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The Evolution of Malaria Treatment: From Quinine to Modern Therapies— A Review

Kartik Sharma[1], Tanya Sharma[2], Zulphakar Ali[3]

[1] Student of B-Pharmacy at Mewar University, Rajasthan, India.
[2] Assistant Professor at Mewar University, Rajasthan, India.
[3] Assistant Professor at Mewar University, Rajasthan, India.

ABSTRACT :

Such malaria is one of the greatest contributors to global health challenges, as it affects millions in a year, most especially in tropical and subtropical homogeneous regions. Blood- stage infection: The use of quinine heralded the earliest phase of antimalarial therapy, and initial developments towards synthetic antimalarials, mainly chloroquine, amodiaquine, and sulfadoxine-pyrimethamine, have followed with a significant stride. On the one hand, these new antimalarials have been proved effective in the treatment of malaria; the appearance of drug-resistant Plasmodium strains clearly limits their long-term usage. The introduction of artemisinin and artemisinin-based combination therapy (ACT) has become a landmark in present-day treatment of malaria, permitting patients to have their parasites cleared quickly with a reduction in death rates. Rapid emergence of evidence on developing resistance to artemisinin and its partner drugs has even made it very urgent for researchers to find next-generation antimalarial drugs as well as new therapeutic paradigms. RTS, S/AS01, and R21/Matrix-M vaccines have indeed been promising alternatives for malaria prevention regarding the recent advancements in malaria vaccine development, while still posing questions when it comes to long-term effectiveness and scaling up of delivery to great numbers of target populations. Such novel approaches may incorporate innovations concerning drug delivery systems, gene editing technologies for vector control, and AI-based surveillance methods that are being explored to bolster malaria management and eradication efforts. But the development of action and sustainability for abandoning malaria will include the following: developing better medicines, improving vaccine coverage, a strong health infrastructure, and integrated vector control measures. This review covers the past, current, and future aspects in the path of therapy for malaria; reviews the successes and failures in importing challenges of a drug-resistant malaria; and casts an eye on innovations on the verge of future malaria eradication.

Keywords: malaria, quinine, artemisinin-based combination therapies (ACTs), drug resistance, malaria vaccines, next-generation antimalarials, vector control, CRISPR, nanotechnology, AI surveillance.

INTRODUCTION

Malaria continues to be one of the world's major global health threats, impacting millions of people every year, particularly in tropical and subtropical areas. The disease is caused by Plasmodium parasites, including P. falciparum and P. vivax, and is transferred through the bites of infected mosquitoes of the Anopheles type. The World Health Organization (WHO) estimates that in 2022, there were approximately 249 million cases of malaria worldwide, with the highest burden in Africa [1]. Although there have been multiple measures to control and eliminate malaria, obstacles such as resistance to treatment, limited access to healthcare, and socio-economic limitations remain significant barriers to progress [2]. The treatment of malaria has evolved immensely over time. 1590-founded remedies, such as natural remedies of cinchona bark and its active component quinine, were the first recorded treatment for malaria. Quinine emerged in the 17th century and remains the main treatment for the disease. In the 20th century, there were more affordable and synthesized options, like chloroquine [3]. Nevertheless, P. falciparum strains began to emerge in the 1950s that were resistant to chloroquine, which necessitated the need for new treatments for malaria. New evidence led to the development of sulfadoxine-pyrimethamine (SP), and later, artemisinin-based combination therapies (ACTs) emerged [4]. The identification of artemisinin from Artemisia annua was a pivotal moment for the treatment of malaria. Since its incorporation into clinical practice in the 1970s, artemisinin-based combination treatments (ACTs) have been widely recognized as the gold standard of malaria treatment, with significant reductions in malaria mortality risk [5]. Nevertheless, the emergence of artemisinin resistance in some locations in Southeast Asia raises questions about the future treatability, viability, and mortality risk of current treatments [6]. Current research has focused on developing new drugs, combination therapies, and future malaria vaccines as a means to address issues of resistance and treatment outcomes [7]. This review will consider the past history of malaria treatment, in terms of early treatments through to current treatment advances, while looking at present- day challenges facing malaria treatments, drug therapies, and future challenges to managing malaria, while also providing the reader with a greater understanding of the historical progression and present- day antimalarial therapies [8].

