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Safety and efficacy of a cytomegalovirus glycoprotein B (gB) vaccine in adolescent girls: A randomized clinical trial

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ABSTRACT

Background: Cytomegalovirus (CMV) is a leading cause of congenital infection and an important target for vaccine development.
Methods: CMV seronegative girls between 12 and 17 years of age received CMV glycoprotein B (gB) vaccine with MF59 or saline placebo at 0, 1 and 6 months. Blood and urine were collected throughout the study for evidence of CMV infection based on PCR and/or seroconversion to non-vaccine CMV antigens.
Results: 402 CMV seronegative subjects were vaccinated (195 vaccine, 207 placebo). The vaccine was generally well tolerated, although local and systemic adverse events were significantly more common in the vaccine group. The vaccine induced gB antibody in all vaccine recipients with a gB geometric mean titer of 13,400 EU; 95%CI 11,436, 15,700, after 3 doses. Overall, 48 CMV infections were detected (21 vaccine, 27 placebo). In the per protocol population (124 vaccine, 125 placebo) vaccine efficacy was 43%; 95%CI: −36; 76, $p = 0.20$. The most significant difference was after 2 doses, administered as per protocol; vaccine efficacy 45%, 95%CI: −9; 72, $p = 0.08$.
Conclusion: The vaccine was safe and immunogenic. Although the efficacy did not reach conventional levels of significance, the results are consistent with a previous study in adult women (Pass et al. N Engl J Med 2009;360:1191) using the same formulation.

1. Introduction

Cytomegalovirus (CMV) is a significant pathogen in congenital infections and in immunocompromised patients. Between 0.5 and 2.0% of infants worldwide are congenitally infected with CMV, including about 0.64% in Western countries [1]. In the United States (US), congenital CMV infections account for about 400 deaths and 5000–8000 significantly impaired children each year [2,3]. It is the most common viral cause of sensorineural hearing loss (SNHL) and developmental delay in the country [4,5]. In 2000, the U.S. Institute of Medicine issued a report that listed a CMV vaccine to prevent congenital infections as the highest priority based on cost savings and health benefits [6]. In 2012 a multidisciplinary meeting was held to discuss priorities related to development of CMV vaccines [7,8].

Multiple approaches to the development of CMV vaccines have been evaluated including live attenuated, plasmid DNA, viral-vectored, and subunit vaccines (reviewed in [9,10]). Most recently, two vaccines have been evaluated in transplant patients. A plasmid DNA vaccine coding for pp65 and gB with a poloxamer adjuvant was found to reduce CMV viremia in hematopoietic cell transplant patients [11] while a subunit gB vaccine administered with MF59 as

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an adjuvant reduced the duration of CMV viremia and the duration of antiviral therapy [12]. The gB subunit vaccine also provided modest (50%) protection in preventing CMV infection in young women [13].

The most important reason for developing a CMV vaccine is to prevent congenital CMV disease. One recognized strategy for the prevention of congenital CMV is to immunize adolescent girls, or perhaps both boys and girls, before the onset of sexual activity as sexual activity is an important mode of transmission after infancy and the toddler years [7,8]. This trial evaluated the gB/MF59 vaccine in adolescent girls.

2. Methods

2.1. Participants and study design

This study was a randomized, double-blind, placebo-controlled, Phase II study designed to assess the safety and efficacy of the experimental CMV gB/MF59 vaccine in healthy adolescent females. Healthy females, age 12 to 17 years at time of screening, were recruited from 5 sites in the USA in order to obtain approximately 400 CMV-seronegative subjects for the vaccine trial ($N = 200$ per group). Enrollment began on July 26, 2006 and the last subject visit was conducted on June 10, 2013. After signing the screening consent and parental consent (if subject was <18 years old), subjects were screened for antibodies to CMV. Subjects who were CMV-seronegative then consented to participate in the vaccine study (with parental consent if <18 years old) and were randomized 1:1 to receive either the vaccine or saline placebo. The randomization sequence used permuted blocks (randomly selected block size of 4 or 8). The randomization list was available only to the unblinded pharmacist and vaccine administrator. All other site staff, subjects, and laboratory staff were blinded to the treatment assignment. In order to participate, subjects had to be using an effective method of birth control if they were sexually active. Subjects also could not be receiving or have a history of receiving any medications or treatments that affected the immune system, could not have received a blood transfusion or blood products within 3 months, or have active or previous drug abuse. A complete description of the inclusion/exclusion criteria can be found in Supplemental Table 1. Subjects received 3 doses of vaccine or saline placebo administered by intramuscular (IM) injection in the deltoid muscle on a 0-, 1-, and 6-month schedule. Collection of sera occurred at screening, study day 0, month 6, month 7 and every three months for two years after month 7 for the analysis of CMV shedding by polymerase chain reaction (PCR) and for assessment of seroconversion to non-vaccine CMV antigens by a gB adsorption assay. Collection of urine occurred at study day 0, month 1, month 2, month 6, month 7 and every three months for two years after month 7 for the assessment of CMV shedding by PCR.

