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CLINICAL CHARACTERISTICS OF POST-TREATMENT REACTIONS TO IVERMECTIN/ALBENDAZOLE FOR *WUCHERERIA BANCROFTI* IN A REGION CO-ENDEMIC FOR *MANSONELLA PERSTANS*

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Abstract. Post-treatment reactions to single-dose ivermectin (200 μg/kg) and albendazole (400 mg) were studied in a filarial endemic region of Mali. The prevalence of *Wuchereria bancrofti* in this region was 48.3% (69 of 143), and coinfection with *Mansonella perstans* was common (30 of 40, 75%). Microfilarial levels of *M. perstans* correlated positively with age ($P = 0.006$) and with *W. bancrofti* microfilarial levels ($P = 0.006$). Forty individuals (28 infected and 12 uninfected) were treated, with mild post-treatment reactions occurring in 35.7% (7 of 28) of the *W. bancrofti*-infected subjects. Reaction severity correlated with pretreatment *W. bancrofti* microfilarial levels ($P = 0.001$). There were no significant differences in the prevalence or severity of post-treatment reactions in those who were co-infected with *M. perstans*. It is concluded that co-infection with *M. perstans* does not significantly alter the post-treatment reaction profile to single-dose ivermectin/albendazole in *W. bancrofti* infection in this community, and that acute post-treatment reactions should not limit patient compliance in community-based programs to eliminate lymphatic filariasis.

INTRODUCTION

Treatment of lymphatic filariasis with anthelmintic drugs is often associated with post-treatment reactions characterized by fever, headache, lethargy, muscle aches, weakness, and, less commonly, pulmonary or gastrointestinal symptoms.[1] These clinical reactions have been studied prospectively in a number of clinical trials. Initial studies examined the effects of diethylcarbamazine (DEC).[2,3] Although DEC is known to produce severe post-treatment reactions in the treatment of onchocerciasis,[4] including life-threatening allergic type reactions and exacerbations of skin and ocular pathology, treatment of lymphatic filariasis has been relatively well tolerated. Since ivermectin was shown to be microfilaricidal in lymphatic filariasis, comparative studies (versus DEC) of post-treatment reactions have shown it to be similarly well tolerated.[5,6] With the discovery that the addition of albendazole may prolong the duration of amicrofilaremia after a single dose,[7] comparative studies again showed a similarly low incidence of moderate or severe post-treatment reactions.[8,9] Annual ivermectin/albendazole has therefore been chosen as the regimen for population-wide distribution in Africa in hopes of eliminating lymphatic filariasis as a public health problem.[10] However, to date, none of these studies have commented on post-treatment reactions in patients co-infected with *Mansonella perstans*.

Although some activity of ivermectin[11,12] and albendazole[13,14] against *M. perstans* has been described, the effects appear to be partial and gradual, with no specific post-treatment reactions having been reported. Closely observing post-treatment reactions in lymphatic filariasis in an area endemic for *Mansonella* is therefore of some scientific interest. If post-treatment reactions result from a drug-induced breakdown of host evasion mechanisms in the parasite, such as the secretion of protease inhibitors or human cytokine homologs,[15] one might predict these reactions would be attenuated in the presence of another filarial species whose ability to modulate the host immune system remains unaltered. Conversely, if post-treatment reactions in lymphatic filariasis result primarily from the release of pro-inflammatory products, such as lipopolysaccharide from endosymbiotic bacteria,[16] the presence of a second bystander filarial parasite would not have an obvious effect on the post-treatment reaction profile. A third possibility is that *M. perstans*, though not as responsive to drug treatment as *Wuchereria bancrofti*, may nevertheless release pro-inflammatory products upon exposure to drug, contributing to an increased post-treatment reaction.

We undertook a study of post-treatment reactions in Sabougou in the Koulikoro District of Mali. Reported here are the results of the clinical evaluation during the five days following treatment with single-dose ivermectin plus albendazole.

