Acta Tropica 158 (2016) 52–58

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Prophylactic effect of artemether on human schistosomiasis mansoni among Egyptian children: A randomized controlled trial

Hala Elmorshedy[a,*], Marcel Tanner[b,c], Robert N. Bergquist[c,d], Soraya Sharaf[e], Rashida Barakat[a,1]

[a] Department of Tropical Health, High Institute of Public Health, University Of Alexandria, Egypt
[b] The Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland
[c] University of Basel, Basel, Switzerland
[d] Ingerod, Brastad, Sweden
[e] Parasitology Department, National Liver Institute, Menoufeya University, Menoufeya, Egypt

ARTICLE INFO

Article history:
Received 29 March 2015
Received in revised form 15 February 2016
Accepted 21 February 2016
Available online 26 February 2016

This paper is dedicated to Professor Rashida Barakat, who not only inspired our team but a generation of scientists committed to better health and well-being for all.

Keywords:
Schistosoma mansoni
Randomized control trial
Praziquantel
Artemether
Prophylaxis
Egypt

ABSTRACT

A double-blind, randomized controlled trial was conducted in an endemic focus for *Schistosoma mansoni* in Kafr El-Sheikh Governorate, Northern Nile Delta, Egypt, to evaluate the prophylactic effect of artemether (ART) given in conjunction with praziquantel (PZQ). The study encompassed 913 primary school children randomly assigned to two treatment groups PZQ/ART and PZQ/ART-placebo. At baseline, both groups received 40 mg/kg body weight of PZQ twice four weeks apart, after which one group received 6 mg/kg body weight of ART every 3 weeks in 5 cycles during the transmission season and the other group received ART-placebo. At the end of the study, prevalence of infection among the PZQ/ART was approximately half that of the PZQ/ART-placebo group, i.e. 6.7% versus 11.6%, and incidence of new infections for the PZQ/ART was 2.7% versus 6.5% for the PZQ/ART-placebo. In conclusion, PZQ/ART combined therapy might be considered as an adjunct measure against human schistosomiasis, by specifically reducing transmission and therefore contribute to disease elimination.

1. Introduction

Schistosomiasis is a neglected tropical disease (NTD) that remains one of the most prevalent parasitic infections in the humid tropics ranking second only after malaria in terms of gravity and public health importance (Chitsulo et al., 2000). The estimated global burden of the three most common schistosome species, *Schistosoma mansoni*, *Schistosoma haematobium* and *Schistosoma japonicum* has been reported to be 4–5 million disability-adjusted life years (DALYs) (World Health Organization, 2002) but would be considerably higher if subtle morbidities were included. The great majority of the world's burden of schistosomiasis is concentrated in the African continent with an overall estimated average prevalence of approximately 10% (Steinmann et al., 2006; Utzinger et al., 2009). In Egypt, both *S. mansoni* and *S. haematobium* species are endemic. Currently, the number of infections due to *S. mansoni* exceeds that of *S. haematobium* due to ecological changes influenced by the shift in irrigation system from basin to perennial following the construction of the Aswan High Dam (Dazo and Biles, 1972; Malek, 1975). In Egyptian hyper-endemic foci of *S. mansoni* infection, the prevalence even approaches 70% and the percentage of heavily infected

Abbreviations: PZQ, praziquantel; ART, artemether; NTD, neglected tropical disease; DALYs, disability adjusted life years; EPG, eggs per gram; WHO, World Health Organization; MDA, mass drug administration; MOHP, the Egyptian Ministry of Health and Population; UNDP, United Nations Development Program; USAID, United States Agency for International Development; KES Governorate, Kafr El Sheikh; GMEC, geometric mean egg count; Swiss TPH, the Swiss Tropical and Public Health Institute; RHU, Rural Health Units; CI, confidence interval; ACTs, artemisinin-based combination therapies.

* Corresponding author: Department of Tropical Health, High Institute of Public Health, 165 Alhorreya Avenue, Alexandria, Egypt.
E-mail addresses: elmorshedyh@hotmail.com, elmorshedyh@gmail.com (H. Elmorshedy), marcel.tanner@unibas.ch (M. Tanner), robert.bergquist@outlook.com (R.N. Bergquist), Soraya_sharaf@yahoo.com (S. Sharaf).
[1] Deceased.

http://dx.doi.org/10.1016/j.actatropica.2016.02.015

individuals, i.e. those excreting more than 400 eggs per gram (EPG) of faeces accounts for 20% of those infected (Barakat et al., 2000).

The World Health Organization (WHO) recommends schistosomiasis control through large-scale mass drug administration (MDA) with PZQ, a key anti-morbidity strategy that remains in place to date (World Health Organization, 1983, 2011). Chemotherapy as a measure of control is feasible and sustainable if distributed repeatedly according to defined, long-term schedules (World Health Organization, 2011). The Egyptian Ministry of Health and Population (MOHP) has implemented a large-scale control programme since the early 1980s supported by international agencies including the United Nations Development Program (UNDP) and the United States Agency for International Development (USAID). The outcome was excellent during the first implementation phase with prevalence rates falling throughout the country (Barakat et al., 2014). However, shortly after cessation of control measures, infection indices increased drastically exceeding baseline levels. In addition, new infection foci appeared in areas claimed to have been secure (Talaat et al., 1999; El-Khoby et al., 2000; Barakat, 2013; Abdel-Wahab et al., 2000). It was also noticed that the age pattern had shifted in the direction of more infections among children and occurring at a younger age (Barakat et al., 1998).

