International Journal of Pharmacology and Clinical Research (IJPCR)

IJPCR |Volume 6 | Issue 3 | July - Sept - 2022
www.ijpcr.net

ISSN: 2521-2206

Review article Clinical Review

Review on current scenario of dengue vaccine

Mohd Wasiullah[1], Syed Yasoob Zaidi[2], Yusuf Quraishee[3], Shashikant Maury[4]

[1]*Professor & Principal, Department of Pharmacy, Prasad Institute of Technology, Jaunpur, Uttat Pradesh, India*
[2,3,4] *Department of Pharmacy Prasad Institute of Technology, Jaunpur, Uttat Pradesh, India*

Corresponding Author: Mohd Wasiullah

ABSTRACT

Dengue fever is the most prevalent arboviral disease, caused by one of four separate but closely related dengue viruses (DENV), and it has a considerable economic and public health impact in endemic areas. A dengue vaccine will be critical in furthering illness management. However, the work has been hampered by the need to induce good protection against all four DENV serotypes, as well as the possibility of an unfavourable effect due to the phenomena that partial immunity to DENV may aggravate symptoms upon future heterotypic infection. The most modern dengue vaccines available today are all tetravalent and based on recombinant live attenuated viruses. Sanofi Pasteur's CYD-TDV vaccine has been licenced for use in people who have previously been infected with dengue. Two other tetravalent live attenuated vaccine candidates: TAK-003 by Takeda and TV003 by National Institute of Allergy and Infectious Diseases, have completed phase 3 and phase 2 clinical trials, respectively.

Keywords: DENV, CYD-TDV, Non-Structural (NS) proteins, Clinical Trials, Tetravalent Vaccine.

INTRODUCTION

Dengue fever is a viral disease spread by mosquitoes that is caused by four antigenically diverse serotypes of dengue viruses (DENV1-4). The yearly global dengue incidence is estimated to be around 100 million, and it is increasing due to the expansion of mosquito habitat.[1]

The annual global cost of dengue amounts to about US $8.9 billion in 2016 and is responsible for almost 40000 disability-adjusted life years. [2]

DENV serotypes are divided into four antigenically related groups: DENV1, DENV2, DENV3, and DENV4. DENV is mostly transmitted by mosquitoes (Aedes aegypti and Aedes albopictus), which are abundant in Southeast Asia, India, and South America. DENV serotypes are divided into four antigenically related groups: DENV1, DENV2, DENV3, and DENV4. DENV is mostly transmitted by mosquitoes (Aedes aegypti and Aedes albopictus), which are abundant in Southeast Asia, India, and South America.[3]

Recently, the area suitable for spread of DENV infection and the population at risk of dengue diseases are expected to increase due to climate changes that promote the replication of host mosquitoes. [4]

DENV is predicted to cause about 390 million infections every year, with over 96 million cases of clinical symptoms reported. Until now, research has focused on developing effective vaccinations to protect humans from DENV infection. Despite Sanofi Pasteur's successful commercialization of a dengue vaccine, many are apparently hesitant to get vaccinated due to the vaccine's low efficiency and adverse effects.[5]

The importance of viral Antigens (Ags) and candidate materials in the development of dengue vaccines

DENV is made up of genes that code for the capsid protein, membrane (M) protein, envelope (E) protein, and non-structural (NS) proteins such as NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5 [6]. E protein, which is involved in DENV entry into the host cell, and NS1, which is present on the host cell surface, is now significant prospective Ags for use in a vaccine to induce effective antibodies (Abs) and prevent DENV infection. Furthermore, NS3 and NS5, which

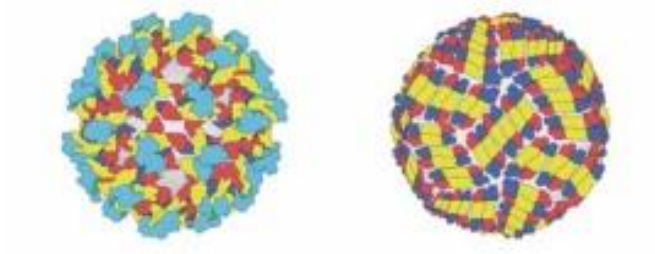
include peptide sequences recognised by human major histocompatibility complex class I, are thought to be key candidate Ags for inducing a cellular immune response to DENV infection. The primary candidate is the basic functions of the DENV proteins. [7]

