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Revisiting Chloroquine In Malaria Treatment: A Pharmacological Perspective

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Abstract:
Malaria remains a major global health challenge, with artemisinin-based combination therapies (ACTs) serving as the current gold standard for treatment. However, the growing reports of ACT resistance, particularly in regions like sub-Saharan Africa and Southeast Asia, have raised concerns about their long-term efficacy. This review revisits chloroquine, a previously widespread antimalarial drug, to evaluate its potential for reintroduction in areas facing ACT resistance. A comprehensive literature review was conducted, focusing on chloroquine's historical efficacy, safety, and pharmacoeconomic. Emerging studies suggest that in regions where chloroquine has been withdrawn for several years, malaria strains have regained sensitivity to the drug. By comparing chloroquine's pharmacological benefits and safety profile with ACTs, this review explores whether chloroquine could serve as a viable alternative in the context of rising ACT resistance. The findings suggest that chloroquine merits reconsideration in specific regions, particularly where resistance to current therapies is becoming an increasing concern.

Keyword: *Chloroquine; ACT resistance; malaria treatment; pharmacoeconomics; patient compliance; drug availability.*

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I. Introduction

Malaria is endemic in many parts of the world, with Sub-Saharan Africa carrying the highest burden. Chloroquine, once a first-line treatment for Plasmodium falciparum, was phased out due to widespread resistance, particularly in Africa (N. White, 1999) .The advent of ACTs marked a significant advance in malaria management, but recent reports of ACT-resistant Plasmodium falciparum strains raise concerns about future treatment efficacy (Maiga et al., 2021). This review aims to assess whether chloroquine could be revisited in light of these challenges or if it should remain in disuse.

Malaria continues to be one of the most significant global health challenges, particularly in sub-Saharan Africa, Southeast Asia, and parts of South America. Despite substantial progress in reducing malaria-related morbidity and mortality, the disease still claims hundreds of thousands of lives annually, with the majority being children under five years of age. For decades, chloroquine (CQ) was the cornerstone of malaria management due to its efficacy, safety, low cost, and ease of use. However, by the late 20th century, widespread resistance to CQ, particularly against Plasmodium falciparum, led to its replacement by artemisinin-based combination therapies (ACTs), which have since become the gold standard for malaria treatment (White, 1999).

Despite the success of ACTs in combating malaria, increasing reports of ACT resistance and treatment failure have surfaced, particularly in Southeast Asia. Resistance to artemisinin is driven by mutations in the kelch13 gene, which compromises its ability to clear parasites quickly, leading to prolonged parasite clearance times and, in some cases, outright treatment failure (Ashley et al., 2014). These emerging challenges have triggered concerns about the long-term efficacy of ACTs, especially in regions where resistance is rapidly increasing. As a result, there is an urgent need to explore alternative or complementary antimalarial therapies.

One of the proposed solutions is to revisit chloroquine, a drug once discredited due to resistance but now showing potential for reintroduction in certain regions. Studies have demonstrated that in areas where CQ has been withdrawn for several years, Plasmodium falciparum has regained susceptibility to the drug. For example, in Malawi, a country that discontinued chloroquine use in 1993, chloroquine-sensitive malaria has re-emerged, with studies confirming the restoration of CQ efficacy in more than 99% of cases by 2006 (Laufer et al., 2006) Similar observations have been made in Sudan, parts of Nigeria, and other areas where CQ resistance had previously been widespread (Maiga et al., 2021; Niba et al., 2021; Rana et al., 2022). This review aims to

assess whether chloroquine could be revisited in light of these challenges with the objective to determine whether the case against chloroquine is sufficient to discredit its use entirely or whether it merits reconsideration as an alternative therapy in regions where ACT resistance is on the rise; by exploring the pharmacological arguments for and against the reintroduction of chloroquine, focusing on effectiveness, safety, pharmacoeconomic, patient compliance, availability, and acceptance.

II. Methods

To assess the potential reintroduction of chloroquine in malaria treatment, this review followed a structured narrative approach. The first step involved a comprehensive literature search across various academic databases, including PubMed, Scopus, and Google Scholar. Specific keywords, such as "chloroquine resistance," "ACT resistance," "malaria treatment," and "chloroquine reintroduction," were used to identify relevant studies.
Inclusion criteria focused on research that explored chloroquine's efficacy, safety profile, and the resurgence of its effectiveness in areas where it had been previously discontinued. Additionally, studies examining the growing resistance to artemisinin-based combination therapies (ACTs), particularly in sub-Saharan Africa and Southeast Asia, were incorporated to provide context on current treatment challenges.

