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Ivermectin for causal malaria prophylaxis: a randomised controlled human infection trial

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Abstract

OBJECTIVE Ivermectin is safe and widely used for treating helminth infections. It also kills arthropods feeding on treated subjects, including malaria vectors. Thus, ivermectin mass drug administration as an additional tool for malaria control is being evaluated by WHO. As *in vitro* data, animal experiments and epidemiological observations suggest that ivermectin has a direct effect on the liver stages of the malaria parasite, this study was designed to assess the prophylactic effect of ivermectin on *Plasmodium falciparum* controlled human malaria infection.

METHODS A total of 4 volunteers were randomised to placebo, and 8 volunteers were randomised to receive ivermectin 0.4 mg/kg, orally, once 2 h before being experimentally infected intravenously with 3200 *P. falciparum* sporozoites. The primary endpoint was time to parasitaemia detected by positive thick blood smear; RT-qPCR was performed in parallel.

RESULTS All but one volunteer became thick blood smear positive between day 11 and day 12 after infection, and there was no significant effect of ivermectin on parasitaemia.

CONCLUSION Ivermectin – at the dose used – has no clinically relevant activity against the pre-erythrocytic stages of *P. falciparum*.

keywords Malaria, ivermectin, controlled human malaria infection

Sustainable Development Goals (SDGs): SDG 3 (good health and well-being), SDG 17 (partnerships for the goals)

Introduction

Early diagnosis and prompt malaria treatment, prevention through long-lasting insecticide-impregnated mosquito nets and other vector control tools, such as indoor residual spraying, are the main components of malaria elimination strategies. Malaria vaccines are in development but not a single one is fully approved for marketing yet [1,2]. Increased prevention and control measures have led to a 29% reduction in malaria mortality rates globally since 2010. However, these gains are threatened by the emergence of drug and insecticide resistance and residual transmission [3].

Both indoor residual spraying and impregnated bednets affect mosquitoes that are endophagic night biters. This leaves an opportunity for exophilic vectors biting at dawn to escape from insecticide-treated surfaces and to maintain residual transmission [4].

Ivermectin has become interesting for global health scientists as an approach to reducing residual transmission of malaria [5]. This long-known drug was originally identified as a natural substance by Satoshi Ōmura of the Kitasato Institute and further developed by William Campbell of Merck Laboratories as a potent anthelmintic, at first for use in veterinary health and targeting more than 20 species of helminths [6]. When ivermectin's ability to kill microfilaria was recognised, it was also approved for use in humans. Through donation programmes, more than 2.5 billion doses have been distributed in mass drug administration campaigns over the past 30 years. Onchocerciasis and lymphatic filariasis have been eliminated in several endemic areas, and Ōmura and Campbell were awarded the Nobel prize in physiology or medicine for their achievement in 2015 [7].

Ivermectin is an 'endectocide' targeting endoparasites as well as ectoparasites. Famous are early field trials on faeces of ivermectin-fed calves which failed to degrade in the normal way. This failure was associated with the absence of dung-degrading insects [8].

Ivermectin has also the capacity to kill mosquitos – such as *Anopheles* species – that feed on treated subjects. This property makes mass drug administration with ivermectin a potential complementary tool to reduce malaria transmission. Such an intervention would have the potential to reduce residual transmission because it reaches malaria vectors whilst feeding on humans and in such a way fill the temporal and spatial gaps left by core vector control [9].

For this purpose, WHO convened a technical consultation [10] and published a Preferred Product Characteristics guide for the product development of ivermectin as vector control tool. The Bill and Melinda Gates Foundation funded the development of a technology roadmap for ivermectin and malaria [11]. Ivermectin is a topic of the updated Malaria Eradication Research Agenda (MalERA) [12].

Besides its effect on mosquitoes, ivermectin impairs the development of sexual and asexual stages of *P. falciparum in vitro* [13], and a direct prophylactic effect on malaria parasites through the inhibition of *Plasmodium* liver stage infection has been observed: a library screen of 1037 drugs for their ability to inhibit *Plasmodium* hepatic stage development showed that ivermectin reduces the infection of human liver cells *in vitro* and *in vivo* in a dose-dependent manner. This liver parasite reduction translated in a delay and reduction of parasitaemia with 20% of ivermectin-treated mice protected from malaria 10 days post-challenge [14].

