Evidence of protection against malaria by MSP3 candidate vaccine

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In 2007 we conducted a double-blind, randomized Phase 1b clinical trial in 45 children 12- 24 months old using the Merozoite Surface Protein 3 (MSP3) vaccine in a malaria endemic area. Children were randomized 1:1:1 to receive 3 doses on days 0, 28 and 56 of either MSP3 15μg, MSP3 30μg or Hepatitis B vaccine. Details of ethical approval, study vaccines, safety and immunogenicity results have been reported previously (1).

The trial was not designed to measure vaccine efficacy. However, to monitor safety, passive surveillance of all illness episodes, including clinical malaria, was maintained during the ensuing malaria transmission season in a blinded fashion. As numerous malaria attacks were recorded, we considered examining the possibility of a vaccine-induced protective effect. An analysis plan comparing clinical malaria incidence between the three arms was agreed on before undertaking the analysis. Given the high transmission rate in the study area (> 200 infected bites/person/year)(2), clinical malaria was defined as a fever ≥ 37.5° C in the presence of *P. falciparum* parasitemia at a density ≥ 5000 / μl (3). The risk period analysed was from four weeks after the 3rd vaccine dose until the end of the transmission season.

The incidence rates of clinical malaria were found to be substantially lower in each of the 2 vaccinated groups, 1.2 and 1.9 per 100 days respectively, compared to 5.3 in the control group (P=0.01, Figure). Thus, despite the small sample size and the high cumulative incidence in all groups, there is some indication that MSP3 vaccine protects against clinical malaria, at least in the short term. A sensitivity analysis using a threshold parasite density of 10000 produced broadly similar results (P=0.03). The similar incidence rates in the two MSP3 vaccine groups are consistent with their similar immune responses (1). Results are in keeping with the reduction in malaria attacks associated with naturally occurring MSP3 antibodies. (4)

It is unlikely that other malaria control efforts influenced these results. Data from the demographic surveillance system indicate that bednets were used in only 5–10 % of households. Neither indoor insecticide spraying, nor intermittent preventive treatments were practised in the area. The study clinic provided free diagnosis and treatment 24 hours a day so it is likely that most or all episodes of symptomatic malaria were detected.

Despite the limitations in sample size and study design, we believe that the findings of this trial, conducted in accordance with ICH GCP guidelines, justify further evaluation of this vaccine candidate.

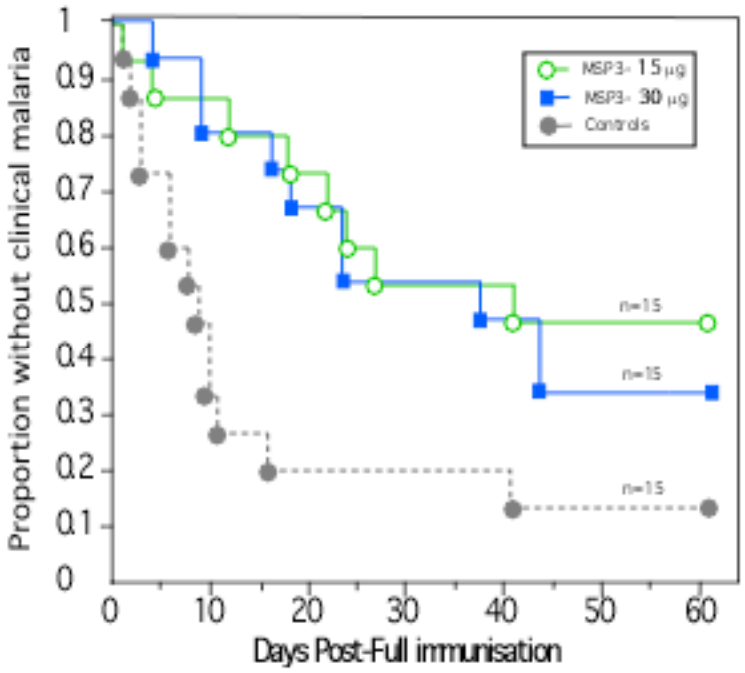

Figure legend: Kaplan-Meier plot of time to first episode. The number of days at risk (until first episode or end of risk period) were 660, 519 and 244 for MSP3-15µg (open circles), MSP3-30µg (open squares) and Engerix B (plain circles) groups respectively, yielding an incidence rate/100 days of 1.2, 1.9 and 5.3 respectively. The numbers of children experiencing an epsiode were 8, 10, and 13 respectively. A log rank tests indicates evidence of a difference in the experience of the three arms (P=0.01). When a threshold density of 10 000 parasites per microl was used similar results were obtained with periods at risk of 715, 563, and 296 respectively, and incidence rates/100 days of 1.0, 1.6 and 4.1 respectively

(P=0.03). The period of analysis shown here, starts after full immunization, (ie 4 weeks after the 3rd immunization when antibody titers peak), and goes up to the end of transmission.

References

1. Sirima S., Tiono A., Ouedraogo A. et al. Safety and Immunogenicity of the Malaria Vaccine Candidate MSP3 Long Synthetic Peptide in 12–24 Months-Old Burkinabe Children, PLoS ONE, 2009, 4(10): e7549. doi:10.1371/journal.pone.0007549

2. Ilboudo-Sanogo E, Tiono BA, Sagnon N, Cuzin Ouattara N, Nébié I, Sirima SB. Temporal dynamics of malaria transmission in two rural areas of Burkina Faso with two ecological differences. J Med Entomol. 2010 Jul;47(4):618-24

3. Smith T. et al, An epidemiologic model of the incidence of acute illness in Plasmodium falciparum malaria. Am.J.Trop.Med.Hyg.2006, 75(suppl2), 56-62.

4. Roussilhon C, Oeuvray C, Muller-Graf C, et al. Long-term clinical protection from falciparum malaria is strongly associated with IgG3 antibodies to merozoite surface protein 3. PLoS Med 2007;4:e320

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