EARLY TREATMENTS AND THE DISCOVERY OF QUININE

Prior to the advent of powerful antimalarial agents, malaria was treated using traditional herbal medicines derived from plants. Various civilizations practiced phytomedicine, using either Chang Shan plant (Dichroa febrifuga) extracts in China or herbal decoctions in the Ayurvedic tradition for all febrile complaints [9]. However, efficacy was limited and these indigenous remedies were not scientifically established, hence leading to inconsistent treatment outcomes [10].Major advances were made in malaria treatment with the discovery of quinine (an alkaloid derived from the bark of the cinchona tree, Cinchona officinalis) which is a South American native plant. It was the indigenous Peruvians who first used cinchona bark to treat febrile illnesses, a practice later brought to Europe in the 17th century by Jesuit missionaries [11]. The active ingredient was first isolated from its bark in 1820 by French chemists Pierre Joseph Pelletier and Joseph Bienaimé Caventou, and so the quinine of cinchona bark became the first scientifically validated treatment for malaria [12].

Quinine promptly turned out to be the first antimalarial, which had an indispensable part in the context of colonial medicine and military warfare in the 19th and early 20th centuries. In order to ensure a consistent supply of quinine, large-scale cinchona plantations were established by European nations, mainly the British and the Dutch, in India and Indonesia [13]. However, this has often been accompanied by side effects like cinchonism (tinnitus, nausea, and visual disturbances), and more importantly, World War II, which witnessed far greater demand than supply, shifted attention to synthetic alternatives [14]. The inability of quinine to satisfy the requirements of therapeutic effectiveness as well as safety had given rise to much effort towards the searching of synthetic substitutes for antimalarial drugs that came into being during the 1930s, chloroquine being discovered as the most effective and less toxic antimalarial agent [15]. Although quinine is being outpaced by newer therapies, it is still a valuable drug in the treatment of cases of severe malaria where resistance to modern therapies has been developed [16].

DEVELOPMENT OF SYNTHETIC ANTIMALARIALS

The quest for effective synthetic antimalarial drugs was keenly felt with respect to quinine, which had the limitations of being at times unavailable, costly, and side effects such as cinchonism (tinnitus, nausea, dizziness, and visual disturbances) [9]. Although the demand for new treatments was always there, during World War II it became almost acute when supplies of natural quinine were threatened by Japanese occupation of the key producing regions in Indonesia. The whole crisis, therefore, triggered immense research intto synthetic antimalarial alternatives, hence one of the greatest events in the history of discoveries related to malaria treatments [14].

1. The Discovery and Widespread Use of Chloroquine

One of the earliest and one of the most important synthetic antimalarial agents, chloroquine, being a 4-aminoquinoline derivative, was synthesized in 1934 by Hans Andersag and his colleagues at Bayer Laboratories in Germany [15]. At that time chloroquine was considered too toxic for therapeutic use. During World War II, American scientists rediscovered the drug and found it to be safe and effective against Plasmodium falciparum and much safer than quinine [17]. Just after the war, chloroquine became the first-line treatment for malaria around the world because it was cheap, easy to use, and provided long-term protection.

By inhibition of heme detoxification in the malaria parasite, a toxic amount of heme would accumulate within the parasite's digestive vacuole and cause its death [18]. For decades, chloroquine was the backbone of malaria treatment and prophylaxis, considerably alleviating the disease burden in endemic areas. But in the late 1950s, chloroquine resistance (CQR) arising in Southeast Asia and South America proved to be a stupendous hurdle. Resistance was further linked to mutations in the PfCRT gene allowing the parasite to expel the drug and survive treatment [19]. Resistance developed widely by the 1980s, rendering chloroquine ineffective in large areas of the world, thus bringing forth the need for alternate therapies.

2. Overview of Introductory Antifolate Drugs

Pyrimethamine, Proguanil, and Sulfadoxine-Pyrimethamine. The birth of a new class of synthetic antimalarials for the treatment of resistance to chloroquine will be the folate biosynthesis pathway inhibitors of Plasmodium species. These inhibitory effects of these drugs were mediated through the enzyme dihydrofolate reductase (DHFR), which is required for the parasite's DNA synthesis and replication [5] :

Pyrimethamine was one of the earliest antifolate drugs used for the treatment of malaria, having been developed around the 1950s. Initial hopes of its having monotherapeutic value were dashed as it proved ineffective after monotherapy due to rapid resistance. Proguanil was developed during that same period as an antifolate mainly used for malaria prophylaxis, and it usually had to be administered with chloroquine to improve efficacy. Sulfadoxine-pyrimethamine emerged on the market during the 70s and was fast turned to for use in place of chloroquine in many areas; it was sulfadoxine (under dihydropteroate synthase) and pyrimethamine (under dihydrofolate reductase) combined because there was dual inhibition of the folate pathway, delaying the development of resistance [20].

Notwithstanding the initial success, resistance to SP was created at a fast pace in Africa and Southeast Asia, mainly through mutations in the dhfr and dhps genes of Plasmodium falciparum that rendered the drug useless in many endemic areas owing to the emergence of the urgent need for new treatment strategies [21].