METHODS

Study site. The village of Sabougou in the Kolokani District of Mali has a population of 1,757 according to an unpublished census performed by the Malaria Research and Training Center of the University of Mali in May 2002. The village is located outside the coverage area for the Onchocerciasis Control Program. Few, if any, of the inhabitants have previously received anti-filarial chemotherapy. The study design and consent procedures were reviewed and approved by the Institutional Review Board of the National Institutes of Health and by the Institutional Ethics Committee of the University of Mali School of Medicine, Pharmacy, and Dentistry.

Pre-treatment assessment. Healthy individuals between the ages of 18 and 65 who were not pregnant or breast-feeding were eligible for the treatment portion of the study. One hundred fifty individuals were screened with a questionnaire regarding symptoms of lymphatic filariasis and the types of symptoms commonly associated with post-treatment reactions (Figure 1). An immunochromatographic card test (ICT) for circulating filarial antigen (CFA) (Binax, Portland, ME) using whole blood was performed; each was read at exactly 10 minutes according to the manufacturer's instructions.[17] Screening also included a urine pregnancy test (Foremost Pregnancy One-Step; Biotron Diagnostics, Hemet, CA) and

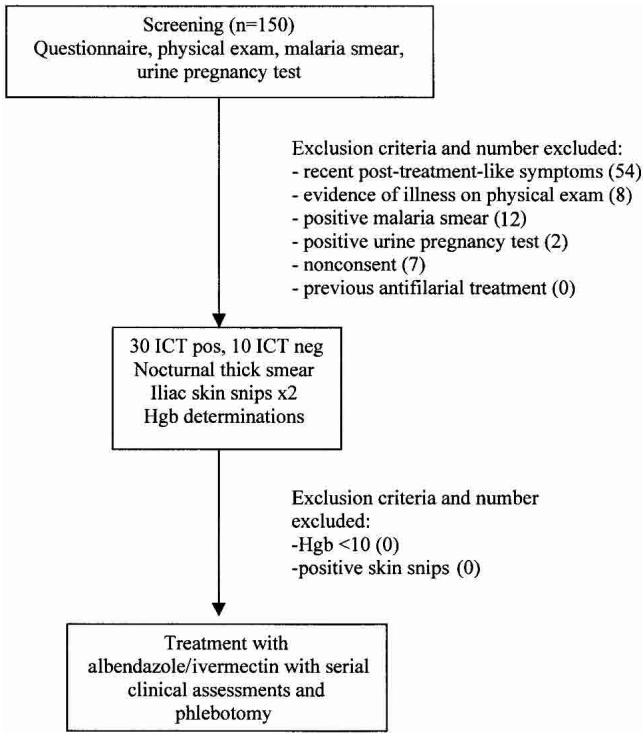

FIGURE 1. Schematic overview of the study. ICT = immunochromatographic card test; pos = positive; neg = negative; Hgb = hemoglobin.

thick blood smears for malaria. Forty subjects (30 card test positive and 10 negative) were selected to be treated using the following selection criteria: no symptoms in the preceding three days that might be consistent with post-treatment reactions, negative malaria smear, and negative pregnancy test result. Antigen testing on the same serum samples was later performed using an enzyme-linked immunosorbent assay (ELISA) kit (TropBio Pty. Ltd., Townsville, Queensland, Australia) performed according to manufacturer's instructions both to confirm the ICT card test results and to quantitate the level of CFA.

Calibrated nocturnal thick smears were made prior to treatment on all 40 subjects between 9:00 PM and midnight. Twenty microliters of finger stick blood was spread on each of three slides. Slides were defibrinated and air-dried. Subsequent staining with unmodified Giemsa enabled the quantification of microfilariae in 60 μL of blood, providing a lower limit of detection of 17 microfilaria (mf)/mL. Skin snips for microscopy and a polymerase chain reaction (PCR) for *Onchocerca volvulus* were preformed, and hemoglobin concentrations were obtained prior to treatment.

Treatment and post-treatment assessments. Individuals were administered ivermectin (200 μg/kg) and albendazole (400 mg). Serial clinical assessments and phlebotomy were performed at 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, and 120 hours post-treatment. Clinical assessments were made by clinicians fluent in the local language (Bambara) who were unaware of the infection status of the volunteers. A scorecard was used to quantify reactions based on measurements of temperature and blood pressure and responses to a questionnaire that specifically asked about rash, fatigue, diarrhea, changes in appetite, vomiting, scrotal pain, headache, myalgias, cough, and dyspnea. Scoring was based on a modification of a World Health Organization system for which a mild adverse event is assigned a value of 1, a moderate event a 2, a severe event a 3, a life-threatening or disabling event a 4. Scores for individual patients were then calculated by adding up all the scores assigned for all parameters over all time points. A follow-up clinical assessment, phlebotomy, and nocturnal thick smears were performed on 37 of the study subjects at eight months post-treatment.

