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A phase 1 study of safety and immunogenicity following intradermal administration of a tetravalent dengue vaccine candidate

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ABSTRACT

Background: As part of the ongoing search for an effective dengue vaccine, Takeda performed a phase 1b study to investigate the safety and immunogenicity of an early low-dose tetravalent dengue vaccine candidate formulation (LD-TDV), based on an attenuated serotype 2 backbone, when administered intradermally with an injector device (PharmaJet®), or needle-syringe.
Methods: The study was performed in two centers in the US, in healthy 18–45 year old subjects with no history of dengue vaccination or disease. One or two vaccine doses were given on Day 0, and another dose or placebo on Day 90. Neutralizing antibodies were measured up to Day 270; safety was assessed as laboratory measurements and solicited and unsolicited adverse events on diary cards.
Results: Changes in World Health Organization prequalification guidance for new vaccines concerning storage conditions favored the use of lyophilized preparations, and led to the early cessation of enrolment, but not before 67 subjects were enrolled in four treatment groups. Sixty-five subjects completed the planned schedule. There were no safety signals or serious adverse events. All vaccination regimens elicited neutralizing antibodies. Titers of neutralizing antibodies against serotypes 1 and 2 were higher than those against serotypes 3 and 4. There were no consistent increases in responses with two doses given either concomitantly or 90 days apart.
Conclusions: Simultaneous injection of two LD-TDV doses was shown to have the potential to improve seroconversion rates to serotypes 1 and 2, and to increase serotype 2 antibody titers. A primary dose of LD-TDV administered by PharmaJet was shown to induce more rapid seroconversion to serotypes 1, 2, and 3 compared with administration by needle-syringe (ClinicalTrials.gov: NCT01765426).

1. Introduction

Dengue is a systemic viral infection transmitted between humans by *Aedes* mosquitoes and is the most common mosquito-borne viral disease in man [1]. The majority of infections are subclinical, however dengue can present as an acute febrile illness [2]. Severe disease can include life-threatening dengue hemorrhagic fever and dengue shock syndrome [3]. Prevention currently replies on vector control measures, because there is no specific therapy available for dengue infection; this creates an urgent medical need for effective vaccines. Primary infection with any of the four serotypes (DENV-1, -2, -3, -4) induces homotypic life-long immunity but not long-term heterotypic protective immunity against the other serotypes. Subsequent infection with another serotype is associated with an increased risk of severe disease. Therefore, protection against all 4 dengue serotypes is an important consideration in the development of a dengue vaccine and has led to investigation of tetravalent formulations that contain antigens specific for each of the four serotypes [4].

Abbreviations: LD-TDV, low-dose tetravalent dengue vaccine; AE, adverse event; DMID, Division of Microbiology and Infectious Diseases; SAE, serious adverse event; CPK, creatine phosphokinase; ALT, alanine transaminase; AST, aspartate transaminase; GMT, geometric mean titer; PFU, plaque forming units.

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Takeda's live tetravalent dengue vaccine (TDV) candidate is based on a molecularly characterized attenuated serotype 2 strain (TDV-2) [5]. Three chimeric strains (TDV-1, TDV-3, and TDV-4) were engineered by substituting the pre-membrane (prM) and envelope (E) structural genes of the respective DENV strains into the attenuated TDV-2 backbone [6].

Studies in dengue-seronegative adults showed the low-dose TDV formulation (LD-TDV) used in the present study is safe and well-tolerated when administered by subcutaneous or intradermal injection in a two-dose schedule, 90 days apart [7,8]. This phase 1b study was designed to assess the safety, tolerability, and immunogenicity of intradermal administration of different schedules of LD-TDV using either an investigational needle-free injector (PharmaJet®; PharmaJet Inc., CO, USA) or a syringe and needle.

2. Methods

This randomized, partially-blinded, phase 1b study was performed from February 2013 to June 2014 at two US sites. The protocol was approved by the Institutional Review Board of each site. All participants provided written informed consent. The study was conducted according to GCP and ICH guidelines. A total of 21 (31%) subjects were enrolled at the site in Texas, and 46 (69%) subjects at the site in Washington (ratio ~ 1:2). Staff at both study sites underwent training on the correct use of the PharmaJet device. Co-primary objectives were comparisons of the immunogenicity, safety, and tolerability of different schedules and modes of administration. Secondary objectives included the measurement of viremia and levels of neutralizing antibodies after each vaccination (ClinicalTrials.gov: NCT01765426).