3. The Development of Mefloquine and Atovaquone-Proguanil

The three stages of the development of mefloquine and atovaquone-proguanil showed how new synthetic antimalarial drugs were introduced as resistance to chloroquine and antifolates spread. Mefloquine was a drug developed by the United States Army in the 1970s to be a long-acting antimalarial drug for both treatment and prophylaxis. It inhibited the heme detoxification pathway in the parasite similar to chloroquine, but because of different chemical structures, resistance could be avoided. Mefloquine is effective, but side effects such as dizziness, psychiatric problems as anxiety, vivid dreams, and rare instances of a person going psychotic as well were met in a divided use of mefloquine [22]. Malarone, the atovaquone-proguanil introduced in the early 1990s, was a much safer and effective alternative. It affects the mitochondrial electron transport chain in the parasite and inhibits folate synthesis, making proguanil an effective drug having very little resistance. Due to this, Malarone suits especially as an antimalarial prophylaxis for travelers because of its mild side effects, as well as duration more so compared to mefloquine [23].

4. The Rise of Artemisinin-Based Combination Therapies (ACTs)

ACTs were born: as synthetic antimalarials facing ever-increasing resistance, major breakthroughs occurred with the rediscovery of some old antimalarial compounds such as artemisinin. This discovery did provide hope for the direct revival of a component that had long been relegated to relative obscurity due to the plant's importance in traditional Chinese medicine. Tu Youyou's research led to isolating artemisinin in the 1970s, which changed everything regarding malaria treatment [5].ACTs were adopted in the early 2000s and became the gold standard for malaria treatment due to their rapid clearance from parasites, high efficacy, and ability to reduce the transmission of resistance. ACTs involve combinations of artemisinin derivatives, such as artesunate, artemether, or dihydroartemisinin, with longer-acting synthetic partner drugs, such as lumefantrine or mefloquine, to prevent resistance development [24].In any case, artemisinin resistance still exists in some areas of Southeast Asia, which constitutes a greater challenge to global efforts to control malaria. Mutations in the Kelch13 (K13) gene of Plasmodium falciparum have been linked to a delayed parasite clearance, thus threatening the very basis of efficacy for ACTS against malaria [25].

ARTEMISININ AND COMBINATION THERAPIES

Artemisinin probably defined the turning point in treatment for malaria, thus becoming the ultimate weapon in the fight against Plasmodium falciparum\textit{, }especially in areas where any traditional antimalarial drug would have failed by all standards of resistance. Since then, artemisinin-based combination therapy (ACT) has become the hallmark of malaria chemotherapy, put forth worldwide by the WHO on grounds of efficacy, rapidity of parasite clearance, and prevention of further development of ACT resistance [26].

1. Discovery and Mechanism of Action of Artemisinin

Artemisinin is a sesquiterpene lactone derived from Artemisia annua (sweet wormwood), a plant used for centuries in traditional Chinese medicine. In the 1970s, Tu Youyou, a Chinese scientist who received the 2015 Nobel Prize in Physiology or Medicine for her extraordinary work, was able to isolate the compound \textit{[5].} Artemisinin and its derivatives-ar tesunate, artemether, and dihydroartemisinin-are potent against malarial parasites and have rapid action even in the midst of resistance.Antimalarials not used before: Artemisinin itself has an unusual mechanism of action. It acts by cleaving the endoperoxide bridge to generate reactive oxygen species (ROS), which subsequently damage parasite proteins, lipids, and membranes in a massive manner. Hence, the rapid clearance of parasites makes artemisinin, among others, the fastest-acting antimalarial available \textit{[27].} Moreover, there is an accumulation of artemisinin within the digestive vacuole of Plasmodium falciparum and disrupts the detoxification of heme, which is an important survival mechanism of the parasite \textit{[28].}

2. The Emergence of Artemisinin-Based Combination Therapies (ACTs)

Although artemisinin is a very efficacious agent, its very short half-life necessitates its combination with long-acting partner drugs in order to complete clearance of the parasites and prevent re-infection. Such combination therapy led to the development of artemisinin-based combination therapies (ACTs), which have an artemisinin derivative partnered with a second antimalarial with longer duration of action. The rationale behind ACT is to improve efficacy, reduce resistance by parasites, as well as make it therapeutically longer with the artemisinin derivatives [24].

