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Efficacy of Moxidectin Versus Ivermectin Against *Strongyloides stercoralis* Infections: A Randomized, Controlled Noninferiority Trial

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Background. Infections with *Strongyloides stercoralis* are of considerable public health relevance. Moxidectin, a well-established drug in veterinary medicine under consideration for regulatory submission for the treatment of onchocerciasis, might serve as an alternative to the widely used ivermectin.

Methods. We conducted an exploratory, randomized, single-blind trial to evaluate the efficacy and safety of moxidectin (8 mg) vs ivermectin (200 μg/kg) against *S. stercoralis* infections. Cure rate (CR) against *S. stercoralis* was the primary outcome. Safety and efficacy against coinfections with soil-transmitted helminths and *Opisthorchis viverrini* were secondary outcomes. Noninferiority required the lower limit of the 95% confidence interval (CI) of the differences in CRs not exceed 7 percentage points.

Results. A total of 127 participants were enrolled and randomly assigned to the 2 treatments whereby 1 participant per arm was lost to follow-up. We observed a CR of 93.7% (59/63) for moxidectin compared to 95.2% (59/62) for ivermectin. Differences between CRs were estimated as –1.5% percentage points (95% CI, –9.6 to 6.5), thus the lower limit of the CI exceeds the noninferiority margin of 7 percentage points. No side effects were observed. CRs against hookworm infection were 57% (moxidectin) and 56% (ivermectin). Low efficacy for both drugs against *O. viverrini* was observed.

Conclusions. Moxidectin might be a safe and efficacious alternative to ivermectin for the treatment of *S. stercoralis* infection, given that only slight differences in CRs were observed. However, noninferiority could not be demonstrated. Larger clinical trials should be conducted once the drug is marketed.

Clinical Trials Registration. Current Controlled Trials: ISRCTN11983645

Keywords. *Strongyloides stercoralis*; moxidectin; ivermectin; *Opisthorchis viverrini*.

Strongyloides stercoralis is a soil-transmitted nematode and one of the most overlooked helminths among the neglected tropical diseases. It exists throughout the world, excluding only the far North and South, yet estimates of its prevalence (about 100 million people) are often only little more than educated guesses and probably largely underestimated [1–3]. Compared to other major soil-transmitted helminths (STHs), information on *S. stercoralis* is scarce [4]. *Strongyloides stercoralis* is an exception among helminthic parasites as it can reproduce within a human host (endogenous autoinfection), which may result in long-lasting infections. Some studies have reported on individuals who had *S. stercoralis* infections sustained for more than 75 years. *Strongyloides stercoralis*' ability to cause systemic infection is another exceptional feature of this threadworm [3]. However, most infections, chronic, low-intensity infections in particular, remain asymptomatic. It has been found that *S. stercoralis* infection occurs often in adults [4, 5].

The current recommended treatments are a single dose of ivermectin or albendazole for 3 consecutive days, which has a lower efficacy [1, 5, 6]. Ivermectin is highly effective against *S. stercoralis* infection, characterized by a high cure rate (CR). Several trials conducted in Southeast Asia on *S. stercoralis* reported a CR for ivermectin of 97%–99% [6–10]. Despite this, new drugs are needed. Among new candidates in the human anthelminthic drug development pipeline is moxidectin, a macrocyclic lactone that is well established in veterinary practice [11]. In vivo studies on *Strongyloides fuelleborni* conducted on rhesus macaques infections reported the efficacy of moxidectin to be similar to that of ivermectin [12]. Moxidectin is currently under consideration by the US Food and Drug Administration (FDA) for use against onchocerciasis in humans. The drug

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might offer some advantages over ivermectin. First, moxidectin use is weight independent at an 8-mg fixed dose, simplifying administration, especially when treating large communities. Second, moxidectin has been shown to have a lower neurotoxic potential than ivermectin [13]. Finally, and most importantly, moxidectin has been used successfully in veterinary medicine against ivermectin-resistant strains of *Haemonchus contortus* [14].

Our aim in this study was to assess, for the first time, the efficacy of moxidectin against *S. stercoralis* infections. Ivermectin served as the comparator. The safety of moxidectin and its efficacy against coinfections with *Opisthorchis viverrini* and STHs were evaluated as secondary outcomes.