2.1. Subjects

Subjects were healthy 18–45 year old male and female adult volunteers with no indications of HIV, Hepatitis B, or Hepatitis C infections. Female volunteers had to have a negative pregnancy urine test prior to each vaccination and agree to use approved contraception from 30 days before the first study vaccination until the final blood sample. Main exclusion criteria included any Grade 2 or above abnormality in the screening laboratory tests (hematology, serum chemistry, urinalysis) [9]; any history of dengue fever, Japanese encephalitis, West Nile or yellow fever disease, or baseline seropositivity to West Nile or dengue viruses.

2.2. Study vaccine

The study vaccine (Lot number: 00809) was a liquid formulation (Shantha Biotechnics Ltd., Medchal, India) stored at ≤minus 60 °C. Each 0.1 mL dose contained 8×10^3 plaque forming units (pfu) of TDV-1, 5×10^3 pfu TDV-2, 1×10^4 pfu TDV-3, and 2×10^5 pfu TDV-4. Placebo was sterile phosphate-buffered saline solution. Placebo or study vaccine were administered by intradermal injection in the upper arm using needle (25–27 gauge) and syringe or PharmaJet injector. Simultaneous doses were given in opposite arms. Methods of vaccine administration were consistent across both the study sites.

2.3. Study design

The original sample size of 96 subjects (24 per group) was selected empirically based on similar vaccine studies at this stage of development. Subjects were screened within 28 days before enrolment to assess general medical and laboratory parameters, including seropositivity for dengue, West Nile, human immunodeficiency, or hepatitis C viruses, then randomized at enrolment to four equal groups to receive their first injections of LD-TDV or placebo on Day 0 (in different arms based on dosing schedule and delivery device) and second injections on Day 90 (Fig. 1).

2.4. Safety – adverse events

Participants were observed for immediate reactions for 60 min, and then recorded any solicited local or systemic adverse events (AEs) in diary cards for 14 days after each vaccination. The severity grading criteria applied to local and systemic AEs, serum chemistry analyses, hematology tests, and urinalysis were defined by the US National Institutes of Health, Division of Microbiology and Infectious Diseases (DMID). Any solicited AEs not graded according to the DMID-defined criteria were graded for severity (mild, moderate, and severe) by study participants based on impact on daily living. Unsolicited AEs within 28 days of each vaccination were also reported on the diary cards. Serious adverse events (SAE) were collected throughout the study. Rates of solicited and unsolicited AEs were calculated by maximum severity, and by event type as percentages of subjects in each group with at least one event.

2.5. Clinical laboratory evaluation

Hematology, serum chemistry testing and urinalysis were performed at screening and on Days 7, 14, 90, 97, and 104 to assess shifts in established severity grades from baseline. Parameters studied included eosinophils, hemoglobin, neutrophils, platelet count, white blood cell counts, activated partial thromboplastin time, fibrinogen, creatine phosphokinase (CPK), alanine transaminase (ALT), and aspartate transaminase (AST).

2.6. Immunogenicity

Serum dengue neutralizing antibodies were measured on Days 0, 28, 90, 118, and 270 by plaque reduction neutralization assay [7,8]. Antibody titers were defined as the reciprocal of the dilution at which 50% of plaques were neutralized ($PRNT_{50}$), seropositivity being defined as a $PRNT_{50} \geq 10$. As baseline seropositivity was a predefined exclusion criterion, seroconversion was defined as any post-vaccination value ≥10. Seroconversion rates, the percentages of each group achieving seroconversion, with exact 95% CI calculated by the Clopper-Pearson method, and geometric mean titers (GMTs) with 95% CI were calculated for each group at each time point. To calculate GMTs, $PRNT_{50}$ titers <10 were assigned a value of 5.

2.7. Vaccine viremia

Vaccine viremia was assessed as viral RNA in blood on Days 0, 7, 10, 14, 21, 90, 97, and 104, using qRT-PCR as described previously [7,8]. Where replication competent, infectious, plaque-forming virus could be isolated from the serum samples which tested positive for viral RNA by qRT-PCR (note, not all qRT-PCR positive samples produced plaques), additional spot sequencing analysis [7,8] was performed on each plaque-forming isolated vaccine serotype (note, in some cases plaques failed to yield a sufficient quantity of viral RNA for sequencing analysis to be performed). Spot sequencing analysis was performed on a total of 20 serum samples to monitor for the occurrence of reversion at any of the three nucleotide mutations (in the 5′ NCR, NS-1, and NS-3 genes) known to contribute to the attenuated phenotype of the vaccine virus strains. If after vaccination plaque-forming virus could be isolated on more than one day, sequencing analyses were performed on the sample with peak viral RNA levels and the sample from the last day that the subject was positive for RNA from plaque-forming vaccine virus.

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