Protective efficacy of a trivalent recombinant hemagglutinin protein vaccine (FluBlok®) against influenza in healthy adults: A randomized, placebo-controlled trial

John J. Treanor, Hana El Sahly, James King, Irene Graham, Ruvim Izikson, Robert Kohberger, Peter Patriarca, Manon Cox

ABSTRACT

Background: Development of influenza vaccines that do not use embryonated eggs as the substrate for vaccine production is a high priority. We conducted this study to determine the protective efficacy a recombinant, baculovirus-expressed seasonal trivalent influenza virus hemagglutinin (rHA0) vaccine (FluBlok®).

Methods: Healthy adult subjects at 24 centers across the US were randomly assigned to receive a single injection of saline placebo (2304 subjects), or trivalent FluBlok containing 45 mcg of each rHA0 component (2344 subjects). Serum samples for assessment of immune responses by hemagglutination-inhibition (HAI) were taken from a subset of subjects before and 28 days after immunization. Subjects were followed during the 2007–2008 influenza season and combined nasal and throat swabs for virus isolation were obtained from subjects reporting influenza-like illness.

Results: Rates of local and systemic side effects were low, and the rates of systemic side effects were similar in the vaccine and placebo groups. HAI antibody responses were seen in 78%, 81%, and 52% of FluBlok recipients to the H1, H3, and B components, respectively. FluBlok was 44.6% (95% CI, 18.8%, 62.6%) effective in preventing culture-confirmed influenza meeting the CDC influenza-like illness case definition despite significant antigenic mismatch between the vaccine antigens and circulating viruses.

Conclusions: Trivalent rHA0 vaccine was safe, immunogenic and effective in the prevention of culture confirmed influenza illness, including protection against drift variants.

Safety and immunogenicity of a baculovirus-expressed hemagglutinin influenza vaccine: a randomized controlled trial

John J. Treanor, MD, Gilbert M. Schiff, MD, Frederick G. Hayden, MD, Rebecca C. Brady, MD, C. Mhorag Hay, MD, Anthony L. Meyer, BS, Jeanne Holden-Wiltse, MPH, Hua Liang, PhD, Adam Gilbert, PhD, Manon Cox, PhD

ABSTRACT

Context: A high priority in vaccine research is the development of influenza vaccines that do not use embryonated eggs as the substrate for vaccine production.

Objective: To determine the dose-related safety, immunogenicity, and protective efficacy of an experimental trivalent influenza virus hemagglutinin (rHA0) vaccine produced in insect cells using recombinant baculoviruses.


Interventions: Participants were randomly assigned to receive a single injection of saline placebo (n = 154); 75 µg of an rHA0 vaccine containing 15 µg of hemagglutinin from influenza A/New Caledonia/20/99(H1N1) and influenza B/Jiangsu/10/03 virus and 45 µg of hemagglutinin from influenza A/Wyoming/3/03(H3N2) virus (n = 153); or 135 µg of rHA0 containing 45 µg of hemagglutinin each from all 3 components (n = 153). Serum samples were taken before and 30 days following immunization.

Main Outcome Measures: Primary safety end points were the rates and severity of solicited and unsolicited adverse events. Primary immunogenicity end points were the rates of 4-fold or greater increases in serum hemagglutinin inhibition antibody to each of the three vaccine strains before and 28 days after inoculation. The prespecified primary efficacy end point was culture-documented influenza illness, defined as development of influenza-like illness associated with influenza virus on a nasopharyngeal swab.

Results: Rates of local and systemic adverse effects were low, and the rates of systemic adverse effects were not different in either vaccine group than in the placebo group. Hemagglutinin inhibition antibody responses to the H1 component were seen in 3% of placebo, 51% of 75-µg vaccine, and 67% of 135-µg vaccine recipients, while responses to B were seen in 4% of placebo, 65% of 75-µg vaccine, and 92% of 135-µg vaccine recipients. Responses to the H3 component occurred in 11% of placebo, 81% of 75-µg vaccine, and 77% of 135-µg vaccine recipients. Influenza infections in the study population were due to influenza B and A(H3N2), and influenza A infections were A/California/7/2004-like viruses, an antigenically drifted strain. Seven cases of culture-confirmed CDC-defined influenza-like illness occurred in 153 placebo recipients (4.6%) compared with 2 cases (1.3%) in 150 recipients of 75 µg of vaccine, and 0 cases in recipients of 135 µg of vaccine.

