Filaria Journal

BioMed Central

Research

Open Access

Treatment of co-infection with bancroftian filariasis and onchocerciasis: a safety and efficacy study of albendazole with ivermectin compared to treatment of single infection with bancroftian filariasis

William H Makunde*[1], Leo M Kamugisha[2], Julius J Massaga[2], Rachel W Makunde[3], Zakana X Savael[2], Juma Akida[2], Fred M Salum[2] and Mark J Taylor[4]

Address: [1]Bombo Research Field Station, P.O. Box 950, Tanga, Tanzania, [2]Amani Medical Research Centre, P.O. Box 4, Amani, Tanzania, [3]Bombo Regional Hospital, P.O. Box 452, Tanga, Tanzania and [4]Liverpool School of Tropical Medicine, Pembroke Place, Liverpool, L3 5QA, UK

Email: William H Makunde* - hwmakunde@hotmail.com; Leo M Kamugisha - hwmakunde@hotmail.com; Julius J Massaga - hwmakunde@hotmail.com; Rachel W Makunde - hwmakunde@hotmail.com; Zakana X Savael - hwmakunde@hotmail.com; Juma Akida - hwmakunde@hotmail.com; Fred M Salum - ; Mark J Taylor - mark.taylor@liv.ac.uk

* Corresponding author

Published: 06 November 2003

Filaria Journal 2003, **2**:15

Received: 20 December 2002
Accepted: 06 November 2003

This article is available from: http://www.filariajournal.com/content/2/1/15

Abstract

Background: In order to use a combination of ivermectin and albendazole for the elimination of lymphatic filariasis, it is important to assess the potential risk of increased adverse events in individuals infected with both lymphatic filariasis and onchocerciasis. We compared the safety and efficacy of albendazole (400 mg) in combination with ivermectin (150 micrograms/kg), for the treatment of co-infections of *Wuchereria bancrofti* and *Onchocerca volvulus* with single infection of *W. bancrofti*.

Methods: The safety study on co-infections was a crossover, double blind design, while for the single infection of bancroftian filariasis an open design comparing two treatments was used. For co-infection, one group was allocated a single dose of ivermectin (150 micrograms/kg) plus albendazole (400 mg) (Group A). The other group received placebo (Group B). Five days later the treatment regime was reversed, with the Group A receiving placebo and Group B receiving treatment. For the single bancroftian filariasis infection, one group received a single dose of albendazole (400 mg) plus ivermectin (150 μg/kg) (Group C) while the other group received a single dose of albendazole (400 mg) alone (Group D). Blood and skin specimens were collected on admission day, day 0, and on days 2, 3, and 7 to assess drug safety and efficacy. Thereafter, blood and skin specimens were collected during the 12 months follow up for the assessment of drug efficacy. Study individuals were clinically monitored every six hours during the first 48 hours following treatment, and routine clinical examinations were performed during the hospitalisation period and follow-up.

Results: In individuals co-infected with bancroftian filariasis and onchocerciasis, treatment with ivermectin and albendazole was safe and tolerable. Physiological indices showed no differences between groups with co-infection (*W. bancrofti* and *O. volvulus*) or single infection (*W. bancrofti*). The frequency of adverse events in co-infected individuals was 63% (5/8, Group A, albendazole + ivermectin) and 57% (4/7, Group B, placebo) and of mild or moderate intensity. In single *W.*

bancrofti infection the frequency of adverse events was 50% (6/12, Group C, albendazole + ivermectin) and 38% (5/13, Group D, albendazole) and of a similar intensity to those experienced with co-infection. There were no differences in adverse events between treatment groups. There was no significant difference in the reduction of microfilaraemia following treatment with albendazole and ivermectin in groups with single or co-infection.

Conclusion: Our findings suggest that ivermectin plus albendazole is a safe and tolerable treatment for co-infection of bancroftian filariasis and onchocerciasis.

Background

Bancroftian filariasis and onchocerciasis are important causes of clinical disease and progressive disability in the tropics and subtropics, affecting more than 120 and 17.6 million people respectively [1,2]. In Tanzania, more than 10 million people live in areas endemic for bancroftian filariasis, and of these 11.7% are affected by the infection [3]. Eleven foci for onchocerciasis have been established in Tanzania in which it is estimated 2 million people are at risk and of these 400,000 are already infected [4]. Studies conducted in Tanzania showed that bancroftian filariasis is prevalent along the entire coastal belt of the Indian Ocean, its islands, and in the regions around the Great Lake [5]. The clinical manifestations of the disease are hydrocoele, lymphoedema, orchitis, adenolymphangitis and elephantiasis. The acute and chronic pathologies caused by these diseases impose a significant impediment to socio-economic development [6,7].

