Evaluating memory B responses and antibodies induced variant surface antigen recognition of a vaccine candidate for malaria in pregnancy using in vitro assays

T HOUNTOHOTEGBE[1,2], D BERRY[2], K GBEDANDE[2], S Rogerson[4], A JF Luty[1,3]

[1] Université Paris DESCARTES, Paris, France
[2] Institut de Recherche Clinique du Bénin, Centre d'Etude et de Recherche sur le Paludisme Associé à la Grossesse et à l'Enfance, Cotonou, Bénin
[3] Institut de Recherche pour le Développement, UMR216-MERIT
[4] University of Melbourne, Department of Medicine, Laboratory of Immunology and Microbiology, Australie

Background

Placental malaria is caused by infected erythrocytes binding to chondroitin sulfate A (CSA) in the placenta. Approximately 25 million pregnancies are at risk of placental malaria infections in sub-Saharan Africa each year.
The interaction between the parasite protein VAR2CSA and CSA in the human placenta is a key element in the pathogenesis of placental malaria. A protective vaccine should elicit the type of immunoglobulins that block the binding of VAR2CSA to CSA.
The PAMVAC vaccine is a VAR2CSA protein-based vaccine, aiming to protect fetus and mother against the adverse effects of placental malaria during pregnancy. In animal models immunoglobulin G molecules (IgGs) induced by immunization with the recombinant PAMVAC antigen are able to inhibit homologous parasite-infected erythrocyte adhesion to CSA *in vitro* and are also cross-inhibitory, inhibiting CSA adhesion erythrocytes infected with other parasite strains.
The objective of this study is to access the immunogenicity of the vaccine candidate during a Phase Ib clinical trial.

Methods

The study took place at Institut de Recherche Clinique du Bénin in Benin from November 2016 to September 2017. From forty eligible volunteers, 21 healthy nulligravid female adults, living in endemic area were enrolled and randomized to receive 50 µg PAMVAC adjuvanted with either Alhydrogel, or GLA-SE, or placebo. Three injections with the same dosage and adjuvant were done, each 28 days apart (Day 0, 28 and 56). Control subjects received physiological saline instead of the vaccine. Blood samples collection were performed before immunization and at each visit. Plasma samples and PBMC were harvested at D0, D56, D84, D168, D252 and store either -20°C or in nitrogen liquid for Immunoassays.
ELISpot assays for antibodies secreting memory B cell were quantified using the vaccine antigen, CIDR antigen, Tetanus toxoid antigen and anti-human IgG. Functional antibodies induced by the vaccine were quantified for variant surface antigen (VSA) expressing infected red blood cells recognition and opsonic phagocytosis using FACS.

Results

21 female nulligravidae received 3 doses of 50µg of PAMVAC vaccine and were randomized in 3 groups (9 PAMVAC & Alhydrogel, 9 PAMVAC & GLA-SE, 3 Placebo). The mean age of our study population was 19. At the time of submission, only ELISpot data have been analysed.
PAMVAC vaccination induced a memory B response that increased noticeably after the 2nd dose of vaccine and persisted over time at levels equivalent to or substantially higher than those we have previously measured in multigravid Beninese. The frequency of PAMVAC-specific antibody-secreting B cells was notably higher with the one of the new adjuvants than with alum, and responses were stable between D56 and D84 (110 days after the 3rd dose). Immunization with PAMVAC did not appear to affect B cell responses to other antigens tested. The latter were stable both in the absence and presence of PAMVAC vaccination. Also notable was the fact that PAMVAC-specific B cell responses were undetectable in unvaccinated nulligravid Beninese women who have been exposed to infection with P. falciparum since birth.

Conclusions

The combination of PAMVAC with one of the new adjuvants rather than alum is associated with the strongest B cell responses to the vaccine in women of childbearing age before their first pregnancy. At the time of writing, functional antibody responses are undergoing analysis.

Keywords: Placental Malaria, vaccine, immunity