Antimicrobial resistance

OC - (8743) - THE GENERATION AND TESTING OF A GENETICALLY ATTENUATED MALARIA PARASITE (GAP) VACCINE

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Background

Immunization with radiation-attenuated *Plasmodium falciparum* sporozoites (SPZ) (Sanaria® PfSPZ Vaccine) can protect >90% of vaccinees against controlled human malaria infection (CHMI) and protects against naturally-transmitted *P. falciparum* in Africa for at least 6 months. Immunization with sporozoites of genetically attenuated parasites (GAPs), which completely arrest after liver-cell invasion can be potentially safer and more potent than irradiated sporozoite vaccines. As part of a collaboration between 2 Dutch research groups (LUMC and Radboud University) and the US company, Sanaria, we describe the generation and first-in-man testing of a GAP vaccine,

Methods

We screened single and multiple gene deletion parasites in order to identify parasites that can invade hepatocytes but are unable to complete liver-stage development. Informed by rodent studies we created *P. falciparum* double gene-deletion mutant, Δb9Δslarp; sporozoites of this line were infective to human hepatocytes *in vitro* and to humanized mice but they completely arrest after invasion. PfΔslarpΔb9 PfSPZ (Sanaria® PfSPZ-GA1 Vaccine) was manufactured in compliance with cGMPs and released for human clinical trials in the EU under a conditional release GMO license. This GAP vaccine was used to perform phase 1 (safety) and phase 2a (efficacy) clinical CHMI trial in the Netherlands.

Results

In a dose escalating phase 1 clinical trial, the vaccine showed an excellent safety profile. All adverse events related to the vaccine were mild (grade 1). Based on this indication of safety, vaccine efficacy was examined by CHMI; 48 subjects were subsequently enrolled into phase 2a study and were immunized with either PfSPZ-GA1 or PfSPZ Vaccine or saline placebo.

Conclusions

In conclusion, PfSPZ-GA1 Vaccine is the first injectable genetically attenuated malaria vaccine assessed in humans. The accomplishment to manufacture, obtain regulatory approval and to demonstrate an excellent safety profile for this vaccine is unprecedented and holds a promise for PfSPZ vaccines with increased potency.