The review extracted data on chloroquine's historical significance in malaria treatment, its pharmacological properties, and its comparative advantages in terms of cost-effectiveness, patient compliance, and long-term safety. Emerging patterns of ACT resistance and their implications were also analyzed.

Effectiveness of Chloroquine

Chloroquine, a 4-aminoquinoline derivative, was highly effective against Plasmodium falciparum for decades, until the emergence of resistance significantly diminished its use in the treatment of malaria. By the late 20th century, the widespread presence of chloroquine-resistant P. falciparum strains, especially in sub-Saharan Africa and Southeast Asia, prompted its replacement by ACTs (Wellems & Plowe, 2001). However, more recent research from areas such as Malawi, where chloroquine was discontinued, has shown that the drug may regain efficacy as resistance wanes in the absence of selective drug pressure (Laufer et al., 2006). In this regard, Mwendera et al., (2017) suggest that CQ may be a valuable alternative in regions where ACTs are beginning to fail.

Re-emergence of Chloroquine Sensitivity

Beyond Malawi, similar findings have been documented in other parts of sub-Saharan Africa. In Senegal, for instance, research conducted by (Njiro et al., 2022) found a significant reduction in the prevalence of chloroquine-resistant alleles after CQ was withdrawn from routine use. This study demonstrated that over 90% of P. falciparum isolates had reverted to CQ sensitivity, suggesting that the removal of drug pressure could restore chloroquine efficacy in these areas.

Furthermore, in a clinical trial conducted in Guinea-Bissau, chloroquine showed an impressive 98% efficacy against P. falciparum infections, even after several years of disuse (Frosch et al., 2011). This reversion to sensitivity provides a compelling argument for reconsidering CQ in regions experiencing rising resistance to ACTs.

ACT Resistance and Limitations

The growing resistance to artemisinin-based combination therapies (ACTs) has become a major concern in malaria-endemic regions, warranting a reevaluation of older treatments like chloroquine (CQ). Recent reports, particularly from areas like Southeast Asia and parts of Africa, show the emergence of ACT resistance through mechanisms such as mutations in the pfkelch13 gene. These mutations result into delayed parasite clearance and treatment failure (Juliano et al., 2023.; Maiga et al., 2021)

The situation is further complicated by resistance to partner drugs used in combination with artemisinin, such as piperaquine, leading to decreased efficacy in some cases (Maiga et al., 2021). In regions such as Mali, ongoing monitoring reveals similar concerns, indicating that ACT efficacy is no longer guaranteed, making alternative therapies an urgent priority (Maiga et al., 2021)

Artemisinin-based combination therapies, initially celebrated for their rapid clearance of Plasmodium parasites, are facing growing resistance challenges. The kelch13 mutation, which mediates delayed parasite clearance, has been increasingly observed in Southeast Asia, notably in Cambodia, Thailand, Vietnam and some African countries (Ariey et al., 2014; Roper et al., 2014). Resistance to partner drugs, such as lumefantrine and piperaquine, is compounding the problem, resulting in declining cure rates for ACTs in these regions (Thu et al., 2017).

In Africa, resistance to ACTs, although not yet as widespread, has been reported in countries like Rwanda, where delayed clearance times associated with kelch13 mutations have been documented (Uwimana et al., 2020, 2021). The concern is that the emergence of ACT-resistant P. falciparum strains could spread more

broadly, leading to a resurgence of malaria morbidity and mortality if alternative treatment options, such as chloroquine, are not explored.

Chloroquine for Non-Falciparum Species

Chloroquine remains highly effective against non-falciparum species, particularly P. vivax and P. ovale, which are still sensitive to the drug. In a study conducted in Indonesia, (Ratcliff et al., 2007) demonstrated that CQ had an efficacy of over 95% in treating P. vivax malaria. This continued sensitivity in non-falciparum malaria provides a strong case for its use in mixed infections or regions where P. vivax is co-endemic with P. falciparum.

