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CURRENT STATUS ON ARTEMISININ RESISTANCE: THE KENYAN NARRATIVE

Medical Science

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ABSTRACT

Antimalarial drug resistance threatens the gains made on malaria elimination as per the United Nations' sustainable development goals. Emergence if artemisinin resistance ahs been observed in part of the greater Mekong region hence frequent monitoring should be done in areas endemic for malaria. Mapping the prevalence and occurrence of mutation in Africa and Kenya in particular is important for resistance management.Electronic databases were searched for randomized clinical trials evaluating the efficacy of artemisinin combination therapy. Independent reviewers assessed the quality of the trials selected, calculated the risk of bias and a Jadad score assigned t all the trials reviewed.Seven (7) randomized clinical trials that evaluated the efficacy of both Artemisinin Lumefantrine and Dihydroartemisin Piperaquine were identified. The median parasite clearance rates in these studies were 2.3 hours(IQR 2.0-2.9) for Artemether Lumefantrine and 2.2 hours(IQR 1.9-2.5) for Dihydroartemisin piperaquine. Although some non-synonymous mutations were reported in some of these studies, no evidence of mutation associated with resistance to *pk13* was reported.The efficacy of AL and DP is still high in Africa and particularly Kenya with no reported incidences of failure. However, continuous monitoring needs to be done so as to inform policy on interventions and treatment regimen of uncomplicated malaria in Kenya.

KEYWORDS

Plasmodium falciparum, Artemisinin resistance, parasite clearance rates, Artemisinin combination therapy.

INTRODUCTION

Malaria remains to be a global burden with an estimated 3.2 billion people at risk of malaria worldwide. WHO estimates that a total of 219 million malaria cases occurred worldwide in 2017 with 435000 deaths being reported. The larger proportion of these cases occurred in Sub Saharan Africa with 200 million cases and 404000 deaths recorded. It is estimated that in 2017, 11 countries accounted for approximately 70% of the total mortality and morbidity, 10 of the being in SSA.(WHO, 2018).

In SSA, which accounts for more than 90% of the diseases' mortality, 70% of these cases occur in children under 5 years of age. However, there has been a 66 % decline in the number of malaria cases between 2000-2016.

In Kenya, it has been estimated that the population at risk of malaria morbidity and mortality is 70%. (Kenya Ministry of Health, 2014). In Kenya and around the world steps have been taken to reduce the burden of this disease and these are in line with the United Nations' SDGs and more specifically in Kenya, Vision 2030.

Treatment of malaria has changed drastically over the years from chloroquin to sulphadoxine-pyrimethamine and finally to Artemisisnin combination therapy. The change in policy was as a result of reported resistance to these drugs.(Dondorp et al., 2010). Most countries in which malaria is endemic have adopted this policy, and ACTs are the recommended first line treatment for uncomplicated *Plasmodium falciparum* malaria. In Kenya, the guideline is that uncomplicated malaria be treated with ACTs while pregnant women receive a dose of SP during their first trimester of pregnancy.(MOPHS, 2016).

The artemisinin component of these combinations produces a characteristic rapid reduction in parasite biomass immediately after treatment, but these compounds are metabolized in hours and thus combination with a partner drug is required to provide complete parasite clearance with short treatment regimens and to minimize the opportunity for evolution of parasites resistant to either component drug.(Tahar & Ringwald, 2009) The artemisinin compounds act through heme-depended cleavage of Endoperoxide Bridge by iron-sulphur oxido-reduction within the food vacuole of the parasite and production of free radicals leading to alkylation and inhibition of functional parasite proteins.(Tahar & Ringwald, 2009).

Exposure to of the parasite population to artemisinins monotherapy in sub therapeutic doses for over 30 years and the availability of substandard artemisinins are the main driving force in the selection of the resistant phenotype.(Laura N. Wangai et al., 2011) Studies with murine malaria model demonstrated increased resistant to artemisinins.(Laura N. Wangai et al., 2011) Strong evidence shows that resistance depend on SNPs in the drug putative chemotherapeutic target, the SERCA-type ATPase protein (pfATP6) though large scale epidemiological evaluation of gene copy numbers inatural parasite populations have not been carried out. Studies from French Guyana, Senegal and Cambodia identified parasites with reduced in vitro sensitivity and prolonged parasites clearance times after treatment with artemisinin, raising concern around the world.(Gama et al., 2010)

