Article Review
International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Dengue Vaccine Development at The Dengue Virus Serotypes

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ARTICLE INFO

Keywords:
Dengue hemorrhagic fever (DHF), DENV, Vaccine

Submission,
15 November 2019
Review,
30 November 2019
Publish,
9 December 2019

ABSTRACT

Dengue hemorrhagic fever (DHF) is a disease caused by dengue virus (DENV1-4) and is transmitted by the Aedes aegypti mosquito. However, in 2015, official data from the member countries, WHO reported more than 3.2 million cases, including 10,200 severe dengue cases and 1181 deaths. The protein encoded by the genome of dengue virus. Major structural and non structural proteins making up the genome of dengue. From genomic data several studies found that mechanism of vaccine that can use in dengue virus. Several vaccines was establish in the world for example Live attenuated Vaccine, Chimera Vaccine, Subunit Vaccine, DNA vaccines DENV, Activated DENV Vaccine - Whole Virus Particles, Activated DENV Vaccine - Recombinant Subunit DENV, and DENV Vaccine 5.

Introduction

The incidence of dengue fever are increasing each year and increase dramatically over the last few years. Existing data indicate approximately 50-100 million cases of dengue fever and 500,000 cases of dengue hemorrhagic fever occur worldwide, with 22,000 deaths (especially in children). In 2015, official data from the member countries, WHO reported more than 3.2 million cases, including 10,200 severe dengue cases and 1181 deaths. An estimated 2.5-3 billion people (about 40% -50% of the world population) are estimated at risk of dengue infection. Recent estimates have found that 128 countries around the world at risk of dengue infection, which includes 36 countries once classified as dengue fever free. The only continent that has not undergone the transmission of dengue fever is Antarctica. (Darvin, 2019).

Dengue hemorrhagic fever (DHF) is a disease caused by dengue virus (DENV1-4) and is transmitted by the Aedes aegypti mosquito. DENV belong to the genus Flavivirus and family Flaviviridae and consists of four serotypes that is DENV1, DENV-2, DENV-3 and DENV-4 (Guzman and Harris, 2015). DENV infection can occur with varying intensity, ranging from asymptomatic to severe with symptoms such as Dengue Shock Syndrome (DSS). The vaccine is expected to induce a humoral response against the proteins contained in the vaccine causing a protective immune response against dengue virus (Khetarpal and Khanna 2016).

The Genome of Dengue

Dengue vaccine development efforts of an Open Reading Frame (ORF) were faced with the challenge capable of creating encodes two different proteins are structural and non-vaccine for all serotypes of Dengue virus, the dengue-1, dengue-2, dengue-3 and dengue-4. Monovalent vaccine is a vaccine for one serotype of dengue virus serotypes other, so the vaccine is not effective. Infection with one serotype immunity against the virus causing serotypes, but no cross-protection against other serotypes.

Dengue vaccine development is inseparable from the study of genome structure of Dengue itself to be able to find suitable vaccine candidate targets. Dengue virus particles comprising a ribonucleic acid genome that surround the "ecosehedral" nucleic capsule wrapped with a 10 nm thick fat derived from the host cell wall membranes comprising envelope proteins and membrane walls. Dengue virus is composed of 10,700 bases in the genome consists of a positive sense single-stranded RNA (ssRNA). The genome of dengue virus has an Open Reading Frame (ORF) which encodes two different proteins are structural and non-structural (NS), namely NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5 characterized by a 5 'and 3' non-translated region (NTR) at both ends. Non-structural proteins largest portion (75%, Figure 1. A) consisting of NS-1 to NS-5 (Figure 1.B and 1.C). The ability to stimulate the formation of antibodies (immunogenicity) is the highest among strukturaladalah protein envelope protein (E) then precursore Membrane (PRM) and capsid (C). In the non-structural proteins that were most responsible is NS1 (Figure 1.B and 1.C).

