



DENGUVAXIA VACCINE: EFFECTIVE AGAINST DENGU DISEASE.

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ABSTRACT:

Dengue fever is one of the most common mosquito-borne diseases worldwide, affecting an estimated 390 million people per year. Over the past two decades, efforts to prevent dengue virus (DENV) infections have faced several challenges , primarily related to the complexity of conducting long – term studies to evaluate the effectiveness and safety of exclusion vaccines and the associated risk is related to vaccine -related DHS/DSS , especially in children .At least seven DENV vaccine have progressed through various phases of clinical trials ; However ,only three of them (Dengvaxia ,TV003 and TAK-003) have shown promising results and are discussed in detail in this review in terms of their molecule design ,efficacy and immunogenicity .Safety challenges in developing the DENV vaccine are also discussed.

KEY WORDS:

Dengu fever, mosquito born diseases,DENV,DHS/DSS, DENV vaccine.

INTRODUCTION:

Dengue fever represents a major burden on public health systems worldwide and is considered the most widespread mosquito -borne disease in tropical and subtropical regions of the world increasing rapidly every year due to various factors such as climate changes and deforestation is associated ,among other things ,with uncontrolled urbanization ,overpopulation and the emergence of mosquitoes that are resistant to common insecticides .Dengue fever is caused by dengue virus (DENV) , which belongs to the genus Flavivirus of the family Flaviviridae and it transmitted by mosquitoes of the genus aedes , mainly aedes aegypti and aedes albopictus .Four genetically distinct DENV serotypes (DENV-1,DENV-2,DENV-3,and DENV-4) have been reported to circulate among humans worldwide . Dengue fever is characterized by a wide spectrum of clinical manifestation ,ranging from mild febrile illness to severe dengue ,increasing the risk of developing dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS)secondary DENV infection (e.g., exposure to a heterotypic serotype) is the greater risk factor for severe disease due to the phenomenon of antibody - dependant enhancement (ADE) .Briefly ,cross -reactive antibodies arising after the exposure to the first DENV serotype associate with second DENV serotype and form infectious immune complexes that invade Fc receptor – bearing cells. This increases the number of infected cells and the amount of viruses produced.

At least seven DENV vaccine based on various platform ,including live attenuation viruses ,DNA and recombinant proteins , have been developed and are currently in various phase of clinical trails . preclinical phase investigation .In this review, We discussed the recent advance of the three most advanced DENV vaccine (Dengvaxia,TV003 /TV005 and TAK-003) ,focusing on the molecular characteristics of each vaccine

and the available clinical data on their effectiveness and immunogenicity . Finally ,we highlight the safety challenges associated with the risk of vaccine -related DHS/DSS.

Development and Preclinical Evaluation of Dengue Virus [DENV] vaccines .

This vaccine was originally developed in the early 2000s by the national institutes of health (NIH), the University of St. Louis and Acambis Inc. and was subsequently licensed by Sanofi Pasteur .It uses chimerivax technology .This technology is based on a vaccine strain (17D) of yellow fever virus (YFV)in which the premembrane (prM) and envelope (E) genes of YFV were replaced with the homologous genes of each of the four DENV-derived DENV serotype to produce four chimeric ones YF-DEN viruses recovered in Thailand and Indonesia between 1978 and 1988 and used in the formulation of a tetravalent DENV vaccine (chimerivaxDENV 1-4). Preclinical evaluation of the safety and immunogenicity of the tetravalent chimerivax DENV 1-4 vaccine showed a reduced neurovirulence profile in mice compared to the parental YFV vaccine strain (YF-VAX) .Furthermore ,neurovirulence tests conducted on macaca fascicularis confirmed that the tetravalent chimerivax DENV serotype , as well as limited viremia compared to the DENV parental strains , following a single administration of a high or low dose of the vaccine in cynomolgus monkeys. Interestingly ,challenges studies found that 92% of vaccinated monkeys were protected from challenges with wild animals .

Development of the live attenuation DENV vaccines ,designated TV003/TV005, began in 1996 at the infectious diseases laboratory (LID) of the National Institute of Allergy and Infectious Diseases (NIAID) , Given the importance of untranslated regions (UTRs) in replications of the DENV genome , the initial attenuation strategy focused on deleting 30 contiguous nucleotide (172143)in the TL2 stem -loop from the 3-UTR of DENV-4 (rDEN430). A mutant lacking the same homologous genomic region was also constructed for DENV -1(rDEN130).Both mutant displayed an attenuated phenotype , as demonstrated by their reduced infectivity , and demonstrated their ability to elicit strong neutralizing antibody responses in rhesus macaques that correlated with protection when challenged with wild type of DENV -1 and DENV-4 .Further Efforts The searches for a tetravalent DENV vaccine led to the generation of the attenuated DENV -2 component by using backbone of rDEN430 to generate two attenuated DENV -4 and DENV 2 chimeric viruses in which the membrane and envelope genes (rDEN2/4 30 (ME)) or the capsid , membrane and envelope genes (rDEN-2 /4 30(CME)) of DENV-4 were replaced by the homologous genes of DENV -2 . preclinical studies of the two chimeras showed that both exhibit a highly attenuated phenotype in SCID -HuH-7 mice and in rhesus monkey, in which the chimerization and the 30 deletion were additive , rendering the virus non- infectious to monkey . A chimeric DENV3- DENV4.