In another study, three doses of 1 mg/kg within 36 h reduced parasite liver burden. A 75% reduction in the intensity of liver infection was seen. Ivermectin also significantly reduced parasitaemia and improved animal survival after malarial infection [15].

A direct prophylactic effect of ivermectin was also suspected in a pilot cluster randomised trial which investigated ivermectin (0.2 mg/kg) every three weeks for a total of six doses (total 1.2 mg/kg). The outcome measure was malaria incidence in children under 5 years. In some subgroups a marked and highly significant malaria incidence reduction (50%) could be observed; the authors attributed this observation to a partial prophylactic effect of ivermectin [16].

We investigated ivermectin for causal malaria prophylaxis in a trial using controlled human malaria infection.

Methods

This study was carried out at the clinical trial platform at the Institute of Tropical Medicine at the University of Tübingen, Germany. The study complied with the International Council for Harmonisation Good Clinical Practice guidelines and the German Medicines Law and was approved by the ethics committee of Eberhard Karls University and the University Hospital as well as the regulatory authorities at the Federal Institute for Medicines and Medical Products and the Government Presidency Tübingen. A Safety Monitoring Committee reviewed the study to evaluate the safety of individual volunteers. The study was registered with the European Clinical Trials Register (EudraCT-Nr. 2017-002723-16).

Volunteers were eligible for the study if they were healthy, malaria-naïve adults, aged 18–45 years with a body-mass index between 18 kg/m^2 and 30 kg/m^2. Female participants had to have a negative pregnancy test and were required to practice effective contraception. Further inclusion criteria were as follows: no clinically significant findings in history, physical examination and basic laboratory parameters, being reachable at all times by mobile phone during the whole study, agreement to share medical information with his or her general practitioner, and understanding of study procedures and risks, assessed by a multiple-choice test, willingness not to take drugs or substances which could have an impact on ivermectin blood levels (this includes all drugs inducing or inhibiting Cytochrome P450 3A4). Additionally, willingness to undergo controlled human infection with *Plasmodium falciparum* sporozoites NF54 strain (Sanaria®PfSPZ Challenge), to take a curative malaria treatment if necessary, and being able to comply with all study requirements.

Exclusion criteria were as follows: a history of malaria or *Loa loa* infection; plans to travel to malaria-endemic regions during the study; participation in another clinical trial within 30 days before enrolment or during the study; previous participation in a malaria vaccine trial; history of serious psychiatric conditions, convulsions, or severe head trauma; any malignancy and diabetes mellitus. Any symptoms, physical signs, and laboratory values suggestive of systemic disorders, or of conditions that could interfere with the interpretation of the study results, or compromise the health of the volunteers, or compromise the use of systemic antibiotics with known antimalarial activity within 30 days of study enrolment excluded participation.

Randomisation (2:1 ivermectin:placebo) was carried out as described elsewhere [1]. Both placebo and verum tablets were administered by a physician who was not involved in the study. Thus study participants, study physicians and study staff were unaware of group allocation. Administration of 0.4 mg/kg ivermectin (with water) was directly observed and under fasting

conditions. Fasting conditions were chosen as most pharmacokinetic investigations on ivermectin have been done under fasting conditions. The full study protocol with further details is available from the corresponding author upon request.

All volunteers were infected with 3200 *P. falciparum* sporozoites by direct venous inoculation two hours after drug intake. Previous dose-finding studies had shown that this was the number of sporozoites needed to guarantee that all placebo recipients get thick blood smear positive. The inoculated parasite strain (NF54) is susceptible to all clinically used antimalarials [17]. Volunteers who became parasitaemic by thick blood smear (or on day 21 after infection) were treated immediately with atovaquone/proguanil or artemether/lumefantrine.