Chemotherapy is now considered as the most cost-effective tool to potentially interrupt transmission [8]. The most common strategy adopted is mass treatment of populations with either diethylcarbamazine (DEC) or ivermectin. DEC mass distribution has been the main strategy for lymphatic filariasis control programmes for many years in endemic areas based on annual or semi-annual administration [2]. However, DEC is contraindicated in individuals with onchocerciasis because of potentially severe treatment adverse reaction [1]. The severity of such reactions is reduced in ivermectin, which is considered safe and effective against either disease [1]. Recently albendazole has been introduced for use in combined chemotherapy with either ivermectin or DEC as the treatment regime for the global elimination of lymphatic filariasis [8]. Albendazole combined with either ivermectin or DEC has been demonstrated to effectively clear bancroftian microfilaraemia [9]. The new anti-filarial drug combinations are expected to improve compliance, coverage and reduce costs by introducing simple efficient drug delivery and distribution methods.

In Tanzania, albendazole and ivermectin have been adopted as the combination treatment for the community-based control of bancroftian filariasis. In order to determine whether this treatment can be used safely and effectively in areas of co-endemicity with onchocerciasis, we examined the safety, tolerability, and efficacy of albendazole with ivermectin for the treatment of individuals with concurrent infections of bancroftian filariasis and onchocerciasis and single infection of bancroftian filariasis.

Methods

Patients

The Ethics Committee of the National Institute for Medical Research, Tanzania, the Research Ethics Committee of the Liverpool School of Tropical Medicine, UK and the Ethics committee of the World Health Organisation (WHO) approved the study. The clinical trial was conducted from April 1998 to May 1999 in Muheza district, Tanga, northeastern Tanzania, where bancroftian filariasis and onchocerciasis co-exist. Candidates for the trial were selected from rural communities of Maramba "A" and Mhinduro, which is the first time the co-existence of both diseases has been reported in the Western Usambara Mountains. The majority of the inhabitants are Moslems and their main source of income is farming, petty trade and animal husbandry. The villages have not previously been included in control activities against bancroftian filariasis, onchocerciasis or other helminths.

Fifteen males aged between 15 and 55 years with co-infection of bancroftian filariasis and onchocerciasis and 25 (11 male and 14 female [age range 15–55]) for single infection of bancroftian filariasis were recruited (see Trial Profile, Figure 1). Individuals were screened for inclusion into the study by finger-prick blood samples (100 μl) for bancroftian filariasis and by skin snip for onchocerciasis. Clinical evaluation was conducted at Bombo Regional Hospital, Tanga. The inclusion criteria for admission into this study included; apparently healthy individuals aged between 15 and 55 years, able to give oral consent to participate, weighing more than 31 kilograms, have no papular onchodermatitis and itching, with no history of taking herbal medication, anthelminthic or anti-filarial drugs three months prior to recruitment, microfilaria counts of ≥ 100 mf/ml in *Wuchereria bancrofti*, and/or *Onchocerca volvulus* microfilaria counts of ≥ 5 mf/skin snip. Women were excluded from the co-infection group due to the risk of inadvertent pregnancy and the potential effects of