In the late 1990s, the MOHP followed up with more vigorous control strategies based on MDA and providing chemotherapy to all individuals in hyper-endemic foci annually regardless of infection status. However, transmission continued unabated as snail control had been abandoned and PZQ does not affect the immature stages of the parasite leaving new infections to mature and start egg production (World Health Organization, 2011; Cioli and Pica-Mattoccia, 2003; Pica-Mattoccia and Cioli, 2004). Although snail control measures affect disease transmission, application is not always feasible due to the high cost of molluscicides and their broad-spectrum effect on the fauna, e.g. fish, as well as administrative and logistic limitations of its use, particularly as preventive chemotherapy is now the recommended main approach (Taylor, 2008).

Artemether (ART), a methyl-ether derivative of dihydroartemisinin (Li and Wu, 2003), in addition to its excellent anti-malarial properties, also exhibits activity against the immature stages of *Schistosoma* spp. (Shuhua et al., 2000; Utzinger et al., 2001, 2000; Utzinger and Keiser, 2004; Xiao et al., 2002; Bergquist et al., 2004; N'Goran et al., 2003). The administration of a dose of 6 mg/kg once every 2–4 weeks, reduces the incidence of schistosome infection significantly (Utzinger et al., 2001; Utzinger and Keiser, 2004). Peak efficacy of the drug varies from two weeks after cercarial skin penetration for *S. japonicum* to four weeks for *S. haematobium*. ART complements PZQ as its effect is focused on the juvenile stage, thereby blocking the development of new adult stages (Shuhua et al., 2000; Utzinger et al., 2001; Utzinger and Keiser, 2004; Xiao et al., 2002). Theoretically, combined drug therapy should completely wipe out schistosome infection in the human host as there would be no replacement of the adult worms by those maturing, as is the case after exclusive PZQ treatment. This type of combined treatment should ultimately impact transmission by reducing overall egg excretion from the human host. It is worth noting that ART treatment might also have an effect comparable to a vaccine as shown in a previous experimental study, where ART treatment in the second and third week after infection resulted in immune responses that protected mice at the level of 58% and 81% respectively (Bergquist et al., 2004).

After initial Chinese trials of artemisinin derivatives for prevention of *S. japonicum* infection (unpublished in the international literature), several clinical trials have confirmed the effect of ART against the three most common species (Utzinger et al., 2000; N'Goran et al., 2003; Li et al., 2005). A comprehensive meta-analysis from 2011, refers to 52 trials and 38 articles on the antischistosomal efficacy of different medication strategies with various artemisinin derivatives including combination therapy with PZQ (Liu et al., 2011). According to this systematic review, it is preferable to use complementary treatment regimen which includes PZQ and multiple doses of ART or artesunate (Liu et al., 2011). Given these facts and since field studies evaluating the ART effect on Egyptian *Schistosoma* species do not exist so far, we set the following objectives:

1. Evaluate the prophylactic effect of ART chemotherapy on schistosomiasis mansoni in a double-blind randomized controlled trial.
2. Assess the safety and efficacy of combined PZQ and ART versus PZQ only.

2. Methods

2.1. Ethical approval and financial support

The study protocol was approved by the Ethical Review Board, Ministry of Health and Population (MOHP), Egypt. Before the implementation of the study, written informed consents were obtained from the guardians of the children. The study was funded by the Special Programme for Research and Training in Tropical Diseases (TDR) (ID No.: SGS02/39).

2.2. Study area

The study was conducted in a hyper-endemic area for *S. mansoni* in the north-western region of the Metobas District, Kafr El-Sheikh Governorate (KES), which is located in the northern part of the Nile Delta (Fig. 1). It is bordered by the Mediterranean Sea to the north, the Rosetta Nile Branch to the west, the Dakahleya Governorate to the east, and the Gharbeya Governorate to the south. One of the main geographical features of the coastal area of KES is the El-Borolos Lake which is located in the northern part of the Nile Delta and connected to the Mediterranean Sea by the Boghase-El-Borolos canal. The whole study area is free from malaria.

2.3. Study design and study sample

A randomized, double blind controlled trial was conducted during the period 2003–2005. The study encompassed a total of 913 primary school children attending grades 1–5, aged 6–11 years. The children were randomized into two treatment groups using a computer generated random list. The PZQ/ART-placebo group included 453 children, and the combined-therapy group (PZQ/ART) included 460 children. Both the investigators and the study participants were blinded as to which participants were given ART or ART-placebo. Considering an attrition rate of 10%, the sample size was estimated to give the study at least 80% power at 0.05 level of significance to detect the difference between the two treatment groups.