Active survey of lymphatic pathology. In addition, we also sought to identify individuals with evidence of lymphatic pathology in the village. Local health care providers arranged for those with suspected lymphedema or hydrocele to be evaluated by our team on the last day of our stay there.

Statistical analyses. The Mann-Whitney U test was used for unpaired comparisons and the Spearman rank correlation was used to examine the relationship between two parameters. Response rates were assessed by Fisher's exact test. Microfilarial counts and circulating filarial antigen levels pre- and post-treatment were compared using the Wilcoxon signed rank test.

RESULTS

Of the 150 individuals who were enrolled in the screening portion of the study, 143 completed the questionnaire. More than one third of the population surveyed (54 individuals) had experienced one or more symptoms that have been associated with post-treatment reactions in the preceding three days, the most common being gastrointestinal symptoms in 31 and headache in 26.

Sera were available for 143 of the participants. The overall prevalence of filarial antigen positivity was 48.3% (69 of 143). There was a trend towards a higher prevalence of infection in men (52.9% [37 of 70] versus 43.8% [32 of 73] of the women), but this was not statistically significant. The geometric mean (GM) age was 38.0 years (range = 20–60) for the antigen-positive group and 36.6 years (range = 18–62) for the antigen-negative group (P = not significant). Malaria trophozoites were seen on thick blood films from seven of 69 of the antigen-positive individuals and five of 74 of the antigen-negative individuals (P = not significant).

Immunochromatographic card testing of this population for filarial antigen showed 70 antigen-positive and 69 antigen-negative reactions, with four indeterminate colorimetric reactions. Compared with the ELISA (which subsequently showed 69 positive results and 74 negative results), the card test showed a false-positive rate of 24.3% (18 of 74) and a false-negative rate of 23.2% (16 of 69).

According to our study design, 40 individuals were selected for treatment, 30 patients who were card test positive and 10 card test-negative controls. Subsequent antigen testing revealed that 28 of these subjects were antigen positive and 12 were antigen negative (Figure 1). None of these individuals had clinical signs of filarial infection. None had hemoglobin levels < 10 g/dL or microfilariae of *O. volvulus* seen on skin snips (or subsequent PCR[18]), and all consented to the treatment portion of the study.

Of 28 *Wuchereria*-infected individuals, 23 were found to be microfilaremic with *M. perstans* on nocturnal thick smears, compared with seven of 12 who were not infected with

Wuchereria. Microfilarial counts ranged from 0 to 1,467 mf/mL for *W. bancrofti* and from 0 to 7,433 mf/mL for *M. perstans*. Microfilarial counts for *M. perstans* were positively correlated with age ($P = 0.006$, $\rho = 0.437$), while those for *W. bancrofti* were not ($P = 0.16$). There was a significant positive correlation for microfilarial levels between the two species, ($P = 0.006$, $\rho = 0.445$). Of the 15 patients who were microfilaremic with *W. bancrofti*, 14 were also microfilaremic with *M. perstans*.

Post-treatment symptoms were reported by one of the 12 antigen-negative individuals (headache 36 hours after treatment) and 10 of 28 *Wuchereria*-infected individuals. These are shown in Figures 2 and 3. No patient developed hemodynamic instability or any reaction more than grade 1 in severity. The time course of symptom onset was similar to that reported previously,[1] with few symptoms occurring in the first 12 hours and maximum reactions occurring at 24 hours post-treatment.