Global efforts toward controlling malaria are greatly challenged by the increasing spread of antimalarial drug resistance particularly in sub-Saharan Africa. To ensure that malaria control strategies and malaria treatment policies rely on the deployment of effective anti- malarials, there is a need for systematic monitoring of anti-malarial drug efficacy and drug resistance.(WHO, 2006) Methods commonly used include in vivo test, which involves the repeated assessment of clinical and parasitological outcomes of treatment during a fixed period of follow-up to detect any reappearance of symptoms and signs of clinical malaria and/ or parasites in the blood and recently through monitoring parasites clearance times. In vitro studies of parasite susceptibility to drugs in culture and molecular methods of gene mutations or gene amplifications that are associated with parasite resistance.(WHO, 2006)

Therapeutic efficacy trials are the standard monitoring tool for the efficacy of antimalarials although they are restricted by financial constraints. Emergence of resistance to ACTs provided more opportunities for these kinds of studies with an aim of improving monitoring studies.(Collet et al., 2016).

Emergence of artemisinin resistance has been reported in parts of the Greater Mekong Sub-region (GMS) particularly in Cambodia which was among the first countries to adopt ACTs.(Dondorp et al., 2010). In Africa however, there have been no confirmed reports of ART-R. Routine TES have reported delayed parasite clearance rates, but these reports have not been consistent with the most frequent allele observed being A572S which has no association with mutation in *pk13*.(WHO, 2017). A recent study carried out in five countries in SSA also confirmed presence of A572S in all the five countries in which sampling was done.(Kamau et al., 2015).

To date, there have been 200 non-synonymous mutations associated with the K13 domain of plasmodium with evidence of the mutation in different geographical areas. These emerging events have mostly been reported in South-east Asia with the KARMA project reporting frequent mutations in C580Y, R539T and Y439H. In Africa, however, these mutations are rare and highly diverse with a very low prevalence of non-synonymous mutations being reported in Kenya particularly.(WHO, 2017).

This review is meant to present any evidence of resistance to ACTs through the clinical trials that have been conducted in Kenya since introduction of the combined therapy.

Methodology.

Study eligibility criteria and identification of trials.

An electronic search was conducted on 5 databases Pubmed, Cochrane CENTRAL, EMBASE, Medline, Popline as well as manual searches of relevant journals on Google scholar. The trials were identified in the database through the search terms "*Plasmodium sp* K13 resistance, Kenya" and "mutation in K13 gene in *Plasmodium sp,* Kenya". All randomized clinical trials which were either one arm (AL only) or two arm (AL and DHA-PQ) conducted after 2006, in Kenya, were included in the study. All the trials included for this review investigated uncomplicated malaria caused Plasmodium falciparum. The reference list of all the trials included were searched to identify those studies that had not been published. A total of 6 trials were included for this review.

Outcomes

The primary outcome was to determine the parasite clearance times recorded in studies involving the administration of ACTs to participants which was a common outcome to all but 1 trial. The secondary outcome of all the trials included was to determine the prevalence of mutations associated to ART-R to K13 propeller domain in Kenya.

Risk of bias

The Cochrane collaboration tool for accessing risk of bias was used and bias classified into four categories; selection, attrition, detection, performance, reporting and other bias.

Data Processing.

For the trials evaluating the efficacy of ACTs in Kenya, we recorded information on the recruitment process, randomization procedures as well as supervision of the investigational product during the trial. We also gathered information on loss to follow-up trends in all the trials and the nature in which blood test examination was carried out. In addition, the inclusion and exclusion criteria as well as the response of participants towards treatment with either Artemether Lumefantrine or Dihydroartemisinin Piperaquine.

Assessment of the quality of the studies included for this review was done based on the generation of the allocation sequence and concealment. Quality of these trials was also assessed based on the degree of loss to follow up reported for the primary end point. This assessment was scored using a Jadad score by two independent reviewers and the score harmonized.(Jadad et al., 1996) However blinding of the quality assessment could not be done as all the reviewers were familiar with most of the trials included in this review.

Data Analysis.

A candidate and validated mutation of pk13 was defined in two ways: a statistically significant association($p<0.05$) between a k13 mutation and positive parasitaemia at 72 hours via a chi squared test. It was also defined through confirmation of >1% survival using ring stage survival assay, in at least five individual isolates in a given mutation.(WHO, 2017)

The status of artemisinin resistance was analyzed and the trials grouped into two groups based on a number of factors. The first group comprised of all those trials that were two-armed studies pitting the first line Artemether Lumefantrine against Dihyroartemisnin Piperaquine. This group also included all the trials that had the rate of parasite clearance times of the drug as a primary outcome. The other classification of trials was those that sought to assess the prevalence of *pk13* in Kenya and this was a secondary outcome to all but one trial included in this review.