The primary objective of the study was to assess whether ivermectin could affect *P. falciparum* development in the liver resulting in protection or prolonged time to microscopically detectable parasitaemia. The primary endpoint was time to parasitaemia (pre-patent period), detected by thick blood smear microscopy. Secondary endpoints were mean parasite density at day 12, mean parasite density at day of treatment (when thick blood smear became positive), proportion of infected individuals at days 12–20 (infectivity), parasite multiplication rate and kinetics, estimation of infected liver cells and safety.

Thick blood smears were performed as previously described [18] every 12 h (+/-4 h) during the period of intense observation from day 9 to treatment, or to day 21. Blood smears were also performed daily during treatment and during the follow-up visits on day 35 and day 90. Slides were considered positive when at least two independent readers detected two parasites each. A negative slide was defined as no observed parasites in the volume of blood required to detect with 95% probability <10 parasites per µl. In case of discordance, a third reading was performed.

Purification of nucleic acids for molecular assay was automated on the QIAsymphony SP using QIAsymphony DSP DNA kit (Qiagen, Hilden, Germany). Reverse-transcription quantitative PCR (RT-qPCR) was performed as previously described at screening and then from day 6.5 every 12 h (+/-4 h) to treatment or to day 21. The ultra-sensitive RT-qPCR assay consistently detects low-density parasitaemia with a lower limit of detection of 6 parasites per ml. RT-qPCR results were not reported to the clinical and microscopy teams during the study period to avoid bias.

Sample size and statistical methods: In a recent infection trial conducted in Tübingen with 13 volunteers, the mean time to microscopically detectable parasitaemia was 12.1 days (range 11–18, SD 2.10, variance 4.41), thus the sample size (12 volunteers; eight verum, four placebo) was determined to consider a 33% delay in time to diagnosis from 12.1 to 16.1 days as a potentially relevant outcome (80% power at 5% significance). The Wilcoxon–Mann–Whitney test was used for comparisons of non-parametric variables.

Results

Participants were recruited in screening visits between 8 May and 18 May 2018. Twelve of 26 screened volunteers were randomly allocated to receive either ivermectin as a single dose of 0.4 mg/kg ($n = 8$), or placebo ($n = 4$) (Figure 1).

The average age of the 12 volunteers was 28 years (range: 23–37 years). The groups were similar in respect to age, weight, height and BMI (Table 1).

After infection, all volunteers stayed under observation for two hours; no adverse event related to drug intake or infection was observed during this time period and thereafter for 6 days.

All but two volunteers (10/12) became RT-qPCR-positive on day 7 after infection. All but three volunteers (9/12) became blood smear positive on day 11 after challenge; two became smear positive on day 12 and one on day 14 (volunteer no. P002) (Figure 2a,b).

All but one volunteer received a full therapeutic course of atovaquone/proguanil beginning on the day of smear positivity. Treatment of one volunteer (volunteer no. P002) was changed to artemether/lumefantrine after the second dose of atovaquone/proguanil. Treatment was swiftly successful in all cases.

Unblinding was done on day 20. At this time point, all volunteers had become blood smear positive and all volunteers had been cured. Only two follow-up visits (day 35 and day 90 after the inoculation of sporozoites) were pending after unblinding.

Primary endpoint: median time to microscopically detectable parasitaemia was 263 h (mean: 277 h) in the ivermectin group and 262 h (mean: 262 h) in the placebo group, respectively. There was no significant difference between the two groups.

Secondary endpoints: Median parasite density at day 12 was 464 parasites/ml in the ivermectin group and 361 in the placebo group, with no significant difference between the groups. Median parasite density at day of treatment was 5640 parasites/ml in the ivermectin group and 3139 in the placebo group, with no significant difference between the groups. On day 12, all individuals were RT-qPCR-positive, and 7/8 individuals and 4/4 individuals were smear positive in the ivermectin and placebo group, respectively.