If subjects seroconverted or had CMV detected by PCR at any time on or after Day 0 of the study, they were eligible to enter the shedding portion of the study. The subject and her parent (if subject was <18 years old) signed another informed consent detailing this portion of the study. The shedding sub study included monthly visits for 4 months to obtain urine, saliva, and blood samples for quantification of CMV by PCR and then every other month for 8 months for the same purpose.

2.2. Study objectives

The primary objective for the efficacy analysis was protection from a systemic infection, defined as identification of CMV from the urine or blood evaluated by PCR. The secondary efficacy objective was protection from CMV infection, defined as systemic infection or seroconversion to non-vaccine CMV antigens. The primary safety outcomes were the incidence of local and systemic reactions within 7 days of vaccination, adverse events (AEs) occurring within the 30-day period (±2 days) after vaccination, and serious adverse events (SAEs) observed at any time throughout the study.

Additional secondary outcomes included CMV shedding in infected subjects measured by the duration and magnitude of CMV replication in the urine and blood and CMV antibody measurements by CMV gB enzyme-linked immunoassay (ELISA).

2.3. Vaccine

CMV gB/MF59 is a subunit gB glycoprotein of human CMV (strain Towne) expressed in Chinese Hamster Ovary (CHO) cells. The CMV gB/MF59 vaccine (20 μg CMV glycoprotein gB and 10.75 mg MF59) was provided by Sanofi Pasteur as 2 separately vialed components, which were combined prior to administration. The 20 μg dose was based on prior evaluations [14]. Sterile Saline (Sodium Chloride 0.9%) was used as the placebo.

2.4. Assessment of safety

Local and systemic signs and symptoms including temperature were collected the day of vaccination and for 6 follow-up days after each vaccination, recorded by the subject on a memory aid. For thirty days after each dose, all AEs were collected. SAEs were collected for the duration of the study. A Safety Monitoring Committee monitored the study progress and addressed any specific safety concerns. Unsolicited AEs were coded to Medical Dictionary for Regulatory Activities Terminology (MedDRA) version 14.0 or later terms.

2.5. Assessment of immunogenicity

Blood for immunogenicity testing was obtained at baseline, prior to the third vaccination at 6 months, and at months 7, 13, 19, 25 and 31.

2.6. Laboratory tests

2.6.1. Screening for anti-CMV IgG antibody

Anti-CMV IgG antibodies were detected by use of the Wampole CMV IgG enzyme immunoassay (EIA) kit (Fisher Scientific, Pittsburg, PA). This assay was performed, at a central site, according to the manufacturer's instructions to determine if the subject was eligible for the study.

2.6.2. CMV gB IgG ELISA assay to determine CMV anti gB antibody response

IgG antibody titers to gB were measured using an ELISA assay developed and validated at Cincinnati Children's Hospital Medical Center (CCHMC). Serum antibody levels were determined using 0.75 μg/mL gB (vaccine preparation) diluted in coating buffer (pH 9.5) to coat plates overnight at 4 °C. After plates were washed with phosphate-buffered saline plus 0.05% Tween 20 (wash buffer), plates were blocked using 0.89% Bovine Serum Albumin (Sigma, St. Louis, MO) in wash buffer. A human gB positive serum, assigned an arbitrary value of 5120 units was used to generate a standard curve by starting at a dilution of 1:400. Samples were run in a series of two fold dilutions. After washing the blocking solution from the plates, standards and samples were added to wells and incubated for 45 min at 37 °C. After washing, peroxidase conjugated goat anti-human IgG (KLP, Inc., Gaithersburg, MD) was added and incubated for 30 min at 37 °C. Plates were washed and 3,3′,5,5′-tetramethylbenzidine (TMB), peroxidase substrate system (KLP, Inc.) was added for 30 min at room temperature. The reaction was