Pharmacological Benefits of Chloroquine

Another pharmacological advantage of chloroquine is its relatively long half-life, which offers post-treatment prophylaxis by continuing to protect individuals from reinfection for weeks following a course of therapy (N. White, 1999). This property is especially useful in high-transmission areas, where reinfections are common shortly after completing treatment with shorter-acting drugs like ACTs.

Additionally, chloroquine has a broad spectrum of immunomodulatory properties, which have been utilized in treating autoimmune diseases such as lupus and rheumatoid arthritis (Touret & de Lamballerie, 2020). These additional benefits may enhance its overall acceptance and utility in healthcare systems.

Safety Profile

Chloroquine (CQ) has an established safety record, particularly at therapeutic doses, and it has been widely used for decades. Common side effects include gastrointestinal disturbances such as nausea, vomiting, and diarrhea, along with headaches and pruritus. Pruritus is particularly notable in African populations but is generally well tolerated and not life-threatening . One key advantage of chloroquine is its safety in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, as it does not induce hemolysis, unlike other antimalarials such as primaquine (Beutler, 2008). This makes CQ a safer option in areas where G6PD deficiency is prevalent.

However, at higher doses or with prolonged use, CQ is associated with significant toxicity risks, including retinopathy, cardiotoxicity, and neurotoxicity. Retinopathy, characterized by irreversible damage to the retina, is a well-documented adverse effect that can lead to permanent vision loss in cases of chronic use or overdosing (Yusuf et al., 2023). Cardiotoxicity, manifested as conduction abnormalities and arrhythmias, can be life-threatening, especially when CQ is used at supratherapeutic levels. Neurotoxicity, including seizures and confusion, has also been reported but is more common with excessive dosing (AlKadi, 2007) .

In contrast, while ACTs have revolutionized malaria treatment, their safety profile is not without concerns, especially as resistance emerges and prolonged or higher-dose regimens are required. Artemisinin derivatives, a key component of ACTs, are associated with neurotoxicity, particularly when used in high doses over extended periods (Efferth & Kaina, 2010). Artemisinin-induced neurotoxicity is characterized by damage to the brainstem, leading to symptoms such as unsteadiness, dizziness, and in severe cases, brainstem dysfunction. Moreover, ACTs, especially those combined with drugs like mefloquine, are known for psychiatric side effects such as anxiety, vivid dreams, and even psychosis (Croft et al., 2010).

Another growing concern with ACTs is delayed hemolysis, particularly in cases of P. falciparum malaria treated with intravenous artesunate. Post-treatment hemolysis occurs as the body clears damaged red blood cells after the parasite is killed, leading to anemia in some patients (Abanyie et al., 2023; Jaita et al., 2023; Kurth et al., 2023; Rolling et al., 2014). This side effect can be serious in individuals with limited access to medical follow-up or blood transfusions. Additionally, reports of prolonged QT intervals and cardiac effects with some ACT combinations, such as artemether-lumefantrine, raise concerns about their safety in certain populations, especially in those with pre-existing cardiac conditions (N. J. White, 2007).

While both CQ and ACTs have established safety profiles, the emerging toxicities associated with ACTs, particularly in the context of drug resistance, make CQ's relative safety at therapeutic doses noteworthy. As resistance necessitates higher doses or prolonged use of ACTs, the risk-benefit ratio may shift in favor of revisiting older drugs like CQ, especially in areas where chloroquine sensitivity is returning.

Pharmacoeconomics and Cost Considerations

Chloroquine's low cost is a significant advantage, especially in low-resource settings where healthcare budgets are often constrained. Historically, chloroquine was one of the most affordable antimalarials available, and even today, it costs a fraction of what artemisinin-based combination therapies (ACTs) cost. While a full course of ACTs can range from several dollars to more, depending on the country and the specific combination, chloroquine treatments cost just a few cents per dose (Dondorp et al., 2009). This price difference becomes

particularly relevant in regions where malaria is endemic and the population may not have access to subsidized treatments.

The affordability of chloroquine is further highlighted by the fact that international programs, such as the Global Fund and other public health initiatives, heavily subsidize ACTs to ensure their availability in resource-limited regions. However, despite these subsidies, logistical challenges, high demand, and fluctuating funding levels sometimes result in shortages or uneven distribution of ACTs, making chloroquine an attractive alternative in situations where healthcare systems are already stretched (N. White, 1999).