Challenges in DENV vaccine Development .

Immunopathological events are a common feature of DENV infection , with multiple underlying mechanism such as: B, an overview proinflammatory cytokines such as granulocyte – macrophage colony -stimulating cytokines growth factor (GM-CSF), macrophage inflammatory protein 1 beta (MIP -1) , interferon gamma (IFN-) and interleukin 10 IL-10, Eventually leading to vascular leaks ,bleeding and some other thrombotic event .Molecular mimicry with E and NS1 viral proteins has been documented to activate cross reactive antibodies against platelets and endothelium ,leading to severe dengue . Furthermore , naturally infected individuals with a DENV serotype who have low levels of anti -DENV antibodies (<1:80) suffer complications from secondary infection with a heterologous DENV serotype . specific antibodies produced during infection represent an essential part of the immune response to neutralize invaders ; However , for the pathogens such as DENV, under certain conditions , antibodies produced during a first encounter can potentiate further .Interestingly ,patient who develop high titres of anti-DENV antibodies (>1:320) show protections against further symptomatic DENV infections.

The infection enhancement process known as antibody -dependant enhancement (ADE)in dengue is well documented , but the details of this event in dengue are not yet known .viral entry is known to be facilitated by Fc and mediates activations of T cells and release of TNF and other cytokines that cause endothelial dysfunction . Therefore , effective DENV serotype to avoid vaccine induced immunopathological events.

Safety issue with Dengue vaccines.

To develop vaccine against dengue fever, it is important that they recognize the four existing serotypes; The three more advanced vaccine have taken this into account in their design. An important consideration in natural infection is that a primary infection with one DENV serotype would established long term memory against that specific serotype, but could result in a short, subneutralizing and enhancing response with the other serotypes. The enhancing phenomenon in subsequent dengue infection with a different DENV serotype could be due to previous heterotypic exposure, and prevention of these events is an ongoing concern in the field of dengue vaccine.

Dengvaxia construct:

Dengvaxia® is a live attenuated tetravalent vaccine consisting of chimeras composed of structural pre-membrane (prM) and envelope (E) genes of the four DENV types in combination with the non-structural genes of yellow fever vaccine strain 17D (chimeric yellow fever dengue – CYD). The chimeric approach originated at St. Louis University and was first used to develop a vaccine construct against Japanese encephalitis.¹² The chimeric technology was later applied to dengue fever at Acambis, Inc., which later became part of Sanofi Pasteur.¹³ The Dengvaxia® parental strains consist of Type 1: Thailand PUO-359/TVP-1140, Type 2: Thailand PUO-218, Type 3: Thailand PaH881/88 and Type 4: Indonesia 1228 (TVP-980).¹⁴ Each monovalent CYD DENV was obtained separately via recombinant deoxyribonucleic acid (DNA) technology. The four chimeric vaccine DENVs were cultured in Vero cells and then combined into a single vaccine formulation.

Phenotypic characterizations showed stable plaque size for each DENV in all production steps. The CYD genomes (DENV-1–4) were fully sequenced according to Good Manufacturing Practices (GMP) standards at various stages of vaccine batch production, from initial passages through pre-master seed batches (PMSL) to master seed batches (MSL), and bulk, and finally at a later step in the process (bulk + 10 passages).¹⁵ Nine point mutations across all DENV types were identified; five at late passage (p10–p21), three in a mixed population with the original sequence, and one silent mutation (all but one were in the nonstructural (NS) regions). The virus morphology observed by electron microscopy was typical of a flavivirus in various stages of maturation (round, smooth particles of about 52–54 nm and barbed or partially barbed particles of about 54–56 nm).^{16,17} The ratio of non-infectious to infectious particles were consistent throughout all production steps.^{18,19} Additional studies examined consistency of protein content using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis, replication potential in insect C6/36 cells, temperature sensitivity, and replication in dendritic cells. Specific intercellular adhesion molecule-3 grabbing of non-integrin-transfected (DC SIGN) cell lines and glycosylation status.

The vaccine is provided in powder and solvent form to prepare a suspension containing an infectious cell culture dose of approximately 5 log₁₀ of 50% (CCID₅₀) of each live, attenuated DENV type. Dengvaxia is a sterile and freeze-dried product that is reconstituted with a sterile solution of 0.4% sodium chloride before injection. The vaccine (freeze-dried product) and diluent are available in a single-dose vial. After reconstitution, a dose (0.5 mL) is administered using a needle into the subcutaneous space (SC). Three doses of vaccine are administered 6 months apart; 0, 6 and 12 months.

