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Simvastatin Enhances Clinical Response to Quinine against *Plasmodium falciparum*

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Abstract
3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitors exhibit both *in vivo* and *in vitro* anti-plasmodial effects, independent of their hypolipidemic action. This study sought to evaluate the synergistic effect of quinine and simvastatin combination in enhancing clinical response in the treatment of malaria infection. Subjects with clinically characterized malaria (n=60) confirmed by thick blood film and immunological tests, were categorized into test and control groups after obtaining informed consent. Ethical clearance certification was obtained from UNTH Research Ethics Committee (NHREC/05/01/2008B). The quinine + simvastatin (test) group received oral quinine and simvastatin, while the quinine alone (control) group received only quinine. The subjects were followed up on days D0, D3, D7, D14 and D28 post-treatment. The assessment of clinical response was carried out in line with WHO criteria. GraphPad Prism 4.0 was employed in the analysis of data. Statistical test of significance between test and control groups determined using two-tailed Student *t*-test, $p<0.05$ considered as significant and data presented in tabular and graphical forms. A statistically significant difference ($p<0.05$) exists between test and control groups across the various parameters assessed. The mean early treatment failure and late treatment failure given as 7.8% and 5.9% in the test subjects were significantly decreased relative to 18.9% and 16.4% in the control. Adequate clinical and parasitological response given as 86.3% in the test group was significantly elevated relative to 64.7% in the control. The mean parasite clearance time and fever clearance time given in the test group as 3.2 days and 46.7 hours were significantly reduced relative to 6.8 days and 74.7 hours recorded in the control. The clinical clearance rate was significantly increased in the test group relative to controls. These were given as 90.5% for test subjects and 64.7% recorded in the control. The recrudescence rate of 8.0% recorded for test subjects was significantly reduced relative to 19.5% recorded for control. The enhancement in clinical response in this study is attributable to modulating influence of statin therapy. Thus, the 3-HMG-CoA reductase inhibitor, simvastatin, is a potential candidate for combinational anti-malarial chemotherapy.

Keywords: Antimalarial effect, Clinical response, HMG-CoA reductase inhibitors, Malaria, *Plasmodium falciparum*, Quinine, Simvastatin.

1. Introduction
Quinine is an alkaloid derived from the bark of cinchona tree and has been used in the effective treatment of malaria for over 400 years. Poor clinical response to use of quinine has been reported over 3 decades ago in South-East Asia and Africa [1-3]. The use of quinine in combination with doxycycline, tetracycline or clindamycin as a 2nd line treatment for uncomplicated malaria and, in combination with clindamycin as the preferred choice for treatment of malaria in first trimester of pregnancy; is in line with World Health Organisation (WHO) recommended guideline [4]. Quinine is still widely used for treatment of severe malaria in Africa [5]. However, recent studies carried out have sought drug interactions with a view of enhancing the anti-malarial effectiveness of quinine [6, 7]. Simvastatin, a 3-hydroxy-3-methyl glutaryl CoA reductase inhibitor, belongs to a group of drugs known as statins employed in the treatment of hyperlipidemia. The immunomodulatory and pleiotropic effects of statins, which are independent of its lipid lowering effects, may significantly influence infection-related survival [8, 9]. Simvastatin has been reported to exhibit *in vitro* anti-parasitic effects against *Plasmodium falciparum* with IC_{50} in the range of 10 to 20 µg/ml [10]. A recent study has revealed that adjunctive treatment with statins resulted in prevention of cognitive impairment in patients with cerebral malaria [11]. Experimental evidence from animal and *in vitro* studies has revealed that statins reduce the release of tumour necrosis factor-alpha (TNF-α) and interleukin-1β involved in the pathophysiology of malaria [12, 13]. It is hypothesized that a significant difference exists in clinical response between patients treated with simvastatin plus quinine and those treated with quinine alone. This study, therefore, aimed at evaluating the

synergistic effect of quinine and simvastatin combination in enhancing clinical response in the treatment of malaria infection.

2. Materials and methods

2.1 Subjects

Patients with clinically characterized frank malaria (n=60) confirmed by thick blood film and immunological test (Paracheck PI®) in a double blind randomized controlled study, were selected. Paracheck PI® is a rapid qualitative two site sandwich immunochromatographic dipstick assay employed for the determination of *Plasmodium falciparum* specific histidine rich protein-2 (PfHRP-2) in whole blood samples. This was necessary in order to supplement the classical method of diagnosis by microscopy involving examination of thin and thick blood smears; which is time consuming and prone to false negative readings.

