ORIGINAL ARTICLE

Field-Based Evidence of Single and Few Doses of Annual Ivermectin Treatment Efficacy in Eliminating Skin Microfilaria Load after a Decade of Intervention

Hudu O. Osue*

Affiliation and Correspondence:
[1]Nigerian Institute for Trypanosomiasis (and Onchocerciasis) Research (NITR), Kaduna, Nigeria
*Email: osueho@yahoo.com

ABSTRACT

BACKGROUND: Impact assessment of community-based ivermectin treatment control of onchocerciasis is required to determine its effectiveness. This study was conducted to evaluate geographic coverage and demographic ivermectin treatment compliance.
METHODS: The number of village dosage were obtained from the community based distributors. Bioclinical data of participants comprising gender, age, number of treatment received from inception and dosage were obtained. Each participant was subjected to physical examination for palpable nodule and other skin clinical signs and symptoms of onchocerciasis. Visual acuity test was done using the Snellen illiterate E-chart. Eye examination was performed using touch loop and handheld ophthalmoscope. Skin snips from both iliac crests were incubated overnight at 28-32ºC and emerged micrifilaria enumerated under an inverted microscope. The changes in epidemiological indices at post-decade of mass drug administration were compared with baseline data.
RESULTS: Village annual ivermectin treatment doses averaged 62%, ranging between 10-100%. Individual treatment compliance rate was generally low with an average of 4 treatments and a range between 0-10. Despite variations in treatment compliance, there were significant improvements in some onchocercal morbidities. These include reduced number and severity of itching, visual impairment, papular onchodermatitis, onchocercomata (palpable nodules) and leopard skin. Ivermectin treatment halted development of new blind cases, except the case of a man who had optic nerve disease and became blind 2 years after ivermectin treatment had commenced. There was a significant overall reduction in parasite burden with very low mean skin microfilaria load of 1.7mf per skin snip and 3.7% skin mf prevalence, compared to baseline data of 17.7mf and 37.9% respectively. The palpable nodule was also drastically reduced from 14.5% to 6.4%. Outcome of this study has practically demonstrated that even a single dose ivermectin treatment is capable of clearing skin mf load on a long-term basis. This assertion is exemplified by the result obtained from Bomjock village that had taken treatment only at inception, and the prevalence rate was reduced from 70% to about 9.0% at post-decade of intervention.

CONCLUSION: It can be inferred that high demographic coverage with annual treatment doses, it is feasible to attain a shorter time (within a decade) contrary to the anticipated longer-term projection.
KEYWORDS: Ivermectin,   Microfilaria, Treatment   Compliance,   Onchocerciasis, Onchodermatitis, Visual Impairment

INTRODUCTION

Concerted efforts to control onchocerciasis had relied on strategies directed at reducing or eliminating the vector using insecticides (larvicides). Its setback includes the vast landmass, negative environmental effects and huge costs to sustain the project (1). Secondly, two drugs, diethyl carbamazine (DEC) and suramin available for treatment were very toxic. Thirdly, nodulectomy campaign embarked upon to eliminate adult worms could not achieve the desired results because not all nodules can be detected by palpation as cryptic infections made this control approach not feasible. A foreseeable effective and affordable control strategy emerged when ivermectin previously patented for veterinary use was proven to have microfilaricidal activity (2). More importantly, the drug was not found associated with serious side effects and therefore suited its use as mass drug administration (MDA) through mass distribution to endemic rural and often remote human settlements. Prior to implementing MDA with Mectizan or ivermectin or Stromector, over 40 million Nigerians were exposed to Onchocerciasis; 20 million were infected and about 120,000 went blind from the disease (3). Coincidentally, most of the people infected or at risk of infection were poor peasant farmers who cannot afford the drug and have no access to health facility. Therefore, the development of a novel control strategy called community directed treatment with ivermectin (ComDTI) was highly welcome. With the biannual treatment strategy adopted in six Latin American onchocerciasis endemic countries have proved adequate in eliminating the disease (4,5) within a record time frame.