Dengvaxia® is considered a genetically modified organism and risk assessments (humans and environment) have been completed.²³ (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-clinical-aspects-live-recombinant-viral-vectored-vaccines_en.pdf, accessed 7 MAY 2019) (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessments-medicinal-products-consisting-containing-genetically_en.pdf, accessed 7 MAY 2019) (https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonization-technical-requirements-registration-pharmaceuticals-human-use_en-10.pdf) (https://www.who.int/biologicals/Clinical_guidelines_revised_IK_29_Oct_2015.pdf, accessed 7 MAY 2019) The possibility of CYD viruses entering the environment was assessed by excretion of vaccine viruses after administration. There were no safety concerns regarding viral RNA shedding in urine and saliva. Dengvaxia® contains no adjuvants or preservatives. A proprietary stabilizer is included in the finished

product. Accelerated stability studies have shown that the vaccine from the phase 3 batches of CYD TDV (single-dose presentation) was stable at 25 ± 2 °C for up to one month and that the virus titer decreased by less than 0.5 log₁₀ CCID₅₀ 7 days at $+37 \pm 2$ °C. The reconstituted vaccine was found to be stable at $+5 \pm 3$ °C for up to 6 hours.¹⁸ No material of biological origin (animal or human) uses drug substance (DS) and drug product (DP). Dengvaxia® does not contain any material of pig origin. Extensive testing for adventitious agents is carried out using in vivo animal testing, in vitro cell substrate testing and molecular assessments of the manufacturing process of seed batches, cell banks and DS.

Preclinical in vitro studies:

When an infected female Aedes mosquito seeks a blood meal and virus particles are introduced intracutaneously, dendritic cells (DCs) are among the first immune cells to come into contact with the virus. DCs are efficient antigen-presenting cells (APCs) and initiate the immune response cascade following DENV infection or immunization. Quote³⁸ The CYD viruses were examined for their infectivity against immature human myeloid DCs and showed that they induced DC maturation with a limited inflammatory cytokine response and expression of type I antiviral interferon (IFN).Quote²¹ These in vitro Results suggest that the vaccine triggers a controlled inflammatory response that promotes efficient antigen presentation, potential adaptive immunity and possibly the safety of acute vaccination.

Conclusion:

Dengvaxia® took more than 20 years to develop and license and cost more than \$1.5 billion. The breadth and depth of the preclinical and clinical development pathways addressed a variety of real and theoretical risks inherent in all vaccine development efforts, some of which were dengue specific. Although two large Phase 3 efficacy trials met the primary efficacy endpoints, long-term follow-up revealed a very concerning safety signal in seronegative vaccine recipients. Additional data generation and analysis confirmed the signal, resulting in a change to the sponsor's requested indication, WHO use recommendations and regulatory approvals. The current storm of political, legal and social disputes continues without a clear understanding of the end result.

Future perspectives:

DENVs are naturally produced as heterogeneous populations. Variations in the prM and E sequences, virion maturation state, and viral respiration strongly impact epitope presentation and interactions with human antibodies, leading to either virus neutralization or enhancement of infection. Most importantly, the presence of anti-DENV antibodies is not sufficient for neutralization and protection; Instead, stoichiometry is influenced by the heterogeneity of the virion surface. Given the well-established correlates of protection against TBE, YFV and JEV vaccines based on measurement of neutralizing antibody titers (1:10 each), this clearly shows that the quality of the antibody response is an important element of protection provided by flavivirus vaccines. Citation 107, Citation 108 Therefore, improving the quality and quantity of anti-DENV NtAbs is a primary goal in the development of next-generation dengue vaccines.

Although a LATV dengue vaccine is currently preferable, it remains a challenge to reproduce all four component strains equally at the correct dosage and to induce balanced serotype-specific NtAbs. If an individual with repeated exposure to different DENV serotypes generally develops a broad immune response sufficient to provide protection against all DENV serotypes, a strategy to induce such broad NtAbs in the next generation dengue vaccine should be developed Be considered.Quote 13 A monovalent universal dengue vaccine capable of broadly inducing NtAbs or a heterologous prime-boost vaccination strategy combined with LAV such as Dengvaxia for immune refocusing could potentially be an alternative solution.

Using systems vaccinology to guide vaccine design through reverse engineering, vaccines that were previously difficult to produce, such as: B. Vaccines against the human immunodeficiency virus (HIV) or the respiratory syncytial virus (RSV). presents quaternary structures and EDE epitopes for the induction of broadly cross-reactive NtAbs with rational help from the current understanding of immune responses in natural DENV infection and is full of potential. Quote¹¹⁰ VLP antigens with repetitive proteins on the

surfaces of antigens enable “cross-linking” of multiple receptors on the surface of B cells. VLPs may be the best candidates for a dengue vaccine because they elicit the strongest and most durable antibody responses, including LLPCs. Citation 111 However, the lack of immune correlates of protection against DENV infection hinders the development of other potential DENV vaccines. Currently, dengue LAVs are still preferred because they trigger both cellular and humoral immune responses similar to those elicited by natural infection. We believe it is essential to apply fundamental knowledge of memory B cell biology, more broadly NtAbs, and virion structural biology to current problematic infections to better guide vaccine design and future research and development.

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