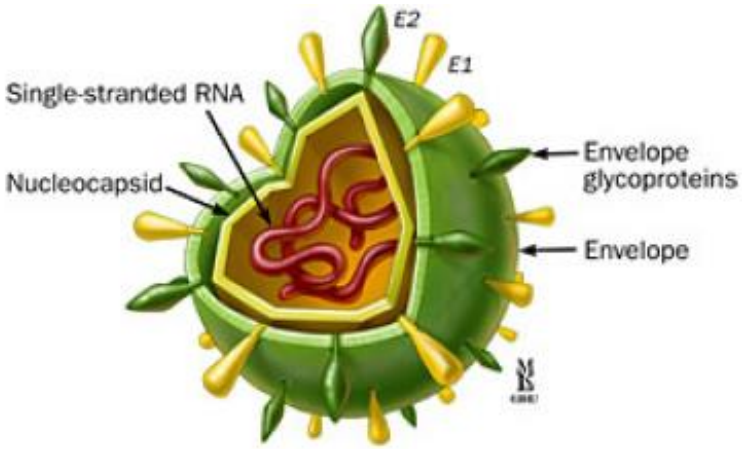

Figure 1.A: protein flavivirus

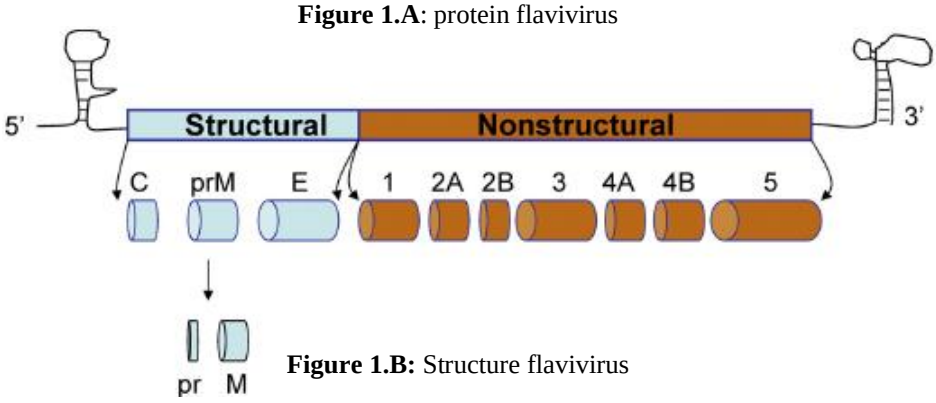

Figure 1.B: Structure flavivirus

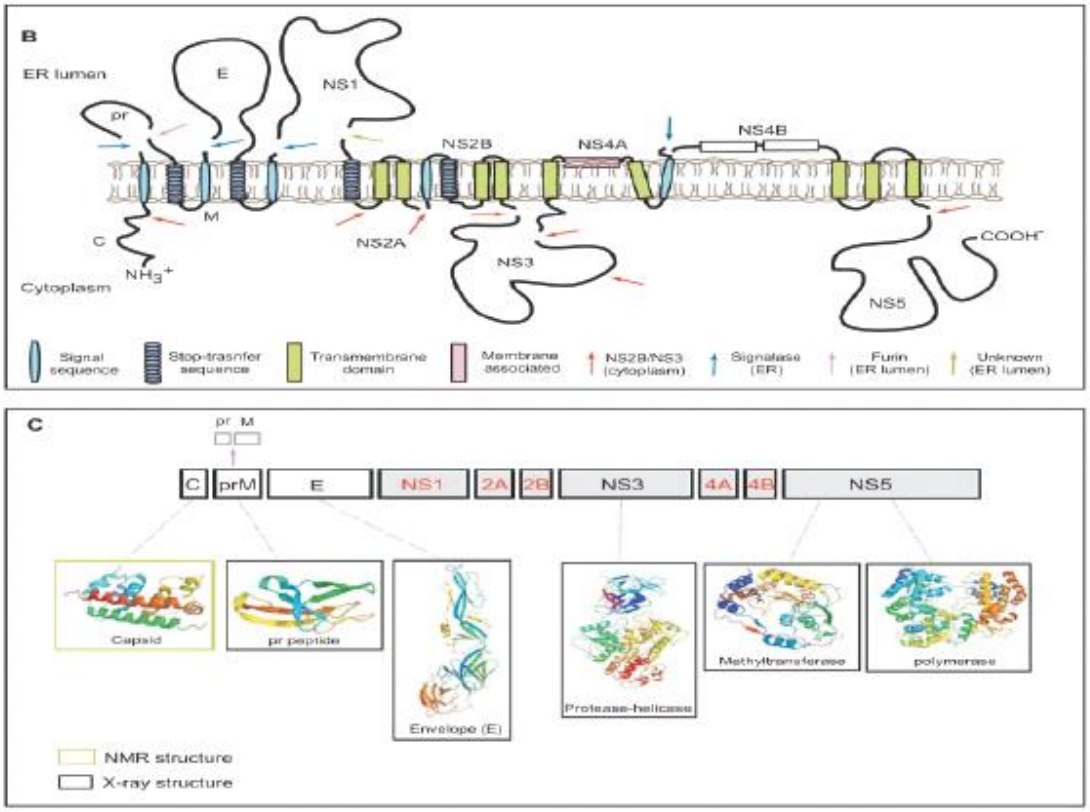

Figure1.C: The protein encoded by the genome of dengue virus. Major structural and non structural proteins making up the genome of dengue (A), dengue virus polyprotein cutting scheme to remove a single protein (B), Schematic three-dimensional protein making up the genome of dengue (C)

