Efficacy and Safety of a Naphthoquine-Azithromycin Coformulation for Malaria Prophylaxis in Southeast Asia: A Phase 3, Double-blind, Randomized, Placebo-controlled Trial

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Background. A prophylactic antimalarial drug that is both effective for protection and improves compliance is in high demand.

Methods. We conducted a randomized, placebo-controlled, double-blinded phase 3 trial to evaluate the 1:1 fixed-dose combination of naphthoquine-azithromycin (NQA) for safety and protection against *Plasmodium* infections in villages along the China-Myanmar border. A total of 631 residents, 5–65 years of age, were randomized into the drug group (n = 319) and the placebo group (n = 312) to receive NQA and placebo, respectively, as a single-dose monthly treatment. Follow-ups were conducted weekly to monitor for adverse events and malaria infections.

Results. Of the 531 subjects completing the trial, there were 46 and 3 blood smear-positive *Plasmodium* infections in the placebo and treatment groups, respectively. For the intent-to-treat analysis, the single-dose monthly NQA treatment had 93.62% protective efficacy (95% confidence interval [CI]: 91.72%–95.52%). For the per-protocol analysis, NQA treatment provided a 93.04% protective efficacy (95% CI: 90.98%–95.1%). Three smear-positive cases in the NQA group were all due to acute falciparum malaria. In comparison, NQA treatment provided 100% protection against the relapsing malaria *Plasmodium vivax* and *Plasmodium ovale*. The treatment group had 5.6% of participants experiencing transient elevation of liver aminotransferases compared with 2.2% in the placebo group ($P > .05$).

Conclusions. Monthly prophylaxis with NQA tablets was well tolerated and highly effective for preventing *Plasmodium* infections. It may prove useful for eliminating *P. vivax* in areas with a high prevalence of glucose-6-phosphate dehydrogenase deficiency in the population.

Clinical Trials Registration. ChiCTR1800020140.

Keywords. naphthoquine-azithromycin; malaria; prophylaxis; protective efficacy; safety.

Chemotherapy plays an essential role in managing and preventing malaria infections [1]. Artemisinin-based combination therapy is the recommended first-line treatment of falciparum malaria in all endemic countries by the World Health Organization (WHO). However, the emergence of artemisinin resistance in *Plasmodium falciparum* is threatening malaria control and elimination [2]. Artemisinin resistance in *P. falciparum*, first identified in Cambodia [3, 4], has been confirmed in all countries of the Greater Mekong Subregion (GMS) [5–10].

In addition, there is a global trend of increased prevalence of *Plasmodium vivax* malaria [11]. In most endemic areas, chloroquine/primaquine remains the front-line treatment for *P. vivax*. Substantial evidence indicates the emergence of chloroquine resistance in *P. vivax* [12, 13]. Managing resistance in all *Plasmodium* species is critical for effective malaria control and elimination.

Malaria chemoprophylaxis by both suppressive and causal pathways is an important strategy to prevent malarial infections among both endemic populations and travelers. Suppressive prophylactic drugs act on the sexual blood-stage malaria parasites, whereas causal prophylactic drugs kill asexual parasites attempting development in the liver [14]. Currently, suppressive chemoprophylaxis with blood schizontocides dominates travel medicine practice [15]. For travelers to endemic areas, atovaquone-proguanil (Malarone), mefloquine, and doxycycline are the recommended drugs for suppressive prophylaxis [16]. However, these drugs are associated with various problems

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such as drug resistance, neurotoxicity, and compliance issues. Although suppressive chemoprophylaxis is effective for falciparum infections, it does not address the significant problem of delayed attacks of relapsing malaria. Primaquine and the recently United States Food and Drug Administration–approved tafenoquine [17] are the only drugs with proven causal prophylactic activity against latency in vivax malaria [18, 19]. However, a key disadvantage of these 8-aminoquinoline drugs is their hemolytic toxicity in people with glucose-6-phosphate dehydrogenase (G6PD) deficiency [19].