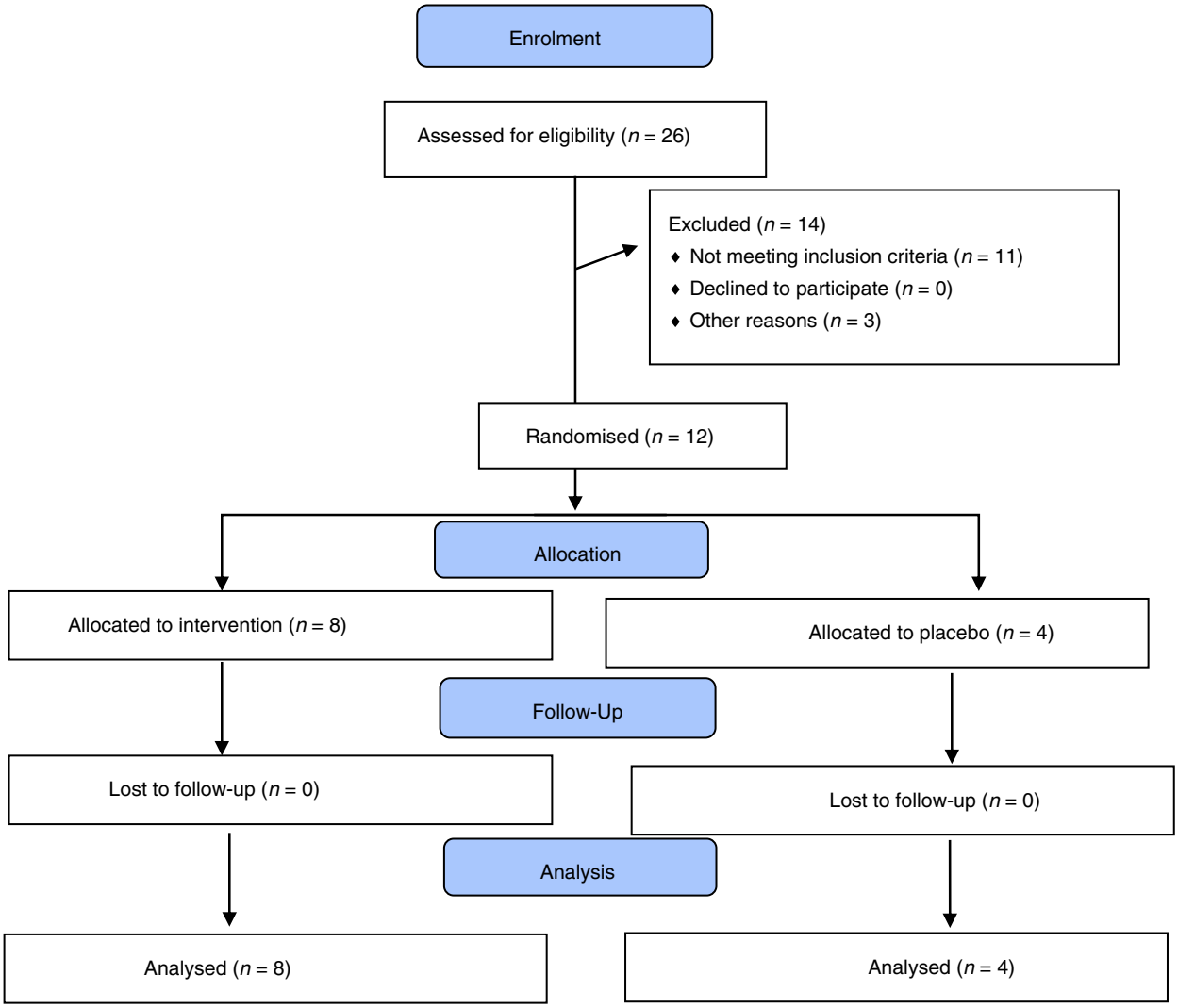

Figure 1 Flow diagram of recruitet of volunteers. [Color figure can be viewed at wileyonlinelibrary.com]

Table 1 Baseline characteristics of volunteers

	Ivermectin (n = 8, 4 male)		Placebo (n = 4, 2 male)	
	Average	Range	Average	Range
Age (years)	27	23–37	30	25–34
Weight (kg)	69	53–93	68	53–97.5
Height (cm)	171	162–180	167	161–182
BMI (kg/m^2)	23	20–30	24	20–29

Altogether, 110 adverse events (71 grade 1, 31 grade 2 and 8 grade 3) occurred in the twelve volunteers of the study. 103 of 110 (94%) events were possibly or probably associated with malaria or with antimalarial treatment. The most frequent adverse events were lymphocytopenia (n = 15), headache (n = 9) and fatigue (n = 8). No difference was detected between verum and placebo group.

