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Editorial: The First Monoclonal Antibody Vaccine to Prevent Malaria Heralds a New Era of Malaria Vaccines to the *Plasmodium falciparum* Circumsporozoite Protein (PfCSP)

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Abstract Malaria affects more than 3 billion people in 95 countries, with an estimated mortality rate of 400,000 per year. The female Anopheles spp mosquito most commonly transmits malaria, and the main burden of disease is due to *Plasmodium falciparum*. The most abundant antigen on the sporozoite surface is the *Plasmodium falciparum* circumsporozoite protein (PfCSP). PfCSP is required for parasite development and attachment to host hepatocytes. The first potential protein vaccine, RTS,S/ASO1, consists of a recombinant fusion antigen based on PfCSP. Initial findings from a phase 3 trial of RTS,S/ASO1 were promising but resulted in recommendations for further evaluation in large-scale trials. R21, a circumsporozoite protein-based vaccine, combined with an adjuvant, Matrix-M (MM), was recently evaluated in a phase 2 investigational study in children between 5-17 months of age in Burkina Faso. The R21/MM candidate vaccine resulted in high titers of malaria-specific antibodies. On August 26, 2021, the findings from a phase 1 trial on a new monoclonal antibody to PfCSP, CIS43LS, showed that a single dose of the CIS43LS monoclonal antibody resulted in protection against malaria. These new findings have implications for the seasonal control of malaria in endemic regions and a possible future role in public health strategies to eliminate malaria. This Editorial aims to provide the background to developing and evaluating the new malaria vaccines that target PfCSP, including the first monoclonal antibody vaccine to malaria.

Keywords: ***Plasmodium falciparum*** • **Malaria** • **Monoclonal Antibody** • **Vaccine** • **Editorial**

Malaria affects more than 3 billion people in 95 countries, with an estimated mortality rate of 400,000 per year [1]. Malaria is most commonly transmitted by a bite from the female Anopheles spp mosquito, with rare cases from materno-fetal transmission, blood transfusions, contaminated needles, and organ transplants [2-4]. The main burden of disease is due to *Plasmodium falciparum* [1]. *Plasmodium falciparum* malaria occurs mainly in sub-Saharan Africa, Haiti, the Dominican Republic, and New Guinea [1]. In 2019, the World Health Organization (WHO) reported 229 million cases and 409,000 deaths from malaria [1]. More than 94% of cases were reported in sub-Saharan Africa, 4% in Southeast Asia and the Eastern Mediterranean, and 2% in the Americas and Western Pacific regions [2,3]. In 2017, there were 2,161 cases of malaria reported in the US, which was the highest rate recorded, possibly due to increased international tourism [4]. More than 76% of cases were due to infection with *Plasmodium falciparum*, and more than 86% of cases were associated with travel to West Africa [4]. In 93% of cases, the US tourist did not take antimalarial chemoprophylaxis [4].

Prevention of malaria has relied on public health measures and infection control, with the aims of eradication, and global elimination [5]. Currently, intermittent preventive treatment (IPT) is advised by the WHO to reduce the risk of malaria infection among individuals at high risk [5]. In 2008, the WHO divided the 104 countries affected by malaria into three groups that included 25 countries with the recent elimination of malaria, 32 countries amenable to control and elimination, and 47 countries with stable malaria transmission but poor public health infrastructure [6]. The World Health Organization Strategic Plan, 2016-2030, recommends IPT and seasonal chemoprophylaxis of target groups [7]. Infection control aims to reduce the incidence to levels managed by community public health measures [7]. Elimination aims to reduce the incidence and transmission to zero in a defined geographic area [7]. Eradication is the global elimination of human malaria [7].

The development of a successful malaria vaccine increases the possibility of reducing the global disease burden of malaria when the vaccine is combined with other control interventions [7]. The malaria eradication research agenda (malERA)

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supports the ultimate hope for vaccines that contribute to disease control, possible eradication, and global elimination of malaria [8]. In areas where malaria transmission is low, highly seasonal, or localized, full protective immunity from malarial infection is not acquired, resulting in symptomatic disease at all ages [9]. In these populations, morbidity and mortality are exceptionally high in infants and children, which is why recent clinical trials for malaria vaccines have begun in infants and children in some geographical regions [9].

