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NOVEL MOLECULAR TARGET IN MALARIA PARASITE CHEMOTHERAPY: LIMITATIONS AND FUTURE PROSPECTS

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ABSTRACT
Approximately one-fourth of the world's population suffers from anemia. While anemia can be caused by several factors, Iron-deficient anemia is the most common type. As people age,[1] the prevalence of anemia increases, and it is more predominant in females.[2] This study assessed adherence to transfusion guidelines at tertiary care referral hospitals. The study was conducted for three months, and the data was analyzed retrospectively. A total of 150 anemic patients who received packed red blood cells (PRBCs) were included in the study. Most patients had nutritional anemia caused by deficiencies in Iron, Vitamin B12, and Folic acid. The O +ve patients had a high incidence of anemia, with 57 patients (38%) affected, and there was 100% adherence to PRBC transfusion criteria (where Hb <8 for non-cardiac patients and <10 for cardiac patients). This study sheds light on the primary causes of anemia in the Indian setting. It emphasizes the need for adequate treatment to reduce morbidity and healthcare costs borne by society and the government.

KEYWORDS: Blood Transfusion, Anemia, Adherence, Guidelines.

INTRODUCTION

Recent antimalarial drug discovery has been a race to produce new medicines that overcome emerging drug resistance, whilst considering safety and improving dosing convenience. Discovery efforts have yielded a variety of new molecules, many with novel modes of action, and the most advanced are in late-stage clinical development. These discoveries have led to a deeper understanding of how antimalarial drugs act, the identification of a new generation of drug targets, and multiple structure-based chemistry initiatives. The limited pool of funding means it is vital to prioritize new drug candidates. They should exhibit high potency, a low propensity for resistance, a pharmacokinetic profile that favours infrequent dosing, low cost, preclinical results that demonstrate safety and tolerability in women and infants, and preferably the ability to block Plasmodium transmission to Anopheles mosquito vectors.[1]

Malaria is a tropical threatening disease caused by Plasmodium parasites, resulting in 409,000 deaths in 2019. The delay of mortality and morbidity has been compounded by the widespread of drug resistant parasites from Southeast Asia since two decades. The emergence of artemisinin-resistant Plasmodium in Africa, where most cases are accounted, highlights the urgent need for new medicines. In this effort, the World Health Organization and Medicines for Malaria Venture joined to define clear goals for novel therapies and characterized the target candidate profile. This ongoing search for new treatments is based on imperative labor in medicinal chemistry.[2]

The malaria parasite resistance to the existing drugs is a serious problem to the currently used antimalarials and, thus, highlights the urgent need to develop new and effective anti-malarial molecules. This could be achieved either by the identification of the new drugs for the validated targets or by further refining/improving the existing antimalarials; or by combining previously effective agents with new/existing drugs to have a synergistic effect that counters parasite resistance; or by identifying novel targets for the malarial chemotherapy. In this review article, a comprehensive collection of some of the novel molecular targets has been enlisted for the antimalarial drugs. The targets which could be deliberated for developing new anti-malarial drugs could be: membrane biosynthesis, mitochondrial system, apicoplasts, parasite transporters, shikimate pathway, hematin crystals, parasite proteases, glycolysis, isoprenoid synthesis, cell cycle control/cycline dependent kinase, redox system, nucleic acid metabolism, methionine cycle and the polyamines, folate metabolism, the helicases, erythrocyte G-protein, and farnesyl transferases. Modern genomic tools approaches such as structural biology and combinatorial chemistry, novel targets could be identified followed by drug development for drug resistant strains providing wide ranges of novel targets in the development of new therapy. The new approaches and targets mentioned in the manuscript provide a basis for the development of new unique strategies for antimalarial therapy with limited off-target effects in the near future.[3]

Malaria is a protozoal infection caused by certain species of Plasmodium. It is transmitted from person to person through the bite of infected female anopheles' mosquito which carries the plasmodium parasite. The key stages of the malaria parasite in the human host involve: 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. 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 parasite, in the form of 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. 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. 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 is thus continues. A summary of this cycle and the various targets of current antimalarial is shown in figure 1 as adapted from Siqueira-Neto et al., 2023.[1]