DENV proteins, like those expressed by other viruses, are classified as structural and NS proteins, with the former including capsid, M, and E proteins. After synthesis, the capsid protein is pre-sent in the cytoplasm and is cleaved by viral proteases (NS2B-NS3). The capsid protein then forms a nucleocapsid and participates in DENV assembly [8]. The E and M proteins are important components of the DENV surface and play a role in DENV infection of host cells. The major protein component of the virus surface is E protein, which occurs as a dimer. E protein is made up of three ectodomains and three transmembrane segments, and each E protein domain (ED) has a different purpose. Domain II of E protein (EDII) is the only ED with a dimerization interface, two glycosylation sites, and a fusion loop. DENV binds to its cognate receptor, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), via a contact between DC-carbohydrate SIGN's recognition domain and the mannose-rich N-glycan on E protein amino acid residue N67 [9].

CD4+ and CD8+ T cell target epitopes are found in NS proteins. CD4+ T cells in humans respond mostly to the capsid, followed by the E, NS3, NS2A/B, and NS5 proteins [10]. CD8+ T cells primarily respond to the NS3 protein, as well as the capsid, NS5, and NS4A/B proteins. As a result, because T-cell epitopes are dispersed in numerous DENV structural and non-structural proteins, both structural and non-structural proteins elicit powerful DENV specific T-cell immune responses. T-cell activity is necessary for virus defence, but T cells also influence immunopathology during heterologous infection. Suboptimal T-cell receptor activation following infection with heterologous DENV serotypes resulted in elevated TNF- and poor antiviral effectiveness, possibly contributing to immunopathology [11].

Selection of candidate vaccine immunogens based on DENV maturation and breathing

Understanding virus maturation is critical in Ab-mediated protection against virus infection since it is linked to the binding of neutralising and infection-enhancing Abs to the virus, as well as virus infectivity. DENV's glycoprotein shell is made up of 180 copies of the E and M proteins with icosahedral symmetry [12]. Because the two proteins have different conformations in immature and mature DENV particles, they contribute distinct structural properties to both immature and mature DENV particles. Premembrane (prM) and E proteins form 90 heterodimers in the immature virion, extending as 60 trimeric spikes from the viral particle's surface. In contrast, E protein in the mature virion is made up of 90 homodimers that lie flat against the viral surface, forming a ring. [13]



Cryo-electron microscopic structure of the mature DENV1 particle with 90 E protein dimers (PDB 4CCT) in surface representation (right). An icosahedral asymmetric unit is indicated by a white triangle, and the icosahedral vertices are marked by white symbols: two-fold, ellipse; three-fold, triangle; and five-fold, pentagon. EDI, E protein domain I; EDII, E protein domain II; EDIII, E protein domain III; FL, fusion loop; S, stem region; TM, transmembrane anchor; pr, precursor peptide; M, membrane protein. [14]

Fig 1: Cryo-electron microscopy image of the structure of the immature DENV1 particle carrying 60 trimeric precursor membrane (prM) E spikes (PDB 4B03) in surface representation (left).

PROTECTIVE IMMUNE RESPONSE

Antibody-Mediated Protection

In DENV infection, humoral immunity is thought to play both a protective and a permissive function. Early mouse investigations revealed that antibody, rather than cell-mediated immunity, was essential for recovery from acute DENV infection [15]. Furthermore, epidemiological evidence suggests that maternal antibodies protect infants from DENV infection during the first few months of life. Solid protection against a second infection with a homotypic DENV has been demonstrated for up to 18 months after primary infection, although it is thought to be much longer, possibly even permanent. The evidence for long-term homotypic immunity comes mostly from in vitro investigations that discovered neutralising antibodies in the sera of people infected with DENV more than four decades ago. [16]

The mechanisms of DENV neutralisation are assumed to involve virus attachment inhibition and virus-mediated membrane fusion. The DENV E protein is thought to be the main antigen involved in virus neutralisation by antibody. The E protein triggers the first and longest-lasting immune responses in humans during primary DENV infection. Studies with monoclonal antibodies (MAb) have confirmed the E protein as a target for neutralising antibodies [17].