Another protein which has been developed as a vaccine candidate is the E protein because it has an important role in virus attachment and fusion process on host cells. Protein E is also a major target of neutralizing antibodies. E protein is a structural protein that has the ability to withstand high. The flavivirus E protein has 12 cysteine residues that form intramolecular disulfide bridges 6. E protein mutations have a major impact on the change in the virulence of dengue virus and other flavivirus species. Protein E recognize all strains of the virus and has a molecular weight support as candidate vaccines, but require the carrier as an immunomodulator that stimulates B cells (B lymphocytes) and Th cells (T helper) to induce the production of antibodies through the expression of cytokines, resulting in antibody titer higher. E protein has a high hydrophobic properties, contains a lot of histidine and stable nature. Therefore, developed the E protein recombinant Baculovirus results are then used as a subunit vaccine clones. Epitopes of protein E contains many amino acids that stimulate the formation of antibodies neutralisasi through acidic compartments that are secreted through the Golgi complex. E protein is secreted by cells in vivo tissue has a high reactivity and the level of optimal immunogenicity as vaccine subunit clones. Model Baculovirus expression with security, obtain a stable protein and virus-like particles, making it ideal developed as a multivalent dengue vaccine. Therefore, developed the E protein recombinant Baculovirus results are then used as a subunit vaccine clones. Epitopes of protein E contains many amino acids that stimulate the formation of antibodies neutralisasi

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Classification of vaccine

Live attenuated Vaccine (LAV)

LAV is the vaccine most economical and affordable, especially in developing countries, namely types tetravalent vaccine derived from attenuated live virus, economical because its development is very easy. Conventionally attenuated viruses, ie repeatedly regenerate specific cell lines that power the infection is paralyzed, but the nature of imunogeniknya maintained. Both live attenuated tetravalent vaccine developed produce high seroconversion for all serotypes in clinical trials. Some virus serotypes were combined, may result in an imbalance of the immune response that causes the severity of the dengue patients. Dosage formulations and vaccination schedule is important to adjust the immunogenicity of the four components of the vaccine. Reaktogenisitas related issues, a study by Avantis Pasteur's vaccine candidates temporarily suspended. Meanwhile, a phase II study by GlaxoSmithKline showed reactivity very little research on the subject (Chit Laa Poh, 2018). Tetravalent neutralizing antibody response has also been achieved in 63% of subjects in two doses penggunaan.19 Until now, studies have been conducted to phase III. Around 2015, LAV will be finished and ready to be marketed in accordance with the recommendations of WHO in vaccine development program.

1. Chimera Vaccine

Progress of genetic engineering technology has been able to construct a chimera virus in the form of substitution of

a specific protein from a virus on other viruses. Construction virus protein chimeras with the substitutions PRM / env of each type of gene homologous DENV in the yellow fever virus (YFV) strain 17 D (ChimeriVax- DEN) and LAV DENV2. Chimera tetravalent vaccine that uses YFV 17D strain capable of producing neutralizing antibodies and protection against viremia DENV1-4 in the evaluation of pre-clinical trial studies and phase I. Phase II clinical trials are underway in several countries. Phase III clinical trials being conducted in Australia. Chimera tetravalent vaccines which use DENV2 strain vaccine also proved immunogenic and protective. Clinical trials phase I still do to this day. Chimerisasi strategy can produce an ideal vaccine, but the possibility of genetic recombination with a virus that is virulent can still occur. Construction ChimerVax-DEN vero cells by electroporation with RNA transcription cDNA prepared from virus. Pre-clinical studies indicate that the vaccine candidate is able to replicate, are genetically stable and non neurovirulen on vero cells. The vaccine was also safe and have protective properties in a series of evaluations conducted.

In general, the results showed that the vaccine is safe and well chimera immunogenicity and protective efficacy however, clinical trials need to be done to ensurenew hope for the development of engineering vaccines in other diseases such as tick-born encephalitis, japanese encephalitis (JE) and west nile virus.safety and efficacy of further protective in humans. The development strategy chimera virus intonew hope for the development of engineering vaccines in other diseases such as tick-born encephalitis, japanese encephalitis (JE) and west nile virus.