2.2 Study Design

Informed consent was obtained by formal written documentation after adequate explanation of the purpose of study, type of treatment to be administered and clarification of any likely adverse effects or complication that may arise in the course of treatment. The subjects for this study within the age range of 16 to 65 years inclusive were selected from patients attending eight primary health facilities within Asu Nkanu Local Health Authority in Nkanu East Local Government Area of Enugu State. The subject's physical condition and presence of any confounding ailment were ascertained following routine clinical clerkship and examination. The body weight and axillary temperature were recorded. A table of random numbers statistically generated was employed for the randomization of subjects into test and control groups. None of the study participants including the investigator, microscopist, field supervisor, field assistants, medical officer and nurses had any prior knowledge of the patients' medical records nor the treatment group to which each subject was assigned. Approval for this study was obtained from the Enugu State Ministry of Health, Nigeria while ethical clearance certification (NHREC/05/01/2008B) was obtained from Health Research Ethics Committee, University of Nigeria Teaching Hospital, Enugu, Nigeria; in line with principles guiding human experimentation as enumerated in the Declaration of Helsinki by the World Medical Association General Assembly as last amended (Seoul 2008). Quinine (Malagold® from Medreich, Surrey-England) was administered orally to test subjects as 20mg/kg start then followed by 10mg/kg every 8 hours for seven days and Simvastatin (Simvor® from Ranbaxy Laboratories, Dewas-India) given orally in the dosage 0.6mg/kg/d only in the evening for 3 consecutive days. The control group, however, received quinine alone as indicated above. Subjects who presented with treatment failure and recrudescence were withdrawn from the study and salvaged with Artemether-Lumefantrine (Coartem® from Novartis Pharma AG, Basel-Switzerland). The Artemether component is given as 3.2mg/kg/d while the Lumefantrine as 19.2 mg/kg/d respectively in two divided doses for 3 days. Baseline monitoring of liver function tests was done before commencement and in the course of therapy. The elevation of serum transaminase activity up to three times normal levels will lead to discontinuation of treatment.

2.3 Assessment of Response

The patients were followed up on days D0, D3, D7, D14 and D28. The World Health Organisation (WHO) criteria were applied in the categorization of therapeutic response as follows:

Early Treatment Failure (ETF): Development of danger signs of severe malaria on D1-D3 in the presence of parasitemia. Parasitemia on D2 higher than D0 count irrespective of axillary temperature. Parasitemia on D3 with axillary temperature ≥ 37.5 ^{o}C.

Late Treatment Failure (LTF): Development of the danger signs of severe malaria after D3 in the presence of parasitemia, without previously meeting any of the criteria of early treatment failure. Presence of parasitemia and axillary temperature ≥ 37.5 ^{o}C on any day from D4 to D14, without previously meeting any of the criteria of early treatment failure.

Late Parasitological Failure (LPF): Presence of parasitemia on D28 and axillary temperature <37.5 ^{o}C without previously meeting any of the criteria of early treatment failure or late treatment failure.

Adequate Clinical and Parasitological Response (ACPR): Absence of parasitemia on D14 irrespective of axillary temperature without previously meeting any of the criteria of early treatment failure or late treatment failure

Fever Clearance Time (FCT): The time taken from anti-malarial drug administration until axillary temperature falls below 37.4 ^{o}C and remains at that value for 72 hours.

Parasite Clearance Time (PCT): The time taken from anti-malarial drug administration until no patent parasitemia is detected.

Clinical Clearance Rate (CCR): The proportion of subjects with full resolution of signs and symptoms of malaria on D14.

Recrudescence Rate (RR): The proportion of subjects in which there is incomplete clearance of parasitemia on D14 and D28 of follow-up.

Cure Rate: This is defined as the proportion of patients who remain free of parasitemia on D14 and D28 of follow-up.

2.4 Statistical Analysis

This was carried out using Graphpad Prism version 4.0 (GraphPad Software, Inc., La Jolla, CA, USA) statistical software and data presented in tabular and graphical forms. Statistical test of significance between test and control groups ascertained using two-tailed Student *t*-test assuming equal variance at degree of freedom, df=28.

3. Results

Table 1 depicts baseline characteristics of the test and control groups at presentation. Figure 1 depicts the mean geometric parasite density of test and control subjects on follow-up days D0, D3, D7, D14 and D28. Table 2 depicts statistically significant difference (*$p<0.05$) in treatment failure between subjects treated with quinine and simvastatin (test) and those treated with quinine alone (control). Statistically significant difference (*$p<0.05$) in the mean values of Parasite Clearance Time (PCT), Fever Clearance Time (FCT), Clinical Clearance Rate (CCR), Recrudescence Rate (RR) and Cure Rate (CR) between test and control groups is depicted in Table 3.