2.4. Socio-demographic data

The data form contained the following personal information: name, class, identification number, gender, residence, body weight, compliance to stool sample collection and treatment and results of stool sample analysis. The investigators dealing with the data were unaware about the group identity of the study subjects until the final analysis of data at the end of the study.

2.5. Stool sample evaluation

Since the most intense schistosomiasis transmission in Egypt is from April through October, the study was started in the former month, when stool samples were collected to determine baseline prevalence and intensity of infection. For the assessment of PZQ

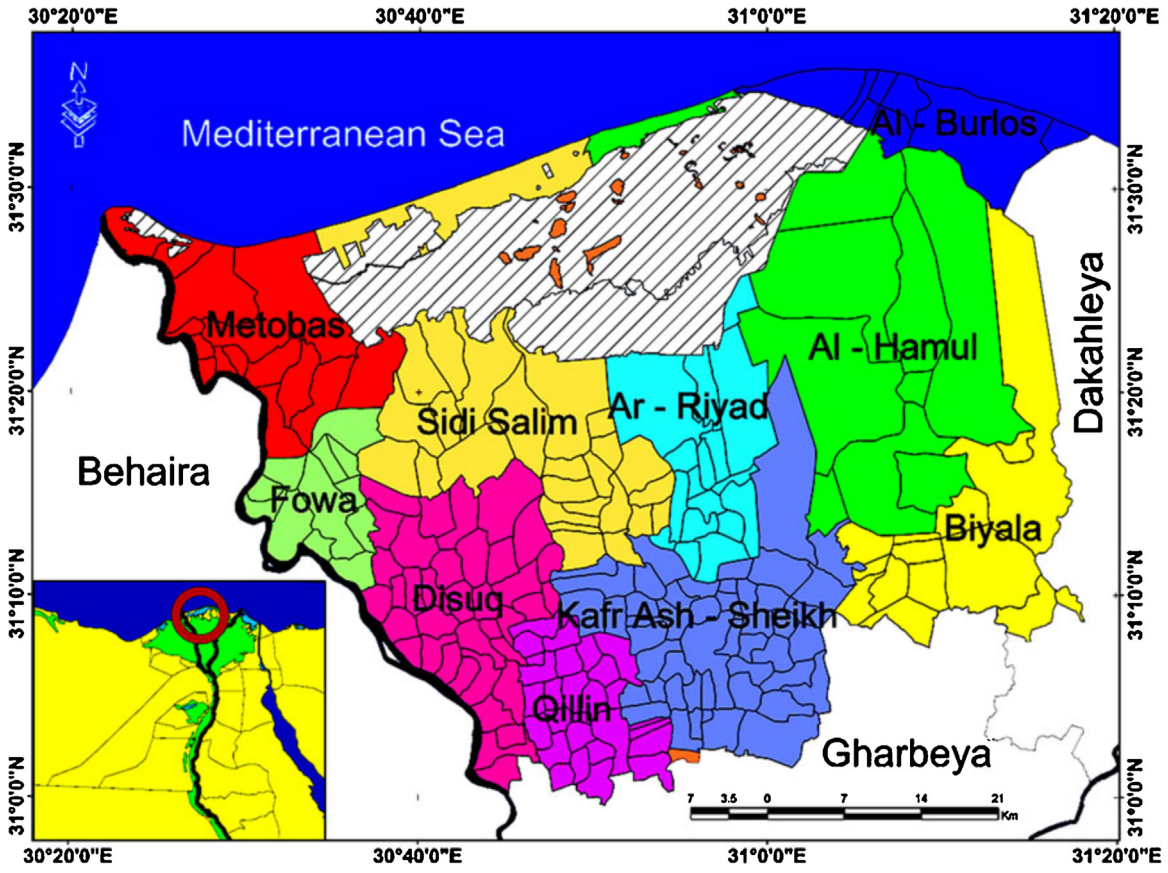

Fig. 1. Kafr El Sheikh Governorate showing the location of the study area (Metobas District).

Table 1
Project activities by date for both treatment and control groups from April 2003 to October 2003.

Dates and tasks performed	Treatment group PZQ/ART	Control group PZQ/ART-placebo
Collection of the1st stool sample April 13–14	√	√
PZQ Mass treatment—1st dose of PZQ April 15–16	√	√
2nd stool sample taken for cure assessment May 11–12	√	√
PZQ Mass treatment—2nd dose of PZQ May 14–15	√	√
1st dose of ART/placebo May 25–26	√	√
2nd dose of ART/placebo June 15–16	√	√
3rd dose of ART/placebo July 6–7	√	√
4th dose of ART/placebo July 27–28	√	√
5th dose of Art/placebo August 17–18	√	√
Stool sample for end-of-intervention assessment October 24–25	√	√

cure rate, a second stool sample was collected four weeks after the first dose of PZQ. At the end of the study in October, stool samples were again collected to evaluate the impact of treatment regimens among the two groups (Table 1). Because schistosomiasis control in Egypt resulted in a substantial, relatively long-term effect, strongly downregulating indices of infection (Barakat et al., 2014), it is justifiable, more feasible and cost-effective to implement control activities every two years. Therefore, stool samples were recollected approximately two years following the latest intervention to evaluate the long-term effect of the combined-chemotherapy regimen.