Annual distribution of Mectizan started in Nigeria in 1992 under the National Primary Health Care. The study area comprised six farming villages located within onchocerciasis meso-endemic focus as described (6). The villages were enlisted into the National Mectizan Distribution Program in 1994. Before the commencement of ivermectin distribution in the study villages, baseline data on prevalence and intensity of onchocercal related clinical manifestations, parasitological (skin microfilarial load and presence of palpable nodule) were obtained (7). Various epidemiological mathematical models have been designed to project the duration for treatment that may likely achieve the eradication of onchocerciasis. Among them are the projection by ONCHOSIM (onchocerciasis simulation model), a microsimulation mathematical model of the dynamics of onchocerciasis transmission, to explore the potentials of a hypothetical macrofilaricidal drug for the elimination of onchocerciasis under different epidemiological conditions (8). In all cases, a 10-year programme of annual macrofilariciding was considered. A modelling stimulation SIMON also predicted that between 10-15 years will be needed to attain eradication of mf (9). Just as it was earlier envisaged, treatment was required to last beyond the adult life span estimated to be between 9-15 years. According to Plaiser *et al*. and Turner *et al*. (10,11), the ONCHOSIM and the epidemiology of onchocerciasis (EPIONCHO) both projected that in mesoendemic areas, the provisional operational threshold for treatment interruption followed by surveillance (pOTTIS) can be reached with annual treatment. The strategy may be insufficient in very highly hyperendemic areas, or would require prolonged continuation of treatment (12). Thus, the principal challenge for onchocerciasis control is to deliver ivermectin treatment to all target communities and to sustain high treatment coverage over a very long period (13). Therefore, the need to evaluate the long-term impact of ComDTI on public health and the transmission potential based on host parasite reservoir is imperative (14). Monitoring is a key issue to ascertain the level of treatment compliance that would impact on this control strategy. More importantly, the observed continued transmission

after a decade of ivermectin treatment intervention in Cameroon (15) and the clear evidence of onchocerciasis elimination in parts of Senegal and Mali, and in Nigeria as variously reported (16,17,18) showed that annual ivermectin treatment can effectively be used in the eradication of onchocerciasis. Impact of different levels of compliance to treatment at post decade of MDA on skin mf load, nodule rate and clinical (eye and skin) manifestations is presented in this report.

MATERIALS AND METHODS

Study area and sample population: The study area included ten villages within Gurara river basin of Kachia Local Government Area (LGA) of Kaduna State, Nigeria. Six sentinel villages had baseline data while four control villages were without baseline data. The area is within latitude 9° 37' to 9° 45' N and longitude 7° 40' to 8° E. The sample population (n=438) from the sentinel communities was comprised of males (n=220) and females (n=218) drawn from among the pre-baseline sample population. Only those who voluntarily consented to participate were examined for skin diseases (including palpation for nodule and skin snipping), and were subjected to visual acuity test for each eye. Subjects were between the ages of 14-90 years. The control study population (n=194) was made up of males (n=90) and females (n=104) between the ages of 15-90 years. Unlike the others, Ibika community was farther away from the study area and was excluded from the MDA at inception based on the outcome of the rapid epidemiological mapping of onchocerciasis (REMO) that was conducted.

Experimental design: Emerged microfilariae from skin snips taken from both iliac crests were incubated at ambient temperature between 28-32°C over night and enumerated under inverted microscope using tally counter. Each patient was examined for skin clinical manifestations according to Murdoch *et al*. (19), and visual acuity (VA) for each eye was assessed using illiterate E-chart and counting of fingers at 6 and 3 meter distance. Eye examination was performed using touch loop and handheld ophthalmoscope. The number of treatment taken and reasons for not taking the treatment were obtained from individuals. Information on the number of annual treatment administered to the village was obtained from the community based distributors and compared to information provided by the village heads.

Ethics: This project was approved by the Research and Development Committee of the Nigerian Institute for Trypanosomiasis (and Onchocerciasis) Research. All procedures in the collection of human samples were obtained in accordance to the Helsinki Declaration of 1975 (as revised in 1983). The villagers were briefed in their local dialect, and only those who volunteered and consented were enlisted to participate in the project.