Neutralization activity linked well with the ability of E monoclonal antibodies to protect. Although prM monoclonal antibodies were likewise protective, their ability to neutralise did not correlate as well. Following primary and subsequent DENV infection, antibodies to the NS proteins can be identified. Following primary infection, antibodies to C, prM, NS1, NS3, NS4A, and NS5 are found, while antibodies to C, prM, NS1, NS3, NS4A, and NS5 can be detected in the convalescent sera of individuals with secondary DENV infection [18].

CURRENT VACCINE CANDIDATES

Live Attenuated Vaccines

In vaccination, live attenuated vaccines (LAV) use live but less aggressive microorganisms. As a result, they can induce the whole repertoire of antigens essential for long-term immune protection . LAVs for additional flaviviruses, such as yellow fever (YF) and Japanese encephalitis virus (JEV), have been produced effectively. With a single dosage, the YF-17D and JEV SA14-14-2 vaccines show more than 90% long-term effectiveness. Because normal dengue infection causes life-long homotypic protective immunity, LAVs are predicted to replicate natural infection and promote both cellular and humoral immune responses to provide long-term protection. The three most advanced dengue vaccines, Sanofi Pasteur's CYD-TDV, Takeda's TAK-003, and the National Institute of Allergy and Infectious Diseases' (NIAID) TV003/TV005, all use recombinant live attenuated dengue virus.[19]

CYD-TDV Dengue Vaccine

The only licenced dengue vaccine at the moment is Sanofi Pasteur's tetravalent live attenuated CYD-TDV vaccine. CYD-TDV starts with the yellow fever 17D (YF17D) vaccine strain and replaces the YF17D prM and E regions with those of the four DENV serotypes. Overall vaccination effectiveness (VE) ranged from 56.5 percent to 60.8 percent. Specific protection against DENV3 and DENV4 was greater than 70%, while protection against DENV1 and DENV2 was 40% to 50%. [20].The baseline serostatus influences VE as well. Because seropositivity rates in an endemic setting normally increase with age, age is frequently utilised as a surrogate for DENV exposure [21]. Despite the fact that vaccine protection can persist up to four years , the risk of hospitalisation for vaccines rose three years after immunisation . Several clinical investigations in Asia and Latin America on CYD-TDV found that it was less effective against DENV2. One probable explanation for the formulation's overall low efficiency is a paucity of DENV non-structural (NS) proteins. The majority of the conserved epitopes across the four DENV serotypes were found in the NS proteins, according to an analysis of the conserved epitopes. The lack of neutralising antibodies (nAb) and CD8 T cell immune responses against the NS proteins may contribute to the CYD-lower TDV's protection and durability [22].

Several ideas have been proposed to explain the higher likelihood of hospitalisation and serious illness in seronegative patients. As previously stated, ADE is a feature of DENV infection caused by increased entry of antibody-virus complexes into phagocytic cells via Fc-gamma receptors. Natural DENV infection or vaccination can induce three types of antibodies: serotype-specific neutralising antibodies (nAb), cross-reactive antibodies, and broad neutralising antibodies (bnAb). Serotype-specific antibodies are preferable to cross-reactive antibodies because they bind serotype-specific epitopes and only neutralise the specific DENV serotype [23]. Serotype-specific antibodies have also been demonstrated to be reliable predictors of protection in human dengue infection. In contrast, cross-reactive antibodies bind but do not neutralise DENV infection [24].