All stool samples were processed according to Katz et al. (1972): two slides each of 43.7 mg faeces were prepared from each sample and examined microscopically by well-trained parasitology technicians (Swiss TPH, April 2005). Egg counts from the two slides were averaged and the EPG of stool was computed. The outcome was used to calculate the geometric mean EPG of stool (GMEC). All EPG values were transformed into log10 +1 to allow for zero counts, and the GMEC was computed as the anti-log10 of the mean of the log10 egg counts.

Validity and reliability of parasitological data were assured by re-examination of 10% of the slides, which were randomly selected. Slides were re-checked by a senior parasitologist if the

re-examination data were not strongly correlated with the original data. In addition, any slide with only one egg was also rechecked by an experienced parasitologist.

2.6. Chemotherapy

After estimating the baseline prevalence of infection and regardless of the infection status, PZQ (donated free-of-charge by the MOHP) was given to all participants in a dose of 40 mg/kg of body weight according to the MOHP policy for hyper-endemic foci (World Health Organization, 2011). Since PZQ is only effective against the adult stage of the parasite, a second dose of the drug was administered four weeks after the first dose and couple of days after the collection of the second stool sample. Administration of PZQ in two doses ensures that almost every participant was free of infection before the start of ART therapy.

ART and ART-placebo, were donated by Kunming Pharmaceutical Industries through the Swiss Tropical and Public Health Institute (Swiss TPH). ART treatment was repeated every three weeks during the transmission season from May to August. The drug was administered in a single oral dose, each of 6 mg/kg of body weight. The PZQ/ART-placebo group followed the same schedule, but here ART-placebo was administered to the participants (Table 1). Poten-

Table 2
Treatment and stool compliance rates.

Compliance to ART			Compliance to stool	
ART dose	N	%	N	%
1st	430	100.0	859	94.1
2nd	423	98.4	854	93.5
3rd	422	98.1		
4th	418	97.2		
5th	403	93.7	855	93.6

tial adverse effects of the drugs were assessed immediately and after 24 h in all participants of the two treatment groups (PZQ/ART and PZQ/ART-placebo). During the school summer vacation, the children were reached through house visits, which necessitated community participation in the form of regular meetings with community leaders, doctors at Rural Health Units (RHU) and parents. In addition, mass campaigns were conducted during the Friday prayers at local mosques to motivate parents to adhere to the treatments scheduled for their children.

2.7. Statistical analysis

Data were analyzed using SPSS, version 16.0 (IBM, New York, NY, USA). Comparisons, presented as percent difference of *S. mansoni* infections between PZQ/ART and PZQ/ART-placebo recipients were subjected to Pearson's Chi-square test (Kirkwood and Sterne, 2003). GMEC values were computed for the positive cases with 95% confidence interval (CI). The unpaired *t*-test was used for comparison of the two treatment groups using log-transformed egg counts, because the distribution of intensity of infection, as measured by EPG following treatment is right-skewed, i.e. in the majority of cases, there are only a few or no parasites left after treatment, while a few individuals showed relatively large parasite burdens, a tendency best described by considering their geometric mean (Kirkwood and Sterne, 2003). All tests were two-sided and the 0.05 level was used as the cut-off value for statistical significance.

3. Results

3.1. Study sample and compliance rates

Overall, a total of 2568 stool samples were collected during the whole study period resulting in a compliance rate of 93.8%. The rates during the various collection occasions were the following: at the baseline in April, 859 (94.1%) samples were collected and in May, 854 (93.5%) samples were collected four weeks following PZQ chemotherapy for cure assessment. At the end of the study, following the peak of transmission season in October 2003, 855 (93.6%) stool samples were collected. As for chemotherapy compliance, 853 children (93.4%) received the two doses of PZQ at the baseline. Among children in the PZQ/ART group, 403 (93.7%) received the 5 scheduled doses of the drug (Table 2).

3.2. Baseline parasitological data

At baseline, there was no significant statistical difference between the indices of infection among the two treatment groups: prevalence rates were 30.2% and 27.3%, and the corresponding GMECs values were 59.8 and 57.6 EPG for the PZQ/ART and the PZQ/ART-placebo, respectively. Following PZQ chemotherapy, the overall cure rate was 83.2%. The difference in cure rate between the two treatment groups was not significant, being 79.5% and 87.2% for the PZQ/ART and the PZQ/ART-placebo respectively. The GMEC of uncured cases was comparable among the two treatment groups with no statistically significant difference. All these data are summarized in Table 3.