In China, chemoprevention has been applied extensively in endemic populations. Drugs that were used for chemoprevention in the past, including dapsone and pyrimethamine, pyrimethamine-sulfadoxine, and piperazine-sulfadoxine, locally named Malaria Prevention I, II, and III, respectively, were recommended to the endemic populations for monthly administrations. In an effort to develop new chemoprevention agents, we evaluated the naphthoquinazithromycin (NQAZ) co-formulation as a 1:1 fixed-dose combination for prophylactic purpose in villages endemic for both *P. falciparum* and *P. vivax* [20]. At a single dose of 400 mg naphthoquinone (NQ)/400 mg azithromycin (AZ), the combination was safe and offered >90% prophylactic efficacy against all malaria species within 1 month. Here, we performed a randomized, double-blind, placebo-controlled phase 3 trial to further assess the prophylactic efficacy of monthly administration of NQAZ in malaria-endemic villages of northeast Myanmar.

METHODS

Test Drugs and Placebos

This study was a randomized, double-blind, placebo-controlled, phase 3 clinical trial to evaluate the prophylactic efficacy and safety of NQAZ (400 mg NQ/400 mg AZ) tablets along the China-Myanmar border in Southeast Asia. Drugs and placebos were provided by the Institute of Microbiology and Epidemiology, Chinese Academy of Military Medical Sciences. Each coformulated NQAZ drug tablet contained 100 mg NQ base and 100 mg AZ. Placebo tablets were indistinguishable from treatment tablets in shape and color. All tablets were preserved in airtight, dark containers. Each package contained 2 small packages of drugs or placebo, which were administered as directly observed treatment to an individual participant monthly at day 0 and day 31.

Study Site and Populations

The studies were conducted in villages along the China-Myanmar border, where malaria transmission is perennial with peaks in May–September [21, 22]. These villages were selected based on an epidemiological survey conducted during a previous season, which showed >10% parasite incidence annually.

A total of 722 residents in 9 villages, all Kachin (or Jingpo) ethnicity, aged 5–65 years, were screened for eligibility. One week prior to the administration of the treatment, participants were subjected to a general physical check and malaria diagnosis by microscopy. Subjects were excluded if they had malaria symptoms or were positive for *Plasmodium* parasites after microscopic examination of a Giemsa-stained blood smear, were febrile (axillary temperature >37.3°C), had a history of malaria in the past 2 weeks, had received malaria prophylaxis in the past 3 months, had a known or suspected allergy to macrolides and NQ, had known or suspected liver and kidney dysfunction, or had an enlarged liver or spleen. Pregnant and lactating women were also excluded. Based on our phase 2 trial suggesting an association of elevated hepatic aminotransferase levels with NQAZ administration [20], blood chemistry analysis was performed, and those with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels outside of the normal range were also excluded.

Randomization, Blinding, Treatment, and Follow-up

Eligible participants were randomly assigned in a 1:1 ratio to either the NQAZ (400 mg NQ/400 mg AZ) or the placebo group using a computer-generated randomization card provided by the regulatory organization (Tigermed Consulting Co, Ltd, Shanghai, China). Drug and placebo packages were all coded and information was concealed until the completion of the study. Participants were administered drug or placebo tablets on days 0 and 31. Adults (≥17 years of age) received 4 tablets at each treatment, whereas younger (5–12 years) and older (13–16 years) children were given 2 and 3 tablets, respectively, at each treatment. They were visited weekly by study team members for 2 months. At each visit, participants were monitored for adverse events and malaria infections. Axillary temperature was measured and thin and thick blood smears were prepared. Parasitological assessment of blood smears by microscopy was performed according to the WHO guidelines [23]. The smears were stained with Giemsa and read by 2 independent microscopists, and discrepancies were settled by a third reader. Blood smears were considered negative after reading 100 fields under the oil-immersion objective (×100). In addition to the scheduled visits, malaria patients were encouraged to visit the local health facility if they felt sick during the follow-up period. Participants with clinical episodes of malaria (axillary temperature >37.5°C) and confirmation of malaria parasites by microscopy as well as those with asymptomatic *Plasmodium* parasitemia (with malaria parasites observed by microscopy but without malaria-related symptoms) during the study were all promptly reported and treated per local malaria treatment guidelines. Efforts were undertaken to document reasons for discontinuation of those lost to follow-up.

Efficacy Indicators

The primary endpoint was defined as protective efficacy of the NQAZ monthly treatment against malaria infection, expressed as $(1 - P_T/P_C) \times 100\%$, where P_T and P_C are the cumulative positive *Plasmodium* incidence in the drug and placebo groups, respectively. The cumulative *Plasmodium* incidence during the trial was the secondary indicator of therapeutic efficacy.