Serious Adverse Event: The volunteer (volunteer no. P002, Ivermectin group) became blood smear positive on day 14 and treatment with atovaquone/proguanil was started. On day 15 after the second administration of atovaquone/proguanil the volunteer was hospitalised because of severe diarrhoea (12 times within two hours), fever (up to 40°C) and hypotension (90/60). Laboratory examinations showed norovirus in stool samples by PCR.

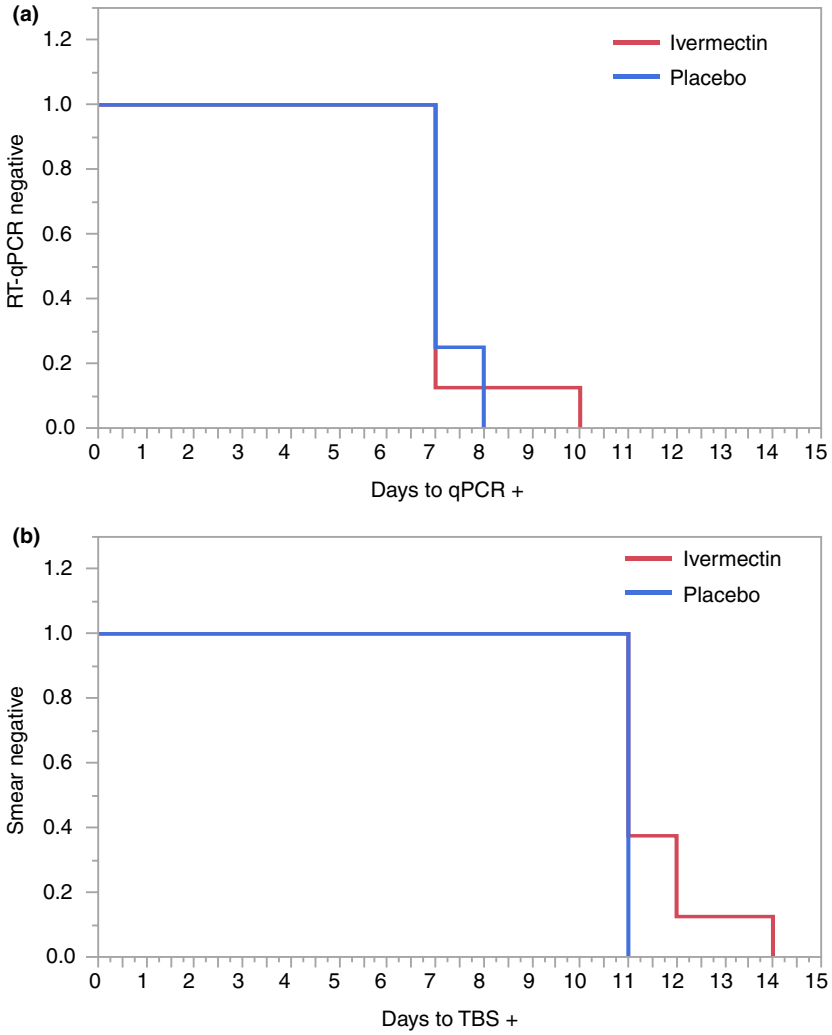

Figure 2 (a) Time to RT-qPCR-positivity. (b) Time to blood smear positivity. [Color figure can be viewed at wileyonlinelibrary.com]

Malaria treatment was continued with a full course of artemether/lumefantrine after the second dose of atovaquone/proguanil. At that time the volunteer had no more detectable parasites in the thick blood smear. The volunteer stayed hospitalised for observation and was discharged after three days in good health. As diarrhoea may have been caused by norovirus, but also by *P. falciparum* parasitaemia and/or atovaquone/proguanil the SAE was classified as possibly related.