Some of the ACTs that are commonly used include:

- Artemether-lumefantrine (Coartem)- of the most commonly used ACTs since lumefantrine provides prolonged parasite suppression after the rapid clear-out of initial infection by artemether [29].
- Artesunate-amodiaquine - This is primarily used in Africa, where amodiaquine still has effective activity against P. falciparum [30].
- Arthesunate-mefloquine - This is the major ACT in Southeast Asia, especially where the intensity of mefloquine resistance is not effectively widespread [31].
- Dihydroartemisinin-piperaquine: A very potent ACT with long post-treatment prophylactic effect due to piperaquine's long half-life [32].

3. Challenges: Artemisinin Resistance and Its Implications

The impressive accomplishment of ACTs in achieving therapeutic results has unfortunately taken an unexpected twist with the development of resistance to artemisinin in Southeast Asia, particularly in the Greater Mekong Subregion. Such resistance is defined mainly by a measured delay in parasite clearance, associating it with mutations in the Kelch13 (K13) gene of Plasmodium falciparum. These mutations lower the susceptibility of the parasites to artemisinin, which resulted in the capacity of a few parasites to escape from the treatment during this phase and pose an even higher risk of treatment failure. Resistance to artemisinin, therefore, becomes a real threat all over the world because there are no adequately effective alternative therapy available at this time. This meant that in Africa, where the highest burden of malaria was found, progress made over decades in controlling malaria would be jeopardized [20]. This event has spurred different research endeavors to develop new-generation ACTs, optimal drug combinations, and alternative therapeutic strategies.

4. Future Perspectives and the Role of Triple-Combination Therapies

In order to counter resistance and improve the treatment efficacy, the researchers now focus on the compromise of two partner drugs along with artemisinin by way of triple artemisinin-based combination therapies (TACTs). Some of the combinations that are attractive include:

- Artemether-lumefantrine-amodiaquine
- Dihydroartemisinin-piperaquine-mefloquine

Early clinical trials suggest that TACTs may provide stronger protection against resistance, prolonging the effectiveness of existing antimalarial drugs [33]. Another way of non-artemisinin treatments is using novel drug classes such as ozonides (e.g., OZ439) and spiroindolones (e.g., KAF156) which target various biological pathways in the malaria parasite [34].

CHALLENGES IN MALARIA TREATMENT

And yet, despite these propositions for the eradication of malaria having made real progress over the decades, much still lies ahead: drug resistance, poor healthcare infrastructure, socioeconomic impediments, and gaps in research and development for vaccines. Contending with these issues is vital if any sustained malaria control and reduction of the disease burden are to be achieved globally.

1. Drug Resistance and Limited Treatment Options

This remains one of the greatest challenges against the treatment of malaria. Drug-resistant strains of Plasmodium, especially Plasmodium falciparum, were noted. Resistance to the early antimalarial drugs, chloroquine and sulfadoxine-pyrimethamine, has seen these drugs not being effective since the late 20th century [35]. The introduction of ACTs, with their very high efficacy, lessened the impact of resistance on malaria treatment; however, artemisinin resistance has now emerged in the Greater Mekong Subregion due to mutations in the Kelch13 (K13) gene [25]. This resistance mechanism leads to a delay in parasite clearance, a condition that fosters treatment failure and transmission of malaria [20]. Any attempts to thwart resistance through development involve triple ACTs and drug candidates such as spiroindolones (KAF156) and ozonides (OZ439). However, possibly the biggest hurdle here is ensuring affordability and availability of the new drugs to all people [34]."

2. Limited Access to Effective Treatment in Endemic Regions

Most malaria-endemic countries, especially in sub-Saharan Africa and some parts of Southeast Asia, fell short on the health infrastructure that would allow timely diagnosis and treatment. Consequently, rural populations living far from healthcare facilities incur an often unnecessary delay to access a health facility for treatment, with mortality severely impacted as a result [36]. Stock-outs of vital antimalarial drugs in poorly equipped and regulated clinics aggravate the barriers so that patients even visit informal providers, where they are likely to receive substandard or counterfeit medicines [37]. Another critical issue is the price of ACTs, which is too high for most lower-income societies. Organizations such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria subsidize these treatments but are also still affected by funding gaps and logistical issues in drug availability [38].

3. Socioeconomic Barriers and Inaccurate Information

Socioeconomic parameters primarily involve poverty, low education, and cultural beliefs that have significant contributions to the results of malaria treatment. In some regions, people do prefer traditional forms of medicine to modern medicine as for long relieving from certain ailments [9]. Misinformation concerning health care systems has also been a contributing factor to low adherence to prescribed treatments, thus increasing the possibility of incomplete parasite clearance and development of resistance [39]. Malnutrition in addition with co-infections with HIV, tuberculosis, etc may depress the immune response so that these individuals would be more susceptible to severe malaria and treatment complications [40]. Community mobilization, Improved health literacy and more robust public health initiatives are important in overcoming these barriers.

