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Long-term follow-up of Japanese encephalitis chimeric virus vaccine: Immune responses in children

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ABSTRACT

Background: A single dose of live attenuated Japanese encephalitis chimeric virus vaccine (JE-CV) was shown to be immunogenic and well tolerated when given either as a booster to formalin-inactivated Japanese encephalitis (JE)-vaccine (mouse brain-derived vaccine [MBDV])-primed 2–5-year-olds, or as a primary vaccination to JE-vaccine-naïve 12–24-month-old toddlers in Thailand. A 5-year follow-up assessment of immune response persistence over time was conducted.

Methods: Four additional visits (at 2, 3, 4, and 5 years) for immunologic assessments were added to the original 12-month open-label crossover study, in which 100 healthy children aged 2–5 years with a history of two-dose primary vaccination with MBDV (according to the Thai Expanded Program for Immunization schedule), and 200 healthy JE-vaccine-naïve 12–24-month-old toddlers, were randomized 1:1 to receive JE-CV, containing $\geqslant 4$ $\log_{10}$ plaque forming units, 1 month before or after hepatitis A control vaccine.

Results: In MBDV-primed 2–5-year-olds ($n = 78$), the immune response to the JE-CV vaccine persisted up to at least 5 years after vaccination with a single dose of JE-CV, with all ($n = 78$) children seroprotected at the year 5 visit (geometric mean titers [GMT]: 252 1/dil). There was no decrease of seroprotection rate over time (100% at 6 months post-vaccination and 96.8% (90.3–98.9) at 5 years post-vaccination). In JE-vaccine-naïve toddlers, a protective immune response persisted up to at least 5 years in 58.8% (50.9–66.4) after a single-dose administration of JE-CV (GMT 26.7 1/dil; sensitivity analysis).

Conclusions: A single-dose of JE-CV as a booster following MBDV administration provided long-lasting immunity. In JE-vaccine-naïve toddlers, despite relatively high seroprotection rates persisting over time, a subsequent booster dose is recommended following a JE-CV primary vaccination for long-term protection.

Conclusions: This study was registered on www.clinicaltrials.gov (NCT00621764).

Abbreviations: AE, adverse event; BMI, body mass index; CI, confidence interval; FAS, full analysis set; FV, flavivirus; GMT, geometric mean titers; JE, Japanese encephalitis; JE-CV, Japanese encephalitis chimeric virus vaccine; JEV, Japanese encephalitis virus; K-M, Kaplan-Meier; MBDV, mouse brain-derived vaccine; NPMLE, non-parametric Maximum Likelihood Estimator; PP, per protocol; SAE, serious adverse event; SD, standard deviation; WHO, World Health Organization.

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1. Introduction

Japanese encephalitis (JE) is a vector-borne (*Culex* mosquito) zoonotic viral disease, which is endemic in most countries of South and East Asia and the Western Pacific. Infection with the JE virus (JEV) is the most common cause of viral encephalitis in children [1,2]. JEV cannot be eradicated, due to the animal reservoirs of infection (pigs and wading birds), therefore good vaccine coverage in endemic areas is of major importance [2]. JE is estimated to be responsible for nearly 68,000 cases of encephalitis, with up to 20,000 deaths, annually. The overall annual incidence in endemic countries has been estimated at 5.4/100,000 in the 0–14-year age group, and 0.6/100,000 in those ⩾15 years [2]. Severe disease is estimated to occur in about one case per 250 JEV infections and may rapidly progress to severe encephalitis, or lifelong neurologic sequelae [2].

JE has also been recognized as a significant cause of childhood morbidity in Thailand since the early 1970s when annual outbreaks produced up to 2400 cases and 400 deaths. However, since the national vaccine program was introduced in the 1990s, the JE incidence has declined to approximately 500 cases a year with 50 deaths [3]. As the burden of JE remains high in the Asia/Pacific region, new and improved vaccines are needed. The duration of effect and adverse reactions of the inactivated JE vaccine, leading to discontinuing immunization, have stimulated research for alternative vaccination methods, and the World Health Organization (WHO) stated that it should be replaced by new generation vaccines [2]. A number of newer inactivated and live attenuated JE vaccines are currently available, based on either the Beijing, Nakayama, or SA14-14-2 vaccine strains.

