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Immunogenicity and safety of a single dose of a live attenuated Japanese encephalitis chimeric virus vaccine in Vietnam: A single-arm, single-center study

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ABSTRACT

Objective: To describe the immunogenicity and safety of the Japanese encephalitis chimeric virus vaccine (JE-CV) in children and adults in Vietnam.
Methods: In this prospective, open-label, single-center, single-arm study, 250 healthy participants aged 9 months to 60 years received a single dose of JE-CV (IMOJEV®). JE neutralizing antibody titers were assessed at baseline and 28 days after vaccination using the 50% plaque reduction neutralization test ($PRNT_{50}$). Safety and reactogenicity were assessed through solicited and unsolicited adverse events.
Findings: Seroconversion (titer ≥10 [1/dil] in participants JE seronegative [titer <10] at baseline [per protocol analysis], or a 4-fold rise from a baseline titer ≥10) and seroprotection (titer ≥10 [1/dil]) rates 28 days after vaccination were both 98.5% (132/134) in the per protocol analysis, and 82.4% (201/244) and 98.8% (242/245), respectively, in the full analysis set. Geometric mean titers (GMTs) increased in all age groups from Day 0 to Day 28; Day 28/Day 0 GMT ratios were 55.3 (95% confidence interval [CI] 38.4–79.8), 348 (95% CI 211–572), 296 (95% CI 152–576) and 194 (95% CI 13.1–2870) in those aged 9 months to 4 years, 5–11 years, 12–17 years and 18–60 years, respectively, in the per protocol analysis. There were no safety concerns during the study.
Conclusion: A single dose of JE-CV in children and adults aged 9 months to 60 years in Vietnam elicited a protective immune response and was well tolerated with no safety concerns.
Registered at www.clinicaltrials.gov (NCT02492165).

Introduction

Japanese encephalitis (JE) virus is a mosquito-borne flavivirus epidemic and endemic in a number of countries across Asia and the Western Pacific region; including India, Indonesia, Thailand and Vietnam (Wang and Liang, 2015). Patients with JE present with high fever, and a range of neurological disorders including: coma, seizures and spastic paralysis (Solomon et al., 2000). Mortality from symptomatic JE can be as high as 10–40%, and a large proportion of those who survive suffer from a range of neurological sequelae (Solomon et al., 2000; Sarkari et al., 2012; Hills et al., 2010). An estimated 67,900 clinical cases of JE occur annually in JE-endemic countries, leading to an estimated 13,600–20,400 associated deaths (Campbell et al., 2011).

JE has been recognized as a public health concern in Vietnam since the first reports of JE epidemics in the 1960s and 1970s (Okuno, 1978). Estimated rates for acute encephalitis syndrome (surrogate used for JE surveillance) of 1–8 cases per 100,000 population were reported between 1985 and 1993 (Yen et al., 2010). In 1997, the JE immunization program was launched in Vietnam using locally produced, inactivated mouse brain-derived vaccine (MBDV) initially targeting children 1–5 years old in high-risk areas (Marks et al., 2012), and subsequently expanded nationwide (Yen et al., 2010). JE surveillance data in Vietnam between 1998 and 2007 showed a decreasing trend in the incidence of acute encephalitis during this period, with a mean annual incidence of 2.4 cases per 100,000 population and a case-fatality rate of 3.8% (Yen et al., 2010). In 2006, the World Health

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Organization (WHO) recommended the gradual replacement of MBDV with new generation JE vaccines due to safety concerns (World Health Organization, 2006).

A live attenuated JE chimeric vaccine (JE-CV; IMOJEV®; Sanofi Pasteur) has been developed for protection against JE. The safety and immunogenicity of primary vaccination with a single-dose JE-CV has been demonstrated in toddlers, children and adults in several endemic and epidemic areas (Chokephaibulkit et al., 2010; Feroldi et al., 2012, 2014; Kim et al., 2014; Chotpitayasunondh et al., 2017; Huang et al., 2014). A single-dose JE-CV provides long-term protection that persists for at least 5 years in children (Chokephaibulkit et al., 2016; Kosalaraksa et al., 2016). The vaccine was initially licensed in Australia in 2010, and is now available or approved in a number of countries in South East Asia. The present study investigated the safety profile and immunogenicity of a single dose of JE-CV in healthy participants aged 9 months to 60 years in Vietnam as part of the registration requirements for this country.

Methods

Study design

This study was a prospective, open-label, single-center, single-arm study, of a single dose of JE-CV in healthy children and adults in Vietnam (www.clinicaltrials.gov; NCT02492165). The study was conducted between 27 June and 24 August 2015, in accordance with the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. The study protocol was approved by the National Institute of Hygiene and Epidemiology Institutional Review Board/Independent Ethics Committee, and the Ministry of Health Ethics Committee, Vietnam. A signed informed consent form was obtained from each participant aged ≥18 years. For participants aged <18 years, the informed consent form was signed by a parent or legal representative; participants aged 12–17 years were additionally required to sign the informed consent form, and those aged 8–11 years were additionally asked to sign an assent form.

