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Clinical development of a Vero cell culture-derived seasonal influenza vaccine

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ABSTRACT

Background: Cell culture technologies have the potential to improve the robustness and flexibility of influenza vaccine supply and to substantially shorten manufacturing timelines. We investigated the safety, immunogenicity and efficacy of a Vero cell culture-derived seasonal influenza vaccine and utilized these studies to establish a serological correlate of vaccine protection.
Methods: Two multicenter, randomized, double-blind phase III trials were undertaken in the US during the 2008–2009 Northern hemisphere influenza season, in young (18–49 years) and older (50–64 years and ≥65 years) adult subjects. 7250 young adults were randomized 1:1 to receive either Vero-derived vaccine or placebo. 3210 older adult subjects were randomized 8:1 to receive either Vero-derived vaccine or a licensed egg-derived vaccine. Serum hemagglutination inhibition antibody titers were assessed 21 days post-vaccination. Vaccine efficacy in preventing cell culture-confirmed influenza infection was determined for the young adult population. Local and systemic adverse events were recorded in both studies.
Results: The Vero-derived vaccine was safe and well tolerated in both young and older adults. All US and European immunological licensing thresholds were comfortably met in both populations. Vaccine efficacy in young adults was 79% against A/H1N1 viruses antigenically matching the corresponding vaccine strain and 78.5% for all antigenically matched influenza viruses. A hemagglutination inhibition antibody titer of ≥1:15 provided a reliable correlate of protection for the Vero-derived influenza vaccine, with no additional benefit at titers >1:30. Bridging of the correlate of protection established in the young adult population to the older adult immunogenicity data demonstrated the likely effectiveness of the Vero-derived vaccine in the older adult population.
Conclusions: A Vero cell culture-derived seasonal influenza vaccine is safe, immunogenic and protects against infection with influenza virus. The novel vaccine technology has the potential to make a substantial contribution to improving influenza vaccine supply.
Clinical trial registration: The studies are registered with ClinicalTrials.gov, numbers NCT00566345 and NCT00782431.

1. Introduction

The continuous accumulation of mutations affecting the antigenic properties of circulating influenza viruses necessitate that seasonal influenza vaccines are manufactured on the basis of a yearly strain selection procedure [1]. Conventional influenza vaccines are produced using viruses adapted to growth in embryonated hens' eggs. These vaccines have been shown to be safe and effective but the use of eggs as a growth substrate is associated with a number of drawbacks. The planning and manufacturing processes necessary for egg-based production of seasonal influenza vaccines require that recommendations for virus strains to be included in the vaccine are based on the prediction of strains considered likely to predominate 9–12 months later [1,2]. Mismatches between vaccine strains and strains circulating during the influenza season can occur as a consequence of this delay, resulting in reduced vaccine effectiveness in some influenza seasons [2–4]. Moreover, some virus strains have adapted poorly to growth in eggs, delaying vaccine production or enforcing the use of antigenically non-matched strains [5–7]. In addition, manufacturing difficulties associated with the susceptibility of egg-based manufacturing processes to microbial contamination have in the past contributed to substantial shortfalls of seasonal influenza vaccine [8–10].

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The use of modern, robust and rapidly scalable cell culture-based vaccine manufacturing technologies offers several advantages over egg-based production methods, including the potential to provide a more reliable supply of effective influenza vaccines and to substantially shorten manufacturing timelines [11,12]. Because naturally occurring influenza viruses grow more readily in mammalian cell culture than in eggs, the generation of high-growth reassortants currently required for egg-based vaccine production may not be needed for cell culture-derived vaccines. Omission of this step would allow vaccine production to be initiated closer to the beginning of the influenza season, reducing the likelihood of mismatches between vaccine strains and circulating strains [11]. Furthermore, since the use of cell culture for the isolation and growth of vaccine virus avoids the selection of antigenic variants associated with adaptation to virus growth in eggs [13–15], cell culture-derived vaccines may have the potential to be more effective than egg-derived vaccines. In animal models, vaccines grown exclusively in cell culture have been shown to elicit better immune responses than egg-derived vaccines and to provide improved protection against challenge with wild-type virus [16,17].

A number of continuous cell lines are being used in the development of influenza vaccines; however, to date only the Vero cell line has universal regulatory acceptance [12,18]. Vero cells have been used to manufacture pandemic influenza vaccines which are well-tolerated and immunogenic [19–22] but, prior to the studies reported here, the safety, immunogenicity and efficacy of Vero cell culture-derived seasonal influenza vaccines had not been investigated in clinical studies.