METHODS

Ethical Considerations

Ethical clearance was obtained from the ethics committee of Northwestern and Central Switzerland and from the Lao National Ethics Committee on Health Research Ministry of Health. The trial is registered with Current Controlled Trials (ISRCTN11983645). Participants aged 12–60 years were eligible for inclusion. Written informed consent was collected from all participants or legal guardians for children before enrollment.

Randomization and Drugs

We used a computer-generated block randomization code (block size of 4) provided by an independent statistician. Enrolled participants were randomly allocated to the following 2 treatment arms: ivermectin 200-µg/kg single dose or moxidectin 8-mg single dose. Moxidectin was administered as an oral suspension (Cydectin 0.1%; Zoetis, Switzerland) mixed with equal amounts of mint syrup (sweetener Premix CY/SA S741 from Sanaro SA, Switzerland) containing E952 (sodium cyclamate), E954 (sodium saccharin), and peppermint aroma (Permaseal from Givaudan AG, Switzerland) to mask the drug's bitter taste. Ivermectin (Iver P; 3-mg tablets), obtained from Elea, Argentina, was administered based on patient weight (200 µg/kg). Only the principal investigator was aware of the treatment assignments, while laboratory technicians were blinded. Patients were not informed whether they would receive ivermectin or moxidectin, though we cannot exclude the possibility that the patients recognized ivermectin tablets if they had been treated with it in earlier treatment campaigns.

Study Procedures and Diagnosis

This exploratory, phase 2, randomized, single-blind study was conducted between April and June 2016 in the district of Pathoumphone, Lao People's Democratic Republic, which is endemic for *S. stercoralis* infection. CR against *S. stercoralis*, determined 21 days after treatment, was the primary outcome. Safety, CR, and egg reduction rate (ERR) against coinfections with STHs and *O. viverrini* were the secondary outcomes. In both locations, village-based recruitment was implemented.

At baseline 2 fecal samples on 2 consecutive days were collected from participants. Samples were examined with the Baermann method for the detection of *S. stercoralis* larvae. The Baermann method was performed following the World Health Organization standard procedure [15]. Only participants positive for the infection were included in the study. Concomitant infections with STHs (*Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm) and *O. viverrini* were assessed using the Kato-Katz method [16]. Height was measured with a standard meter (to the nearest 1 cm) and weight with an electronic balance (to the nearest 0.1 kg). The medical history of participants was assessed with a standardized questionnaire in addition to a clinical examination carried out by the study clinician. Participants who had chronic diseases, were aged <12 years, were pregnant women, or were considered not healthy at physical examination were excluded from the trial but still given the recommended treatment. Side effects were monitored at 3, 24, and 48 hours after treatment.

Between day 21 and day 25 after treatment, we resampled 2 stool specimens for analysis of *S. stercoralis*, STHs, and *O. viverrini*. At the end of the study, all participants who were still positive for *S. stercoralis*, STHs, and/or *O. viverrini* infections were treated with ivermectin (200 µg/kg), albendazole (400 mg) and/or praziquantel (40 mg/kg) according to local guidelines.

Sample Size and Statistical Analyses

This study was designed as a binary outcome noninferiority trial. The sample size determination was based on the assumptions that the efficacy of moxidectin against *S. stercoralis* has not yet been studied and that it is well known that the efficacy of ivermectin is high (97%–99%) [7–10, 17]. Since the mode of action of both drugs is similar, we assumed a CR of 98% for both drugs. The noninferiority limit was set to 7 percentage points. With no difference between both drugs, 100 patients (50 per arm) would yield an upper limit of the 95% confidence interval (CI) that excludes a difference of more than 7% with a power of 80%. The sample size was increased to 60 per arm to account for a potential loss to follow-up of 15%.

We based the screening on reported prevalence data of 40% on Mekong islands [18]. Hence, we anticipated screening 350 participants for the detection of at least 120 infected with *S. stercoralis*, including a safety margin. However, this number had to be increased since the proportion of participants who provided 2 stool samples was lower than expected.

