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TOPICS EXPLORING LOA-LOA, ONCHOCERCIASIS, HOOKWORM, ASCARIS, TRICHURIS (A SANCHEZ AND R FUJIWARA, SECTION EDITORS)

Update on Treatment and Resistance of Human Trichuriasis

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Abstract *Trichuris trichiura* is a common soil-transmitted helminthic pathogen with considerable impact on human health. To achieve appropriate control of trichuriasis from a public health perspective, effective treatments and regular education of populations most at risk such as children and pregnant women are essential. Currently available drugs show however only unsatisfying cure rates when used in short-course regimens, and egg reduction rates are disappointingly low. An improvement in efficacy of drug therapy has been demonstrated for a prolonged 3-day dosing regimen of albendazole as well as for a combination therapy of albendazole and oxantel pamoate or mebendazole and albendazole. However, even these regimens do not reach the widely accepted threshold for a satisfactory cure rate of at least 90 %. While this lack of efficacy of current anthelminthic drugs may be explained by specific single nucleotide polymorphisms in the β-tubulin gene of *T. trichiura*, these findings highlight the need for further research to develop highly efficacious short-course treatments for human trichuriasis.

Keywords Trichuriasis · Treatment · Albendazole · Mebendazole · Resistance · β-tubulin

This article is part of the Topical Collection on *Topics Exploring Loa-Loa*, *Onchocerciasis*, *Hookworm*, *Ascaris*, *Trichuris*

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Introduction

Trichuris trichiura, or whipworm, is a soil-transmitted helminth (STH)—a group consisting of pathogens including *Ascaris lumbricoides*, *Strongyloides stercoralis*, *Necator americanus* and *Ancylostoma duodenale*. STH occurs almost globally with higher prevalence in developing countries and resource-limited regions in the tropics such as parts of sub-Saharan Africa, East Asia, China, India and South America [1–3]. Infection rates typically peak in school children [4–7] and, to a lesser extent, in pre-school children [7]. Importantly, pregnant women constitute another population with increased prevalence and morbidity [8]. Behavioural factors and lack of infrastructure such as safe and reliable water supply and appropriate sanitation in school and at home are the major risk factors for infection [6, 9]. Thus, school children in highly endemic regions represent the target population for appropriate control measures, such as mass drug administration and mass education. Approximately 800 million people are infected with *T. trichiura* globally [10, 11•], and the number of disability-adjusted life years (DALYs) is estimated to range between 40 and 60 million [12, 13]. However, there is controversy with regard to the global burden of STH as most infections are asymptomatic and therefore often overlooked [9]. Lightly infected populations appear generally healthy and will only be aware of their infection status during a routine check-up for STH. However, in settings characterized by co-infections with other pathogens, nutrient deficiencies or in

cases of chronic and high-burden infections with STH, anaemia may be observed in pregnant women [8, 14, 15], and stunting, physical and cognitive retardation and anaemia in school children [16]. Moreover, STH can cause malabsorption leading to impaired digestion and poor absorption of nutrients by alterations of the mucosa of the gastrointestinal tract [17]. Furthermore, an association between STH infection during pregnancy and poor cognitive and gross motor outcomes [18] as well as poor vaccine immune responses [19] in both unborn infants and school-aged children [20–22] has been reported. Thus, STH is considered as an important public health problem in affected tropical regions.

To address STH infection control, the 24th World Health Assembly passed in 2001 a resolution (WHA. 45.19) [23, 24] affirming that the control of schistosomiasis and soil-transmitted helminthiases should be considered as a public health priority [23] and urging the member states to put in place measures including large-scale use of anthelminthic drugs for school-aged children in less developed countries [24]. In daily practice in resource-limited settings, presumptive treatment is therefore commonly administered systematically to target populations without prior examination of stool samples. Such treatments are usually either albendazole (400 mg) or mebendazole (500 mg) single-dose therapy or 3 days twice daily mebendazole (100 mg). Whereas these regimens have satisfactory efficacy against other STH, cure rates for trichuriasis are notoriously poor and rarely exceed 50 % [25•, 26•, 27, 28•, 29•, 30•]. This review summarizes recently published data advancing our knowledge of anthelminthic drug therapy for human trichuriasis.