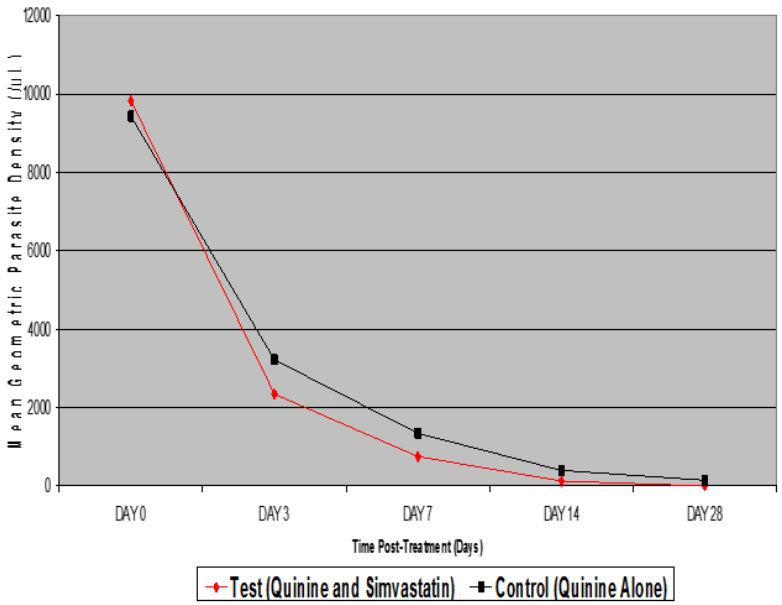

Fig 1: Depicts linear graphical representation of the progressive decline in the level of parasitemia in both test and control groups. It reveals mean geometric parasite density of 9818/µL, 2345µL, 748/µL, 126/µL and 0/µL for days 0, 3, 7, 14 and 28 respectively in respect of test group. This is as compared to the mean geometric parasite density of 9430/µL, 3219/µL, 1342/µL, 398/µL and 144/µL in the control group.

Table 1: Baseline Characteristics of Test and Control Subjects

Characteristics	Test	Control	p-Value
Number of Patients	30	30	-
Male: Female Ratio	2:3	2:3	-
Mean Age (Range: 16-65 years)	37.5±2.6	40.3±2.7	p>0.05
Mean Weight (Range: 43–92 kg)	64.2±4.5	55.8±2.9	p>0.05
Mean Temperature (Range: 37.8–39.2ºC)	39.1±2.1	38.4±1.4	p>0.05
Mean Parasite Density (Range: 1260-21500/µL)	9818±865	9430±569	p>0.05
Mean Hemogram (Range: 4.2 – 11.5g/dL)	7.9±1.4	8.1±1.2	p>0.05
Mean WBC Total (Range: 3000 – 11700 x 10^9/L)	8170±50	8900±50	p>0.05
Mean Alanine Transaminase (Range: 7.8-31.2U/L)	17.1±4.3	14.9±3.8	p>0.05
Mean Aspartate Transaminase (Range: 13.7-28.4U/L)	18.4±5.2	20.8±5.5	p>0.05
Mean Alkaline Phosphatase (Range: 45.2-110.7U/L)	93.6±6.7	87.2±6.9	p>0.05
Mean Total Bilirubin (Range 4.3-13.8µmol/L)	6.9±1.3	7.3±1.1	p>0.05

Table 2: Mean Treatment Failure in Both Test and Control Subjects

Treatment Parameters	Test	Control	P-Value
ETF (%)	7.8±0.22	18.9±0.17	P<0.05
LTF (%)	5.9±0.13	16.4±0.15	P<0.05
ACPR (%)	86.3±0.53	64.7±0.51	P<0.05

ETF: Early Treatment failure
LTF: Late Treatment failure
ACPR: Adequate Clinical and Parasitological Response

Table 3: Mean Clinical Response in Both Test and Control Groups

Clinical Parameters	Test	Control	p-Value
PCT (Days)	3.2±0.14	6.8±0.21	P<0.05
FCT (hours)	46.7±1.7	74.7±2.6	P<0.05
CCR (%)	90.5±0.51	69.8±1.2	P<0.05
CR (%)	86.3±0.9	64.7±0.8	P<0.05
RR (%)	8.0±0.1	19.5±0.2	P<0.05

