Malaria Vaccine and There Intiative

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Abstract- *This paper is an overview of vaccine antigens against malaria produced in plants. Plant-based expression systems represent an interesting production platform due to their reduced manufacturing costs and high scalability. At present, different Plasmodium antigens and expression strategies have been optimized in plants. Furthermore, malaria antigens are one of the few examples of eukaryotic proteins with vaccine value expressed in plants, making plant-derived malaria antigens an interesting model to analyze. Up to now, malaria antigen expression in plants has allowed the complete synthesis of these vaccine antigens, which have been able to induce an active immune response in mice. Therefore, plant production platforms offer wonderful prospects for improving the access to malaria vaccines.*

Keywords- Malaria diseases vaccine cell Properties blood streams death

I. INTRODUCTION

Malaria is an endemic disease that affected 229 million people and caused 409 thousand deaths, in 2019[1]. Disease control is based on early diagnosis and specific treatment with antimalarial drugs since no effective vaccines are commercially available to prevent the disease. Drug chemotherapy has a strong historical link to the use of traditional plant infusions and other natural products in various cultures. The research based on such knowledge has yielded two drugs in medicine: the alkaloid quinine from Cinchona species, native in the Amazon highland rain forest in South America, and artemisinin from Artemisia annua, a species from the millenary Chinese medicine

Development Of Disease

Malaria infection begins when an infected female Anopheles mosquito bites a person, injecting Plasmodium parasites, in the form of sporozoites, into the bloodstream.

The sporozoites pass quickly into the human liver.[2]

The sporozoites multiply asexually in the liver cells over the next 7 to 10 days, causing no symptoms.

In an animal model, the parasites, in the form of merozoites, are released from the liver cells in vesicles, journey through the heart, and arrive in the lungs, where they settle within lung capillaries. The vesicles eventually disintegrate, freeing the merozoites to enter the blood phase of their development.*

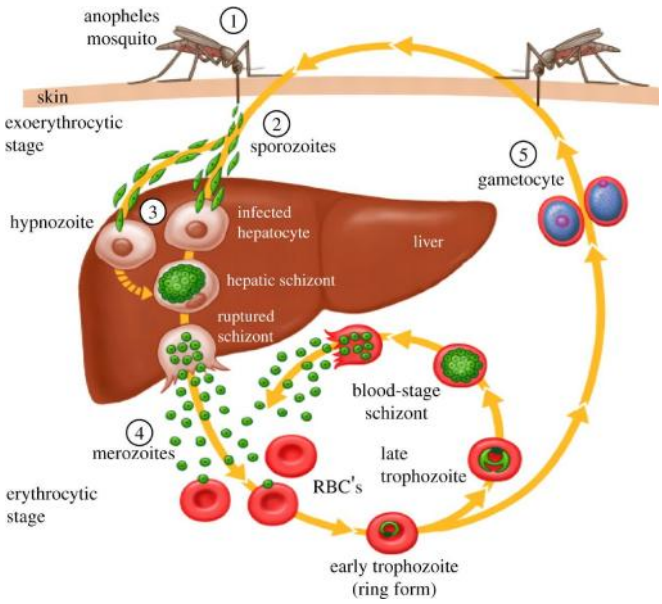
In the bloodstream, the merozoites invade red blood cells (erythrocytes) and multiply again until the cells burst. Then they invade more erythrocytes. This cycle is repeated, causing fever each time parasites break free and invade blood cells.[3]

Some of the infected blood cells leave the cycle of asexual multiplication. Instead of replicating, the merozoites in these cells develop into sexual forms of the parasite, called gametocytes, that circulate in the blood stream.

When a mosquito bites an infected human, it ingests the gametocytes, which develop further into mature sex cells called gametes.

The fertilized female gametes develop into actively moving ookinetes that burrow through the mosquito's midgut wall and form oocysts on the exterior surface.

Inside the oocyst, thousands of active sporozoites develop. The oocyst eventually bursts, releasing sporozoites into the body cavity that travel to the mosquito's salivary glands.



The cycle of human infection begins again when the mosquito bites another person.