Methodology

Medline and Google Scholar were searched for relevant publications of clinical trial data assessing established anthelminthic drugs for human trichuriasis. Publications evaluating potential genetic targets associated with resistance of STH were also identified for this review. Data published between 2010 to mid-2015 are reviewed here.

Results

Clinical Trials of Established Anthelmintics Against *T. trichiura*

The most widely used treatment for *T. trichiura* consists of a single dose of 400 mg of albendazole, despite the fact that this regimen has rarely been systematically evaluated. Albendazole is furthermore currently considered as the drug of choice for repeated mass drug administrations in endemic areas. The choice of albendazole is based on its cost-effectiveness, safety and logistical advantages as a single-dose treatment [25•]. The aim of mass treatment is generally not a complete cure from helminthic infections but rather a significant reduction of worm burden and consecutively egg excretion—potentially leading to a reduction of morbidity and transmission within the community [31]. The target population of such mass treatments remains school children [23, 24, 25•]. For pregnant women, the World Health Organization recommended in 1994 to treat all pregnant women against hookworms due to the concern of hookworm-induced anaemia [32] in highly endemic areas. Besides albendazole, other anthelminthic drugs and drug combinations are also used (e.g. mebendazole or oxantel pamoate) [26•, 33•] or are under evaluation (nitazoxanide) [29•].

Albendazole

Albendazole is a broad-spectrum anthelminthic drug with good efficacy against most soil-transmitted helminths. Chemically, it is a methyl 5-(propylthio)-2-benzimidazolecarbamate ($C_{12}H_{15}N_3O_2S$). Albendazole is used as a single dose (400 mg) in mass drug administration campaigns. Several studies reported its good effectiveness and positive effects in school children such as an increase in haemoglobin levels, improvement of appetite, fitness and cognitive performance [34–36].

In the general population, albendazole is usually well tolerated and the only formal contraindication besides pregnancy is allergy to imidazole derivatives. Some controversy exists in the classification of albendazole for its use during pregnancy. It has been shown to have teratogenic and embryotoxic effects in rats and rabbits. Albendazole must therefore not be administered during the first trimester [10, 37]. Since it is not known whether albendazole has harmful effects on the unborn human child during the second and third trimester of pregnancy, it is considered as a category C substance by the Food and Drug Administration (FDA). The clinical benefit of albendazole in pregnant women must therefore outweigh the potential risks of this drug. However, recent trials in Uganda [37–40], Sri Lanka [41, 42], and Sierra Leone [43, 44] indicate the safety of its use after the second trimester of pregnancy.

Efficacy of albendazole is rather low against *T. trichiura* in comparison to other STH. In clinical trials, cure rates (CR) of single-dose albendazole for *T. trichiura* ranged between 2.6 % [0.0–5.6 %] [26•] and 64.5 % [44.4–84.7 %] [45•], and egg reduction rates (ERR) were between 7 % [−52–78 %] [25•] and 83.1 % [78.5–91.4 %] [28•] (see Table 1). Two doses of albendazole given on two consecutive days resulted in improved CR of 67 % [52–82 %] [25•] and up to 83 % [73–93 %] [25•] when given on three consecutive days. Doubling the dose of albendazole even when administered as a single dose also led to higher CR (43.4 % [32.2–54.6 %]) [46•] compared to the standard dose (15.4 % [8.4–20.6 %]). Thus,

Table 1 Summary of cure rates and egg reduction rate of monotherapies in trichuriasis