Japanese encephalitis chimeric virus vaccine (JE-CV; Imojev®, Sanofi Pasteur) is a live attenuated vaccine, which is approved for prophylaxis of JE in adults and children from 9 months of age. JE-CV is manufactured using the ChimeriVax™ technology based on the YF17D vaccine virus, offering additional advantages such as greater viral stability and a modern production platform using Verocell technology instead of primary cell lines, as well a solid past experience with the backbone vaccine virus used in other flavivirus vaccines (dengue, West Nile). It has been shown to be well tolerated and immunogenic in phase III trials in adults in Australia and the USA [4] and in phase II and phase III trials in children in Asia [5–8]. In two head-to-head comparator studies in adults, adverse reaction rates were significantly lower with JE-CV (67.6%) than with MBDV (82.2%) ($p < 0.001$), and the reactogenicity profile of JE-CV was comparable with that of placebo [4].

JE-CV was first licensed in Thailand in 2010. The current recommended JE-CV schedule in children is a single dose as primary vaccination from 9 months of age and older followed by a booster dose 12–24 months later [7].

The first 12 months of follow-up after vaccination in an open-label crossover study showed that a single dose of JE-CV had a good safety profile and produced a protective immune response in both JE-vaccine-naïve toddlers (12–24 months) and MBDV-primed young children (2–5 years) in Thailand [5]. The study was extended with a 5-year follow-up to further characterize the persistence over time of the immune response induced by JE-CV either as a booster vaccination following a primary immunization with an MBDV 2-dose regimen or as a single-dose primary immunization. This publication reports the immune response to JE-CV vaccination over 5 years (NCT00621764).

2. Methods

The details of the design of this study, patient population, study procedures, investigational products (vaccines), and primary safety, reactogenicity, and immunogenicity assessments, including preliminary persistence results up to 1 year after vaccination, have been reported previously [5].

2.1. Study design and participants

Briefly, this was an open-label crossover study, in which 100 healthy children aged 2–5 years with a history of two-dose primary vaccination with MBDV according to the Thai Expanded Program for Immunization schedule and 200 healthy JE-vaccine-naïve 12–24-month-old toddlers were randomized 1:1 to receive JE-CV, containing ⩾4 $\log_{10}$ plaque forming units, 1 month before or after hepatitis A control vaccine. Here, we report an additional follow-up assessment of the 5-year persistence of the immune response to JE-CV.

Overall, the study involved 13 visits, including: screening, D0 (V01), D4 (V02), D15 (V03), D28 (V04), D43 (V05), D56 (V06), and 6 months (V07) after the last vaccination; and 1 (V08), 2 (V09), 3 (V10), 4 (V11), and 5 years (V12) after the first vaccination. Participants were monitored for the occurrence of JE throughout the 5-year follow-up.

2.2. Immunogenicity assessments

JE antibody assessments were performed using a homologous JE-CV virus (for all time points up to the end of the 5-year follow-up), and one or more wild-type virus strains (Genotype I Strain: 1991 TVP-8236, Genotype II Strain: B 1034/83, Genotype III Strain: Beijing, Genotype IV Strain: JKT 9092 TVP 6265) for all time points up to 6 months after the last vaccination.

JE virus neutralizing antibody measurement was assessed by a $PRNT_{50}$ assay, as recommended by the WHO [9]. Seroconversion was defined as a JE $PRNT_{50}$ neutralizing antibody titer ⩾10 1/dil in subjects who were seronegative (titer <10 1/dil) at baseline. This is considered to be a reasonable threshold antibody level for protection against JE virus [9]. Subjects seropositive (titer ⩾10 1/dil) at baseline required a ⩾4-fold rise in neutralizing antibody titer.

2.3. Statistical methods

This study was descriptive without hypothesis testing and the group sample sizes were determined as reported previously [5].

Persistence of seroprotection up to 5 years after vaccination was assessed on the full analysis set (FAS; all available data). To avoid bias in the antibody measurements over time due to the potential discontinuations of subjects with low neutralizing antibody titers (i.e. below the threshold considered for protection), and who might have received another JE vaccination during the 5-year follow-up period, a sensitivity analysis was performed for the evaluation of the long-term persistence of the immune response from 1 to 5 years post-vaccination.

2.3.1. Sensitivity analysis

If a subject withdrew at a visit (whatever the reason), or missed a visit/blood sample, and he/she was seronegative (i.e. geometric mean titers [GMT] <10 1/dil, homologous virus strain) at the previous visit, the subject was assumed to be seronegative at all the following visits up to the 5-year follow-up visit. In case a subject had positive titer values later (i.e. ⩾10 1/dil) for any reason (i.e. exposure to a JE virus in JE endemic countries) after a visit where he/she was found to be 'negative', this subject was still considered as negative.

In addition to the sensitivity analysis, a Kaplan-Meier (K-M) analysis and interval-censor methods were used to estimate the maintenance of seroprotection over time.

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