Malaria Vaccine Intiative –

Sporozoite Subunit Vaccines

The most extensively tested vaccine candidate for prevention of P. falciparum malaria is RTS,S/AS01; this vaccine directs immune responses against the major circumsporozoite protein (PfCSP) covering the surface of the infecting sporozoite. To accomplish this, RTS,S was designed as a virus-like particle (VLP) comprised of two components: 18 copies of the central repeat and the C-terminal domain of PfCSP fused to hepatitis B virus surface antigen (HBsAg) with extra HBsAg in a 1:4 ratio. RTS,S, formulated with the potent liposomal adjuvant system AS01 from GlaxoSmithKline, is the only vaccine that has demonstrated protective efficacy against clinical malaria in a Phase III clinical trial (Rts, 2015), although protection is partial, wanes over time, and may be age dependent (protection was lower in infants 6–12 weeks of age than in young children 5–17 months old). In the latter, receiving three vaccinations in a 0-1-2 month schedule, the incidence of clinical malaria was reduced by 51% over the first year of follow-up post-dose three [95% CI 48%–55%]. Over 48 months of follow-up, efficacy was 26% [95% CI 21%–31%], and among children receiving a fourth dose at month 20 (18 months post-dose three), efficacy was 39% [95% CI 34%–43%]. A small Phase II study, which followed several hundred children who received the three-dose regimen over 7 years, suggests that there may also be a shifting or[4]

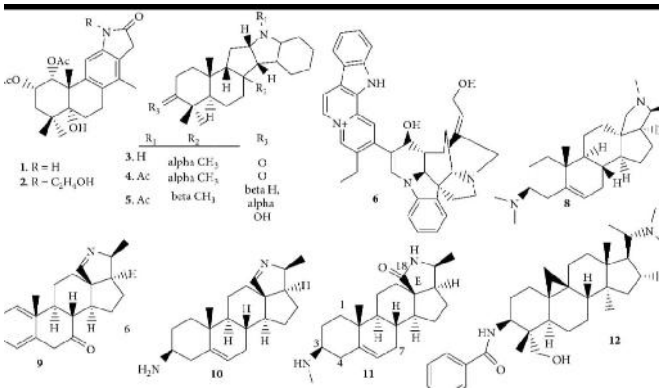
Rebound in malaria incidence 5 years post-vaccination (Olotu et al., 2016). Results of a larger long-term follow-up study to the Phase III efficacy and safety trial are expected later this year. According to the World Health Organization (WHO), two safety signals (meningitis, cerebral malaria) emerged from the Phase III trial, for which the cause is unknown and they noted a confirmed risk of febrile convulsions within 7 days of vaccination in the 5–17 month age category, all of which resolved without long-term sequelae (WHO, 2016).[5]

RTS VACCINE-

One of the most important imperatives for future improvements to RTS,S/AS01, and all next-generation malaria vaccines, is to extend the period of protection, which will require further understanding the mechanisms of vaccine-induced efficacy. While a definitive immune mechanism remains to be determined for RTS,S/AS01, the existing data strongly suggest that high antibody concentrations against the NANP amino acid repeats are closely associated with protection, and waning of such responses is likely to be responsible for decreasing efficacy (White et al., 2015). A direct mechanistic link between a monoclonal antibody (mAb) against the NANP epitope (isolated from a subject immunized with RTS,S [Oyen et al., 2017]) and protection will be tested soon following passive transfer and controlled human malaria infection (CHMI)[6]

Terpenoidal and Steroidal Alkaloids

Several alkaloids having varying terpenoidal backbone, including the cassane-type diterpenes, indoloterpene, and bisindolomonoterpenic alkaloids, have been isolated recently from medicinal plants (Caesalpiniaminax, Polyalthiaoliveri, and Strychnosnux-vomica) and shown to possess good antiplasmodial activity (Figure 2).



Quinine and There Components-Quinine, as a component of the bark of the cinchona (quina-quina) tree, was used to treat malaria from as early as the 1600s, when it was

referred to as the “Jesuits’ bark,” “cardinal’s bark,” or “sacred bark.” These names stem from its use in 1630 by Jesuit missionaries in South America, though a legend suggests earlier use by the native population[2]. According to this legend, an Indian with a high fever was lost in an Andean jungle. Thirsty, he drank from a pool of stagnant water and found that it tasted bitter. Realizing that the water had been contaminated by the surrounding quina-quina trees he thought he was poisoned. Surprisingly, his fever soon abated, and he shared this accidental discovery with fellow villagers, who thereafter used extracts from the quina-quina bark to treat fever [3]. The legend of quinine’s discovery accepted in Europe differs though, and involves the Spanish Countess of Chinchon who, while in Peru, contracted a fever that was cured by the bark of a tree. Returning to Spain with the bark, she introduced quinine to Europe in 1638 and, in 1742, botanist Carl Linnaeus called the tree “Cinchona” in her honour[7]