Immunogenicity of CYD-TDV Tetravalent Dengue Vaccine

In Preclinical Studies: Each recombinant, live-attenuated DENV vaccine expresses the pre-membrane and envelope genes of that specific wild-type DENV on a YF 17D backbone, and is generated in serum-free Vero cells using recombinant DNA technology . The four recombinant DENV serotype viruses are mixed into a single freeze-dried vaccine (i.e. CYD-TDV), which contains no preservatives or adjuvants; the dose of each DENV serotype in the vaccine is 4.5–6 log10 of the 50% cell culture infective dose (CCID50) . The four wild-type DENVs employed in the development of CYD-TDV are the Thai strain PUO-359/TVP-1140 for serotype 1, the Thai strain PUO-218 for serotype 2, the Thai strain PaH881/88 for serotype 3, and the Indonesian strain 1228 (TVP-980) for serotype 4 [24].

In Clinical Trials*:* This section focuses on large (n[150]), observer-blind, placebo-controlled, multicenter, phase 2 or trials in healthy children and/or adults that assessed the immunogenicity of the recommended three-dose regimen of CYD-TDV (given at 0, 6, and 12 months) (Table 1). All research followed WHO criteria for the production of live-attenuated vaccines. These findings are confirmed by findings from phase 2b and protective efficacy trials (n[4000 randomized/trial and single-center, phase 2 immunogenicity trials (n C 150) , which all employed the identical three-dose CYD-TDV vaccination schedule. Evidence from phase 1 research adds to the case for CYD-immunogenicity TDV's. The equivalence of immune responses elicited by three consecutive batches of CYD-TDV from the scaled-up production process was shown in a placebo-controlled, multicentre study in flavivirus-naive adults [25].

The plaque reduction neutralisation test (PRNT) was used to assess immunogenicity at baseline and 28 days after each dose, with geometric mean titres (GMTs) expressed as the highest reciprocal serum dilution (dil-1) at which the mean number of plaques was reduced by 50% compared to control wells (i.e. the PRNT50 antibody titre) . A PRNT50 antibody titre of C10 dil-1 was considered seropositive for each unique DENV serotype. CYD-TDV produced CYD specific cell-mediated T helper 1 (Th1) immune responses and anti YF 17D NS3 specific CD8 responses in clinical trials, with preclinical investigations supporting these findings. [26]

TAK-003 Dengue Vaccine Candidate

Takeda's dengue vaccine candidate (TAK-003) is based on the molecularly defined DENV-2 PDK-53 strain (TDV-2). Three more recombinant chimeric viruses were created utilising the TDV-2 backbone but with the DENV-2 prM and E genes replaced with those from DENV-1 16007 (TDV-1), DENV-3 16562 (TDV-3), and DENV-4 1036 (TDV-4) viruses (44). TDV1-4 are combined to make the tetravalent live attenuated dengue vaccine TAK-003.[27]

Phase 1 Clinical Trials: Based on preclinical investigations and differences in nAb titers against different DENV serotypes, it emerged that the component ratio of the tetravalent vaccination was crucial for vaccine efficacy . In placebo-controlled phase 1 clinical trials, two formulations, a low-dose formulation and a high-dose formulation, were evaluated. The low-dose formulation contained 8 103, 5 103,

1 104, and 2 105 PFU of TDV1, TDV2, TDV3, and TDV4, in a ratio of 3.6 percent: 2.3 percent: 4.5 percent: 91.0 percent, whereas the high-dose formulation contained 2 104, 5 104, 1 105, and 3 105 PFU of TDV1, TDV2, TDV3, and TDV4, respectively, in a ratio of 4.3 percent: 10.6 percent. [28]

Phase 2 Clinical Trials: The DENV-naive subjects were used in the phase 1 trials. However, it is critical to assess the safety and efficacy of dengue vaccinations in people that have already been exposed to dengue (DENV-exposed). As a result, in addition to DENV-naive participants, the high-dose TDV formulation was assessed in phase 2 clinical trials in persons who were seropositive for at least one DENV serotype at baseline (DENV-exposed). Similar to the results of the phase 1 trial, no serious adverse events associated to vaccination were documented, with the majority of adverse events being injection site pain and erythema . There was also no increase in adverse events or vaccination virus replication in DENV-exposed subjects. As a result, it appears that preexisting antibodies did not increase reactogenicity or viral magnitude.[29]