Symptoms associated with post-treatment reactions were significantly more common in subjects who were microfilaremic with *W. bancrofti* (7 of 15) compared with those who were CFA negative (1 of 12) ($P = 0.043$). Post-treatment reaction scores correlated positively with *W. bancrofti* microfilarial counts ($P = 0.001$, $\rho = 0.51$). There was no significant difference in the incidence of reactions between those infected with *W. bancrofti* alone (2 of 5) compared with those infected with both filarial species (8 of 23) (P = not significant) (Table 1), although the group with dual infection also had higher numbers of circulating *W. bancrofti* microfilariae. If we limited the analysis to those individuals who had a circulating *W. bancrofti* microfilarial counts < 100/mL, the incidence of reactions becomes two of 14 in the dually infected group compared with two of five in those with only with *W. bancrofti* ($P = 0.27$).

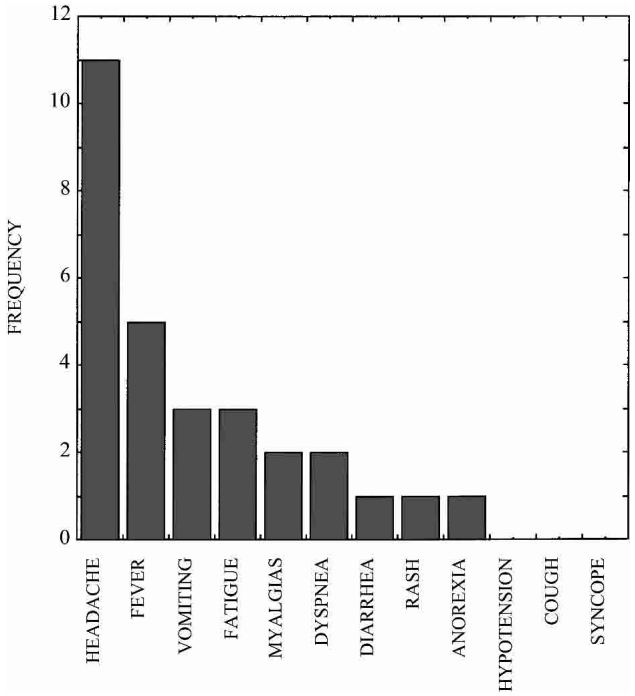

FIGURE 2. Signs and symptoms during the five days following treatment with ivermectin/albendazole in individuals who were positive for circulating filarial antigen.

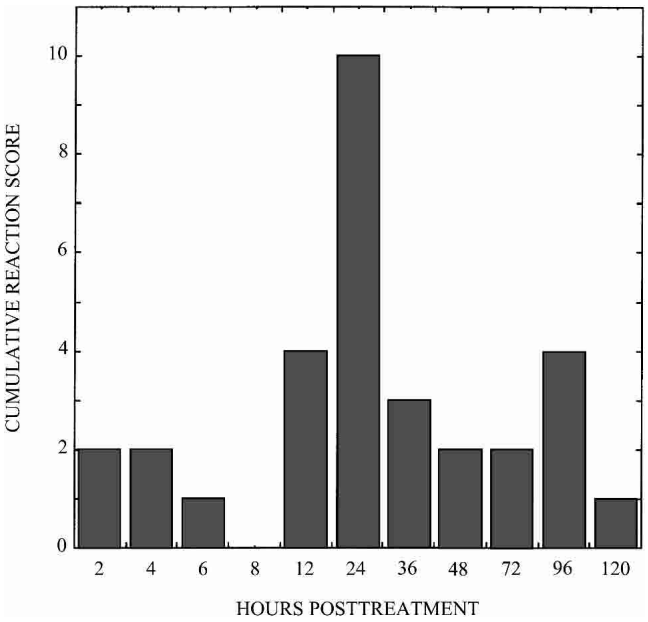

FIGURE 3. Time course of symptom development in infected patients following treatment with ivermectin/albendazole. Bar height reflects the sum of all reactions in all participants at each time point.

Circulating filarial antigen levels eight months post-treatment were significantly lower than those pre-treatment (a GM 39% decrease among those who were antigen-positive pre-treatment, n = 26; $P = 0.010$). Nocturnal thick smears performed eight months after treatment showed a significant decrease in *W. bancrofti* microfilarial counts (a GM 97.5% decrease among those who were microfilaremic pre-treatment n = 15; $P = 0.002$). *Mansonella perstans* counts did not change significantly among those who were microfilaremic for that species before treatment (n = 29; $P = 0.58$).