Before 1820, the bark of the cinchona tree was first dried, ground to a fine powder, and then mixed into a liquid (commonly wine) before being drunk. In 1820, quinine was extracted from the bark, isolated and named by Pierre Joseph Pelletier and Joseph Caventou. Purified quinine then replaced the bark as the standard treatment for malaria [5]. Quinine and other cinchona alkaloids including quinidine, cinchonine and cinchonidine are all effective against malaria. The efficacies of these four alkaloids were evaluated in one of the earliest clinical trials, conducted from 1866 to 1868 in 3600 patients using prepared sulfates of the alkaloids. With the main outcome measure of “cessation of febrile paroxysms”, all four alkaloids were found to be comparable, with cure rates of >98%[6]. However, after 1890 quinine became the predominantly used alkaloid, mainly due to a change in supply from South American to Javan cinchona bark, which contained a higher proportion of quinine [7]. Quinine remained the mainstay of malaria treatment until the 1920s, when more effective synthetic anti-malarials became available.[8] The most important of these drugs was chloroquine, which was extensively used, especially beginning in the 1940s [6]. With heavy use, chloroquineresistance developed slowly. Resistance of Plasmodium falciparum to chloroquine was seen in parts of Southeast Asia and South America by the late 1950s, and was widespread in almost all areas with falciparum malaria by the 1980s. With increasing resistance to chloroquine, quinine again played a key role, particularly in the treatment of severe malaria [6]. To-date quinine continues to play a significant role in the management of malaria. This review, discusses the historical role of quinine, considers its current usage, and provides insight into the appropriate future use of quinine for the treatment of malaria. Information was obtained by searching published literature in the National Library of Medicine via Pub Med and MEDLINE search engines for research articles, reviews, books, and other reports. Identification of published reports was done using key word searches such as quinine and malaria treatment, quinine and drug resistance, quinine in pregnancy, quinine and antibiotic combinations, and quinine and HIV/TB infected populations.

Quinine properties

Quinine is a cinchona alkaloid that belongs to the aryl amino alcohol group of drugs. It is an extremely basic compound and is, therefore, always presented as a salt[6]. Various preparations exist, including the hydrochloride, dihydrochloride, sulphate, bisulphate, and gluconate salts; of these the dihydrochloride is the most widely used. Quinine has rapid schizonticidal action against intra-erythrocytic malaria parasites. It is also gametocytocidal for Plasmodium vivax and Plasmodium malariae, but not for Plasmodium falciparum. Quinine also has analgesic, but not antipyretic properties. The anti-malarial mechanism of action of quinine is unknown.

Quinine is rapidly absorbed both orally and parenterally, reaching peak concentrations within 1-3 hours[8]. It is distributed throughout the body fluids and is highly protein bound, mainly to alpha-1 acid glycoprotein. The binding capacity in plasma is concentration dependent, but also depends on the levels of alpha-1 acid glycoprotein, which therefore makes comparisons between different studies difficult[9]. Quinine readily crosses the placental barrier and is also found in cerebral spinal fluid. Excretion is rapid – 80% of the administered drug is eliminated by hepatic biotransformationOverview of quinine use in the management of malariaQuinine remains an important anti-malarial drug, almost 400 years after Jesuit priests first documented its effectiveness. The 2010 World Health Organisation (WHO) guidelines recommend a combination of quinine plus doxycycline, tetracycline or clindamycin as second-line treatment for uncomplicated malaria (to be used when the first-line drug fails or is not available) and quinine plus clindamycin for treatment of malaria in the first trimester of pregnancy [23]. Based on recent trials, intravenous artesunate should be used for the treatment of severe falciparum malaria in adults :and childrenin preference to quinine.By 2009, 31 African countries recommended quinine as second-line treatment for uncomplicated malaria, 38 as first-line treatment of severe malaria and 32 for treatment of malaria in the first trimester of pregnancy]. In most of Africa, quinine is still used as monotherapy, contrary to the WHO recommendations]; the reason for this practice may be the higher costs of quinine-antibiotic combinations. Quinine continues to play a significant role in the management of malaria in sub-Saharan

Africa and other malaria endemic areas, and its use in routine practice may not be restricted to the stated WHO recommendations.[9]

Cameroon, even one year after the introduction of ACT, quinine continued to be used as first-line therapy, with 45% of adults receiving oral quinine for uncomplicated malaria [25]. Recent surveillance data from sentinel sites in Uganda showed that quinine was prescribed for up to 90% of children < 5 years with uncomplicated malaria .

Conclusion-The use of quinine for uncomplicated malaria cases should have decreased due to toxicities, poor compliance and the implementation of newer and better tolerated therapies such as ACT. However, the limited availability of ACT and the increasing resistance to chloroquine and antifolates have actually increased its use in recent times . Therefore, studies evaluating the role of quinine in the management of malaria have been reviewed

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Abbreviations- **RTS**- Mosquirix**ATS**-Normal activated clotting time**NANP**-National Association of Non-Principals

HIV- human immunodeficiency virus

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