3.3. Impact of chemotherapy

On whole, shortly after treatment, few children complained of mild side effects as nausea and abdominal pain, while no side effects of medical importance were recorded among the two treatment groups. The *S. mansoni* prevalence rate for the combined treatment regimen in the PZQ/ART group was significantly lower than that of the PZQ/ART-placebo. The overall prevalence was 6.7% for the PZQ/ART group compared to 11.6% for the PZQ/ART-placebo group. Accordingly, the reduction in prevalence for the combined therapy group was significantly higher than that for the PZQ/ART-placebo, i.e. 77.8% versus 57.5%. The impact of ART on the incidence of infection was evident, as it was found to be 2.7% versus 6.5% for PZQ/ART and the PZQ/ART-placebo, respectively. The relative risk of developing new infection was 0.42, 95% CI (0.19–0.950), P = 0.024, which indicated that the incidence of infection among the ART/PZQ group is 0.425 times as likely as in the PZQ/ART-placebo group (Table 4). The longitudinal impact of chemotherapy intervention after two years from base line revealed that the prevalence of infection was comparable for the two treatment groups being 6.6% and 8.1% for PZQ/ART and the PZQ/ART-placebo respectively (Table 5).

4. Discussion

The current key strategy to control schistosomiasis relies on PZQ alone (World Health Organization, 1983, 2011). However, this drug fails to prevent reinfection, so transmission continues at high levels in many places (Barakat, 2013; Tchuem Tchuente et al., 2013). Furthermore, reliance on a single drug may ultimately lead to the development of drug-resistant schistosome strains. Reduced susceptibility to PZQ has already been documented under experimental conditions and among humans as reported from Senegal, Kenya and Egypt (Utzinger et al., 2009; Botros et al., 2005; Silva et al., 2005; Doenhoff et al., 2008; Fallon et al., 1995). However, substantial year-to-year variation in drug efficacy is common, so the patterns reported may not be consistent with rapid, progressive emergence of resistance to PZQ (King et al., 2000). Even so, the risk cannot be ignored and the development of new 'fall-back' drugs remains a pressing need.

ART is not a novel discovery, as it has been used for malaria therapy for a long time. However, the surprising finding is that it is also effective against schistosomula of various schistosome species (Utzinger and Keiser, 2004; Xiao et al., 2002; Utzinger et al., 2000; N'Goran et al., 2003; Li et al., 2005) and thus constitutes a novel application. Its effect on immature schistosome stages complements PZQ that only acts against adult worms (Cioli and Pica-Mattoccia, 2003). Drugs acting on different developmental stages of the parasite, such as PZQ and ART, improve cure rate, reduce the risk of developing resistant strains and ultimately block parasite transmission. Since the artemisin group of drugs is important for malaria treatment, the emerging threat of artemisinin resistance should not be ignored (Djimde et al., 2015), and the drug should therefore not be used against schistosomiasis where there is malaria transmission. However, combination therapy against schistosomiasis would be possible in areas close to elimination of the disease, such as North Africa and China where malaria is absent.

The results of our study show that compliance with respect to the five scheduled doses of ART was 93.7%. Concordantly, in an *S. japonicum*-endemic focus in China, the drug was given 9–11 times consecutively with a compliance rate of 84.8% without any adverse effects (Xiao, 2005; Wang, 2006). In our study, the extent of ART impact on *S. mansoni* infection was evident in the combined

Table 3
Matching of the two treatment groups according to the status of infection.

Treatment group	Baseline		GMEC of uncured cases		Cure rate
	Prevalence	GMEC (95%CI)	Number Positive	GMEC (95% CI)	
PZQ/ART	130/431 30.2%	59.8 (47–76)	34	25 (19–34)	101/127 79.5%
PZQ/ART-placebo	117/428 27.3%	56.7 (44–76)	23	25 (18–35)	102/117 87.2%
Test of significance	$X^2 = 0.84$	t = 0.84	t = 0.02		$X^2 = 2.55$
P-value	0.360	0.360	0.983		0.110

Table 4
Impact of treatment on the indices of *Schistosoma mansoni* infection according to drug regimen.

Treatment group	Results after 5 doses of ART (end of transmission season)				
	Prevalence	% reduction*	GMEC of positives (95% CI)	% reduction in GMEC*	Incidence
PZQ/ART	29/427 6.8%	77.5%	27 (18–41)	55.1%	8/299 2.7%
PZQ/ART-placebo	48/421 11.4%	58.2%	28 (21–38)	51.0	20/306 6.5%
Test of significance	$X^2 = 5.46$		t = 0.20		$X^2 = 5.11$
P-value	0.019**		0.845		0.024** Relative risk (RR) (0.425),95% CI (0.19–0.95)

*Percent reduction from the baseline.
**<0.05 = significant.

Table 5
Longitudinal impact of treatment on the percentage of *Schistosoma mansoni* infection according to drug regimen.

Treatment group		Baseline	After two years
PZQ/ART	No.	130/431	23/351
	%	30.2	6.6
PZQ/ART-placebo	No.	117/428	28/347
	%	27.3	8.1
Significance test (X^2)		0.84	0.59
P-value		0.360	0.441

treatment group showing a remarkably higher overall prevalence reduction for ART recipients as compared to the PZQ/ART-placebo group. This can be explained by the effect of ART against immature worms and translating into a protective effect against re-infection all through the transmission season. Experimental studies have revealed that appropriately timed ART administration may not only rely on its direct effect on the infection status, but that the drug also exhibits an effect comparable to a vaccine by destruction of the invading parasites at sites preferential for the generation of protective immunity (Bergquist et al., 2004).