Safety Indicators

All adverse events were monitored and recorded in the clinical report form as well as in the individual subject's medical records. These included unusual physical examination findings and new diseases, as well as laboratory biochemistry data. Expected adverse reactions after treatment with NQAZ included a potentially transient and slight increase of hepatic ALT and AST, which returned to normal after treatment cessation. Accordingly, blood chemistry was performed on day 0, 7, 30, and 60. Adverse reactions/events were rated according to the standards defined in the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, from the National Cancer Institute [24]. Serious adverse events were reported to Tigermed within 24 hours of discovery as well as to the ethics committee and the sponsor.

Statistical Analysis

Sample size calculation was based on the primary outcome of the phase 2 study; assuming a 10% infection rate, a 30-day cumulative malaria incidence rate of 0.88% in the 400 mg NQ/400 mg AZ group, and an expected difference of at least 9% between the 2 groups, the sample size was calculated to be 133 in each group (95% confidence level and 80% power). Participant demographics between the 2 groups were compared using the *t* test and χ^2 test. Adverse events were summarized by counts and compared by Fisher exact test. For the primary outcome analysis, both the per-protocol and the intent-to-treat (ITT) populations were used. Cumulative *Plasmodium* positivity rate was calculated by using a standard life table, corrected for dropouts [25]. Kaplan-Meier cumulative incidence curves were compared between the treatment and placebo groups using the log-rank test. Confidence intervals (CIs) were calculated for the protective efficacy. Statistical analysis was performed using SPSS version 22.

Ethical Considerations

The study protocol was reviewed and approved by China's State Food and Drug Administration and the Ethics Committee of the Yunnan Institute of Parasitic Diseases, Yunnan Provincial Center of Malaria Research. Written informed consent was obtained from all participants or their guardians. Tigermed Consulting Co, Ltd monitored the trial to ensure that the safety and double-blind requirements were met. This trial was

registered with the Chinese Clinical Trial Registry (www.chictr.org.cn; ChiCTR1800020140).

RESULTS

A total of 722 local residents were screened, and 91 who did not meet the eligibility were excluded (Figure 1). Of these 91 individuals, 63 were malaria positive by microscopy, giving an estimated parasite prevalence of 8.7%. All 4 malaria species were detected, among which 46 (73%) were *P. vivax*, 9 (14.3%) *P. falciparum*, 6 (9.5%) *Plasmodium ovale*, and 2 (3.2%) *Plasmodium malariae*. The remaining 631 subjects were randomized to receive drugs ($n = 319$) or placebo ($n = 312$) and were included in the ITT analysis. Per-protocol populations included 281 participants in the drug group and 299 in the placebo group (Figure 1). Baseline demographic characteristics were comparable between the 2 groups (Table 1).

Prophylactic Efficacy

For the 631 subjects, 531 completed the 2-month follow-up. Within the 2-month period, there were a total of 49 microscopy-positive *Plasmodium* infections, 46 in the placebo group and 3 in the NQAZ group (Figure 1). Three subjects in the treatment group had acute *P. falciparum* malaria attacks on day 19, 27, and 28 of the first month of the study. In the placebo group, 37 infections (17 *P. falciparum*, 16 *P. vivax*, and 4 *P. ovale*) occurred in the first month, and 9 (2 *P. falciparum* and 7 *P. vivax*) occurred in the second month (Supplementary Table 1). Among these microscopy-positive infections from the placebo group, 15 *P. falciparum* and 12 *P. vivax* infections were acute symptomatic cases.

For the ITT analysis, the overall slide positivity rate was 0.94% and 14.74% for the NQAZ and placebo groups, respectively, which gave a protective efficacy of 93.62% (95% CI: 91.72%–95.52%). The Kaplan-Meier plots comparing the treatment group with the placebo group showed significantly different curves of cumulative incidence of *Plasmodium* infection ($P < .001$; log-rank test) (Figure 2). For the per-protocol analysis, the total slide positivity rate was 1.07% and 15.38% for the NQAZ and placebo groups, respectively, which gave a protective efficacy of 93.04% (95% CI: 90.98%–95.1%). In the placebo group, there were 27 infections resulting from relapsing parasite species, and the cumulative incidence of smear positivity for *P. vivax* and *P. ovale* was 7.03% (95% CI: 4.15%–9.9%) and 1.3% (95% CI: .03%–2.58%), respectively. No infections from these relapsing parasite species were detected in the NQAZ group, indicating that this monthly treatment regimen provided 100% prophylactic efficacy against *P. vivax* and *P. ovale*. Three cases of *P. falciparum* infections were detected in the NQAZ group vs 19 in the placebo group, suggesting that this treatment offered 84.6% prophylactic efficacy against *P. falciparum* infections (95% CI: 81.75%–87.37%). It is noteworthy that during