4. Gaps in Malaria Vaccine Development

Antimalarial drugs are at the core of the treatment, but vaccines provide a long-term solution to malaria control. The RTS,S/AS01 (Mosquirix) vaccine, which first received widespread approval for malaria vaccination, has been shown to have moderate efficacy (~30-40%) in children but requires more than one dose for adequate protection [41]. Another contender, R21/Matrix-M, has shown higher efficacy (~77%) in clinical trials, raising expectations for better vaccines in the future [42]. These and other matters along with access, affordability, and logistics, will continue being some of the hurdles before widespread immunization efforts.

5. Climate Change and Expanding Areas Endemic to Malaria

Consider the environment; for instance, the climate change factor is spreading malaria to formerly non-endemic geographical locations. The rising temperature in conjunction with the increased rainfall makes a preferable atmosphere for mosquito breeding and this creates a high-risk-transmission condition in new areas, including some parts of South America, southern Europe, and Central Asia [43]. Furthermore, the increased population density in urban centers and the incidence of deforestation further complicates malaria control effort [44].

RECENT ADVANCES AND FUTURE DIRECTIONS

Significant progress has been made in malaria treatment via new antimalarial drug formulations, improved combinations, and vaccine development. Drug resistance and ongoing transmission challenges, however, require new innovations in treatment. Attention for the future will include next-generation antimalarials, new drug delivery systems, and genetic means to cut malaria down to size.

1. Recent advances in antimalarial drug development

Due to issues of artemisinin resistance, KAF156 (Ganaplacide) and OZ439 (Artefenomel) are new antimalarial drugs in clinical trials, which can potentially overcome these resistances and may offer single-dose curative options [45]. The other consideration is the use of triple artemisinin-based combination therapies (TACTs) to remain effective [46].

2. Advances in malaria vaccine

The RTS,S/AS01 (Mosquirix) vaccine has been rolled out as the first widely deployed malaria vaccine, albeit with partial protective efficacy [41]. The recently approved R21/Matrix-M The vaccine has demonstrated superior efficacy (~77%) and may be a key weapon in malaria prevention [42].

3. Innovative Drug Delivery and Nanotechnology

Nanotechnology-based formulations like lipid nanoparticles and polymeric micelles are under investigation to achieve drug stability and enhance targeted delivery, thus improving therapeutic outcomes [47]. These developments will have applications to reduce drug toxicity, thereby increasing availability for improved therapy.

4. Genetic Approaches and Vector Control

Recent gene-editing technologies such as CRISPR-Cas9 have enabled the development of genetically modified mosquitoes that can resist Plasmodium infection; this would thus become a long-term strategy for malaria control [48]. The other systems under consideration are gene drives that effectively lower the population of mosquitoes.

5. Future Directions

- Next-Generation Drugs: Formulating new antimalarials with different mechanisms to avert resistance.
- Improved Vaccines: Research in multi-stage malaria vaccines that confer long-term immunity.
- AI and Data Analytics: AI-based surveillance to predict outbreaks and optimize resource allocation [49].
- Integrated Eradication Strategies: Combining drug therapy, vaccines, and vector control for sustainable malaria management.

CONCLUSION

The treatment of malaria has undergone a marvelous shift from early quinine use to the present-day artemisinin-based combination therapy (ACT) and promising new candidates. The existence of synthetic antimalarials in the past few decades, which have acted as very effective treatment options, has faced stiff challenges primarily due to drug-resistant strains of malaria arising and demanding constant upgrading of therapeutic strategies. While ACTs hold the highest promise in the malaria market currently, the increasing reports of artemisinin resistance from certain regions signal, once again, the pressing need for next-generation antimalarials with totally novel mechanism(s) of action. X- combination therapy, where the investigation of novel drug candidates such as KAF156 and OZ439 will assume an important role, and different alternate therapeutic strategies will play an important part in sustaining effective malaria control. Apart from the launch of new drugs, the introduction of malaria vaccines like RTS,S/AS01 and R21/Matrix-M adds

a whole new dimension to disease prevention. While these vaccines have shown partial protection, their large-scale deployment in conjunction with existing vector control measures could significantly reduce malaria transmission. Exciting opportunities for enabling long-term eradication schemes are offered by gene editing technologies and artificial intelligence-gated surveillance. Going on, the fight against malaria would take a very broad-spectrum approach integrating new therapeutics, improvement in vaccine coverage, vector control strategies, and real-time surveillance. Global collaboration, funding, and research must continue so as to face the immediate challenges and to move towards malaria's ultimate elimination.

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