2. Subunit Vaccine

Subunit vaccine is made from a specific part of microorganisms, such as the use of the E protein of recombinant to get the optimal protection. Analysis of virulence using vero cell culture found 8 strains of all four serotypes, and 4 strains of which was selected as the recombinant material. Once purified and analyzed reactivity, recombinant E protein showed a high immunogenicity properties. The trial vaccine trials in animals also showed the recombinant protein E has antigenitas properties and high immunogenicity. The weakness of the development of this vaccine is more expensive than a live attenuated. Another vaccine development is a DNA vaccine designed to insert multiple genes into a plasmid vector virus, and is packed with other DNA that is immunogenic strong. Structural and genetic elements DNA vaccine consists of two main units. The first unit is a plasmid propagation unit that serves as a control DNA replication of plasmid propagation in vitro in bacterial cells, in accordance with the desired amount and volume at the time of production. The second unit is a DNA fragment containing a gene vaccine that was cloned into plasmid DNA. DNA vaccine is a vaccine that is safe to use in humans.

3. DNA vaccines DENV

Technology in the form of a plasmid DNA vaccine expressing viral antigens in the development of a vaccine to induce an immune response against a variety of viruses including DENV. The first attempt to use DNA in vaccine development DENV done by Kochel et al. In the study conducted env gene cloning and plum on eukaryotic expression plasmid vector then

inoculated intradermally different mice. As a result, there is the formation of anti-dengue antibodies in 60% of experimental mice. Study Putnak et al also reported the induction of a neutralizing antibody to DENV on the use of similar vaccines such as the study of Kochel et al. Furthermore found a regimen consisting of two doses of 1 microgram of DNA can provide protection up to 1 month. For long-term protection is needed revaccination and the higher dose. Raviprakash et al evaluate strategies to increase levels of neutralizing antibodies at the same time protection against viruses. Evaluation of the use of plasmid granulocyte macrophage-colony stimulating factor (GM-CSF), immunostimulatory sequences (ISS), a combination of GM-CSF and ISS. The result is a neutralizing antibody titer is stable for 6 months after vaccination and 87% of the study population are protected from viremia. The highest antibody response was obtained on the use of GM-CSF plasmid.

4. Acctivated DENV Vaccine

Enterprises producing activated DENV vaccine has existed for approximately 60 years but obstacles continue to appear because it is difficult to produce good quality virus through the existing technique. Currently with fetal lung diploid cell culture and vero cells can be generated with a titer tinggi.18 DENV vaccine candidates were prepared from whole virus particles or recombinant subunit protein DENV.

5. Activated DENV Vaccine - Whole Virus Particles

Putnak et al develop DENV purified vero cell culture with sucrose and inactivated in 0.05% formalin at a temperature of 22oC. After inactivation, the virus still has high antigenicity and immunogenicity were seen in high titer neutralizing antibodies in mice experiments. Development of the vaccine provides satisfactory results in the early stages of pre-clinical trials and is currently undergoing clinical trials scheduled phase I.

6. Activated DENV Vaccine - Recombinant Subunit DENV

Progress of molecular biology techniques to facilitate recombinant subunit vaccine for a different virus. Most of the effort was the production of recombinant env and NS1. To trigger an immune response is good, then the recombinant protein is secreted extracellular necessary. This can be done through the env protein expression and PRM. The results show there is a significant protection against DENV infection. Development of a vaccine with these techniques has also been done on the JE and TBE with satisfactory results. Therefore, this type of vaccine is highly promising. Furthermore, required the development of recombinant protein production methods as well as the latest adjuvant and better.

7. DENV Vaccine 5

A study stated DENV-5 has been detected during the inspection of samples of the virus taken from a 37-year-old farmer admitted to hospital in the state of Sarawak Malaysia in 2007. The infection of the farmer originally thought to be an ordinary case of dengue fever caused by sylvatic DENV-4 were circulated among primates and nivalis aedes mosquitoes in the jungles of Southeast Asia. After a phylogenetic analysis spacious, has been hypothesized that the previous four lineages of dengue virus develops in the reservoir primates

thousands of non-human years ago and then jump over these progenitor sylvatic human ancestors for grouping strains of sylvatic with human strains as a result of increased activity human. sylvatic transmission cycle-this DENV ancestor still exists and is maintained in primates and Aedes mosquitoes in the jungles of Southeast Asia and West Africa.

Detection of DENV-5 has also raised speculation that theremight bemore serotypes unidentified till date. More research is being done to address the unanswered questions on the evolution of DENV-5.

Spillover now sylvatic DENV-5 shows that adaptivebarrier for the emergence of sylvatic DENV inhumans is either non-existent or too low to be of significance. Therefore, even if the vaccination program using the tetravalent vaccine capable of controlling dengue is present for a time; which longtermprospect dengue eradicationmaynot feasible because the presence of sylvatic DENV reservoir in the forest canopy. Therefore, the development of dengue vaccines should be seen only as an adjunct to other public health measures such as vector control, community participation and political will (Mustafa, 2015).

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