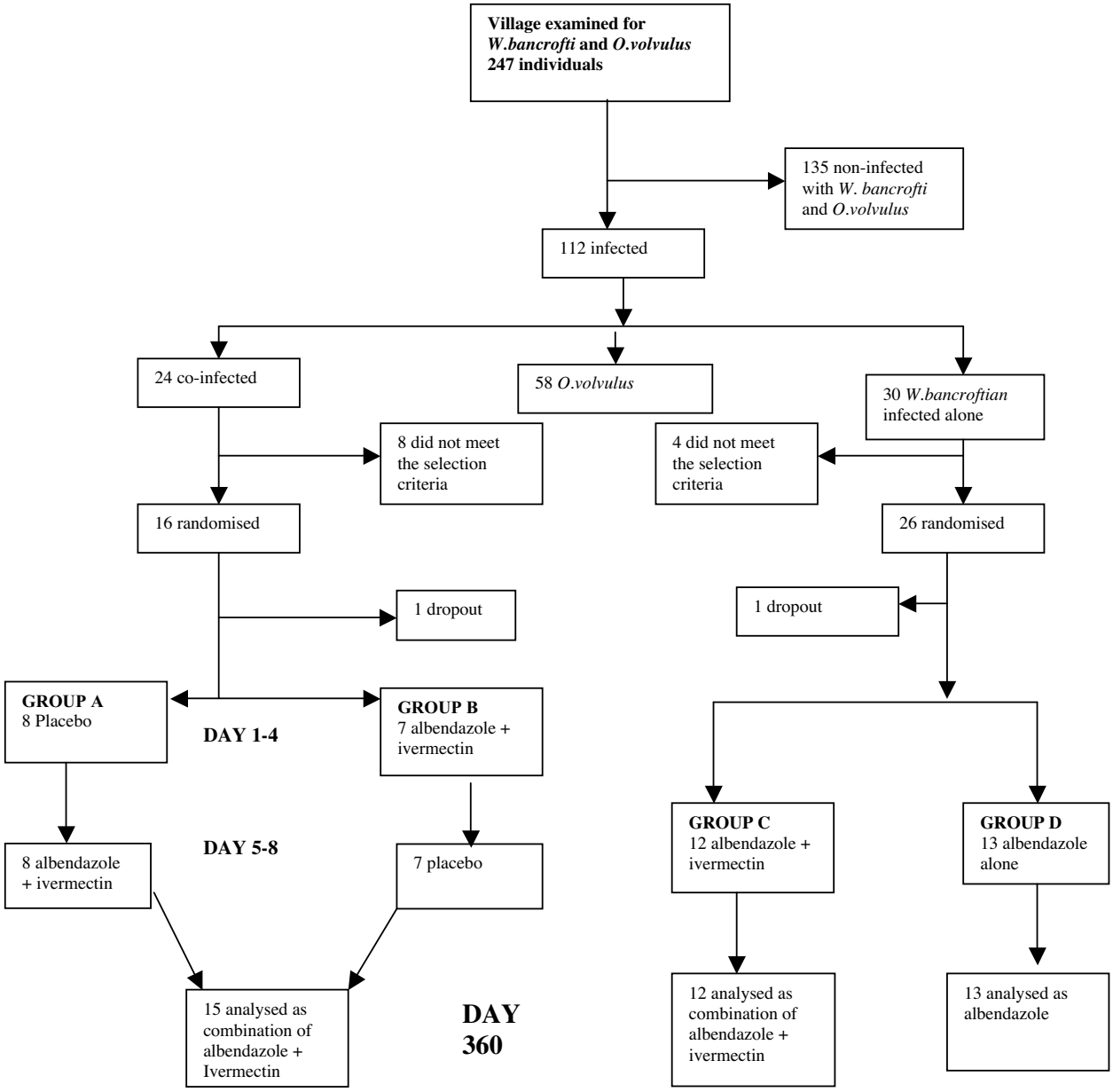

Figure 1
Trial profile for co-infections of *W. bancrofti* and *O. volvulus* and single infection of *W. bancrofti*.

unforeseen adverse events on the foetus. In the single infection of bancroftian filariasis women selected for inclusion were tested for pregnancy.

Clinical examination and laboratory analysis

On admission to the hospital a full medical history was obtained and a physical examination was carried out prior to specimen collection. 7 ml of venous blood was collected into tubes containing ethylenediaminetetraacetic acid (EDTA) as an anti-coagulant between 21:00 and

01:00 h. 1 ml of anti-coagulated blood was thoroughly mixed with 4 ml of normal saline. The suspension was then passed through a membrane filter (3 μm pore; Nuclepore) and the trapped microfilariae (mf) counted. The pre-treatment mf count was calculated in each case by averaging counts of two samples, one-collected three days before admission and the other on day 0 before drug administration at the hospital. The remaining blood specimens were used for biochemical tests to estimate bilirubin, aspartate amino transferase (AST), and creatinine levels and examination of haematological indices, including total leucocyte count, differential white blood cell count and haemoglobin. Skin snips were obtained from the right and left iliac crests using a Walser corneoscleral biopsy punch after disinfecting the site with 70% alcohol. Skin snips were incubated in 0.9% saline overnight. The following day, specimens were microscopically examined for parasite identification and quantification. Blood specimens and skin snips were collected on admission day, Day 0, and on Day 2, 3, and 7 to assess drug safety and efficacy. Thereafter, blood specimens and skin snips were collected during the 12 months follow up for the assessment of drug efficacy. Study individuals were clinically monitored every six hours during the first 48 hours following treatment, and routine clinical examinations were performed during the hospitalisation period and follow-up. Clinical adverse reactions were monitored and assessed by a scoring method. The individuals were assigned scores according to the intensity of adverse reaction, thus a score of 0 = no alteration, no adverse reaction was reported and individuals could perform their usual daily tasks, 1 = mild alteration, mild adverse reaction recorded which individuals are aware of and can easily tolerate and continue with usual daily tasks, 2 = moderate alteration, moderate adverse reaction which can cause discomfort, interfere with usual daily tasks and require rest and/or analgesic before continuing with usual tasks, and 3 = severe alteration, severe reactions which would prevent usual daily tasks and require hospitalisation.

Study protocol

In each sub-study individuals were randomly allocated to one of the treatment regimens. The study on co-infections was a crossover, double blind design, while the study on single infection of *W. bancrofti* was an open comparison of the two treatments (see trial profile Figure 1). For co-infection one group was allocated a single dose of ivermectin (150 μg/kg) plus albendazole (400 mg) (Group A). The other group received 6 saccharine tablets as a placebo (Group B). Five days later the treatment regime was administered in reverse, with the Group A receiving placebo and Group B receiving treatment. For the bancroftian filariasis infection, one group received a single dose of albendazole (400 mg) plus ivermectin (150 μg/kg) (Group C) while the other group received a single dose of albendazole (400 mg) alone (Group D). Trial drugs plus placebo were supplied by WHO/CTD, the Carter Centre (Atlanta, USA) and the Liverpool School of Tropical Medicine (Liverpool, UK).