Conclusions: In this study, a trivalent rHA0 vaccine was safe and immunogenic in a healthy adult population. Preliminary evidence of protection against a drifted influenza A(H3N2) virus was obtained, but the sample size was small. Inclusion of a neuraminidase component did not appear to be required for protection.
Evaluation of the safety, reactogenicity and immunogenicity of FluBlok® trivalent recombinant baculovirus-expressed hemagglutinin influenza vaccine administered intramuscularly to healthy adults 50–64 years of age

R. Baxter\textsuperscript{a,}\textsuperscript{*}, P.A. Patriarca\textsuperscript{b}, K. Ensor\textsuperscript{a}, R. Izikson\textsuperscript{c}, K.L. Goldenthal\textsuperscript{d}, M.M. Cox\textsuperscript{c}

\textsuperscript{a} Kaiser Permanente Vaccine Study Center, Oakland, CA, USA; \textsuperscript{b} Biologics Consulting Group, Inc., Bethesda, MD, USA; \textsuperscript{c} Protein Sciences Corporation, Meriden, CT, USA; \textsuperscript{d} Independent Consultant, Bethesda, MD, USA

ABSTRACT

Background: Alternative methods for influenza vaccine production are needed to ensure adequate supplies. Methods: Healthy adults 50–64 years were assigned randomly to receive one intramuscular injection of trivalent recombinant hemagglutinin (rHA) or U.S. licensed trivalent inactivated vaccine (TIV) containing H1, H3 and B antigens (Ag) derived from 2007 to 2008 influenza virus strains A/Solomon Islands/03/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. Each rHA dose contained 45.g HA/strain of the 2007–2008 FDA-recommended Ag vs. 15.g/strain for TIV. Antibody (Ab) responses were measured using a hemagglutination-inhibition (HAI) assay at baseline and 28 days post vaccination. Respiratory samples for viral culture were collected from subjects with influenza-like illness (ILI) during the 2007–2008 season in the U.S.

Results: 601 subjects were enrolled. Vaccines were well tolerated. Seroconversion (the percentage of subjects with either (a) a pre-vaccination HAI titer \(\leq 10\) and a post-vaccination HAI titer \(\geq 40\) or (b) a pre-vaccination titer \(\leq 10\) and a minimum four-fold rise in post-vaccination HAI antibody titer) in the TIV and rHA groups, respectively, was obtained in 66% vs. 72% for H1; 44% vs. 61% for H3; and 41% vs. 41% for B. Proportions achieving titers \(\geq 40\) were 96% vs. 96% for H1, 75% vs. 85% for H3, and 94% vs. 93% vs. B. Geometric mean titer ratios at day 28 (TIV/rHA) were 0.77 for H1; 0.58 for H3; and 1.05 for B, respectively. ILI frequencies were low and similar in both groups.

Conclusions: Both vaccines were safe and immunogenic. Ab responses vs. H1 and H3 Ags were significantly higher in the rHA group, with similar responses to B. Furthermore, the FluBlok group had a statistically significantly higher seroconversion rate against influenza A/H3N2 compared to the TIV group.


Comparative immunogenicity of recombinant influenza hemagglutinin (rHA) and trivalent inactivated vaccine (TIV) among persons \(\geq 65\) years old

W.A. Keitel\textsuperscript{a,}\textsuperscript{*}, J.J. Treanor\textsuperscript{b}, H.M. El Sably\textsuperscript{a}, A. Gilbert\textsuperscript{c}, A.L. Meyer\textsuperscript{d}, P.A. Patriarca\textsuperscript{e}, M.M. Cox\textsuperscript{f}

\textsuperscript{a} Baylor College of Medicine, Houston, TX, USA; \textsuperscript{b} University of Rochester, Rochester, NY, USA; \textsuperscript{c} Ockham Development Group, Inc., Cary, NC, USA; \textsuperscript{d} Children’s Hospital Medical Center, Cincinnati, OH, USA; \textsuperscript{e} Biologics Consulting Group, Alexandria, VA, USA; \textsuperscript{f} Protein Sciences Corporation, Meriden, CT, USA

ABSTRACT

Alternative substrates for influenza vaccine production are needed to ensure adequate supplies. We evaluated the relative safety and immunogenicity of recombinant hemagglutinin (rHA) or trivalent inactivated vaccine (TIV) among 869 \(\geq 65\)-year-old subjects in a randomized clinical trial. Virologic surveillance for influenza-like illness (ILI) was conducted during the 2006–2007 epidemic. Vaccines were well tolerated. Seroconversion rates vs. influenza A/H1N1 and H3N2 antigens were superior in the rHA group, but were inferior vs. influenza B; however, results for influenza B are confounded since the vaccine antigens were different. ILI frequencies were low and similar in both groups. Studies assessing relative immunogenicity of vaccines using identical B Ags are warranted.