Preventing malaria by administering a monoclonal antibody

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SUMMARY

This study evaluated the administration of L9LS, an IgG1 human monoclonal antibody with an extended half-life, as a strategy for chemoprevention of malaria in high-risk populations such as young children, children with severe anaemia after hospital discharge who are at risk for fatal malaria, and pregnant women. This was a double-blind, placebo-controlled part of a phase 2 trial that evaluated the safety and efficacy of a single subcutaneous dose of L9LS in preventing malaria infections within a 6-month malaria season (June–December) in Kalifabogou and Torodo, Mali.

The study was divided into two parts: Part A and part B. The study participants included healthy adults 18 to 55 years of age and healthy children 6 to 10 years of age. Part A of the study evaluated safety of the L9LS in both adults and children. It included 18 adults who received L9LS subcutaneously at a dose of 300 mg, 600 mg or 20 mg/kg body weight administered intravenously in a sequential manner (*n*=6 per group). The first group received a dose of 300 mg (lowest dose) and was monitored for 7 days. If no safety concerns had arisen for the first group at the end of 7 days, the second group received 600 mg and was monitored for 7 days and the last group was administered 20 mg/kg body weight at the end of the 7-day observation period of the second group and followed up for 7 days. At the end of the adult safety trial, 18 children randomized in a 1:1 ratio received 300 mg of L9LS subcutaneously or saline as placebo.

Part B was an efficacy study to evaluate the antimalarial activity of L9LS subcutaneous infusion in children. Healthy children 6 to 10 years of age (*n*=225) were randomly assigned (in a 1:1:1 ratio) to receive 150 mg of L9LS, 300 mg of L9LS, or saline placebo subcutaneously. Participants were followed up on days 1, 3, 7, 14, 21 and 28 and, subsequently, every 2 weeks through 24 weeks. Physical assessment and microscopic evaluation of blood smears for *Plasmodium falciparum* (*P. falciparum*) infections were done at each time-point. The primary endpoint was microscopic evidence of *P. falciparum* infection in thick blood smears, irrespective of physical symptoms. A secondary efficacy time point was the presence of clinical malaria during scheduled and unscheduled visits. All participants received treatment with artemether–lumefantrine 7–12 days before the administration of L9LS or placebo to ensure clearance of any pre-existing *P. falciparum* infection. Throughout the trial, asymptomatic malaria infections were not treated and symptomatic malaria patients received standard treatment as per the national guidelines of Mali.

In part A of the study, no serious adverse events were observed during the 28-week trial for adults or children after administering L9LS. Mild events included transient swelling at the injection site in adults. In part B of the study, *P. falciparum* infections developed in 48% of the participants who received 150 mg L9LS, in 40% of the participants who received 300 mg L9LS and in 81% of the participants who received saline placebo. Time to first malaria infection was longer in participants who received 150 mg and 300 mg L9LS compared to those who received placebo. Clinical malaria occurred in 28% of the participants who received 150 mg and in 19% of the participants who received 300 mg L9LS compared to 59% of the participants who received placebo. Time-to-event analysis showed that both 150 and 300 mg L9LS were more effective than placebo in delaying the onset of clinical malaria.

COMMENT

Malaria due to *P. falciparum* infections causes >60 000 deaths annually despite the implementation of public health strategies such as the use of insecticide-treated bednets, mosquito-control measures, active screening and chemoprevention.[1] Unlike other pathogens, vaccines against the malaria parasite have been elusive. Two vaccines, the RTS, S/ AS01 (Mosquirix, GlaxoSmithKline), and the R21 Matrix, M against malaria were approved in 2021 by the WHO for use in children 5–17 months of age. However, it was observed that vaccination of children below 6 months of age increased the incidence of malaria in school-age children. School-age children are a major reservoir of asymptomatic malaria infection, aiding malaria transmission, but at the same time are ineligible for the RTS, S/ AS01, and R21 Matrix, M vaccines. The present study provides an alternative approach by proposing L9LS as a safe and effective vaccine candidate for school-age children. Since L9LS was found to delay time to first *P. falciparum* infection and time to clinical malaria, the authors propose that when administered before the malaria season, the vaccine may aid in chemoprevention of malaria infection and therefore, transmission in addition to preventing clinical malaria in this population. This study also suggests that in addition to active immunization by the WHO-approved vaccines, passive immunization by monoclonal antibodies can aid malaria chemoprevention efforts, especially in endemic areas. Seasonal malaria chemoprevention through L9LS monoclonal antibody infusion can also be a strategy for prevention of transmission in addition to malaria transmission-blocking vaccines.