Discussion

The results of this trial were a missing piece for the proper assessment and evaluation of ivermectin as a tool for malaria control and elimination. Our results show that ivermectin given at a dose of 0.4 mg/kg 2 h before inoculation of *P. falciparum* sporozoites has no effect on the course of infection when compared to placebo. Almost all of our hundreds of unprotected volunteers infected with 3200 sporozoites get thick blood smear positive 11 to 12 days after infection, as did 11 of the 12 subjects investigated in this trial. The 3-day delay seen in one of the volunteers in this study is within the normal variation and occurs in approximately 5% of volunteers undergoing experimental infection.

Experimental infections are essential for providing proof of concept for prophylactic and therapeutic interventions and can accelerate their development [19]. *Vice*

versa, negative results can show very early that some interventions are not efficacious even if *in vitro* and *in vivo* animal assays showed promising results. So, with relatively little effort the waste of energy, money and the risk of patients' health can be avoided and thus, resources for the fast and efficient development of other promising interventions can be saved. *P. falciparum* is particularly well suited and can be used as experimental infection to facilitate the development for antimalarial interventions [20].

In 2012, our group established a model using direct venous inoculation of *P. falciparum* sporozoites in malaria-naïve volunteers, which is highly reproducible showing an infection rate of 100% [21]. This was seen in many more trials with all unprotected naïve volunteers having very similar parasitaemia curves [1,20,22–28]. Of note, the same infection model has been used to assess causal prophylaxis at two clinical trial sites and showed that it is adequately powered to detect partial efficacy in small group sizes [24,29].

For the first time in our series of trials using controlled human malaria infection, one volunteer was hospitalised whilst he was blood smear positive, although with extremely low parasitaemia (peak parasitaemia of 13/µl on the day of hospitalisation). Norovirus was the most likely cause of the symptoms, but an individual predisposition for side-effects to atovaquone/proguanil and the malarial parasites cannot be ruled out as partially responsible for the symptoms.

Ivermectin for malaria control is not envisioned as a stand-alone tool. The impact of disease elimination programmes in endemic areas could be improved by integrating several interventions. Ivermectin can be aligned with delivery programmes in which both neglected tropical diseases and malaria are targeted [30].

In this context, the benefit obtained through mass drug administration of ivermectin as a vector control tool would be indirect, that is community benefit. A direct prophylactic effect of ivermectin to individuals at risk of malaria, as hypothesised in this study, would fairly increase the impact of this novel delivery strategy. However, it could be reasoned that the direct effect of ivermectin treatment on prevention of malaria specifically seen in children in observational studies could be due to the fact that ivermectin eliminates helminths and thus directs immune function from a helminth driven T-helper cells type 2 response to a more TH-1 cell type 1 response which is protective against malaria.

The dosage of ivermectin in mass distribution programmes is 0.15–0.4 mg/kg. Therefore, if this study had shown any prophylactic effect of ivermectin on the outcome of malaria, challenge trials using higher ivermectin doses and other treatment schemes would have been justified to adapt both the dose and regimen to achieve better effects.

Moreover, as ivermectin has a relatively short half-life in humans (18 h), combination regimens with other drugs available for mass drug administration could have been considered. For example, as ivermectin is metabolised extensively in the liver via CYP3A4, the time it remains above effective concentrations could be increased by drug-mediated CYP3A4 inhibition as it was shown, for example, for co-administration of azithromycin [31].

However, this trial has shown that ivermectin in the dose of 0.4 mg/kg – given two hours before sporozoite infection – has no causal prophylactic effect on *P. falciparum* malaria. The question remains open whether ivermectin in higher and more frequent dosing has an effect on *P. falciparum* sporozoites. It has to be discussed carefully whether further studies are needed and if so, what kind of studies.

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