Data were digitally collected on tablets using CommCare ODK, version 2.8. The questionnaires and forms were developed in the CommCare server (www.commcarehq.org) and tested previous to the field activity. A mobile user was created for each field data collector allowing access to a specific form. A completed form was immediately synchronized to the server

for real time data monitoring. After fieldwork, data was downloaded from the server into Excel (version 2011). All data was crossed-checked for completeness and consistency. A hard copy of the forms was also completed during data collection and used to cross-check 10% of the electronically collected data. Validated data were cross-checked and analyzed with Stata 12.0 (College Station, Texas). A barcode generating system was applied using a free-barcode generator software available at www.free-barcode.com. A generated barcode containing the UID of each patient was placed on the stool containers before handing them to patients. Once a filled stool container arrived at the research station, a research team member scanned the attached barcode for sample registration and subsequently the system automatically generated a specific form for further data entry. An available case analysis, which included all participants with primary outcome data, and a per-protocol analysis were planned. CRs were calculated as the percentage of participants who became larvae-negative after treatment, being larvae positive at baseline. Bootstrap resampling methods with 2000 replicates were used to calculate 95% CIs for ERRs. CIs indicate statistical significance. For the secondary outcome parameters, the intensity of infection of *O. viverrini* and STHs in terms of eggs per gram (EPG) was assessed by adding up the egg counts from the quadruplicate Kato-Katz thick smears (from baseline and follow-up separately) and multiplying this number by a factor of 6. Geometric and arithmetic mean egg counts were calculated for each group before and after treatment for *O. viverrini* and STHs infections. Intensity of infection for *O. viverrini* was categorized considering 600, 1500, and 6000 EPG as cutoffs [19]. Intensity of infection for hookworm was categorized considering 2000 and 4000 EPG as cutoffs [20]. ERRs were calculated using the following formula: ERR = [1 – (geometric mean at follow-up/geometric mean at baseline)] × 100. CRs for STHs and *O. viverrini* were calculated as the percentage of participants who became egg-negative after treatment, being egg-positive at baseline. Analyses were performed with Stata (version 12.1).

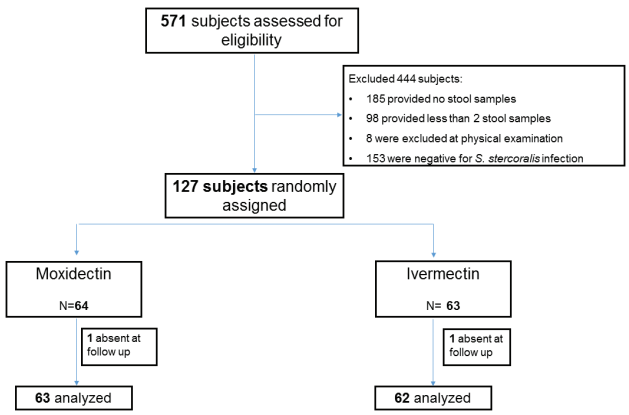

Figure 1. Flow chart of the study conducted in the villages of Morphu and Phakpheo in Champasack Province, Lao People's Democratic Republic, between April 2016 May 2016.

RESULTS

Baseline Characteristics and Study Flow

The study flow chart is presented in Figure 1. We screened 571 participants, of which 153 were negative for infection, 283 did not provide any/enough stool sample, and 8 were excluded at the physical examination because they did not meet the inclusion criteria. In total, 127 participants were enrolled and randomly assigned to 1 of the 2 treatments as follows: 64 received moxidectin (8 mg) and 63 were treated with ivermectin (200 µg/kg). In each treatment arm 1 patient was not present at the follow-up examination (Figure 1). No deviations from the treatment protocol were observed; therefore, the available case analysis is identical with the per-protocol analysis.

Demographic and clinical baseline characteristics are summarized in Table 1. Treatment groups were well balanced in terms of age (mean age, 40 years), sex (51% male participants), weight (mean weight, 54 kg), and height (mean height, 158 cm).

Coinfections were more often observed in the moxidectin arm, in which the proportions of *O. viverrini* and hookworm infections were 89% and 58%, respectively, compared to 75% and 56% of patients, respectively, in the ivermectin arm. Most infections with *O. viverrini* and hookworm were of light infection intensity. No coinfections with other helminths were detected among participants in both treatment arms.

Efficacy Against *S. stercoralis*

We observed a high efficacy of both drugs against *S. stercoralis* infection. Moxidectin achieved a CR of 93.6% (59/63; 95% CI, 84.5 to –98.2) compared to a CR of 95.1% (59/62; 95% CI, 86.5 to 99.0) calculated for ivermectin (Table 2). Differences between CRs were estimated as –1.5 percentage points (95% CI, –9.6 to –6.5). Therefore, the lower limit of the 95% CI exceeds the preset noninferiority margin of 7 percentage points.

