The investigation into merozoite surface protein-1 vaccination in a natural simian host-parasite system

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Abstract:

The immunogenicity and protective efficacy of the C-terminal 19 kDa region of the merozoite surface protein-1 (MSP-1p19), a leading asexual blood stage candidate against malaria, was assessed. The Plasmodium cynomolgi - Macaca sinica (toque monkey) natural host parasite system, which is highly analogous to Plasmodium vivax in man, was used throughout. Three immunization trials (coded Trials MSP 1.05 - 1.07) were conducted, using highly pure and characterized baculovirus-expressed recombinant proteins corresponding to P.cynomolgi ceylonensis (Pcc) MSP-1p19(p19), with four adjuvants. With regard tp the mode pf cja;;emge omfection , Pcc infections induced by infectious mosquito bites (sporozoite-induced) resulted in significantly less intense parasitaemia compared to infections induced by intravenous inoculation of fresh blood containing ring-stage parasites (trophozoite-induced) (P=0.001). This suggested that artificial trophozoite challenge may pose unnecessarily stringent conditions for evaluation of asexual blood stage vaccine candidate antigens, and that a natural sporozoite challenge would provide a more real outcome. Therefore, while trophozoite challenge infections were used in Trials MSP 1.05 and 1.06, a sporozoite challenge infection was used in Trial MSP 1.07. Furthermore, malaria-native animals were used in Trials MSP 1.05 and 1.06, and malaria-exposed animals were used in trial MSP 1.07, to observe the effect of prior exposure to malaria on vaccine efficacy.Immunization with p19 and Freunds's complete and incomplete adjuvant (FCA/FIA) induced a very high p19-specific reciprocal antibody titre of 106, and mediated 100 percent protection against homologous Pcc challenge infection. Intramuscular and subcutaneous immunization resulted in similar immunogenicity and efficacy in two independent trials (Trials MSP 1.05 and 1.06). Furthermore, upon re-challenge of these animals 4 or 8 months after challenge, 97-99 percent protection against homologous Pcc re-challenge infection, and heterologous re-challenge infection of P.cynomolgi Gombak (PcG) was observed. Immunization with p19 and experimental adjuvants. SBAS2 (SmithKline Beecham Biologicals, Belgium) and QS-21 (aquila Biopharmaceuticals, USA), induced reciprocal antibody titres ranging from 103 to 105, and did not mediate significant protection against homologous challenge infection (14 percent and 8 percent respectively). In Trial MSP 1.06, immunization with p19 and an aluminium-based adhyvant (Alhydrogel 2 percent, Superpose Biosecter A/S , Denmark), referred to as AI(OH)3, induced reciprocal antibody titres of 104, and mediated partial protection against Pcc challenge and re-challenge infections (38 percent and 39 percent respectively). Partial protection, in terms of lower peak parasitaemia, was observed against heterologous pcG re-challenge infection. Immunization of p19+FCA/FIA induced significantly higher humoral and cellular responses than immunization with the other adjuvants. Considering immune responses of all immunized animals, the pre-challenge p19 specific antibody titre, significantly and positively correlated with protection against infection, and a pre-challenge reciprocal titre of 1.0x106 was consistently predictive of 100 percent protection. Protective antibodies were however, unable to protect malaria-naIve monkeys upon passive transfer of immune immunoglobulin, indicating that a combined humoral and cellular immune response is required to mediate protection. In Trial MSP 1.07, animals with and without prior exposure to sporozoite-induced natural PCC infection were immunized with p19+AI(OH)3 and challenged via the natural sporozoite challenge system. Animals with prior exposure and p19 immunization were better protected against infection and disease than malaria-naIve, immunized animals. The p19-specific humoral immune responses induced by prior exposure to malaria infection were boosted by immunization, and reciprocal antibody titres of 104 were induced. These results highlighted the

applicability of this MSP-Ip19 based malaria vaccine candidate to malaria endemic populations, where the ultimate goal of reducing malarial disease could be achieved.

Key Words : Antigens, Protozoan / Merozoite Surface Protein 1 / Protozoan Proteins / VACCINATION