For the first classification, parasite clearance rates were compared with respect to the frequency with which blood smears were collected after recruitment. Two trials matched this criterion where blood smears were collected in hourly intervals after recruitment of patients had been done. Parasite clearance curves were compared in each of these trials to determine the rates the parasite clearance half-life. In the same group, trials that were characterized by daily collection (not on hourly basis) of blood smears were also compared. Three trials fell under this sub-group.

The second group was analyzed based on detection of mutations associated to the kelch propeller domain of Plasmodium falciparum. All the trials that were included in this review had this as an outcome.

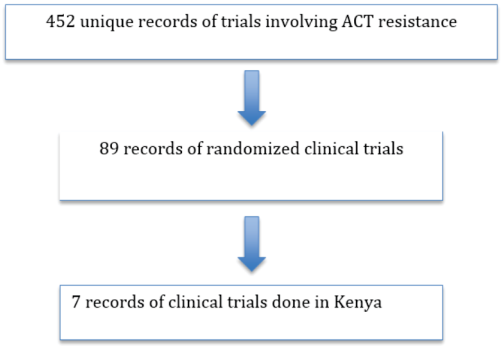
RESULTS.

The database search and the manual searches of relevant articles on Google scholar yielded a total of 454 unique records and included a total of 89 RCTs. However, only 6 trials were conducted in Kenya and this formed the basis of this review, *Figure 2*. All the studies included for analysis were performed in Western Kenya.

Figure 1: Characteristics of Randomized Controlled trials included.

Name of author	Study site	Year	No.of Participants	Transmission intensity
Olubayo et al	Western Kenya	2015	454	High
Fakuda et al	Kisumu, western Kenya	2015	55	High
Muwanguzi et al	Mbita, Western Kenya	2016	69	High
Andagalu et al	Kisumu, Western Kenya	2017	118	High
Khalid et al	Mbita, Western Kenya	2013	154	High
Isozumi et al	Lake victoria, Western Kenya	2015	539	High
Bernhards et al	Kisumu, western Kenya	2014	454	High

Figure 2: database search results and screening



DISCUSSION

From the first group of trials analyzed, it was noted that none of the patients recruited in these studies had early treatment failure except in one trial.(Ngalah et al., 2015). The median parasite clearance rates in these studies were 2.3 hours(IQR 2.0-2.9) for Artemether Lumefantrine and 2.2 hours(IQR 1.9-2.5) for Dihydroartemisin piperaquine. This rate was much higher than the ones previously reported in SEA, which recorded a rate of 7 hours in Thailand.(Ashley et al., 2014). Studies have revealed the association between prolonged PC ½ and pk13 mutations conferring resistance.(Takala-harrison et al., 2015)

RCTs conducted in Africa have generally reported absence of treatment failures post treatment. However, early treatment failure as well as late treatment failures were observed in a randomized clinical trial conducted in Tanzania.(Kamugisha et al., 2012).

In the second group of analysis, which investigated the prevalence of mutation in pk13, no trial reported any mutation that was similar or closely related to the ones conferring ART-R. One study revealed the presence of 4 novel synonymous as well as 5 novel non-synonymous mutations.(Isozumi et al., 2015) However, there were incidences of occurrence of the non-synonymous mutation A578S. This change is known to modify amino acids from hydrophobic to hydrophilic.(Muwanguzi et al., 2016).

Studies have demonstrated that the most frequent allele observed in Africa is A578S that has not been associated with any clinical resistance to Artemisinin.(WHO, 2017). A study conducted in Uganda East Africa, showed that polymorphisms associated with artemisinin resistance were not prevalent in that country, with no evidence of selection of polymorphisms in those genes.(Conrad et al., 2014).

Similar studies carried out in Angola revealed that all samples analyzed for mutation in pk13 exhibited the wild type allele in all analyzed positions.(Kiaco, Teixeira, Machado, do Rosário, & Lopes, 2015). This trend is consistent in other African countries as a study

conducted in Dakar, Senegal also found no evidence of polymorphisms associated with resistance in SEA.(Torrentino-Madamet et al., 2014)

Limitations.

The main limitation in this review was the limited number of randomized clinical trials that have been carried out in Kenya so far.

CONCLUSION

The efficacy of AL and DP still remains high in SSA with only a few cases of failure across the continent. Although there are no reported polymorphisms associated with pk13 resistance seen SEA, there is need to continuously monitor the prevalence of these mutations in Kenya.

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