Until recently, public health measures alone have been available to control malaria, and there has been little hope for the availability of a safe and effective vaccine that may reduce the global public health burden of this disease [10]. Malaria vaccine design and development has been focussed during the past decade to target the stage of development of the parasite at the pre-erythrocytic stage, bloodborne stage, and the transmission stage, with some malaria vaccines targeting multiple stages [11]. The most effective vaccine for malaria would ideally completely prevent the first stages of development of the parasite, block further stages from developing, and prevent infection transmission [11]. Several antigens have been evaluated as potential vaccine targets, mainly based on surface proteins of the *Plasmodium falciparum* sporozoite, combined with an adjuvant [11]. Initial results have been from clinical trials to evaluate a pre-erythrocytic vaccine that targets the circumsporozoite protein on the sporozoite surface to target the *Plasmodium falciparum* parasite before it infects liver cells [11].

Initial approaches to develop malaria vaccines included whole-parasite vaccines with live attenuated sporozoites combined with adjuvants [12]. Because of the possible risk of transmitting malaria, these vaccines were evaluated when combined with antimalarial drugs [12]. More recently, protein-based vaccines that target *Plasmodium falciparum* have begun clinical trials [12]. The most abundant antigen on the sporozoite surface is the *Plasmodium falciparum* circumsporozoite protein (PfCSP) [12]. PfCSP is required to develop the malaria parasite and its attachment to hepatocytes of the host and contains three regions: an N-terminal domain that binds to heparin sulfate proteoglycans on the hepatocyte; a central region containing approximately 40 copies of the NANP or NVDP amino acid sequence; and a C-terminal thrombospondin-repeat domain (dTSR) [12]. Following immunization with PfCSP, antibodies to the sporozoites of *Plasmodium falciparum* prevent their attachment and invasion into hepatocytes *in vivo* [12]. These recent findings have resulted in the development of the RTS,S/AS01 malaria vaccine [12].

RTS,S/AS01 is the first malaria vaccine to be tested in Phase 3 clinical trials and the first to be assessed in routine immunization programs in malaria-endemic areas [13,14]. The RTS,S/ASO1 vaccine consists of a recombinant fusion protein antigen designed from a repetitive sequence of four amino acids based on the circumsporozoite surface antigen of *Plasmodium falciparum* [13,14]. The repeat T epitopes (RTS) are derived from the circumsporozoite protein, the S antigen (S) is derived from the hepatitis B surface antigen (HBSAg), and AS01 is the adjuvant [13,14]. In 2013, the results were reported from a trial of the RTS,S/AS01E vaccine that included 447 children between 5-17 months of age in Kilifi, Kenya, who received three vaccine doses (NCT00872963) [15]. The findings showed a decline of vaccine efficacy between the first year and fourth year of follow-up, from 44% (95% CI; 16-62) to zero [15].

In 2015, findings were reported from a phase 3 trial of the RTS,S/AS01 vaccine [16]. This trial included 15,459 children age 5-17 months from 11 centers in seven countries in sub-Saharan Africa (NCT00866619) [16]. The RTS,S/AS01 vaccine induced partial protection from clinical malaria during the median follow-up period of 48 months and resulted in protection following a booster at 20 months [16]. However, no significant efficacy against severe malaria was found in the 6-12 week age group, even after a booster vaccine [16]. Additional follow-up for children who received four doses of the RTS,S/AS01 vaccine regimen is pending. It has been observed that the RTS,S/AS01 vaccine provides greater protection against malaria from the *Plasmodium spp.* that matches the protein used in the vaccine [17]. Following these initial findings, in 2016, the Malaria Policy Advisory Committee (MPAC) and the Strategic Advisory Group of Experts on Immunization (SAGE) decided not to recommend widespread implementation of the RTS,S/AS01 vaccine, but did advise further clinical trials [18].

In May 2021, Daloo and colleagues reported the findings from a double-blind, randomized, controlled, phase 2b investigational study on the safety and efficacy of a malaria vaccine, R21/MM (NCT03896724) [19]. R21 is a circumsporozoite protein-based vaccine, which is combined with an adjuvant, Matrix-M (MM) [19]. The R21/MM candidate vaccine trial commenced in May and June 2019 in Nanoro, Burkina Faso, West Africa, an area with high seasonal malaria transmission [19]. The trial included 450 children between 5-17 months of age [19]. The children were randomly assigned to receive either three doses of R21/MM, with either a low dose (5 µg R21 plus 25µg MM) or high dose (5 µg R21 plus 50µg MM) of the adjuvant, or rabies vaccine as a control [19]. The vaccine efficacy in the low dose R21/MM group at more than six months was 74% (95% CI; 63-82), and in the low dose, R21/MM group at more than six months was 77% (95% CI; 67-84) [19]. In this trial, there were no serious adverse events associated with vaccination [19]. Children vaccinated with R21/MM developed high titers of malaria-specific antibodies to Asn-Ala-Asn-Pro (NANP) at 28 days after a third vaccination, with doubling antibody levels at the higher adjuvant dose [19]. A fourth vaccine dose, administered after one year, boosted antibody titers to levels similar to