Statistical analysis

Data analysis was done using Epi-Info version 6.04 C and Stata 6. Geometric mean microfilarial intensity (GMI) were calculated as antilog [(log (x+1)/n]-1 where x was the number of mf/ml counted and n is the total number of individuals. A non-parametric test (Mann-Whitney test) was used for comparing GMI of different study days and severity of adverse reactions. Fisher's exact test was used to compare prevalence of infection. P-values of less than 0.05 were considered to be statistically significance.

Results

Pre-treatment parasitological, physiological, haematological and clinical data

Co-infections of W. bancrofti *and* O. volvulus

The pre-treatment microfilaria counts ranged from 108–2232 mf/ml in *W. bancrofti*, and from 5–206 microfilariae/skin snip in *O. volvulus*. The geometric mean microfilarial intensity (GMI) for *W. bancrofti*, was 378.4 mf/ml in Group A, and 465.2 mf/ml in Group B. The microfilarial GMI for *O. volvulus* was 49.1 and 12.9 microfilariae/skin snips in Groups A and B respectively. There was no significant difference in terms of mf GMIs in *W. bancrofti* in the two treatment regimens (P = 0.7). However, the geometric mean microfilarial intensity between the two treatment groups was statistically significant in *O. volvulus* (P = 0.02). The physiological and haematological indices showed no changes for each individual, during the pre-treatment period or at Day 2/3 or Day 7 in both co-infected and single infections. Clinically, there was no significant variation in blood pressure, both systolic and diastolic between the treatment groups (data not shown).

Single infection of W. bancrofti

In the single infection the geometric mean microfilarial intensity in the two-treatment regimens was 508 mf/ml for each treatment group. There was no significant difference in geometric mean microfilarial intensity in the two treatments (P = 0.9).

Post-treatment safety evaluation

Post-treatment levels of the physiological tests and haematological indices in the single and co-infections between the two treatment regimens, placebo, albendazole alone and the combination of albendazole with ivermectin showed no change compared to pre-treatment levels. Likewise, the other parameters assessed, blood pressure, heart rate and body weight also showed no change. The mean level of AST in the co-infections of *W. bancrofti* and *O. volvulus* observed were 18.1 and 27 IU in

Table 1: Post drug administration adverse events experienced by individuals with co-infections of *W. bancrofti* and *O. volvulus*.

Clinical signs / symptoms	(score) Peak intensity*	Group A† (Albendazole + Ivermectin, n = 8) (no. of individuals with symptoms)	Group B† (Placebo, n = 7) (no. of individuals with symptoms)
Fever	1.0	3	0
Adenitis	2.0	1	0
Oedema	2.0	0	1
Palpitations	1.0	0	3
Pruritis	1.0	1	0
Headache	NA	0	0
Dizziness	NA	0	0
Itching	NA	0	0
Chills	NA	0	0
Lethargy	NA	0	0

Table 2: Post-drug administration adverse events experienced by individuals with single infection of *W. bancrofti*

Clinical / Symptoms	(Score) Peak intensity*	Group C (Albendazole + Ivermectin, n = 12) (no. of individuals with symptom)	Group D (Albendazole, n = 13) (no. individuals with symptom)
Fever	1.0	2	0
Itching	1.0	3	0
Palpitation	1.0	1	0
Headache	1.0	0	1
Dizziness	2.0	0	2
Adenitis	2.0	0	1
Oedema	2.0	0	1
Chills	NA	0	0
Lethargy	NA	0	0
Myalgia	NA	0	0
Anorexia	NA	0	0

Scores 0 = no alteration 1 = mild alteration, individual could conduct normal activities without symptom relief. 2 = moderate alteration, individual could proceed with normal daily activity after taking analgesic to alleviate events 3 = severe alteration, individual need be admitted hospital and treated for symptoms. *Mean of highest reaction score for each individual with this sign/symptom. 0, indicates normal, 1 indicates mild; 2 moderate; 3 severe, while fever: 0, indicates 37.0°C – 37.4°C, 1, indicates 37.5°C–37.7°C, 2 indicates 37.8°C–38.8°C, 3 indicates >38.8°C † Group A initially received a single dose of ivermectin (150 μg/kg) plus albendazole (400 mg). Group B received 6 saccharine tablets as a placebo. Five days later the treatment regime was administered in reverse, with the Group A receiving placebo and Group B receiving treatment.

Groups A and B respectively. There was no significant difference in the mean AST levels between Groups A and B (P = 0.07). The mean AST levels for single infection of bancroftian filariasis were 21.9 IU and 23.6 IU for albendazole alone and the combination respectively (P = 0.6).

Adverse Reactions

The adverse reactions occurred at 24 and 48 hours and on day 6 post-drug administration and were generally mild and well tolerated (Tables 1 and 2). These effects lasted for approximately 48 hours. Localised pruritis was observed in the co-infection of bancroftian filariasis plus onchocerciasis. Adverse reactions such as headache, dizziness and itching were reported in individuals with single infection of bancroftian filariasis. In the co-infections 9 out of 15 individuals who experienced adverse reaction, 5 had received albendazole plus ivermectin whereas 4 received placebo.