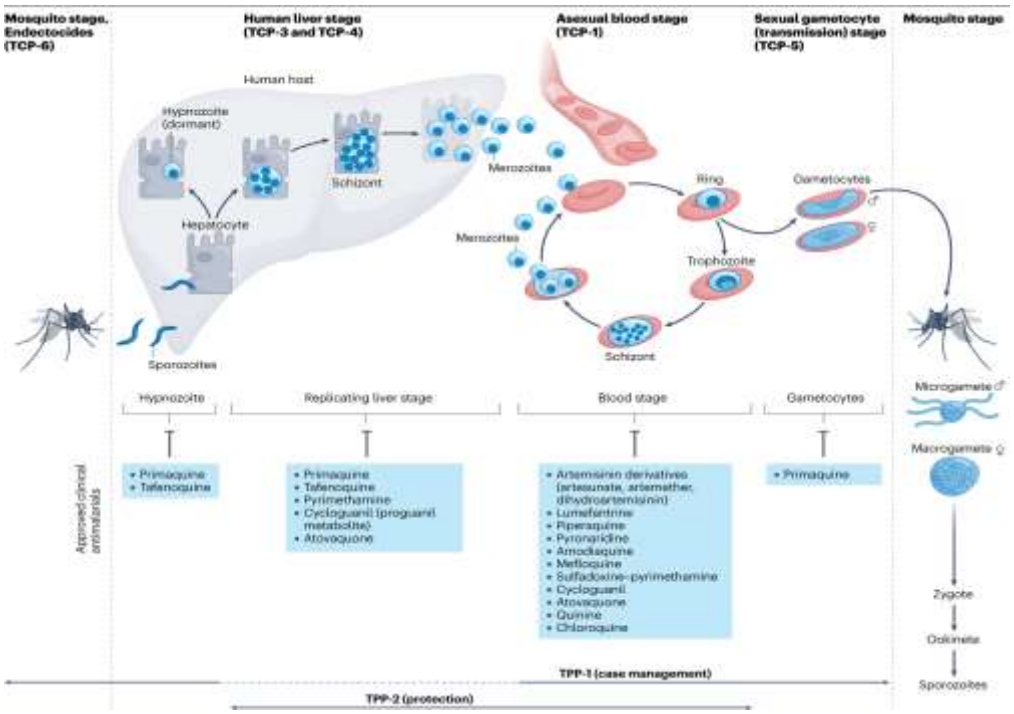

Fig 1: Life cycle of malaria parasite and target stages of current antimalaria (Siqueira-Neto et al., 2023).[1]

CURRENT ANTIMALARIAL DRUGS, THEIR MECHANISIM OF ACTIONS AND THEIR SHORT FALLS/ CHALLENGES

- Chloroquine Phosphate

Chloroquine phosphate is the preferred agent if the infection is considered uncomplicated and works by inhibiting parasite growth by concentrating within the parasite acid vesicles, thereby raising internal PH.[4]

The short falls of chloroquine is that the Plasmodium falciparum parasites harbor mutations against chloroquine due to presence of a transport (P. falciparum chloroquine resistance transporter) on the digestive vacuole membrane. That is in the variant forms can transport these weak-base drugs out of this acidic organelle, thus preventing these drugs from binding heme and inhibiting the detoxification.[5]

- PRIMAQUINE PHOSPHATE

works by eliminating the hypnozoites that remain dormant in the patient's liver, reducing the risk of relapse.[6] This is also an add-on agent (supporting agent) to either chloroquine or hydroxychloroquine against p. vivax or p. ovale.[6] May also say that primaquine is chemically related to chloroquine because both drugs are members of 8-aminoquinolines. But according to Fernando et al, 2011; Thomas et al., 2016.[7,8], P.vivax strains appear to be tolerant to primaquine as relapses have been repeatedly observed in experimental infections treated with standard chloroquine-primaquine regimes in malaria free settings.

- ARTEMISININ DERIVATIVES AND ITS COMBINATIONS

Artemisinin based combination therapy is an alternatives first-line treatment for malaria. Its companion drugs include

- Lumefantrine
- Mefloquine
- Amodiaquine
- Sufadoxine/pyrimethamine
- Piperaquine

Artemisinin derivatives include dihydroartemisinin, artesunate and artemether. Focusing on artemether-lumefantrine(AL), it is used for chloroquine-resistant p.falciparum and works by inhibiting nucleic acid and protein synthesis.[9] Resistance to (AL) is due to increased copy number of plasmodium falciparum multi drug resistance 1 (Pfmdr1) and plasmepsin 2 (Pfpm2) genes which represent validated molecular signature associated with resistance to lumefantrine.[10]