Figure 1. Schematic of the enrollment, randomization, and follow-up of the subjects in the naphthoquine-azithromycin efficacy trial for prophylaxis against *Plasmodium* infections. Abbreviations: ITT, intention to treat; LTF, lost to follow-up; NQAZ, naphthoquine-azithromycin; PP, per protocol.

Table 1. Baseline Demography and Adverse Events

Characteristic	400 mg NQ/400 mg AZ	Placebo	P Value
No. of participants	319	312	
Age, y, mean (SD)	22.7 (17.0)	26.6 (19.6)	.114 ^a
Sex, male	161 (50.5)	137 (43.9)	.111 ^b
Subjects with malaria history	115 (36.1)	109 (34.9)	.803 ^b
Education, y			
0	66 (20.7)	58 (18.6)	>.05 ^c
1–3	67 (21.0)	79 (25.3)	
4–6	139 (43.6)	139 (44.6)	
≥7	47 (14.7)	36 (11.5)	
Adverse events, No.			
Increased AST	14	5	.599 ^b
Increased ALT	3	2	1.000 ^b
Increased ALT/AST	1	0	1.000 ^b
Increased creatinine	0	1	.495 ^b
Proteinuria	2	2	1.000 ^b
Increased eosinophilic granulocytes	0	1	.495 ^b
Total adverse events	20	10	.091 ^b

Data are presented as no. (%) unless otherwise indicated.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; AZ, azithromycin; NQ, naphthoquine; SD, standard deviation.

^at test.

^bFisher exact test.

^cχ² test.

the 2-month follow-up, 80.4% (37/46) of *Plasmodium* infections in the placebo group occurred in the first month, so did the 3 *P. falciparum* cases in the NQAZ group. If the 2 months were considered independently, the overall slide positivity rate for the first month was 0.94% and 11.86% for the NQAZ and placebo groups, respectively, resulting in 92.07% protective

Figure 2. Kaplan-Meier plot comparing the cumulative incidence rates of *Plasmodium* infections between the naphthoquine-azithromycin treatment group and the placebo group. Abbreviation: NQAZ, naphthoquine-azithromycin.

efficacy, while the NQAZ treatment provided 100% protective efficacy for the second month.

Safety

Given that NQ was associated with transient elevation of liver aminotransferases, special attention was paid to these parameters with laboratory chemistry tests. Overall, the treatment was well tolerated; no serious adverse events occurred in either group. No subject dropped out due to adverse events. Adverse events occurred in 20 and 10 subjects in the NQAZ and placebo groups, respectively ($P > .05$, χ^2 test) (Table 1). Potential drug-related adverse events included 18 (5.6%) cases of increased levels of liver aminotransferases in the NQAZ group, compared with 7 (2.2%) in the placebo group ($P > .05$, χ^2 test). These were all grade 1 or 2 adverse events based on the CTCAE definitions, and all were resolved without interventions (Supplementary Table 2). Other adverse events such as proteinuria and increases in creatinine and eosinophilic granulocytes were all grade 1 and occurred either in the placebo group only or in both groups.

DISCUSSION

Malaria prophylaxis is important for both travelers to and residents of malaria-endemic areas. In the past, China has deployed several seasonal prophylactic antimalarial combinations in malaria-endemic areas using a monthly administration regimen. Widespread resistance in malaria parasite to antifolate drugs made these drug combinations obsolete. In recognition of the excellent protective efficacy of NQ against malaria [26–28], and the potential causal prophylactic activity of AZ [29], an NQAZ combination (1:1 naphthoquine phosphate and azithromycin) was developed as a fixed-dose combination. The 1:1 ratio of the 2 drugs was based on maximum synergistic effect of killing blood-stage *Plasmodium berghei* in a rodent malaria model (J. Wang, unpublished data), so further optimization using human malaria parasites is needed. In a phase 2 trial, NQAZ demonstrated a good safety profile and >90% prophylactic efficacy within a month after the drug was administered [20]. Here we conducted a phase 3 evaluation of the 400 mg NQ/400 mg AZ formulation among a local population residing in the malaria-endemic areas of the China-Myanmar border. Consistent with our earlier findings, the drug combination was well tolerated without causing any serious adverse events and with a >90% protective efficacy against *Plasmodium* infections. Given the prevalence of asymptomatic and submicroscopic malaria infections in this region [30], future studies should include molecular detection for low parasitemia.