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peak titers [19]. There remains a need to compare the efficacy of the R21/MM vaccine with the RTS, S/ASO1 vaccine with studies of similar trial design and evaluation of long-term data.

Characterization of the PfCSP protein has resulted in the development of humanized monoclonal antibodies to prevent malaria, in parallel with developing and evaluating protein-based vaccines [20]. Recent studies have characterized more than 200 human monoclonal PfCSP antibodies induced by immunization with the sporozoites to identify the most potent antibodies that bind to the conserved NANP motifs in the core of PfCSP [20]. These initial studies formed the basis for the next generation of PfCSP vaccines that elicit high-affinity antibody responses against the core epitope resulting in protective humoral immune responses to *Plasmodium falciparum* [20].

In 2018, Kisalu and colleagues identified a new monoclonal antibody, CIS43,22, localized to the highly conserved NPDP tetrapeptide at the junction of the N-terminal and central repeat regions of PfCSP [21]. Initially, several human monoclonal antibodies were isolated that were directed against PfCSP from subjects immunized with an attenuated Pf whole-sporozoite (SPZ) vaccine [21]. Following passive transfer experiments, the monoclonal antibody CIS43 conferred protection in two different mouse models of malaria infection and was shown to bind to Asn-Pro-Asn (NPN) [21]. In February 2021, Kisalu and colleagues reported the modification of CIS43 via the Fc domain with the LS mutations (CIS43LS) to increase the binding affinity of CIS43 in a study in rhesus macaques and humans [22]. CIS43LS had a 9-fold to 13-fold increase in binding affinity compared with CIS43 and an increased half-life [22]. Antibody levels were prolonged with the use of adeno-associated virus (AAV) expression, with CIS43LS progressing to clinical trials [22].

On August 26, 2021, Gaudinski and colleagues reported the findings from a two-part phase 1 clinical trial conducted to assess the safety, pharmacokinetics, and efficacy of CIS43LS in healthy adults who had not previously received a vaccine or had malaria infection (NCT04206332) [23]. The first part of the trial assessed the safety and pharmacokinetics of CIS43LS [23]. The CIS43LS human monoclonal antibody was given by subcutaneous or intravenous injection at one of three escalating doses [23]. The second part of the trial included a subgroup of the initial study participants who received a second infusion of CIS43LS, and some additional participants were enrolled and received intravenous dosing [23]. Some trial participants underwent controlled malaria infection, or a controlled human malaria challenge (CHMI), with exposure to mosquitoes carrying *Plasmodium falciparum* sporozoites between 4-36 weeks after infusion of CIS43LS [23]. Parasitemia was detected using polymerase chain reaction (PCR) 21 days after controlled human malaria infection [23]. In 25 adults in the trial, who had no previous history of malaria infection or vaccination, the long-acting monoclonal antibody CIS43LS prevented malaria after controlled infection [23]. There were no safety concerns, and there was a dose-dependent increase in CIS43LS serum concentrations, with a half-life of 56 days [23].

Conclusions

The findings from this first clinical trial of a monoclonal antibody to prevent malaria have resulted in several major advances in preventing this disease. First, the effectiveness of the CIS43LS monoclonal antibody that targets the NPN junctional region of the *Plasmodium falciparum* circumsporozoite protein supports the inclusion of this site as a target for future next-generation vaccines. Also, this clinical trial is the first to demonstrate the potential for passive immune prevention of malaria. A single dose of the CIS43LS monoclonal antibody resulted in protection against malaria, which has implications for the seasonal control of malaria in endemic regions and a possible role in malaria elimination public health strategies. Future developments in malaria vaccines may identify more effective monoclonal antibodies, with new dosing regimens and new application routes, with expanded use for vulnerable populations in endemic geographical areas.

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