Three individuals in Group A experienced fever, while in Group B, 3 reported palpitations and one presented oedema on the right thigh. On day six post-treatment one individual from the albendazole and ivermectin group developed painful swelling on the right inguinal gland, which resolved by the third week post-treatment. In the single infection of bancroftian filariasis, 11 out of 25 individuals reported adverse reactions, of which 5 had received albendazole alone, while 6 had albendazole plus ivermectin. In the albendazole plus ivermectin group, two individuals experienced fever and 3 reported generalised

itching and 1 had palpitations. Of those who received albendazole alone, one individual reported frontal headache, 2 dizziness, 1 adenitis and another 1 oedema of the right arm. Adverse reaction intensity mean score for the single regimen of albendazole alone and the combination of albendazole plus ivermectin in both co-infected and single infection was 1 (mild).

Treatment efficacy

Co-infections of W. bancrofti *and* O. volvulus

The treatment of co-infection with albendazole and ivermectin resulted in a rapid reduction of microfilarial intensity over the first week. For *O. volvulus* and *W. bancrofti* this reduction was sustained throughout the 12 months of the follow up period (Figure 2 & Figure 2b). Microfilarial prevalence of *O. volvulus* and *W. bancrofti* was reduced to 13 and 6% respectively at 14 days post treatment but increased throughout the rest of the follow up ranging from 33–53% for *O. volvulus* and 40–67% for *W. bancrofti* (Figure 2c).

Single infection

Treatment of single *W. bancrofti* infection with albendazole resulted in a sustained reduction of microfilarial intensity throughout the follow up period (Figure 3a). The addition of ivermectin significantly improved efficacy at the time points sampled ($P < 0.05$ for all time points). The prevalence of microfilaraemia showed a dramatic difference between treatment with albendazole and albendazole plus ivermectin. Treatment with albendazole alone resulted in a 15–38% reduction in prevalence, compared to reductions of 73–100% in combined treatments (Figure 3b).

There was no significant difference between single and co-infected individuals in the GMI of *W. bancrofti* during albendazole and ivermectin treatment.

Discussion

This is the first hospital-based trial of a combination of ivermectin and albendazole for the treatment of co-infection of bancroftian filariasis and onchocerciasis. We found that 400 mg of albendazole plus 150 μg/kg of ivermectin were safe and tolerable in individuals co-infected with *W. bancrofti* and *O. volvulus* infections. Due to the relatively low numbers of individuals with co-infection in this endemic area, only a small number of patients could be recruited to the study. Monitoring of haematological indices and physiological functions for liver, heart, muscle, kidney and blood showed no alteration as a result of any treatment regimen. There was no significant variation in AST levels during pre-and post-treatment for both co-infected and single *W. bancrofti* infected individuals in both treatment regimens. The absence of clinical response to treatment may be associated with the lower dosages administered in the current trial as compared to previous studies where higher doses were used, leading to transient elevation of the enzymes and increased frequency and intensity of adverse reaction [10].

Adverse reactions to treatment in patients with co-infection were equivalent to those experienced in individuals with single infection and were categorised as mild. The low frequency and intensity of adverse reactions observed in the study individuals probably reflects the low intensity of infections. Quantitatively it has been shown that the intensity of these adverse reactions is proportional to the pre-treatment microfilarial density [9] and is associated with the release of *Wolbachia* endosymbionts into the blood [11,12]. These results are consistent with the conclusions from a multi-study analysis of the safety of two drug regimens for the treatment of lymphatic filariasis [13] and onchocerciasis [14].

In co-infected individuals albendazole and ivermectin treatment produced a reduction in microfilarial levels over the first week of treatment for both *O. volvulus* and *W. bancrofti*. Thereafter microfilarial levels were sustained at a low level throughout the follow-up period. Prevalence of infection ranged from 33–53% for *O. volvulus* and 40–67% for *W. bancrofti* from 30–360 days after drug administration.

In individuals with a single infection of bancroftian filariasis a similar trend was seen, with a rapid clearance within a week in the albendazole and ivermectin group. Treatment with albendazole and ivermectin was significantly better than treatment with albendazole alone. Reduction in the prevalence of detectable microfilaraemia was observed to be greater in the combination of ivermectin and albendazole (~70–80%) compared to albendazole alone (~20–40%).

Previous studies have shown that 3–6 months post-treatment with ivermectin, when doses of 150 μg/kg or lower are given, mf do gradually return to pre-treatment levels. This is probably due to the lack of adulticidal activity and the transient effect of the drug on embryogenesis [14]. Albendazole alone can have some marginal adulticidal activity and is moderately microfilaricidal, particularly at high doses [10]. However, it is the effectiveness of these drugs in combination, which has led to their use in community-based control strategies [9].