As far as we know, this is the first study to date in Egypt testing the impact of ART on human schistosomiasis in a community setting. In other countries, endemic for human schistosomiasis, randomized controlled trials have shown that ART is effective against the three common schistosome species (Utzinger et al., 2000; N'Goran et al., 2003; Li et al., 2005). Results from a systematic review reveal that PZQ and ART in combination result in a higher protection rate [in general, up to 84%, (95% CI: 64–91%)] than PZQ monotherapy for treatment of human schistosomiasis (Wang, 2006). In accordance with these results, an ART field trial in Côte d'Ivoire showed that *S. mansoni* infection was 50% lower in the children who received 6 doses of ART three weeks apart compared to placebo (Utzinger et al., 2000), while Chinese studies have shown even higher protection rates—one as high as 96% (95% CI: 78–99%) (Liu et al., 2011), and another, carried out in a hyper-endemic focus following the transmission season, where the prevalence was reduced by 92.9% and the intensity of infection was reduced by 96.1% among ART recipients (Li et al., 2005). The difference between the aforementioned studies and the present one could be attributed to strain differences, differences in study design as well as to differences in the indices of infection. In the present study, only 5 doses of ART were used, while between 9 and 11 doses were given in the Chinese study (Xiao, 2005; Wang, 2006). In addition, in the Chinese study, the intensity of infection was calculated for all participants regardless of their infection status, i.e. negative results were included in the calculation of the mean intensity of infection, leading to an overestimation of the impact of ART. In comparison, the GMEC was only calculated for the positive subjects in the present study.

After the transmission season, at the end of the follow-up, both treatment groups showed remarkable GMEC reductions. However the difference between the two treatment groups was not statistically significant. This can be explained by the ongoing annual chemotherapy control programmes adopted by the MOHP leading to modulation of the immune response of the target population. In the Côte d'Ivoire study, GMEC was significantly lower in the ART group than in the placebo ones (Utzinger et al., 2000). However, participants in this study were not subjected to repeated PZQ chemotherapy and no control campaigns had been launched in the area before the start of the study. In addition, children received 6 doses of ART compared to 5 doses in the present study. Other causes, such as genetic variations of schistosome strains and differences in the seasons where the two studies were conducted, might also have been contributing factors.

The impact of the drug on immature infections can be assumed by the difference in incidence rates between the two treatment groups. In our study, the incidence among the ART/PZQ recipients was less than half that of the PZQ/ART-placebo group. The superior effect of ART on the incidence of new infection has been shown previously (Utzinger et al., 2000; N'Goran et al., 2003; Li et al., 2005). In Côte d'Ivoire, incidence of *S. haematobium* in the ART/PZQ group was 49% compared to 65% for the PZQ-only group and the protective efficacy was 0.25, (95% CI: 0.08–0.38, P = 0.007) (N'Goran et al., 2003). In the same region, the incidence of *S. mansoni* was 24% for the group that received ART compared to 49% among the placebo group and the relative risk was 0.5, (95% CI 0.35–0.71, P = 0.00006) (Utzinger et al., 2000). The authors of the Côte d'Ivoire studies recommended the use of ART whenever appropriate as an additional tool for the control of schistosomiasis (N'Goran et al., 2003).

In this study, the longitudinal effect of the combined therapy after two years from the intervention demonstrated that preva-

lence in the group that received PZQ/ART was slightly lower than that among those received PZQ/ART-placebo. Although the difference was not statistically significant, this might indicate the need to schedule treatment repeats on annual basis in high and moderate risk areas. Accordingly, further investigations are needed to carefully determine the schedule of treatment repeats as tailored to the level of disease endemicity.

Finally, it is worth mentioning that the study design did not include a group receiving PZQ only at every time point that would unequivocally have shown if there indeed would be a difference between the two drugs regimens investigated. However, had only PZQ been used, re-infections would not have been cured until the worms reached maturity, while ART would have 'nipped them in the bud' as it were, making sure that no egg-laying worms would appear at all, thus giving this drug the edge. Another fact that speaks in favour of combination therapy, is that neither drug alone has a 100% efficacy. By attacking the parasite with two drugs with different killing mechanisms should augment the efficacy of each drug. Although the available data are not sufficient to settle whether this argument holds, drugs acting on different developmental stages of the parasite should improve cure rates, reduce the risk for drug resistance and ultimately contribute to blocking transmission.

In conclusion, ART is a safe drug that has shown a clear prophylactic effect against *Schistosoma* species through its action on the immature stages. The PZQ/ART combination demonstrated a synergistic effect on prevalence and intensity of infection. The drug should be considered an additional tool for efficacious control of human schistosomiasis in areas where malaria is not endemic and/or in situations where disease elimination is envisioned.

Conflict of interests

The authors declare no conflicts of interest and that they are responsible for the content and writing of this article.