P. falciparum infection occurs in humans when the sporozoite form of the malaria parasite enters the human body via the bite of a female *Anopheles* mosquito.[2] The *P. falciparum* circumsporozoite protein (PfCSP) decorates the cell surface of the invading sporozoite and, is critical to sporozoite development within the mosquito vector as well as, cell invasion in the mammalian host.[3–5] Hence, it has been a leading vaccine candidate for the pre-erythrocytic stages of malaria. L9LS is a

monoclonal antibody targeting a conserved epitope on the *P. falciparum* circumsporozoite protein (PfCSP).[6] The RTS, S/ AS01 vaccine consists of the central and C-terminal domains of PfCSP genetically fused to the hepatitis B virus surface antigen (HBsAg).[7] The R21/Matrix, M vaccine has a virus-like particle containing the central repeats of Asn-Ala-Asn-Pro (NANP) and C-terminal sequence of PfCSP fused to HBsAg (the R21 component) which is administered with a saponin adjuvant Matrix-M.[8] All these therapeutics centre around PfCSP as a target malaria antigen. Therefore, the geographical genetic diversity of PfCSP is an important determinant of efficacy of the PfCSP-centered immunotherapy. Most of the PfCSP-centered vaccines are developed around the PfCSP sequence of the laboratory strain NF54 which may explain the modest vaccine efficacy of the RTS, S/ AS01 vaccine even within Africa.[9,10] Therefore, a combination of approaches must be considered.

What does this mean for India? Genomic data from parasites of Indian origin are limited despite the availability of advanced sequencing technology. Recent datasets of *P. falciparum* whole genome sequences demonstrate the uniqueness of the Indian *P. falciparum* genome compared to African and South East Asian Isolates.[11–13] Since PfCSP is at the centre of global vaccine development efforts, the analysis of PfCSP sequences from the Indian subcontinent is necessary to understand the potential success or challenges of the RTS, S/ AS01, or R21/ Matrix, M or L9LS-based immunotherapeutic approaches in India. In a study that has investigated the genetic diversity of PfCSP in 153 isolates from Madhya Pradesh, India, it is apparent that the PfCSP gene from *P. falciparum* of Indian origin demonstrates a high degree of variability in the central repeat region of PfCSP which harbours B-cell epitopes important for the generation of antibodies.[14] Co-infections of different malaria species and other co-seasonal and co-endemic tropical pathogens further complicate malaria in India.[15–18]

India has made major progress towards malaria control, and the current strategies for malaria treatment include the administration of artemisinin-based combination therapy (ACT) and low-dose primaquine for all confirmed *P. falciparum* cases, as well as a 3-day course of chloroquine and 14-day course of primaquine for all confirmed *P. vivax* cases.[19] Chemopreventive or vaccination strategies are not currently used in India. Vaccination and passive antibody therapy are effective strategies for preventing and eradicating disease and could be combined with existing methods. However, a deeper understanding of the genomic diversity of Indian malarial parasites and the application of immunotherapeutic strategies are critical to further improve malaria elimination efforts in India.