The dosage tested in this trial has been adopted for the community-based treatment of *W. bancrofti* in Tanzania. It has been observed in a study in Ghana using a similar dose, that in single bancroftian infections combinations of ivermectin and albendazole show no significant improvement on ivermectin alone, with albendazole on

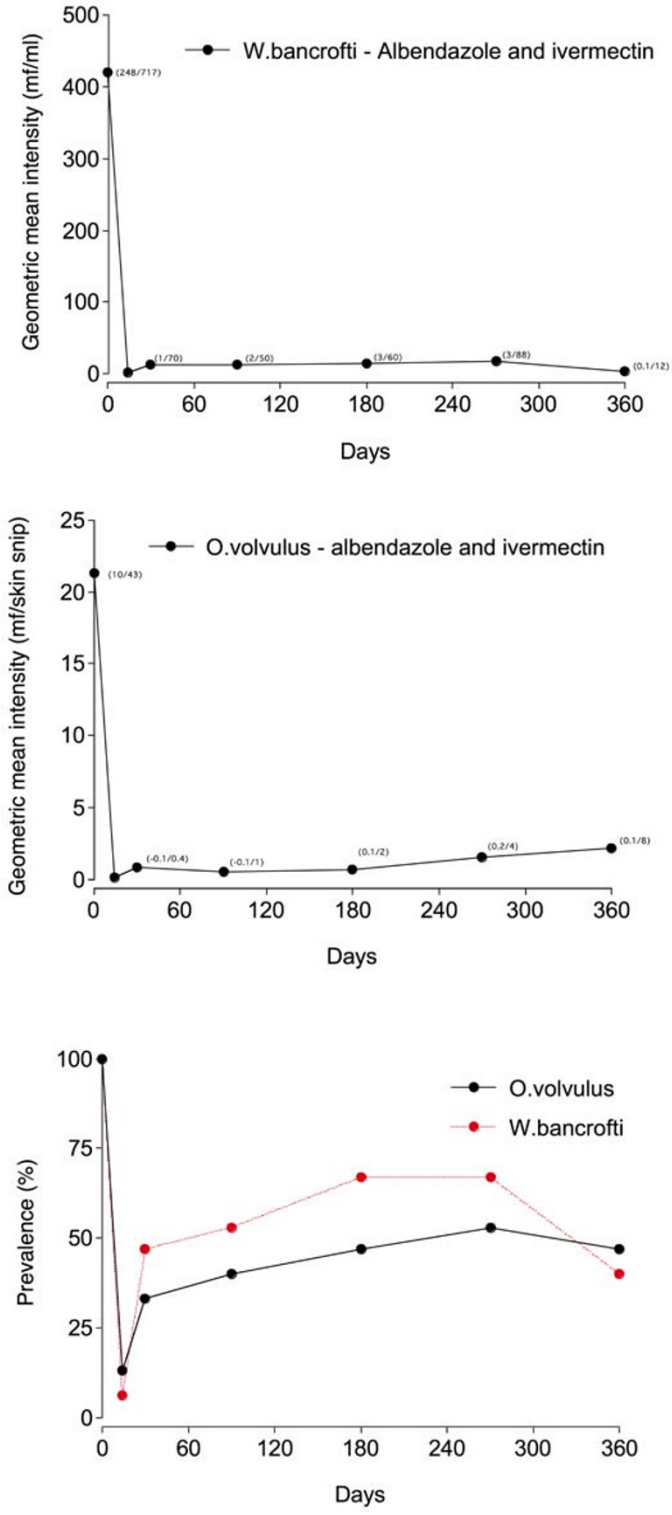

Figure 2
Co-infected individuals treated with albendazole and ivermectin. **a** – Geometric mean intensity (95% confidence intervals) of *W. bancrofti* microfilariae in co-infected individuals treated with albendazole and ivermectin. **b** – Geometric mean intensity (95% confidence intervals) of *O. volvulus* microfilariae in co-infected individuals treated with albendazole and ivermectin. **c** – Microfilarial prevalence (%) in co-infected individuals treated with albendazole and ivermectin.