Phase 3 Clinical Trials: TAK-003's efficacy was assessed in a phase 3 double-blind, randomised, placebo-controlled experiment (ClinicalTrials.gov NCT02747927) (61, 62). This study included healthy children and adolescents aged 4 to 16 years old from eight dengue-endemic countries. Three months apart, two doses of vaccination or placebo were given. TDV-1, TDV-2, TDV-3, and TDV-4 PFU were present in 4 103 (3.6 log10), 1 104 (4.0 log10), 4 104 (4.6 log10), and 1.2 105 (5.1 log10) PFU in each dose of TAK-003. [30]

Comparison of CYD-TDV And TAK-003 Vaccine Efficacies To DENV Serotypes

Both The vaccines CYD-TDV and TAK-003 are tetravalent live attenuated viruses. The prM and E proteins from each DENV serotype are produced from the YF17D backbone and formulated into a tetravalent vaccine in CYD-TDV. However, protective efficiency against different DENV serotypes varied significantly: best against DENV3 and DENV4 and lowest against DENV2. Similarly, in TAK-003, each DENV serotype's prM and E proteins are produced from the DENV2 backbone and made into the same tetravalent vaccine. However, DENV2 protection efficacy was highest and DENV4 protection efficacy was lowest. The observed disparities in protective efficacy between the two vaccinations are most likely due to a combination of variables. The results tend to indicate that the serotype-specific DENV components (prM and E) in the two vaccine formulations have differing immunogenicities. This could be owing to intrinsic variances in immunogenicity of prM and E from distinct DENV serotypes, as well as discrepancies in the four chimeric viruses' infectivity and replication. Antigenic interference or rivalry between the four chimeric viruses in the tetravalent vaccines, particularly when the same amount of each chimaera virus was employed, may also impair the balanced creation of nAb against all four serotypes. Despite Takeda's efforts to modify the formulation component ratios in order to elicit a more balanced response, the improvement achieved was little. Despite adjustments in vaccine composition during phase 2 and phase 3 trials, the geometric mean titer of nAb remained unbalanced, with anti-DENV4 being the lowest and anti-DENV2 being the highest. [30, 24]

Other live-attenuated and inactivated virus vaccines

TDENV-LAV, a tetravalent live-attenuated vaccine, and TDENVPIV, a tetravalent purified inactivated vaccine, are being tested in clinical trials by the US Walter Reed Army Institute of Research (WRAIR) and GlaxoSmithKline (GSK) [31]. TDENV-LAV was tested in a clinical phase II experiment, which included all DENV serotypes in a tetravalent formulation that had been attenuated in PDK and Rhesus lung cells. The findings validated TDENV-safety LAV's and immunogenicity. For example, on days 0 and 180, tetravalent formulation 17 of TDENV-LAV was injected subcutaneously into the deltoid, and sera were collected 28 days later. According to the findings, tetravalent neutralising Abs were produced in 63% of the patients. Subjects with a high level of neutralizing Abs against all DENV serotypes were selected and the presence of type-specific and crossreactive Abs analyzed . The results showed that TDENV-LAV induced type-specific Abs against DENV2 and DENV4. In addition, neutralizing Abs against DENV1 and DENV3 were identified as cross-reactive.[32].

Subunit and virus-like particle vaccines

E protein is involved in DENV binding to host cell receptors, and Abs specific to E protein exert neutralizing effects. Consequently, extensive research has been conducted on the development of subunit recombinant protein vaccine using E protein. Merck and Hawaii Biotech conducted a pre-clinical trial using a C-terminal 80-amino acid-truncated E protein (DEN-80E). Non-human primates were vaccinated with a tetravalent-DEN-80E formulation with ISCOMATRIXTM adjuvant at different concentrations in two immunization regimens (0, 1, and 2 months versus 0, 1, 2, and 6 months). When formulation group 11 (3 μg each of DEN1-80E, DEN2-80E, and DEN4-80 and 6 μg DEN4-80E) was used for vaccination in the regimen conducted at 0, 1, 2, and 6 months, high levels of neutralizing Abs were induced, and viremia was not observed in the DENV1–4 challenge experiment.[32]

Other Dengue Vaccine Candidates

TV003: The National Institutes of Health's National Institute of Allergy and Infectious Diseases (NIAID) in the United States created this vaccine, also known as TetraVax-DV. TV003 is a live attenuated tetravalent dengue vaccine that combines different vaccine formulations for all four dengue serotypes. In a human challenge model, the vaccination previously demonstrated full protection against dengue. As of February 2019, the vaccine is being tested in a Phase II randomised, doubleblind, placebo-controlled clinical trial in Taiwan with 56 healthy adult volunteers. [33].