RESULTS

The number of persons (n=438) who voluntarily participated and were examined in this long-term follow-up study at 10 years after commencement of ivermectin treatment intervention represented about 80% of the baseline sample population. Only few participants (2.5%) of the sample population immigrated into the study area within the period of 1994 to 2003. The number of emigrants could not be assessed. There was low level of annual Mectizan® distribution to some villages. The rate of non-compliance, which include persons who did not take any ivermectin were 17.5% (n=65) while 82.5% (n=373) of the sample population (n=438) had taken one or more doses. There was a decrease from the number of persons who received one dose 17% followed by those that received 2 and 4 doses with 15.9% (n=59), and only one person (0.3%) received 9 doses (Figure 1).
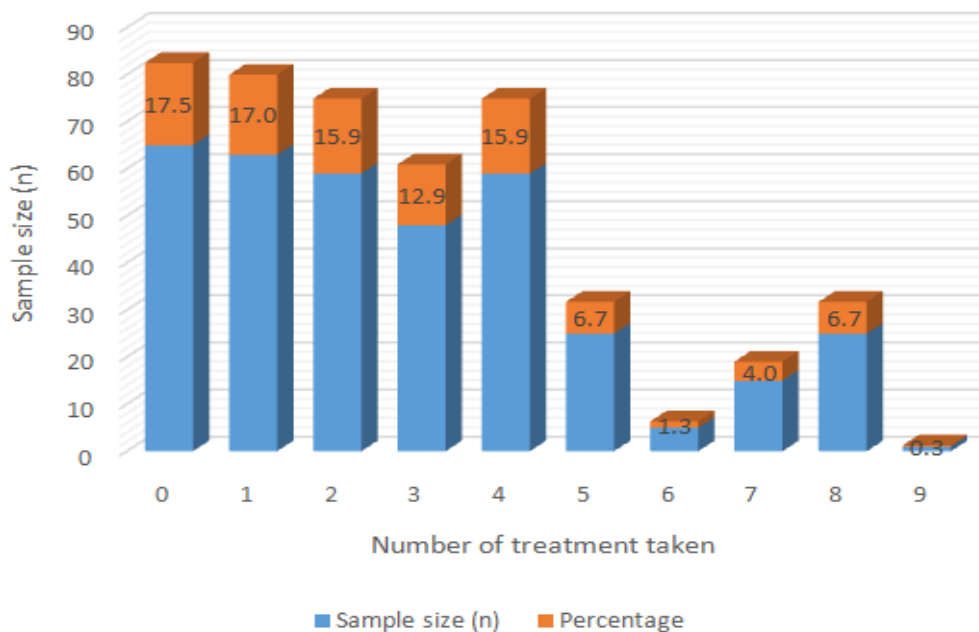
Figure 1: Distribution of annual ivermectin (Mectizan®) treatment compliance. Participants who did not take ivermectin are the non-compliant (0) and those who took between 1-9 doses are the compliant.

At the time of this study, the villages that were expected to have taken ten annual treatments from 1994-2003 had mean of 6.2 (62%) doses with a range of 1 (10%) to 10 (100%). One of the sentinel villages, Bomjock, had one treatment dose at the inception of Mectizan® distribution within the study area in 1994. Kurmin Gwaza and Angwar Maisaje had 4, Gidan Tama had 10 and others had 8. By implication, the individual compliance rates in the 6 sentinel villages were generally very low as shown on Table 1. The average ranging between 7.0 to 78.7 treatment compliance and percentage doses taken were 82.4±6.3% and 34.3%, respectively. Those with palpable nodules were 28(6.4%) and 16(3.7%) microfilaria prevalence in the sentinel sites (n=438). Microfilaria was not seen in Sabon Gantan (n=100) and Gidan Tama (n=61),

1(1.56%) case in Kurmin Gwaza (n=64), 3(4.47%) in Gantan (n=68); 5(7.69%) in Ungwan Shaho (n=65) and 7(9.0%) in Bomjock (n=80). The highest skin microfilaria load was 18 per snip. The changes in parasitological data when compared with baseline data are shown in Table 2. There was a significant reduction ($p<0.05$) in skin microfilaria prevalence from 201(37.9%) pre-treatment baseline compared to 17(4.6%) at post-decade of MDA. Similarly, skin mf density, community microfilaria load and palpable nodule were significantly reduced ($p<0.05$) from 77(14.5%) to 28(6.4%). The palpable nodule rate and skin microfilaria prevalence did not show any strong correlation with both age and number of individual treatments ranging from 2-8 annual doses.