In an area with approximately 8% prevalence of *Plasmodium* infections, the monthly oral administration of 400 mg NQ/400 mg AZ provided an overall >90% protective efficacy of malaria parasitemia during a 2-month follow-up period. Of note, in the second month of the follow-up when cumulative

incidence of *Plasmodium* infection was much lower (~3%), the single treatment provided 100% protective efficacy against all malaria species. In the placebo group, most malaria parasite infections (80%) were detected in the first month of the study. Since both the NQAZ and the placebo populations resided in the same villages, it is possible that drastic reduction of new infections in the treatment group and also treatment of smear-positive cases in the placebo group led to the overall reduction of new blood-stage infections in the second month. Furthermore, 7 of the 9 *Plasmodium* infections detected in the second month were *P. vivax*, the majority of which might be relapses. Although we do not know whether this drug combination possesses causal prophylactic activity against latent malaria either by prevention or therapy, AZ was able to protect 3 of 4 volunteers from mosquito-inoculated *P. falciparum* infection after receiving oral AZ at 500 mg followed by 250 mg daily for 7 days [29]. Thus, the sharp decline in *P. falciparum* cases in the second month could be attributed to both the excellent activity against blood-stage parasites and potential causal prophylactic activity of the drug combination. Regardless of the mechanisms, NQAZ given as monthly prophylaxis could potentially lead to continuous, dramatic reduction and possibly eventual elimination of *Plasmodium* infections in the future.

There were only 3 *P. falciparum* infections detected in the treatment group in the third and fourth weeks of the first month. This may suggest that the NQ concentration during the later weeks of monthly treatment is not high enough to suppress *P. falciparum*. NQ has excellent bioavailability and long elimination half-life of >20 days [31, 32]. Based on the pharmacokinetics of NQ, the NQ dosage used in this study would generate a maximum plasma NQ concentration of >50 nM. In 3 weeks, this level may fall below the concentration inhibiting 50% parasite growth (~10 nM) determined from in vitro drug assays [33]. Thus, future studies to verify the plasma NQ concentrations in those recurrent *P. falciparum* infections after treatment are needed to guide the decision on drug administration intervals. Although we did not genotype the malaria parasites in this study, almost all parasites collected from this region in 2007–2016 carried the Dd2-like mutation haplotype in the *P. falciparum* chloroquine resistance transporter (*pfcr*) gene, which confers high-level resistance to chloroquine [33]. The high efficacy of NQAZ against *P. falciparum* is consistent with the lack of cross-resistance between NQ and chloroquine [33]. The detection of *P. falciparum* infection in the third and fourth weeks in the NQAZ treatment group, as well as the late parasitological failures associated with NQ as monotherapy or in combination with artemisinin [34, 35], suggests that short prophylactic intervals may offer improved protective efficacy. Such a simple prophylactic regimen together with the relative safety of NQ suggests that NQAZ might be an effective drug combination for intermittent preventive therapy (IPT) such as IPT in pregnancy.

In both phase 2 and 3 trials, the 400 mg NQ/400 mg AZ offered 100% protective efficacy against relapsing malaria. Whether this is due to its parasitocidal activity against blood-stage parasites solely (in suppressive mode) or also on the liver stage of the parasites (in causal mode) remains to be determined. Of note, these 2 drugs individually have demonstrated excellent prophylactic activity against vivax malaria [27, 28, 36, 37]. In the study area, *P. vivax* accounted for >70% of the parasites detected at the baseline, and it has become the predominant parasite in the GMS [38]. Though primaquine mass drug administration has been successful in some vivax-endemic regions [39], a similar primaquine mass drug administration in the GMS requires further scrutiny because of the prevalence of G6PD deficiency in these endemic populations [40]. Under this scenario, the excellent safety profile of NQAZ and its superb protective efficacy against vivax malaria make monthly NQAZ an excellent choice for the elimination of vivax malaria in regions with a high prevalence of G6PD deficiency.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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