Antihelminthic	Regimens	Cure rate in % [95 % CI]	Egg reduction rate in % [95 % CI]
Albendazole	1 dose	40 [26–54] [25•];	7 [−52–78] [25•];
		64.5 [44.4–84.7] [45•];	Not available
		30.8 [23, 24, 25•, 26•, 27, 28•, 29•, 30•, 31, 32, 33•, 34–39] [28•];	83.1 [78.5–91.4] [28•];
		33.8 [22.6–46.6] [47•];	76.7 [62.6–86.1] [47•]
		2.6 [0.0–5.6] [26•];	45.0 [32.0–56.4] [26•]
		15.4 [8.0–22.8] [46•];	54.9[46•][d];
		14.5 [8.4–20.6] [46•]	45.6 [25.9–61.0] [46•]
	2 doses	43.4 [32.2–54.6][a] [46•]	89.3[a] [46•][d]
	2 doses	67 [52–82][b] [25•]	58 [29–100][b] [25•]
	3 doses	83 [73–93][c] [25•];	91 [83–100][c] [25•]
		19.6 [12.0–29.1][c] [30•];	88.8 [80.9–94.7][c] [30•];
		56.2 [41.2–70.5][c] [47•]	94.0 [89.4–96.8][c] [47•]
Mebendazole	1 dose	8.4 [3.1–13.8] [33•];	58.5 [45.2–70.9] [33•];
		63.1 [51.6–74.6] [45•];	not available
		39.7 [27.6–52.8] [47•];	82.5 [71.0–89.6] [47•]
		11.8 [5.7–17.9] [26•];	75.0 [64.2–82.0] [26•];
		20.4 [12.4–28.4] [46•]	66.7 [46•][d]
	2 doses	41.9 [31.9–52.0][a] [46•]	94.3[a] [46•][d]
	3 doses	70.7 [57.3–81.9][c] [47•]	97.3 [94.9–98.8][c] [47•]
Oxantel pamoate	1 dose	26.3 [18.1–34.5] [26•]	93.2 [90.0–95.7] [26•]
Nitazoxanide	1 dose	6.6 [2.4–10.8] [29•]	13.4 [0.0–33.7] [29•]

[a] Drugs were given 8 h apart on the same day

[b] Drugs were given on two consecutive days

[c] Drugs were given on three consecutive days

[d] 95 % confidence intervals are missing in this study for ERR

efficacy of albendazole is dependent on the dose and the length of the regimen. This is supported by the fact that the ERR was lowest when given as a single dose 7 % [−52–78 %] [25•] and highest in a regimen of three consecutive doses (94.0 % [89.4–96.8 %]) [47•].

Mebendazole

Mebendazole is a broad-spectrum anthelmintic drug with satisfactory efficacy against most intestinal nematodes with the exception of *Trichuris* spp. Toxicity is low and the drug is usually very well tolerated. Just as albendazole, it is classified as a pregnancy class C drug by the FDA and it has no other formal contraindication other than allergy to imidazole derivatives. Recommended dosing regimens commonly require 3 days twice daily dosing rendering this drug less attractive for mass treatment campaigns compared to albendazole. A single dose of 500 mg is used as well but less efficacious.

Recent clinical trials confirmed the low efficacy of mebendazole against *Trichuris* spp. A one dose 500 mg therapy showed a CR of 8.4 % [3.1–13.8 %] in one trial [33•] and a relatively high CR of 63.1 % [51.6–74.6 %] in another one [45•]. Highest CR and ERR were achieved in a trial with three doses (cure rate of 70.7 % [57.3–81.9 %] and ERR of 97.3 % [94.9–98.8 %], respectively [47•]) (Table 1).

Other Anthelminthic Drugs Against *T. Trichiura*

Oxantel pamoate and nitazoxanide—currently evaluated for the treatment against *T. trichiura*—have shown only poor CR so far (26.3 % [18.1–34.5 %] [26•] and 6.6 % [2.4–10.8 %], respectively). However, the ERR of oxantel pamoate was satisfactory at 93.2 % [90.0–95.7 %] [26•], compared to that of nitazoxanide at 13.4 % [0.0–33.7 %] [29•].