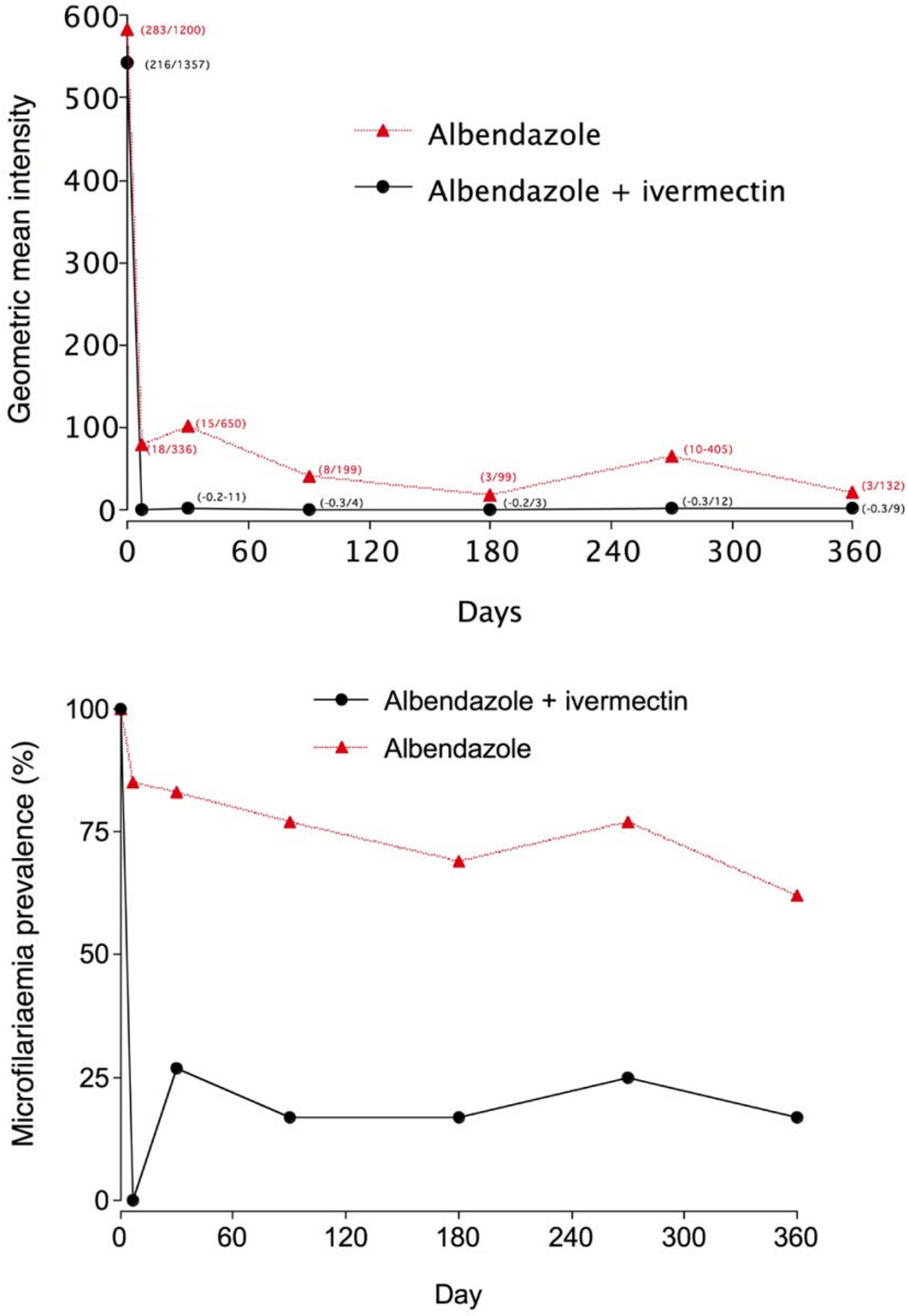

Figure 3
Single infections treated with albendzole or ivermectin. **a** – Geometric mean intensity (95% confidence intervals) of *W. bancrofti* microfilariae in single infections treated with albendazole or albendazole and ivermectin. **b** – Prevalence of microfilariaemia (%) in single infections of *W. bancrofti* treated with albendazole or albendazole and ivermectin.

its own showing only minor effects [15]. In another study in Haiti, combination of albendazole and ivermectin was more effective than treatment with ivermectin only [16]. Our study shows that albendazole and ivermectin is more effective than albendazole alone in the reduction of microfilarial intensity and prevalence. As the interruption of transmission is fundamental to the success of community-based treatments, this emphasises the need for sustained treatments with high community coverage if transmission is to be interrupted.

In Tanzania, the use of combinations of albendazole and ivermectin has been adopted as the strategy for the community-based elimination of lymphatic filariasis as a public health problem. The current study suggests that this combination is safe to be used in areas of co-endemicity with onchocerciasis.

Conclusions

In areas of co-infection of bancroftian filariasis and onchocerciasis, which in Tanzania includes approximately half a million people infected with *O. volvulus*, the use of albendazole (400 mg) and ivermectin (150 μg/kg) appears to be safe and tolerable. Since only a relatively small number of patients could be recruited to this study due to the low prevalence of co-infection, these results should be considered as preliminary and additional studies on individuals with co-infection in other endemic areas should be carried out.

Competing interests

None declared.

Authors' contributions

WHM – Data collection, analysis and manuscript preparation.

LMK & FMS – Data analysis

RWM – Clinical evaluation and monitoring of adverse reactions

JJM – Randomization and treatment allocation

SZX & JA – Parasitological & biochemical examination

MT – PhD supervisor, interpretation of data and manuscript preparation

Acknowledgements

We thank all the Bombo Regional Hospital staff that in one way or another made the clinical assessment of this trial possible. We also acknowledge the assistance given by Mr. Charles Guzo, Ms. Zaina Ali, and Mrs. Bibiana Reuben during the implementation of the trial. We are also grateful to Dr. Alphage Liwa, the former Medical officer in-charge, Bombo Regional Hospital, for providing space for the study and also the villagers of Maramba who participated in this trial. Drs. L.E.G. Mboera, Helen F. McGarry and Professor Chris Curtis are thanked for their useful comments on the earlier version of the manuscript and Dr. Sabine Kläger for statistical advice. Prof. David Molyneux, Dr. Eric Ottesen and Dr. Stefanie Merideth for supplying some of the trial drugs. The study received financial support from the UNDP/World Bank/WHO/ Special Programme for Research & Training in Tropical Diseases (TDR). MJT is a Senior Wellcome Research Fellow in Basic Biomedical Science.