Participants

Healthy participants aged 9 months to 60 years were eligible for inclusion. Exclusion criteria included: pregnancy, lactating or of childbearing potential (non-childbearing potential included use of an effective method of contraception or abstinence for at least 4 weeks before and after study vaccination); vaccination against flavivirus disease including JE, dengue and yellow fever; or receipt of any vaccines in the previous 4 weeks, or planned in the 4 weeks following study vaccination. Other main exclusion criteria included: simultaneous participation in another trial investigating a vaccine, drug or medical procedure/device; receipt of blood, or blood-derived products in the past 3 months; known or suspected congenital or acquired immunodeficiency, or receipt of immunosuppressive therapy within the preceding 6 months, or long-term systemic corticosteroids therapy (for more than 2 consecutive weeks within the 4 weeks preceding vaccination); known or suspected systemic hypersensitivity to any of the vaccine components; history of flavivirus infection confirmed either clinically, serologically or microbiologically; history of central nervous system disorder or disease, including seizures.

Vaccine and procedures

JE-CV (IMOJEV®, Sanofi Pasteur, Government Pharmaceutical Organization — Mérieux Biological Products Co., Ltd., [GPO-MBP], Thailand) was presented as a powder and reconstituted in 0.4% sodium chloride solution immediately before use. Each 0.5 mL dose of vaccine contained between 4.0 and 5.8 $\log_{10}$ plaque forming units of lyophilized virus. Participants received one subcutaneous injection of JE-CV on the day of inclusion (Day 0), into the upper arm. Participants or their parents/guardians received a phone call on Days 1 and 2, and a home visit on Days 3 and 8. Blood samples for immunogenicity were taken on Day 0, before vaccination, and on Day 28.

Immunogenicity assessments and outcomes

JE neutralizing antibody titers were assessed at Day 0 and Day 28 by a JE-CV 50% plaque reduction neutralization assay ($PRNT_{50}$) in Vero cells using 2-fold serial dilutions of serum to be tested and constant challenge dose of JE-CV virus (Focus Diagnostics Inc., San Juan Capistrano, CA, USA), as previously described by Kim et al. (Kim et al., 2014). In brief, the virus-serum test mixtures were incubated at 2–8 °C in 5% CO_2 for 16–20 h to allow neutralization to occur and subsequently inoculated into wells of a 24-well plate of confluent Vero cells and incubated at 37 °C in 5% CO_2 for 1 h. The cell monolayers were then overlaid with methyl cellulose medium, incubated for 5 days and stained with crystal violet/formaldehyde solution. JE-CV infected cells were indicated by the formation of viral plaques that appeared as clear spots on a violet background. The neutralizing antibody (Ab) titer was calculated and expressed as the reciprocal serum dilution reducing the mean plaque count by 50% as compared with mean virus plaque number in the negative control (100% virus load). The assay had a lower limit of quantification titer of 10 (1/dilution). Internal quality control samples, consisting of samples with high, medium or low titers against JE-CV were utilized from serum collected after JE immunization, or a negative control sample from serum collected from JE naïve donors from a non-endemic region (USA).

Immunogenicity outcomes were summarized using geometric mean titers (GMTs) and by seroconversion and seroprotection rates. Seroconversion at Day 28 was defined as JE virus neutralizing antibody titer ≥10 (1/dil) in participants considered seronegative (titer <10 [1/dil]) at baseline, or a ≥4-fold increase in neutralizing antibody titers in participants seropositive (titer ≥10 [1/dil]) at baseline. Seroprotection was defined as JE-CV neutralizing antibody titers ≥10 [1/dil] (Hombach et al., 2005). GMT ratios (Day 28/Day 0) were also calculated.

Reactogenicity and safety

Participants were observed for 30 min after vaccination to record any immediate adverse events (AEs). Participants or their parents/guardians were provided with diary cards, a flexible ruler and a digital thermometer to record any solicited injection site and systemic reactions. The occurrence and intensity of solicited reactions (prelisted in the participants' diary card and case report form [CRF]) were recorded; injection site reactions (pain, tenderness, erythema and swelling) up to 7 days post-vaccination, and solicited systemic reactions (fever, headache, malaise, myalgia, vomiting, abnormal crying, drowsiness, appetite loss and irritability) up to 14 days post-vaccination.

Unsolicited AEs, including serious AEs (SAEs), were recorded up to 28 days post-vaccination. For each unsolicited AE, study investigators assessed the causal relationship with vaccination and rated seriousness. Unsolicited, non-serious AEs were classified based on the following intensity scale: no interference with activity (Grade 1), some interference with activity (Grade 2) and significant interference that prevents daily activity (Grade 3). All injection site AEs (solicited and unsolicited) and all solicited systemic reactions were considered to be related to vaccination. AEs of special interest (AESI), including hypersensitivity/allergic