- **QUININE**

Quinine is a second- line option for treating malaria. It works by intercalates into DNA, disrupting the parasites replication and transcription to exert its antimalarial effects.[11] Quinine resistance was first in demonstrated 1910, in the 19th century.[12] Furthermore, quinine resistance appear to share common characteristics with chloroquine resistance (i.e mutation in Pfmdr1 and Pfcrt).[13]

NOVEL MOLECULAR TARGETS IN MALARIA PARASITE CHEMOTHERAPY

By definition, molecular targets are biomolecules which are involved in metabolic pathways usually specific to that disease.[14]

a) Glucose transporter

As a drug target, they are two types

I. glut 1 transporter: which transport only D-glucose from the blood into the parasitized erythrocyte and is abundant in the erythrocyte.[15]
II. P.falciparum Hexose Transporter: which is the main transporter of glucose of D-glucose and D-fructose and is essential for malaria parasite's growth and survival.[16]
III. Thus, the difference between the above transporters in their interaction with the substrate, which proposed that selective inhibition of P.falciparum hexose transporter is a potential novel target for the discovery of new antimalarial agent.[17]

b). Mitochondrial respiratory chain as a drug target

The plasmodium mitochondrial respiratory chain has formed resistance due to gene mutations against several drug. This is because most drugs targets single active site of cytochrome bc1 complex. According to Yang et al., 2021,[18] a selective inhibitor (RYL-581) was developed P.falciparum nicotinamide adenine dinuleotide with simultaneous inhibition on both active sites of PfNDH2.

c). Targeting the parasite protein Kinase

Kinases are involved in phosphorylation transcriptional control, post-transcriptional control and protein degration in the parasite life cycle and as a result could be the strategic targets for development of antimalarial drugs.[19]

Flavopiridol and lomoucine are examples of drugs that have shown inhibition against the P.falciparium protein kinase[19]

d). Heat shock protein as a molecular drug target.

Recently, in an American study, Cobb et al., 2021[20] identified P.falciparium Hsp40 chaperone termed Pfj2 and protein disulfide isomerases (PDIS). Furthermore, it was revealed that knocking down of the gene encoding PD1s showed a PfpD18 which was essential for parasite growth and survival at the asexual erythrocyte stages.

The investigators demonstrated that interaction between Pfj2 and PfPD18 could be blocked by covalent inhibitors through oxidative folding process in Falciparum ER and this served as a potential drug target.

e). Food vacuole as a drug target

Food vacuole is accountable for the degration of 60-80% of the host red cell hemoglobin, which has a key role in the attainment of amino acid which is essential for parasite development and growth.[21] Investigation of this degradation pathway can be a promising method for the discovery and development of novel antimalarial agents.

f). Apicoplast as drug targets

Recently, blocking the P.falciparium ribosome and other parts of the translated machinery accountable for protein synthesis are becoming a promising target for the discovery and development of novel antimalarial agents, apicoplast, nuclear and mitochondrial.[22]

The apicoplast resulted from endosymbiosis, leading to an organelle that maintains certain specific functions, probably including fatty acid, heme and amino acid metabolism,[21] Human beings do not have these metabolic biochemical pathways which are important for ideal drug targeting,[21,23,24] Other targets includes the haemoglobin trafficking pathway and vitamins.

NEW DRUGS UNDER CLINICAL DEVELOPMENT

- Tefenoquine: a single dose relapse prevention
- Artefenomel-ferroquine: fast and long-acting synthetic-ozonide
- Lumefantrine: lumefantrine solid dispersion formulation is being studied in a trial, to be administered once daily, since its fat-dependent and dose-limited
- Cipargamin: a blood schizontidide under evaluation as a single agent.
- DSM-265: a long acting dihydroorotater dehydrogenase inhibitor with blood and liver stage activity
- AQ-13: a substituted 4-aminouindine, which has been in clinical development for more than 10 years.
- Fosmidomycin-Piperaquine: uncomplicated P.falciparium blood schizonticide
- MMV 390048: an aminopyridine plasmodium phosphatidylinositol 4-Kinase inhibitor.
- Methylene Blue: P.falciparium blood schizonticide and potent gametocytocidal agent.

Another treatment prospect is DDD 107498 which has activity against all stages in the malarial life cycle.[25]

In conclusion, due to the resistance of antimalarial agents globally, searching for novel cellular targets and developing new therapeutic agents targeting old targets is both imperative aspects in fighting drug-resistant malaria. The future antimalarial drug development with better target medicines and a distinctive mechanism of action is a new hope.

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