Local health care providers identified three individuals with mild lymphedema (one unilateral and two bilateral), one elderly man with unilateral lymphedema with early elephantoid changes, and three men with hydrocele among a population of more than 1,700. Each of these individuals was ambulatory and working.

DISCUSSION

Overall, 35.7% (10 of 28) of the *Wuchereria*-infected individuals and 47% (7 of 15) of those who were microfilaremic with *W. bancrofti* experienced a post-treatment reaction. This appears to be significantly less than the prevalence of post-treatment reactions reported in Haiti,[19] French Polynesia,[20]

TABLE 1
Mean reaction scores based on infection status of *Wuchereria bancrofti* (Wb) and *Mansonella perstans* (Mp)*

Infecting species	Wb+Mp+	Wb+Mp−
Number of patients	23	5
GM Wb mf count (range)	19.9 (0–1,467)	1.3 (0–67)
Mean reaction score (Σ reaction scores ÷ n)	0.95	1.00
Reaction prevalence	8/23 (35%)	2/5 (40%)

* GM = geometric mean; mf = microfilaria.

India,[21] and Brazil,[22] where post-treatment reaction prevalences in response to ivermectin in microfilaremic individuals have been reported as 90%, 68%, 97%, and 95%, respectively. However, our results are consistent with what was reported in Ghana, where 36.3% of microfilaremic individuals treated with ivermectin/albendazole experienced a symptom during the post-treatment period, despite having higher numbers of circulating microfilariae than our study (GM intensity = 1,585 mf/ml with a 95% confidence interval of 1,069 to 2,350).[9] No hydroceles or increases in lymphedema were reported during the post-treatment period in our study, just as no localized inflammatory reactions were found in Ghana.[9]

The positive correlation between numbers of circulating microfilariae of the two species is of interest. Previous epidemiologic studies have documented other areas of co-infection,[23,24] but the overall prevalences were lower than in the village in the present study, and the investigators did not comment on any relationship between microfilarial counts of the two species. Other studies have examined areas where *Loa loa* and *M. perstans* are co-endemic;[25,26] similar positive correlations of *Mansonella* with age are described,[25] but again circulating microfilarial levels of the two filariae were not discussed in relation to each other. Occupational risks for intensity of exposure might coincide to explain this correlation. Another intriguing possibility is that the immunomodulating effects of one filarial species benefit the other and *vice versa* (concomitant susceptibility).

The correlation between ICT card tests and the TropBio ELISA antigen kit for circulating filarial antigen in our study was lower than previously reported.[27] Even when taking pains to read the tests at exactly 10 minutes,[17] a significant number of false-positive and false-negative results were encountered.

The absence of debilitating symptoms and relative rarity of even mild lymphatic pathology in an area where *W. bancrofti* is so prevalent was unexpected. A recent survey of the clinical manifestations of lymphatic filariasis in Ghana showed a wide variability in both the prevalence and sequelae of infection, including areas with >20% prevalence but no identifiable pathology.[28] Whether this variability is due to different strains of the parasite, differences in the genetic background of the hosts, recent introduction or increase of *Wuchereria* in these areas, or co-infecting organisms remains to be elucidated. Such variability prevents us from drawing any firm conclusions about the role of co-infection on chronic lymphatic pathology in this region of Mali.

Despite the obvious hypothetical possibility that infection with one filarial species could modify the clinical course or response to treatment of another, few investigators have explored this possibility. In our study, those who were dually infected showed a similar prevalence and severity of post-treatment reactions as those infected with *W. bancrofti* alone. This, along with the stable *M. perstans* microfilarial counts eight months after treatment, suggests that *M. perstans* is not a source of clinically significant pro-inflammatory products during the post-treatment period. Our data fall short of suggesting an immunomodulating effect of *M. perstans* on post-treatment reactions because 1) our numbers are too small to demonstrate a difference in reactions between groups and 2) there is currently no way to identify amicrofilaremic *M. perstans* infections, making a strict distinction between singly and dually infected patients impossible. It is hoped that further molecular and immunologic analyses of the samples collected from individuals in this community will shed further light on the interaction between these two filarial species.

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