Acknowledgements

The authors gratefully acknowledge the participation of the study communities in the trial and all local authorities and field workers for their efforts, commitment and support. We acknowledge Professor Mona Hassan, High Institute of Public Health for her valuable assistance in the statistical analysis of data. We also gratefully acknowledge the support of Professor Shuhua Xiao the long term partnership in studies on the anti-schistosomal drugs, but particularly also for his great support by providing artemether for this study from the Kunming Pharmaceutical Company, Kunming, People's Republic of China.

References

Abdel-Wahab, M.F., Esmat, G., Ramzy, I., Narooz, S., Medhat, E., Ibrahim, M., et al., 2000. The epidemiology of schistosomiasis in Egypt: Fayoum Governorate. Am. J. Trop. Med. Hyg. 62 (Suppl. 2), 55–64.

Barakat, R., Farghaly, A., El Morshedy, H., Hassan, M., Miller de, W., 1998. Impact of National Schistosomiasis Control Program in Kafr El-Sheikh governorate, Nile Delta, Egypt: an independent evaluation. J. Egypt. Public Health Assoc. 73 (5–6), 737–753.

Barakat, R., Farghaly, A., El Masry, A.G., El-Sayed, M.K., Hussein, M.H., 2000. The epidemiology of schistosomiasis in Egypt: patterns of Schistosoma mansoni infection and morbidity in Kafer El-Sheikh. Am. J. Trop. Med. Hyg. 62 (Suppl. 2), 21–27.

Barakat, R., El Morshedy, H., Farghaly, A., 2014. Human Schistosomiasis in the Middle East and North Africa Region. In: Neglected Tropical Diseases—Middle East and North Africa. Springer Verlag Wien, Mary Ann McDowell, Sima Rafati http://link.springer.com/book/10.1007/978-3-7091-1613-5.

Barakat, R.M.R., 2013. Epidemiology of schistosomiasis in Egypt: travel through time: review. J. Adv. Res. 4 (5), 425–432, http://dx.doi.org/10.1016/j.jare.2012.07.003.

Bergquist, R., Utzinger, J., Chollet, J., Shu-Hua, X., Weiss, N.A., Tanner, M., 2004. Triggering of high-level resistance against *Schistosoma mansoni* reinfection by artemether in the mouse model. Am. J. Trop. Med. Hyg. 71 (6), 774–777.

Botros, S., Sayed, H., Amer, N., El-Ghannam, M., Bennett, J.L., Day, T.A., 2005. Current status of sensitivity to praziquantel in a focus of potential drug resistance in Egypt. Int. J. Parasitol. 35 (7), 787–791.

Chitsulo, L., Engels, D., Montresor, A., Savioli, L., 2000. The global status of schistosomiasis and its control. Acta Trop. 77 (1), 41–51.

Cioli, D., Pica-Mattoccia, L., 2003. Praziquantel. Parasitol. Res. 90 (Suppl. 1), S3–S9.

Dazo, B., Biles, J., 1972. The Present Status of Schistosomiasis in the Nile Valley North of the Aswan High Dam. World Health Organization, Geneva (Contract No.: PD/72.14).

Djimde, A.A., Makanga, M., Kuhen, K., Hamed, K., 2015. The emerging threat of artemisinin resistance in malaria: focus on artemether-lumefantrine. Expert Rev. Anti Infect. Ther. 13 (8), 1031–1045, http://dx.doi.org/10.1586/14787210.2015.1052793.

Doenhoff, M.J., Cioli, D., Utzinger, J., 2008. Praziquantel mechanisms of action, resistance and new derivatives for schistosomiasis. Curr. Opin. Infect. Dis. 216 (659), 67.

El-Khoby, T., Galal, N., Fenwick, A., Barakat, R., El-Hawey, A., Nooman, Z., et al., 2000. The epidemiology of schistosomiasis in Egypt: summary findings in nine governorates. Am. J. Trop. Med. Hyg. 62 (Suppl. 2), 88–99.

Fallon, P.G., Sturrock, R.F., Niang, A.C., Doenhoff, M.J., 1995. Short report: diminished susceptibility to praziquantel in a Senegal isolate of Schistosoma mansoni. Am. J. Trop. Med. Hyg. 53 (1), 61–62.

Katz, N., Chaves, A., Pellegrino, J., 1972. A simple device for quantitative stool thick-smear technique in *Schistosomiasis mansoni*. Rev. Inst. Med. Trop. Sao Paulo 14 (6), 397–400.

King, C.H., Muchiri, E.M., Ouma, J.H., 2000. Evidence against rapid emergence of praziquantel resistance in *Schistosoma haematobium*, Kenya. Emerg. Infect. Dis. 6 (6), 585–594.

Kirkwood, B.R., Sterne, J.A.C., 2003. Essential Medical Statistics, 2nd edition. Blackwell Science Ltd., Massachusetts, Oxford, Australia.

Li, Y., Wu, Y.L., 2003. An over four millennium story behind qinghaosu (artemisinin)—a fantastic antimalarial drug from a traditional Chinese herb. Curr. Med. Chem. 10 (21), 2197–2230.