PCT: Parasite Clearance Time
FCT: Fever Clearance Time
CCR: Clinical Clearance Time
CR: Cure Rate
RR: Recrudescence Rate

4. Discussion

The fever clearance time reported in the current study in respect of the test and control groups was as already depicted in Table 3. A previous study, which evaluated the efficacy of quinine reported mean fever clearance time of 4.2 days (100 hours) [14]. However, the only patient in the said study with a recrudescent infection also had a relatively long fever clearance time of 4.8 days (116 hours). It has been documented that peripheral parasitemia in *Plasmodium falciparum* infection declines as a result of sequestration; indeed much of the early decline in parasite counts following administration of quinine results from sequestrations [15]. The result of *in vivo* studies indicates that the process of parasite clearance can best be described by a first-order process [16]. Thus, provided that the drug concentration remains above the maximum effect value, there is a constant fractional decline in the parasite biomass with each asexual cycle. This log-linear decline continues until all parasites have been removed, numbers are reduced low enough such that host defenses can contain the remainder or until the drug concentration has fallen below the minimum parasiticidal concentration. The rate of clearance of the parasite population depends on the time profile of the blood concentration of quinine and the concentration-effect relationships for the residual number of parasites [17]. Similar profiles are observed in experimental cultures *in vitro*, provided sufficient parasites are studied and the experiment continues for long enough to document re-expansion of the parasite population after removal of the drug [18]. Another study reveals that quinine pharmacokinetic is time-dependent; the apparent elimination half life is shorter in the accumulation than in elimination phase [19]. A study reported cure rate of <70% in patients treated with quinine alone [20]. However, the clinical clearance rate given in the test group as compared to control correlated closely with the cure rates in the present study for the test and control respectively as depicted in Table 3. The present study adopted a 7-day treatment course regimen in respect of quinine therapy. This has been shown to be effective, as evidenced by the cure rate and clinical clearance rate in the present study particularly in the test group. It is possible that release of merozoite into the blood from the pre-erythrocytic (hepatic) phase of development may be discontinuous and could be delayed until after treatment had stopped [21].

The 3-hydroxy-3-methyl glutaryl-CoA (HMG-CoA) reductase inhibitors otherwise known as statins have been shown to inhibit *in vitro* growth of *Plasmodium falciparum* [10]. Notwithstanding BLASTX analysis of *P. falciparum* sequence with other protozoal HMG-CoA protein sequences could not identify HMG-CoA homolog [22]. The growth of other protozoan parasites belonging to the Trypanosoma and Leishmania species is disrupted by statins [23, 24]. Drug combination is a useful strategy in reducing the morbidity and mortality associated with malaria infection. The combination of quinine with statins presents a potential and promising prospect in malaria chemotherapy. It has been shown that at relevant concentrations, statins improved the *in vitro* activity of quinine [25]. Simvastatin extended the survival time of mice in an experimental model of sepsis [26]. Sepsis exhibits similar pathophysiological features with cerebral malaria. Local neuroinflammation, apoptosis, breakdown of blood-brain barrier, impaired blood and microvascular plugging are consequences of pro-inflammatory cytokines and chemokines, which activate leukocyte and endothelial cells; observed in animal models of malaria and sepsis [27-29]. It has been noted that the 3-HMG CoA reductase inhibitor simvastatin exerts inhibitory effects on the hepatocytic development of malaria parasite. This may be attributed to the tendency of simvastatin to concentrate in the liver, thereby blocking the transformation of sporozoites to hepatocytic schizonts [10]. Multiple organ dysfunction associated with falciparum malaria may be attributable to excessive stimulation of inflammatory and immunopathological pathways mediated by pro-inflammatory cytokines [30]. Simvastatin has been shown to reduce levels of the pro-inflammatory cytokines, tumor necrosis factor α (TNF-α) and interleukin-1β [31]. No incidence of adverse reactions associated with increased transaminase levels or rhabdomyolysis was reported in this study. It is however, instructive to note that clinical trials of intensive statin therapy for periods ranging from 2 weeks to 5 years did not result to any significant increase in incidence of rhabdomyolysis, elevated serum transaminases or creatine kinase [32-33].

In conclusion, the foregoing observations lend credence to the fact that the enhancement of clinical response in this study could possibly be attributed to statin therapy. Thus, the 3-HMG-CoA reductase inhibitor, simvastatin, is a potential candidate for combinational anti-malarial therapy. There is, therefore, a dire need for further clinical trials to evaluate the use of statins as adjuvant treatment in combination with known anti-malarials to enhance clinical response.

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8. Declarations

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