Table 1: Village treatment compliance, palpable nodule and skin microfilaria prevalence rates at post-decade intervention

Study village	Sample size (n)	Dosage (1-10)	Treatment compliance		Prevalence rates (%)	
A. Sentinel			Population coverage δ (%)	Percentage doses §	Nodule	Skin mf
Bomjock	80	1	45 (56.3)	7.0	5 (6.3)	7 (8.75)
Gidan Tama	61	10	57 (93.4)	78.7	9 (14.8)	0
Ungwar Shaho	65	8	57 (87.7)	40.3	6 (9.4)	5 (7.8)
Kurmin Gwaza	64	4	53 (82.8)	22.7	4 (6.0)	1 (1.49)
Gatan	68	10	54 (79.4)	18.5	1 (1.5)	3 (4.54)
Sabon Gatan	100	7	95 (95.0)	38.5	3 (3.0)	0
Total (Mean±Stdev)	**438**	**6.7**	**361 (82.4±6.3)**	**34.3±21.4**	**28 (6.8±4.8)**	**16 (3.8±3.0)**
B. Control Villages						
Rami Kura*	42	2	12 (28.6)	3.6	6 (14.3)	1 (2.38)
Ungwar Maisaje*	57	10	48 (84.2)	20.5	2 (3.5)	0
Ungwar Kongo*	33	9	23 (69.7)	20.0	7 (21.2)	0
Ibika	62	0	1 (1.6)	0	3 (4.8)	0
Sub-total	**194**	**5.3**	**84 (43.3±32.8)**	**11.0±9.3)**	**18 (9.3±7.2)**	**1 (0.5)**
Total (Mean±Stdev)	**632**	**6.1**	**445 (67.8±30.8))**	**25.0±23.1**	**46 (8.5±6.4)**	**17 (2.5±3.4)**

The sign δ represent sample sizes that took 1-9 Mectizan® treatment doses. The percentage values of total actual doses divided by total expected doses of the sample population (§). *These control villages were enlisted for mass drug administration but had no baseline data. Standard deviation from mean (Stdev).

Table 2: Comparing baseline with post-decade treatment parasitological data

Parameter	Baseline data (n=531)	Post-Treatment data (n=438)	Significant difference	Remarks
Skin mf prevalence	201 (37.9%)	17 (4.6%)	p<0.05)	Reduced mf due to clearance.
Skin mf density	17.7	1.7	p<0.05	Effect on female fecundity to release mf.
Highest skin mf density	145	18	p<0.05	Skin snip mf count
CMFL	1.7	0.06	p<0.05	Geometric mean mf load
Palpable Nodule	77 (14.5%)	28 (6.4%)	p<0.05	Probable remission of nodules

CMFL= Community microfilaria load, mf= microfilaria

Moderate or not too serious form of itching was the main complaint among 14.8% (n=55), and few patients claimed that it was more intense after ivermectin treatment. Eight persons (2.2%) had leopard skin, and few, 15(4.0%), showed one or more forms of onchocercal skin changes as shown in Table 3. They include papular onchocercal dermatitis, chronic onchocercal dermatitis, 2; hernia, 3; a case of elephantiasis of the scrotum at the earlier stage of development. Thirty persons (8.0%) had visual impairment based on VA of 6/18 and above, with 2 partial and 7 total blind cases (2.4%) which included one new blind case. Moderate or not too serious form of itching was the main complaint among 23.53% (n=60) of the four control villages. Five persons (1.96%) had leopard skin, and few, 10(4.0%), showed one or more forms of onchocercal related skin changes. Twenty-five persons (9.8%) had visual impairment based on VA of 6/18 and above. Most cases of blindness were due to accident, old age and childhood disease. Those with palpable nodules were 24(9.41%), and the microfilariae prevalence of the control sample population was 1(0.4%) with 18 and 7 microfilariae per right and left iliac skin snip respectively.

