Vaccine (2008) **26**, 2191–2202

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Phase 2a trial of 0, 1, and 3 month and 0, 7, and 28 day immunization schedules of malaria vaccine RTS,S/AS02 in malaria-naïve adults at the Walter Reed Army Institute of Research☆

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Received 13 December 2007; received in revised form 14 February 2008; accepted 22 February 2008
Available online 13 March 2008

KEYWORDS
RTS,S;

Summary
Background: Immunization with RTS,S/AS02 consistently protects some vaccinees against malaria infection in experimental challenges and in field trials. A brief immunization schedule

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0264-410X/$ – see front matter. Published by Elsevier Ltd.
doi:10.1016/j.vaccine.2008.02.048

Malaria;
Vaccine;
Falciparum;
Adjuvant System;
AS02;
Circumsporozoite protein;
Hepatitis B;
Antibody;
Clinical trials;
Rapid immunization;
IFN-γ;
ELISPOT

against falciparum malaria would be compatible with the Expanded Programme on Immunization, or in combination with other prevention measures, interrupt epidemic malaria or protect individuals upon sudden travel to an endemic area.

Methods: We conducted an open label, Phase 2a trial of two different full dose schedules of RTS,S/AS02 in 40 healthy malaria-naïve adults. Cohort 1 ($n = 20$) was immunized on a 0, 1, and 3 month schedule and Cohort 2 ($n = 20$) on a 0, 7, and 28 day schedule. Three weeks later, 38 vaccinees and 12 unimmunized infectivity controls underwent malaria challenge.

Results: Both regimens had a good safety and tolerability profile. Peak GMCs of antibody to the circumsporozoite protein (CSP) were similar in Cohort 1 (78 μg/mL; 95% CI: 45—134) and Cohort 2 (65 μg/mL; 95% CI: 40—104). Vaccine efficacy for Cohort 1 was 45% (95% CI: 18—62%) and for Cohort 2, 39% (95% CI: 11—56%). Protected volunteers had a higher GMC of anti-CSP antibody (114 μg/mL) than did volunteers with a 2-day delay (70 μg/mL) or no delay (30 μg/mL) in the time to onset of parasitemia (Kruskal—Wallis, $p = 0.019$). A trend was seen for higher CSP-specific IFN-γ responses in PBMC from protected volunteers only in Cohort 1, but not in Cohort 2, for ex vivo and for cultured ELISPOT assays.

Conclusion: In malaria-naïve adults, the efficacy of three-dose RTS,S/AS02 regimens on either a 0, 1, and 3 month schedule or an abbreviated 0, 7, and 28 day schedule was not discernibly different from two previously reported trials of two-dose regimens given at 0, 1 month that conferred 47% (95% CI: −19 to 76%) protection and in another trial 42% (95% CI: 5—63%). A strong association of CSP-specific antibody with protection against malaria challenge is observed and confirms similar observations made in other studies. Subsequent trials of adjuvanted RTS,S in African children and infants on a 0, 1, and 2 month schedule have demonstrated a favorable safety and efficacy profile.

Introduction

Malaria, especially malaria caused by deadly *Plasmodium falciparum* infection, is most threatening to individuals without pre-existing anti-malaria immunity. The largest vulnerable populations are infants and women during their first pregnancy living in endemic lands [1]. But malaria-naïve individuals exposed to epidemic malaria or upon travel to malaria-endemic regions are also at risk of severe disease and death [2,3].

Protection against this mosquito-borne disease is simple in concept, but difficult in practice. The present public health crisis, demonstrated by the fact that more than three children die from malaria every minute [4], is further exacerbated by the inadequate use of proven control measures, such as selective use of house-hold DDT for indoor residual spraying [5], judicious intermittent presumptive treatment [6], and sleeping under insecticide-treated bed nets to avoid nocturnal exposure [7]. The global spread of multiple drug-resistant *P. falciparum* [8] has sharply limited the choice of chemoprophylactic drugs and has worsened the chronic shortages of affordable, effective treatment drugs [9].

A malaria vaccine would be a critically important addition to the present arsenal of malaria prevention measures. Although many candidate vaccines are in development [10], only the RTS,S antigen formulated with either the AS01 or the AS02 Adjuvant System consistently confers partial protective immunity against infection by the *P. falciparum* parasite in malaria-naive ([11—13], Kester, unpublished) and malaria endemic populations ([14,15], Polhemus, unpublished), and in one trial, reduced clinical and severe malaria in young African children for 18 months [15,16]. Most recently, RTS,S/AS02 given in an Expanded Programme on Immunization compatible schedule at 10, 14, and 18 weeks of age was shown for the first time to protect infants against infection and clinical malaria for a 3-month period [17].

At the time the presently reported trial was conducted, we had evaluated three doses of adjuvanted RTS,S in Phase 2a trials in malaria naïve adults using either a 0, 1, and 9 month [10] or a 0, 1, and 6 month schedule [11], but not on the shorter schedules presented here. Importantly, RTS,S/AS02 had also displayed a promising safety and tolerability profile. We had also previously conducted two Phase 2a trials in which we evaluated the preliminary efficacy of two doses of RTS,S/AS02 given at 0 and 1 months in malaria-naïve adults [11,12]. We undertook the present trial to determine if improved efficacy might be achieved by the administration of three doses of RTS,S/AS02 when given on one of two briefer schedules of immunization; either at 0, 1, and 3 months or at 0, 7, and 28 days.

Material and methods

Ethics

The trial was conducted according to Good Clinical Practices under a protocol approved by the Human Use Review Committee of the Walter Reed Army Institute of Research and by the US Army Surgeon General's Human Subjects Research Review Board, Fort Detrick, Maryland under US Food and Drug Administration Investigational New Drug application BB-6043. Written informed consent was obtained prior to screening and enrollment.

Participants

Healthy malaria-naïve civilian and military adult men and women, age 18—45 years, were recruited by non-coercive