Efficacy Against Coinfections

A moderate efficacy was observed against hookworm infection in both treatment arms. The CRs and ERRs for moxidectin and ivermectin were 56.7% (21/37; 95% CI, 55.9% to 79.7%) and 55.9% (19/34; 95% CI, 52.1% to 84.7%) and 74.6% (95% CI, 61% to 90%) and 79.4% (95% CI, 61% to 88%), respectively. None of the drugs showed activity against *O. viverrini*. CRs were 17.8% (10/56; 95% CI, 11.2% to 32.2%; moxidectin) and 6.5% (3/46; 95% CI, 6.4% to 25.4%; ivermectin) with corresponding ERRs of 12.5% (95% CI, –2% to 30%) and 0% (95% CI, –40% to 2%; Table 2).

Safety

At clinical examination, 37 (29.1%) participants reported symptoms before treatment. Most had vertigo (13.4%) and headache (8.6%). In addition, a few participants reported

Table 1. Baseline Characteristics of *Strongyloides stercoralis*–Infected Participants Stratified by Treatment Group

Characteristic	Moxidectin (N = 64)	Ivermectin (N = 63)
Age [y], mean (SD)	39.4 (12.9)	40.7 (10.9)
Males, N (%)	31 (48.4)	34 (54.0)
Weight [kg], mean (SD)	54.4 (10.2)	52.5 (9.3)
Height [cm], mean (SD)	157.5 (7.5)	158.2 (7.5)
Temperature [°C], mean (SD)	36.4 (0.5)	36.4 (0.4)
Coinfection with *Opisthorchis viverrini*, N (%)	57 (89.1)	47 (74.6)
Coinfection with hookworm, N (%)	37 (57.8)	35 (55.6)

Abbreviation: SD, standard deviation.

nausea, diarrhea, abdominal discomfort, and skin lesions. One adult reported blood in stool. Participants were checked at 3, 24, and 48 hours after drug administration for side effects. None of the participants reported any side effect from treatment at any time point.

DISCUSSION

This is the first randomized trial to assess the efficacy of moxidectin against *S. stercoralis* infection, which is a neglected yet considerable public health problem. Despite the high efficacy and safety of ivermectin, which is the current drug of choice, it is crucial to develop and find alternative treatments in case ivermectin resistance arises. Other available drugs, that is, the benzimidazoles (albendazole), need longer treatment courses and are less efficacious [6]. No new drugs are under development for *S. stercoralis* infection [21]. Repurposing of drugs currently used or under registration for different indications might be a fast and cost-effective way to discover novel molecules effective against this infection [22].

Moxidectin, which is widely used in veterinary medicine [11], is a "low hanging fruit" to be repositioned for treatment of *S. stercoralis* infection, given the good results observed in vivo against *S. fuelleborni* infection in macaques [12] and the nearly completed FDA registration for treatment of onchocerciasis in humans.

Moxidectin showed promising efficacy against *S. stercoralis* infection in our trial, comparable to that of ivermectin (94% vs 95%, respectively). Of note, although CRs for ivermectin of between 97% and 99% have been repeatedly reported in similar settings [9, 10], the sample size relied on the optimistic assumption of 98% CR. Since the observed CRs were lower, the study was underpowered and noninferiority could not be demonstrated at the prespecified margin.

Both drugs were very well tolerated in our study; none of the participants reported side effects after treatment. As reported in the literature, ivermectin was well tolerated, with a similar number of side effects observed in the ivermectin and placebo groups [23–25]. A recent study that used the same formulation

Table 2. Efficacy of Moxidectin and Ivermectin Against *Strongyloides stercoralis* and Coinfections

Study Parameter	Moxidectin (N = 63)	Ivermectin (N = 62)
Strongyloides stercoralis		
Participants cured, N (%) (CI)	59/63 (93.6) (84.5 to 98.2)	59/62 (95.1) (86.5 to 99.0)
Opisthorchis viverrini		
EPG before treatment AM (CI)	276.7 (51.3 to 502.1)	248.1 (65.5 to 430.8)
EPG after treatment AM (CI)	169.1 (51 to 287.2)	191.2 (58.6 to 323.7)
EPG before treatment GM (CI)	44.6 (27.1 to 73.2)	32.1 (17.1 to 59.3)
EPG after treatment GM (CI)	27.6 (15.7 to 47.9)	49.7 (23.8 to 65.8)
Egg reduction rate (%) (CI)	12.5 (–2 to 30)	0 (–40 to 2)
Participants cured, N (%) (CI)	10/56 (17.8) (11.2 to 32.2)	3/46 (6.5) (6.4 to 25.4)
Hookworm		
EPG before treatment AM (CI)	149.1 (47.9 to 250.3)	432.9 (0 to 1192.2)
EPG after treatment AM (CI)	34.8 (11.9 to 57.7)	23.7 (8.1 to 39.3)
EPG before treatment GM (CI)	11.4 (5.7 to 22.1)	7.3 (3.6 to 13.9)
EPG after treatment GM (CI)	2.9 (1.0 to 4.4)	1.5 (0.6 to 3.0)
Egg reduction rate (%) (CI)	74.6 (61 to 90)	79.4 (61 to 88)
Participants cured, N (%) (CI)	21/37 (56.7) (55.9 to 79.7)	19/34 (55.9) (52.1 to 84.7)