References

1. Kale OO: **Onchocerciasis: the burden of disease.** *Ann Trop Med Parasitol* **92:**S101-S115.
2. WHO: **Global programme to eliminate lymphatic filariasis.** *WHO/CDS/CPE/CEE/2002.28* 2002 [http://www.filariasis.org].
3. Michael E, Bundy DAP, Grenfell BT: **Re-assessing the global prevalence and distribution of lymphatic filariasis.** *Parasitology* 1996, **112:**409-428.
4. Maegga BTA: **Onchocerciasis.** In: *Health and Disease in Tanzania* Edited by: *Mwaluko GMR, Kilama WL, Mandara MP, Murru M and Macpherson CNL. London, Harper Collins Academic Press*; 1991:159-176.
5. McMahon JE, Magayuka SA, Kolstrup N, Mosha FW, Bushrod FM, Abaru DE, Bryan JH: **Studies on the transmission and prevalence of Bancroftian filariasis in four coastal villages of Tanzania.** *Ann Trop Med Parasitol* 1981, **75:**415-431.
6. Evans BD, Gelband H, Vlassoff C: **Social and economical factors and the control of lymphatic filariasis a review.** *Acta Trop* 1993, **53:**1-26.
7. Workneh W, Fletcher M, Olwit G: **Onchocerciasis in field workers at Bay farm, Teppi coffee plantation project, south-western Ethiopia: prevalence and impact on productivity.** *Acta Trop* 1993, **54:**89-97.
8. Ottesen EA, Duke BOL, Karam M, Behbehani K: **Strategies and tools for the control/elimination of lymphatic filariasis.** *Bull World Health Organ* 1997, **75:**491-503.
9. Ottesen EA, Ismail MM, Horton J: **The role of albendazole in programmes to eliminate lymphatic filariasis.** *Parasitol Today* 1999, **15:**382-386.
10. Ismail MM, Jayakody RL, Weil GJ, Nirmalan N, Jayasinghe KSA, Abeyewickrema W, Rezvi Sheriff MH, Rajaratnam HN, Amarasekara N, DeSilva DCL, Michalski ML, Dissanaike AL: **Efficacy of single dose combination of albendazole, ivermectin and diethylcarbamazine for the treatment of bancroftian filariasis.** *Trans R Soc Trop Med Hyg* 1998, **92:**94-97.
11. Keiser PB, Reynolds SM, Awadzi K, Ottesen EA, Taylor MJ, Nutman TB: **Bacterial endosymbionts of *Onchocerca volvulus* in the pathogenesis of posttreatment reactions.** *J Infect Dis* 2002, **185:**805-811.
12. Cross HF, Haarbrink M, Egerton G, Yazdanbakhsh M, Taylor MJ: **Severe reactions to filarial chemotherapy and release of *Wolbachia* endosymbionts into blood.** *Lancet* 2001, **358:**1873-1875.
13. Horton J, Witt C, Ottesen EA, Lazdins JK, Addiss DG, Awadzi K, Beach MJ, Belizario VY, Dunyo SK, Espinel M, Gyapong JO, Hossain M, Ismail MM, Jayakody RL, Lammie PJ, Makunde W, Lenoble-Richard D, Selve B, Shenoy RK, Simonsen PE, Wamae CN, Weerasooriya MV: **An analysis of the safety of the single dose, two drug regimens used in programmes to eliminate lymphatic filariasis.** *Parasitology* 2000, **121:**S147-S160.
14. Awadzi K, Edwards G, Duke BO, Opoku NO, Attah SK, Addy ET, Ardrey AE, Quartey BT: **The co-administration of ivermectin and albendazole – safety, pharmacokinetics and efficacy against *Onchocerca volvulus*.** *Ann Trop Med Parasitol* 2003, **97:**165-78.
15. Dunyo SK, Nkrumah FK, Simonsen PE: **Single-dose treatment of *Wuchereria bancrofti* infections with ivermectin and albendazole alone or in combination: evaluation of the potential for control at 12 months after treatment.** *Trans R Soc Trop Med Hyg* 2000, **94:**437-443.
16. Addiss DG, Beach MJ, Streit TG, Lutwick S, LeConte FH, Lafontant JG, Hightower AW, Lammie PJ: **Randomised placebo-controlled comparison of ivermectin and albendazole alone and in combination for *Wuchereria bancrofti* microfilaraemia in Haitian children.** *Lancet* 1997, **16:**480-484.