Malaria is a disease caused by parasites. As we know that parasites have 3 life cycles while it’s on the human host: pre-erythrocytes phase, blood-stage phase, and transmission-blocking phase. As for now, the medicine for malaria disease is artemisin combination therapy which is going to be resistant, so people try to develop a vaccine for malaria to meet the goal of malaria eradication. One of the vaccines developed is RTS,S/AS01. RTS,S/AS01 is pre-erythrocytic vaccine that confers efficacy against controlled human malaria infection in about 22% in healthy malaria 5 months after vaccination. In clinical trial phase 3, RTS,S/AS01 was 26% in young infants and 36% in children (Ishizuka et al., 2016). Eradication of malaria needs vaccine protection of more than 80% and has protective efficacy for more than 6 months. Therefore, the development of a malaria vaccine is still needed. Another malaria vaccine is PfSPZ. PfSPZ is pre-erythrocytic stage vaccine similar to RTS,S/AS01. It is whole attenuated sporozoite Plasmodium falciparum.

The study performed in volunteers subject vaccinated showed 13/14 subjects protected against controlled human malaria infection 2 to 10 weeks after last vaccination, 5/6 were protected 10 months and 7/7 were protected against controlled human malaria infection heterologous strain of Plasmodium falciparum (Hoffman, Vekemans, Richie, & Duffy, 2015). As a new vaccine development, PfSPZ is in process of a Clinical Development Plan (CDP). There are 4 stages of CDP, (1) to establish the safety and efficacy, (2) to test the vaccine on elderly and HIV seropositive populations, (3) clinical trials, (4) to use the vaccine for mass administration. PfSPZ currently undergoes the first stage to establish: (1) Reproducibility of the tolerability, immunogenicity, safety, and efficacy, (2) Durability of its protection for minimal 6 months after vaccination, (3) Its protection against Plasmodium falciparum’s heterologous strain after Controlled Human Malaria Infection (CHMI) and from natural Plasmodium falciparum’s infection in Africa, (4) protective efficacy and immunogenicity after previous exposure in Africans, (5) predictive protection immunological assay, (6) route feasibility of mass administration, (7) predictive efficacy of a decreased number of doses, (8) tolerability, safety, efficacy and immunogenicity of IV injection and Direct Venous Inoculation (DVI) (Hoffman et al., 2015).

PfSPZ has a protective mechanism by enhancing CD8 T cell and CD4 T cell. PfSPZ vaccine induces PfSPZ specific antibody and cytokine TH1 produce CD4 T cell and γδ cell in the blood. Plasmodium falciparum specific antibody was determined by stimulating peripheral blood mononuclear cell (PBMCs) for CD4 T cell responses or Pf infected erythrocytes (PfRBC) for CD8 T cell (Ishizuka et al., 2016). The protective efficacy of PfSPZ depends on the dose per vaccination and the number of vaccinations. In the study about protection and immunogenicity after 1-year PfSPZ vaccination, the estimated vaccine efficacy against Controlled Human Malaria Infection done 3 weeks after immunization was 24% with 3 doses of 2.7x105 compared to 4 doses of 2.7x105 was 73%. Similarly, 4 or 5 doses of 1.35x105 conferred 25% efficacy compared to 4 doses of 2.7x105 conferred 55% efficacy. It shows that the greater number of frequency and dose, the greater vaccine efficacy.

Route of administration influenced vaccine efficacy. For the first time clinical trial, PfSPZ was administered by subcutaneous and intradermal. The safety of administration is tolerability but the result shows poor immunogenicity. It was unknown whether the vaccine was not potent or the route of administration was not efficient. Therefore, the next study was performed in nonhuman primates by intravenous. The result showed a better immunogenicity effect. The study of protection against malaria at 1 year and immune correlation following PfSPZ vaccination by Ishizuka et al in 2016 assessed immunogenicity based on the route of administration. The trial compared immunogenicity by subcutaneous, intradermal, intravenous, and intramuscular. The results showed that intravenous administration gives immunogenicity better than subcutaneous and i.d. at dose 1.35 x 105 PfSPZ. Intramuscular administration was found less effective than intravenous administration (8/8 parasitemic subject by i.m. administration at 4 doses of 2.2 x 106 versus 5/11 parasitemic by i.v. administration at 4 doses 2.7 x 105). In the trial with Mali adult as subject, PfSPZ vaccine gives by Direct Venous Inoculation. This route of administration was safe, protective, and well-tolerated for the subject. The vaccine protective efficacy was about 48% at first positive blood smear (Sissoko et al., 2017)

Based on Ishizuka et al’s trial in 2016, the efficacy of PfSPZ vaccine, after first CHMI (3 weeks after last vaccination) show the antibody responses were highest and subject may reduce PfSPZ’s number successfully invade hepatocytes, followed by rapid elimination of the remaining parasites in the liver by cellular responses. At the time of second CHMI (21-25 weeks and 59 weeks), the level of antibody was lower and more parasites reach the liver after CHMI. At this time, there was an activation of PfSPZ specific CD4 T cell to eradicate sporozoite in the liver stage (Ishizuka et al., 2016).

PfSPZ vaccine trial in Tanzanian evaluates the safety and T cell responses and differential antibody in different ages (infant, children, adolescent, and adult), the subject was injected with the PfSPZ vaccine by direct venous inoculation with 3 doses of 9.0 x 105. PfSPZ vaccine was safe for all group ages. T cell responses were highest in the 6-10 year
group after 1 dose and 1-5 years after 3 doses. No significant T cell responses in infants. These poor responses of T cells may be caused by the skewed Th2 responses in infants. Since PiSPZ vaccine is thought to rely on T cell responses for its protection mechanism (Jongo et al., 2019). This study may indicate that children will be protected against Plasmodium falciparum infection after 3 doses at 8 weeks intervals but not infants. The differential antibody for different ages does not significantly differ by statistical analysis due to the small sample size, but the level of antibodies was 31 times lower in Mali adults than in US adults and 4.3 times lower in Tanzanian adults. The result could be due to an immune dysregulation after long-term exposure to Plasmodium falciparum parasites and antibody responses would be higher in children and infants than in adults with long-term exposure in malaria-endemic areas (Jongo et al., 2019).

PiSPZ not only tested against Plasmodium falciparum parasites homologous but also heterologous strain. the study done by six of the nine subjects who were not parasitemic after homologous CHMI underwent heterologous CHMI. 5 subjects of 6 subjects vaccinated remained non-parasitemic (95% CI, 36-99%) (Lyke et al., 2017).

References