TDENV-LAV: TDENV-LAV stands for tetravalent dengue live-attenuated vaccine, and it comprises all four dengue serotypes. The Walter Reed Army Institute of Research (WRAIR) in the United States and GlaxoSmithKline collaborated to create this vaccine (GSK). It is currently undergoing two clinical trials, both in Maryland, USA. The Phase I clinical trial has enrolled 40 healthy volunteers aged 18 to 42 years and is scheduled to

conclude in January 2022. The Phase I/II clinical trial has enrolled 140 healthy volunteers aged 20 to 49 years and is scheduled to conclude in June 2019.[34]

TDENV-PIV: TDENV-PIV stands for tetravalent dengue purified inactivated vaccine, and it consists of a tetravalent vaccine formulation comprising all four dengue serotypes. This vaccine, like TDENV-LAV, was developed together by GSK and WRAIR, USA. It has already completed a Phase I randomised, open-label, single-center clinical trial with 100 healthy volunteers aged 18-39 years. This experiment was conducted in Maryland, USA, and concluded in September 2018.[35]

V180: This is a recombinant protein-subunit dengue vaccine produced in cells of the fruit fly (Drosophila melanogaster). This vaccine, developed by Merck Sharp & Dohme (MSD), has completed Phase I clinical trials in 98 healthy volunteers aged 18-49 years. The trial was completed in December 2014. [36]

TVDV: This is a tetravalent "shuffled" prM/E-expressing plasmid DNA vaccine, developed by WRAIR and the US Naval Medical Research Centre (NMRC), USA. This DNA vaccine has completed Phase I clinical trials in 40 healthy volunteers aged 18-50 years in Maryland, USA. The trial was completed in December 2013.[36]

OBSTACLES TO DENGUE VACCINE DEVELOPMENT

In contrast to the well known kinds of infection associated with other viruses, DENV demonstrates ADE. In ADE, non-protective or less neutralising pre-existing Abs that bind to DENV promote DENV infection. DENV ADE has recently been characterised as extrinsic and intrinsic ADE. DENV-induced prM and fusion-loop Abs, for example, promote immature DENV entrance into host cells via the Fc receptor and drive greater DENV uptake into host cells, allowing for an increase in viral reproduction (extrinsic ADE). The immune-complexed DENV enters host cells via the Fc receptor, suppressing intracellular cytokine signaling and promoting a permissive environment for increased DENV reproduction (intrinsic ADE).[37]

Impediments towards Development of an Ideal Dengue Vaccine

Several dengue vaccine candidates have been developed over the last few decades, but none have proven to be successful, until now. Creating a dengue vaccine is a difficult task. This is due to the fact that four dengue virus serotypes (DENV-1 to DENV-4) circulate, with one type predominating during each dengue season. It is difficult to chemically weaken the virus so that it does not cause sickness while yet eliciting an immune response that gives protection. This is because all four serotypes require similar levels of attenuation. Sanofi Pasteur has overcome this barrier by developing the world's first licenced dengue vaccine.

CONCLUSION

According to the preceding discussion, several promising dengue vaccine candidates are now in the pipeline, both in the governmental and private sectors. Dengvaxia® is the only WHO-approved dengue vaccine available to date. Regardless of the current controversy, if this vaccine is integrated into overall dengue prevention programmes in dengue-endemic countries, it has the potential to achieve the WHO targets of lowering mortality by 50% and morbidity by 25% by 2020. Although there are many challenges in generating successful dengue vaccines, successful vaccine development is getting closer thanks to major recent research efforts.

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