Trials Evaluating Combination Therapy

Several regimens with a combination of drugs have been assessed over the past years [26•, 29•, 33•, 46•] (Table 2). The combination yielding the highest efficacy for *Trichuris* spp. was albendazole plus oxantel pamoate with a CR of 68.5 % [59.6–77.4 %] [33•] followed by combinations of

Table 2 Summary of cure rates and egg reduction rate of combination therapies in trichuriasis

	Cure rate in %[95 % CI]	Egg reduction rate in %[95 % CI]
Albendazole+ivermectin	27.5 [19.0–36.0][a] [33•]	94.5 [91.7–96.3][a] [33•]
Albendazole+oxantel pamoate	68.5 [59.6–77.4][a] [33•];	99.2 [98.7–99.6][a] [33•];
	31.2 [22.5–40][b] [26•]	96.0 [93.5–97.6][b] [26•]
Albendazole+mebendazole	8.4 [3.1–13.8][a] [33•];	51.6 [35.0–65.3][a] [33•];
	54.2 [43.6–64.8][a] [46•]	94.3[a] [46•][d]
Albendazole+mebendazole/ albendazole+mebendazole	56.5 [46.4–66.7][c] [46•]	95.9[c] [46•][d]
Mebendazole+mebendazole	41.9 [31.9–52.0][c] [46•]	94.3[c][46•][d]
Albendazole+nitazoxanide	16.0 [9.7–22.4][a] [29•]	54.9 [37.7–67.9][a] [29•]

[a] Drugs were given once at the same time

[b] Drugs were given on two consecutive days

[c] Drugs were given 8 h apart on the same day

[d] 95 % confidence intervals are missing in this study for ERR

two albendazole doses of 400 mg plus two mebendazole doses of 500 mg administered 8 h apart, which achieved a CR of 56 % [46.4–66.7 %] [46•], and albendazole plus ivermectin which achieved a CR of 27.5 % [19.0–36.0 %]. The poorest CR was achieved with a combination of albendazole plus nitazoxanide (16.0 % [9.7 %–22.4 %]) [29•] (Table 2). The same trend also applies to ERR, where the highest reduction was seen with albendazole plus oxantel pamoate (99.2 % [98.7–99.6 %]) [33•]. The lowest ERR was observed for a combination of albendazole and mebendazole (51.6 % [35.0–65.3 %]) [33•] (see Table 2). In summary, repeated doses as well as combination therapy yield better efficacy in comparison to a single-dose regimen.

Resistance of *T. trichiura* to Anthelmintic Drugs

Benzimidazole drugs have been widely used against STHs for decades in the treatment of individual patients and in mass drug administration programmes. Selection pressure caused by these drugs raised the question of potentially emerging resistant populations of STHs. Drug resistance may explain the poor cure rates in infection with *T. trichiura* using a benzimidazole therapy alone or in combination with other drugs. Benzimidazole drugs are broad spectrum anthelmintics that bind to tubulin, causing interference with tubulin polymerization and destabilization of microtubules [48]. In veterinary studies, it has been observed that the substitution of a single amino acid (from phenylalanine (Phe, TTC) to tyrosine (Tyr, TAC) in the β-tubulin at position 200 may be associated with benzimidazole resistance) [49]. In cattle trichuriasis, several single nucleotide polymorphisms (SNPs) in the β-tubulin isotype 1 gene of various nematodes correlate with resistance to benzimidazoles [50]. In humans, occurrence of TAC SNP at codon 200 in *T. trichiura* is suspected to be potentially associated with resistance to benzimidazoles [51•]. Hence, these findings may potentially explain the poor cure rates in the treatment of *T. trichiura* infestation using benzimidazole drugs, if further substantiated. However, more data, prospective studies and close monitoring of cure rates and genetic markers of drugs resistance are necessary [11•].

Conclusion

Human *T. trichiura* is highly endemic in tropical regions, and most current therapeutic regimens require either prolonged treatment courses or have unsatisfactory cure rates. These poor outcomes may potentially be explained by the presence of genetic markers including a SNP in the beta-tubulin gene at codon 200 which was reported to be associated with benzimidazole drug resistance. Further clinical research aiming to improve cure rates and shortening treatment regimens is therefore warranted as well as studies adding to our knowledge of genetic markers for clinical drug resistance.

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Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interests.

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