Li, Y.S., Chen, H.G., He, H.B., Hou, X.Y., Ellis, M., McManus, D.P., 2005. A double-blind field trial on the effects of artemether on Schistosoma japonicum infection in a highly endemic focus in southern China. Acta Trop. 96 (2-3), 184–190.

Liu, R., Dong, H.F., Guo, Y., Zhao, Q.P., Jiang, M.S., 2011. Efficacy of praziquantel and artemisinin derivatives for the treatment and prevention of human schistosomiasis: a systematic review and meta-analysis. Parasite Vectors 4, 201, http://dx.doi.org/10.1186/1756-3305-4-201.

Malek, E.A., 1975. Effect of the Aswan High Dam on prevalence of schistosomiasis in Egypt. Trop. Geogr. Med. 27 (4), 359–364.

N'Goran, E.K., Utzinger, J., Gnaka, H.N., Yapi, A., N'Guessan, N.A., Kigbafori, S.D., Lengeler, C., Chollet, J., Shuhua, X., Tanner, M., 2003. Randomized, double-blind, placebo-controlled trial of oral artemether for the prevention of patent *Schistosoma haematobium* infections. Am. J. Trop. Med. Hyg. 68 (January (1)), 24–32.

Pica-Mattoccia, L., Cioli, D., 2004. Sex- and stage-related sensitivity of *Schistosoma mansoni* to in vivo and in vitro praziquantel treatment. Int. J. Parasitol. 34 (4), 527–533.

Shuhua, X., Chollet, J., Weiss, N.A., Bergquist, R.N., Tanner, M., 2000. Preventive effect of artemether in experimental animals infected with Schistosoma mansoni. Parasitol. Int. 49 (1), 19–24.

Silva, I.M., Thiengo, R., Conceicao, M.J., Rey, L., Lenzi, H.L., Pereira Filho, E., et al., 2005. Therapeutic failure of praziquantel in the treatment of *Schistosoma haematobium* infection in Brazilians returning from Africa. Mem. Inst. Oswaldo Cruz 100 (4), 445–449.

Steinmann, P., Keiser, J., Bos, R., Tanner, M., Utzinger, J., 2006. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infect. Dis. 6 (7), 411–425.

Swiss Tropical Institute, Basel. Methods in Parasitology: 8. Kato-katz technique for helminth eggs. April 2005. Available at http://www.tropeduweb.ch/parasitology_methods_pdf/8_stool_kato-katz.pdf. (accessed 16.02.15.).

Talaat, M., El-Ayyat, A., Sayed, H.A., Miller, F.D., 1999. Emergence of *Schistosoma mansoni* infection in Upper Egypt: the Giza governorate. Am. J. Trop. Med. Hyg. 60 (5), 822–826.

Taylor, M., 2008. Global trends in schistosomiasis control. Bull. World Health Organ. 86 (10), 738.

Tchuem Tchuente, L.A., Momo, S.C., Stothard, J.R., Rollinson, D., 2013. Efficacy of praziquantel and reinfection patterns in single and mixed infection foci for intestinal and urogenital schistosomiasis in Cameroon. Acta Trop. 128 (2), 275–283.

Utzinger, J., Keiser, J., 2004. Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. Expert Opin. Pharmacother. 5 (2), 263–285.

Utzinger, J., N'Goran, E.K., N'Dri, A., Lengeler, C., Xiao, S., Tanner, M., 2000. Oral artemether for prevention of *Schistosoma mansoni* infection: randomised controlled trial. Lancet 355 (9212), 1320–1325.

Utzinger, J., Xiao, S., N'Goran, E.K., Bergquist, R., Tanner, M., 2001. The potential of artemether for the control of schistosomiasis. Int. J. Parasitol. 31 (14), 1549–1562.

Utzinger, J., Raso, G., Brooker, S., De Savigny, D., Tanner, M., Ornbjerg, N., et al., 2009. Schistosomiasis and neglected tropical diseases: towards integrated and sustainable control and a word of caution. Parasitology 136 (13), 1859–1874.
Wang, Z.H., 2006. Chemical treatment of schistosomiasis japonica in China. J. Clin. Intern. Med. 23, 302–304 (in Chinese).
World Health Organization, 2002. Prevention and control of schistosomiasis and soil-transmitted helminthiasis. World Health Organ. Tech. Rep. Ser. 912 (i–vi), 1–57 (back cover).
World Health Organization, 2011. Report of an Informal Consultation on Schistosomiasis Control. Geneva, WHO, Switzerland (30 March–1 April 2011).
World Health Organization, 1983. The Role of Chemotherapy in Schistosomiasis Control. WHO, Geneva (70).
Xiao, S., Tanner, M., N'Goran, E.K., Utzinger, J., Chollet, J., Bergquist, R., et al., 2002. Recent investigations of artemether, a novel agent for the prevention of schistosomiasis japonica, mansoni and haematobia. Acta Trop. 82 (2), 175–181.
Xiao, S.H., 2005. Study on prevention and cure of artemether against schistosomiasis. Chin. J. Schisto Control 17, 310–320 (in Chinese).