The reintroduction of chloroquine, if resistance remains low or continues to decrease in certain regions, could provide significant economic relief for healthcare systems. For instance, a single country's malaria treatment program could save millions of dollars annually by reverting to chloroquine, reducing the burden on both governments and international aid programs. This could free up funds for other essential health services or even increase the number of patients treated for malaria. In Malawi, where chloroquine sensitivity has returned, studies suggest that switching back to chloroquine could be a cost-effective strategy compared to the more expensive ACTs (Laufer et al., 2006).

However, the cost-effectiveness of chloroquine must be carefully evaluated in light of potential resistance. While initial savings from reintroducing chloroquine might be substantial, the long-term financial implications of a resurgence in chloroquine-resistant malaria (CQR) could negate any short-term economic benefits. Resistance monitoring would be critical to ensure that chloroquine remains an effective option. This would involve ongoing investments in surveillance systems and the development of quick-response strategies to address any re-emergence of resistance, which could erode cost savings over time (Shretta et al., 2018).

Furthermore, while the low cost of chloroquine is undoubtedly attractive, ensuring equitable access to both chloroquine and ACTs is crucial. The effectiveness of any treatment program depends not only on affordability but also on infrastructure, supply chains, and public health policies to prevent stockouts and ensure timely availability. Therefore, although chloroquine’s price tag is appealing, it must be weighed against the broader healthcare context to ensure sustainable malaria control.

Compliance and Ease of Use

Chloroquine (CQ) stands out for its simplicity of administration, particularly when compared to the more complex dosing regimens of artemisinin-based combination therapies (ACTs). CQ is typically administered as a once-daily oral dose over a three-day course, which greatly enhances patient compliance. This simplified regimen reduces the likelihood of incomplete or incorrect treatments, a significant problem with multidose therapies like ACTs (Yeka et al., 2016). In contrast, ACTs often involve more intricate dosing schedules—many require twice-daily dosing over three days, and in some cases, follow-up doses of partner drugs to clear remaining parasites. This complexity increases the risk of missed doses, incomplete treatment, and ultimately, treatment failure.

Poor compliance with ACT regimens is especially problematic in rural or low-resource settings, where patients may not have easy access to healthcare facilities or may struggle with understanding and adhering to the multi-step instructions required by ACTs. For instance, artemether-lumefantrine (one of the most widely used ACTs) demands specific timing between doses and must be taken with food, particularly fats, to enhance absorption. Failure to adhere to these guidelines can significantly reduce the drug’s effectiveness (Bassat et al., 2015)

Moreover, chloroquine’s pharmacokinetics offer an additional advantage in terms of compliance and protection. Chloroquine has a long half-life (up to 30–60 days), providing a "post-treatment prophylactic" effect, meaning that it remains in the body for an extended period after treatment, offering ongoing protection against reinfection. This long-acting effect is particularly beneficial in highly endemic areas where reinfection is common. In contrast, most ACTs have shorter half-lives and do not offer this same level of post-treatment prophylaxis, increasing the risk of recurrent infections soon after treatment.

Availability and Global Acceptance

Before the development of widespread resistance, chloroquine was readily available in nearly all malaria-endemic regions. Its withdrawal from many markets led to a significant reduction in its production. Nonetheless, CQ remains widely available for non-malarial indications such as rheumatoid arthritis and lupus. Acceptance of chloroquine as a malaria therapy would require both policy changes and public health education, especially in regions where ACTs have become the mainstay of treatment. However, CQ's reintroduction would face significant resistance unless clear evidence of renewed efficacy emerges.

Other Pharmacological Benefits Apart from its antimalarial effects

Apart from its well-known antimalarial effects, chloroquine (CQ) possesses a range of pharmacological benefits that extend its therapeutic applications. One of the most important additional

properties of chloroquine is its anti-inflammatory and immunomodulatory action. For decades, CQ has been successfully used to treat autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE). It achieves this by reducing the production of pro-inflammatory cytokines and inhibiting pathways that promote inflammation, including the inhibition of toll-like receptors (TLRs) and the downregulation of MHC class II expression (Cai et al., 2022; Dima et al., 2022). These anti-inflammatory effects make chloroquine and its derivative hydroxychloroquine (HCQ) valuable agents in managing chronic inflammatory diseases, providing an additional rationale for their continued use, especially in regions where malaria and autoimmune diseases overlap.

