 = <20 mm, 2 = 2–50 mm, and 3 > 50 mm). They also recorded solicited systemic AEs, including fever, feverishness, fatigue, myalgia, headache, nausea, weakness, and chills for 7 days after immunization. Fever was scored on a scale of 0–3 (0 = not present, 1 = ≥37.8 °C to <38 °C, 2 = >38 °C to < 39 °C, and 3 = ≥39 °C).

During the 10-day post-immunization period, women recorded solicited AEs experienced by their infants, including fever, difficulty breathing, nasal congestion, runny nose, cough, irritability/fussiness, drowsiness, and loss of appetite. Fever was scored on the same scale used for maternal fever. Unsolicited AEs occurring in women and infants from baseline until 28 days after immunization also were recorded. Women were contacted by telephone 6 weeks and 6 months after immunization to inquire about the occurrence of serious adverse events (SAEs) for themselves and their infants.

The mother and infant were requested to return for evaluation within 72 h of symptom onset if either experienced an influenza-like illness (ILI) [20] between baseline and 28 days after maternal immunization. Examination(s) were performed on the ill individual(s) and nasal swabs were collected from both to test for the presence of influenza viruses.

Women submitted expressed milk and serum specimens, both for antibody assays, at baseline and 28 days post-immunization. Expressed milk (women) and nasal swabs (women and infants) were collected at baseline, 2 and 8 days after influenza immunization to assess influenza virus presence by polymerase chain reaction (PCR) and cell culture. Days 2 and 8 were chosen because the highest proportion of healthy adult LAIV vaccinees shed one or more vaccine strains on days 2–3 post-vaccination and few shed past day 7 [11].

2.3. Immunizations

Licensed IIV (Fluzone®, Sanofi Pasteur, Swiftwater, PA) and LAIV (FluMist®, MedImmune, Gaithersburg, MD) were used as recommended each year. For the 2011–12 season [21], IIV contained 15 μg hemagglutinin (HA) of the A/California/07/2009 (H1N1)-like virus, A/Perth/16/2009 (H3N2)-like virus, and B/Brisbane/60/2008-like virus. FluMist® [11,21] contained $10^{6.5\text{-}7.5}$ FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the three strains found in IIV.

For the 2012–13 season [22], IIV contained 15 μg HA of the A/California/07/2009 NYMC X-179A (H1N1)-like virus, A/Victoria/361/2011 IVR-165 (H3N2)-like virus, and B/Texas/6/2011 (a B/Wisconsin/1/2010-like virus). FluMist® [11,22] contained $10^{6.5\text{-}7.5}$ FFU of live attenuated influenza virus reassortants of each of the strains: A/California/07/2009 (H1N1)-like virus, A/Victoria/361/2011 (H3N2)-like virus, and B/Wisconsin/1/2010-like virus. The intranasal placebo was sucrose phosphate buffer and the intramuscular placebo was sterile saline.

2.4. Antibody assays

Breast milk and serum were stored at ≤ -65 °C until time of performance of the antibody assays at the Laboratory for Specialized Clinical Studies (LSCS) at Cincinnati Children's Hospital Medical Center (CCHMC). The pre- and post-vaccination samples were run on the same day in the same assay and on the same plate to allow direct comparisons. Enzyme-Linked Immunosorbent Assay (ELISA) to detect hemagglutinin (HA)-specific Immunoglobulin A and G (IgA and IgG) in human milk and serum samples was performed as described by Schlaudecker, et al. [8]. A reference standard was used for each assay and assigned an arbitrary value. The amount of HA-specific antibody in the samples was derived by extrapolation from a standard curve assayed simultaneously using the reference standard and expressed as units per mL. The lower limit of detection was 5.82 units/mL for IgA and 2.56 units/mL for IgG. Titers below the limit of detection were reported as one-half the limit of detection.