REFERENCES

1 Venkatesan P. The 2023 WHO World malaria report. *Lancet Microbe* 2024;**5:**e214.
2 Acharya P, Garg M, Kumar P, Munjal A, Raja KD. Host–parasite interactions in human malaria: Clinical implications of basic research. *Front Microbiol* 2017;**8:**889.
3 Cerami C, Frevert U, Sinnis P, Takacs B, Clavijo P, Santos MJ, *et al*. The basolateral domain of the hepatocyte plasma membrane bears receptors for the circumsporozoite protein of *Plasmodium falciparum* sporozoites. *Cell* 1992;**70:**1021–33.
4 Frevert U, Sinnis P, Cerami C, Shreffler W, Takacs B, Nussenzweig V. Malaria circumsporozoite protein binds to heparan sulfate proteoglycans associated with the surface membrane of hepatocytes. *J Exp Med* 1993;**177:**1287–98.
5 Ménard R, Sultan AA, Cortes C, Altszuler R, van Dijk MR, Janse CJ, *et al*. Circumsporozoite protein is required for development of malaria sporozoites in mosquitoes. *Nature* 1997;**385:**336–40.
6 Wang LT, Pereira LS, Flores-Garcia Y, O'Connor J, Flynn BJ, Schön A, *et al*. A potent anti-malarial human monoclonal antibody targets circumsporozoite protein minor repeats and neutralizes sporozoites in the liver. *Immunity* 2020; **53:**733–44.e8.
7 Gordon DM, McGovern TW, Krzych U, Cohen JC, Schneider I, LaChance R, *et al*. Safety, immunogenicity, and efficacy of a recombinantly produced *Plasmodium falciparum* circumsporozoite protein-hepatitis B surface antigen subunit vaccine. *J Infect Dis* 1995;**171:**1576–85.
8 Datoo MS, Dicko A, Tinto H, Ouédraogo JB, Hamaluba M, Olotu A, *et al*. Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: A multicentre, double-blind, randomised, phase 3 trial. *Lancet* 2024;**403:**533–44.
9 Allouèche A, Milligan P, Conway DJ, Pinder M, Bojang K, Doherty T, *et al*. Protective efficacy of the RTS,S/AS02 *Plasmodium falciparum* malaria vaccine is not strain specific. *Am J Trop Med Hyg* 2003;**68:**97–101.
10 Feng G, Kurtovic L, Agius PA, Aitken EH, Sacarlal J, Wines BD, *et al*. Induction, decay, and determinants of functional antibodies following vaccination with the RTS,S malaria vaccine in young children. *BMC Med* 2022;**20:**289.
11 Choubey D, Deshmukh B, Rao AG, Kanyal A, Hati AK, Roy S, *et al*. Genomic analysis of Indian isolates of *Plasmodium falciparum*: Implications for drug resistance and virulence factors. *Int J Parasitol Drugs Drug Resist* 2023;**22:** 52–60.
12 Tyagi S, Pande V, Das A. Whole mitochondrial genome sequence of an Indian *Plasmodium falciparum* field isolate. *Korean J Parasitol* 2014;**52:**99–103.
13 Kumar S, Mudeppa DG, Sharma A, Mascarenhas A, Dash R, Pereira L, *et al*. Distinct genomic architecture of *Plasmodium falciparum* populations from South Asia. *Mol Biochem Parasitol* 2016;**210:**1–4.
14 Zeeshan M, Alam MT, Vinayak S, Bora H, Tyagi RK, Alam MS, *et al*. Genetic variation in the *Plasmodium falciparum* circumsporozoite protein in India and its relevance to RTS,S malaria vaccine. *PLoS One* 2012;**7:**e43430.
15 Kaur C, Pramanik A, Kumari K, Mandage R, Dinda AK, Sankar J, *et al*. Renal detection of *Plasmodium falciparum*, *Plasmodium vivax* and *Plasmodium knowlesi* in malaria associated acute kidney injury: A retrospective case–control study. *BMC Res Notes* 2020;**13:**37.
16 Mandage R, Kaur C, Pramanik A, Kumar V, Kodan P, Singh A, *et al*. Association of dengue virus and leptospira co-infections with malaria severity. *Emerg Infect Dis* 2020;**26:**1645–53.
17 Pandey S, Rai P, Guha SK, Maji A, Ghosh S, Halder P, *et al*. Outcome of adult malarial co-infections in eastern India. *J Glob Infect Dis* 2022;**14:**57–63.
18 Rao MR, Padhy RN, Das MK. Prevalence of dengue viral and malaria parasitic co-infections in an epidemic district, Angul of Odisha, India: An eco-epidemiological and cross-sectional study for the prospective aspects of public health. *J Infect Public Health* 2016;**9:**421–8.
19 Narain JP, Nath LM. Eliminating malaria in India by 2027: The countdown begins! *Indian J Med Res* 2018;**148:**123–6.

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