Abbreviations: AM, arithmetic mean; CI, 95% confidence interval; EPG, eggs per gram; GM, geometric mean.

of moxidectin in children infected with *Schistosoma mansoni* and *Schistosoma haematobium* reported mild side effects including nausea, headache, and abdominal discomfort [26]. One possible explanation might be related to the age of participants (adults vs school-age children) who perceive symptoms and physical discomfort in different ways. Moreover, adults better understand physical symptoms and are more critical and reliable in reporting them. Another possible reason might be linked to the fact that in the cited study, all participants reported similar symptoms before and after treatment, hence it cannot be determined whether symptoms are treatment related or not.

As highlighted above, one key advantage of moxidectin over ivermectin is that it might be effective against ivermectin-resistant *S. stercoralis*. Fortunately, anthelminthic resistance has not yet been observed in humans. Nevertheless, it is worth highlighting that resistance has been demonstrated in sheep infected with *Strongyloides* spp. (40%) following treatment with ivermectin, even at low frequency [27]. Different studies in veterinary medicine have demonstrated that moxidectin is effective against ivermectin-resistant strains of parasites [14]. One trial conducted on lambs showed an efficacy of >99% against resistant *Haemonchus contortus*, whereas the CRs of

ivermectin were only 38%–53% [28]. Resistance against ivermectin was found to be a dominant trait, while it might be rendered incompletely dominant or recessive for moxidectin [29]. Cross-resistance among macrocyclic lactones has been reported in livestock; this impairs efficacy of multiple compounds [14, 27, 30]. Despite this fact, it has been shown that drugs develop resistance at different speed, and resistance toward moxidectin occurs more slowly than for ivermectin. Moreover, moxidectin at recommended dosages was shown to be effective against ivermectin-resistant parasites as well as several macrocyclic lactone–resistant parasites [27].

We evaluated the efficacy of moxidectin against coinfections with hookworm and *O. viverrini*. A low efficacy was observed against *O. viverrini* for both drugs (CRs of 18% for moxidectin and 6.5% for ivermectin). Moderate CRs of 57% and 56% against hookworm infection were recorded for moxidectin and ivermectin, respectively. Of note, we did not distinguish the activity against different hookworm species, including *Ancylostoma ceylanicum*, which is common in the study area [31] and should be evaluated in follow-up studies. Studies on the efficacy of ivermectin against hookworm infections in humans are scarce. Three studies revealed low CRs of 11.8%–33.1% for ivermectin against hookworm infections [32–34]. In veterinary medicine, on the other hand, both drugs are successfully used for the treatment of *Ancylostoma* spp. and other gastrointestinal parasites [35, 36]. In dogs, for example, ivermectin was administered against *Ancylostoma caninum* infections, yielding CRs of 100% [35]. Similarly, moxidectin as pour-on or oral formulation demonstrated a high efficacy against gastrointestinal nematodes in beef cattle [36]. The most widely used strategy for protecting against drug resistance is to use drug combinations [37]. Hence, it might be worth exploring the use of moxidectin in combination with albendazole. Considering the moderate effect of moxidectin against hookworm and the moderate efficacy of albendazole against *S. stercoralis* together with the similar distribution of these parasites, the combination might be effective in tackling the mentioned infections, while potentially delaying drug resistance.

We conclude that moxidectin might be a safe and efficacious alternative to ivermectin for the cure of *S. stercoralis* infection. We did not observe any ancillary benefit against coinfection with *O. viverrini* and moderate efficacy against hookworm. Larger trials are needed to confirm our findings once the drug has successfully passed FDA registration and is marketed for human use.

Notes

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