More recently, CQ and HCQ have garnered attention for their antiviral properties, notably during the COVID-19 pandemic. Early studies indicated that CQ and HCQ could inhibit viral replication in vitro by interfering with the glycosylation of viral proteins and preventing viral entry into host cells (Touret & de Lamballerie, 2020). Additionally, CQ can increase endosomal pH, potentially preventing the fusion of viruses with host cell membranes, which is a critical step for the entry of several viruses, including SARS-CoV-2, into host cells. However, the clinical effectiveness of CQ and HCQ in treating COVID-19 remains controversial, as later clinical trials failed to demonstrate significant benefits in terms of reducing mortality or preventing disease progression. Despite these controversies, the antiviral and immunomodulatory effects of CQ may still provide therapeutic advantages in other settings. For instance, in regions with high co-endemicity of malaria and autoimmune diseases, chloroquine could offer dual benefits by addressing both conditions with a single therapy. This dual-indication advantage could streamline treatment, reduce healthcare costs, and improve compliance, as patients with malaria who also suffer from autoimmune conditions may benefit from the extended use of CQ for both diseases.

Moreover, research into the antiviral effects of chloroquine continues to explore its potential role in treating other viral infections such as hepatitis C and HIV, though clinical data in these areas remain limited (Savarino et al., 2004). In this context, the non-malarial benefits of chloroquine offer a compelling case for its reconsideration in malaria-endemic regions, particularly where healthcare systems struggle with the dual burden of infectious and non-infectious diseases.

P. falciparum Mechanism of Resistance to Chloroquine

The primary mechanism of chloroquine resistance in P. falciparum is linked to mutations in the pfcrt gene, which encodes the chloroquine resistance transporter. Mutations in pfcrt reduce drug accumulation in the parasite's food vacuole, diminishing its efficacy (Da, 2000). The spread of CQR has varied geographically, with Southeast Asia and South America being the first regions affected. In Africa, resistance spread more slowly but became widespread by the late 1990s (Roux et al., 2021).

Despite the persistence of CQR, several studies indicate that resistance may be declining in areas where chloroquine use has been discontinued, likely due to the fitness cost associated with the pfcrt mutations (Ecker et al., 2012). Surveillance in regions like Malawi, Nigeria, and Sudan has shown mixed results, with some areas reporting decreased resistance levels.

Global Pattern of Resistance

Resistance to chloroquine initially emerged in Southeast Asia and spread rapidly to Africa and South America. This pattern is similar to that observed with ACT resistance, driven by mutations in the kelch13 gene. Current WHO guidelines still recommend ACTs as the first-line treatment, but the increasing resistance patterns observed in Southeast Asia are concerning (WHO, 2023). The resurgence of chloroquine-sensitive P. falciparum in some African countries offers a unique opportunity for research into the potential reintroduction of CQ, particularly where resistance to ACTs is rising.

II. Conclusion

In conclusion, the re-evaluation of chloroquine for malaria treatment presents a multifaceted discussion around the drug's historical significance, evolving effectiveness, and contemporary challenges. Although chloroquine was once a mainstay in antimalarial therapy due to its affordability, safety profile, and global acceptance, the emergence of widespread resistance drastically limited its use. However, recent studies showing potential benefits of chloroquine in regions with lower resistance, coupled with its anti-inflammatory properties and affordability, have sparked renewed interest.

The global resistance patterns, pharmacological advantages, and the need for cost-effective treatments in resource-limited settings warrant deeper investigation into how chloroquine might fit into future malaria control strategies. If resistance patterns can be managed or reversed, chloroquine could once again play a significant role in malaria treatment, especially when combined with other therapies to enhance its efficacy and mitigate resistance. However, further research is essential to confirm its viability within the current landscape of malaria management, considering newer therapies and evolving resistance mechanisms.

Ultimately, the consideration of chloroquine for malaria treatment must balance factors such as safety, pharmacoeconomics, compliance, and regional resistance patterns to determine its place in modern antimalarial regimens.

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