Here we review the pivotal clinical data from phase III studies of a novel Vero cell culture-derived trivalent seasonal influenza vaccine in young adult and older adult populations. Seasonal influenza vaccines are generally licensed on the basis of safety and immunogenicity data since the induction of hemagglutinin-specific antibodies in the assay for hemagglutination-inhibition (HI) is an established serological correlate of protection for these vaccines [23–27]. However, it remained to be confirmed that this correlate of protection is equally applicable to cell culture-derived influenza vaccines. We therefore sought to directly investigate the clinical efficacy of the Vero-derived vaccine compared to placebo, using culture-confirmed influenza infection and antigenic typing to provide a stringent assessment of the ability of the vaccine to prevent clinical disease caused by infection with seasonal influenza virus. We also investigated whether HI titer can be used as a serological correlate of protection against culture-confirmed influenza infection for the Vero cell culture-derived vaccine. At the time these clinical studies were undertaken, seasonal influenza vaccination was recommended for pediatric and older adult populations [28], thus it was only feasible to perform a placebo-controlled efficacy study in the young adult population. A serological correlate of protection established in this study was therefore used to bridge to the immunogenicity results of an actively controlled trial performed in older adult subjects, such that the likely effectiveness of the vaccine could also be demonstrated in this population.

2. Methods

2.1. Study design and objectives

Two randomized, double-blind phase 3 clinical trials were undertaken during the 2008–2009 Northern hemisphere influenza season at multiple centers throughout the US. A placebo-controlled trial was conducted at 36 centers in healthy young adults aged 18–49 years to investigate the efficacy, immunogenicity and safety of the investigational trivalent Vero cell culture-derived influenza vaccine (VCIV). An active-controlled trial using a licensed trivalent egg-derived influenza vaccine (EIV) as comparator was performed at 30 centers in subjects ≥50 years of age to determine the immunogenicity and safety of VCIV in the older adult population. Participants enrolled in the older adult study were stratified into subjects aged 50–64 years and those of 65 years or above. The primary study objective for the young adult study was to demonstrate the efficacy of VCIV in preventing cell culture-confirmed influenza infection (CCII) due to an influenza virus that was antigenically matched to one of the vaccine strains. Secondary objectives were to compare the safety of VCIV with placebo and to establish a correlation between VCIV induced HI antibody titers and CCII-determined vaccine efficacy.

The co-primary study objectives for the older adults study were to assess the antibody response to VCIV as characterized by seroprotection and seroconversion 21 days after the vaccination. Secondary objectives included the geometric mean fold increase (GMFI) from baseline of HI titers and the incidence of local and systemic reactions.

The Sterling Institutional Review Board, Atlanta, Georgia, approved the study protocols and consent forms used in both studies. The studies were conducted in compliance with Good Clinical Practice guidelines, the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the Uniform Requirements for manuscripts submitted to Biomedical journals. Both studies employed a four member independent Data Monitoring Committee. Individuals who understood the study procedures and provided written informed consent after the nature and possible consequences of the study had been fully explained were accepted as potential study volunteers.

Prior to randomization potential volunteers provided the investigator with a medical history and received a physical examination, including a urinary test for β-human chorionic gonadotropin for women of childbearing potential, and blood was drawn for assessment of pre-vaccination HI antibody titers. Individuals were excluded from participation if they had a history of severe allergic reaction to any vaccine component, had a history of surgical or functional asplenia, had received live vaccine within 4 weeks or an inactivated vaccine within 2 weeks of study entry, had been treated with any blood product or immune globulin in the previous 90 days, had a pathologically or pharmacologically induced immune deficiency or had a dermatological condition or tattoo that could interfere with assessing local reactions to vaccination. Volunteers for the placebo-controlled trial in healthy young adults were excluded from participating in the study if they were in a risk category for complications of influenza illness as defined by the Centers for Disease Control and Prevention (CDC) [28]. Participants in either study who had previously been vaccinated against influenza for the 2008/2009 season were also excluded but immunization in prior seasons was not recorded or judged to be exclusionary.

2.2. Randomization

Participants in the young adult trial were randomized in a 1:1 ratio to receive either VCIV or placebo (phosphate-buffered saline). Participants in the older adult study were randomized to receive either VCIV or EIV in an 8:1 ratio. Randomization was done via a centralized, telephone accessible, Interactive Voice Response System. Separate randomization lists were prepared for each of the two age strata in the older adult study. The allocation sequences were generated by Baxter with the random number generator algorithm of Wichmann and Hill [29], as modified by Mcleod [30]. Randomization was done in blocks, with block sizes greater than two and nine for the studies in younger and older adults, respectively. To ensure masking, participants were enrolled by investigators who were not involved in the randomization process. Because the syringes containing the test and the control products were different in