Among the post-decade onchocercal related skin manifestations such as onchodermatitis, leopard skin and the ocular clinical symptoms of poor visual impairment and blindness were significantly higher (p<0.05) in sentinel villages compared with control villages. Unlike the sentinel villages, all cases of blindness in the control villages were not due to onchocercal related causes. Evidence of itching of 14.8% (n=55) and palpable nodule rate 28(6.4%) in sentinel villages were lower compared with 23.53% (n=60) and 9.41% (n=24) recorded in control villages. Observed differences were not statistically significant (p>0.05). However, the skin mf prevalence was significantly higher (p<0.05) in the sentinel villages than in the control villages with 17 (4.6%) versus 1 (0.4%), respectively. The only microfilaria positive case was in a 35-year-old male who had taken ivermectin twice. A case of an individual with nine palpable nodule without any skin microfilaria took Mectizan four months before the study.

Table 3: Comparing baseline with post-treatment clinical data

Clinical signs and symptoms	Baseline data (n=531)	Post-Treatment data (n=438).	Difference	Remarks
Dermal changes	51 (9.6)	15 (4.0)	Significant (p<0.05)	Decrease in overall skin clinical signs
Itching	382 (72)	55 (14.8)	Significant (p<0.05)	Reduction in severity of itching
Papular Onchodermatitis	38 (7.2)	2 (0.5)	Significant (p<0.05)	Remission of reactive skin rashes
Chronic Onchodermatitis	26 (4.9)	2 (0.5)	Significant (p<0.05)	Remission of chronic rashes
Leopard Skin	10 (1.9)	14 (3.8)	Significant	Increase in leopard skin
Visual Impairment VA of 6/18 & above	20 (3.8)	30 (8.0)	Not significant (p>0.05)	Increased poor vision and eye lesions
Blindness	6 (1.1)	7 (2.4)	Not significant (p>0.05)	Halted the development of new blind cases

The probability values (p<0.05) show statistical significance by unequalled data t-test. Figures in parenthesis are percentages.

DISCUSSION

Assessment of the long term impact of annual ivermectin treatment of endemic communities is needed to determine the feasibility of controlling and eventually eradicating onchocerciasis. The impact of ComDTI on public health in onchocerciasis endemic communities has been reported to be impressive (20,21,22). It was observed that the skin clinical symptoms including palpable nodules dropped over the base line figures. Many expressed having been relieved from severe skin itching which was widespread before the Mectizan distribution started in these areas. The few who experienced itching reaction did not report any serious limitations to warrant discontinuing with treatment.

These results were in total contrast to baseline figures which ranges between 25-72% for the villages (7). In addition to this impressive performance by the drug, it seems that the fear that non-compliance may adversely affect the control method may not be a serious problem as hitherto assumed. The absence of infection and clinical manifestations among the younger age group below 30 years was a confirmation of a possible break in disease transmission cycle. An early study undertaken by Boussinesq et al. (23) showed that the pretreatment community microfilarial loads (CMFL) decreased from 5.5 and 25.1 microfilariae per snip after 32 months to only 24 and 51% of the initial values, respectively. In a third village treated once had the mean microfilaria density 28 months after treatment to be only 12% of the initial value.

From our finding, the incidence of visual impairment showed remarkable increase over those of baseline data. This could be attributed to the fact that those hitherto seen to have one form of eye lesion now manifest as poor visual acuity. Just like the only new case of blindness recorded was in a man who was said to be blind 2 years after the treatment started. This is not unexpected as non-reversible lesion will not be affected by treatment (24,25). The patient already had optic nerve disease before treatment started. Another notable observation was the claim of disappearance of nodules and remarkable improvement in severity of itching. A typical case

was that of a man who claimed that the severity of the leopard skin had improved along with reduced severe itching. Similar findings have been documented in other studies by Ogbuagu et al. and Emuka et al. (26,27). This is contrary to report (28) that after three doses, 44% of the patients remained skin snip positive. A long term effect of the treatment was not assessed.

It is plausible for the continued presence of palpable nodules and skin microfilaria despite varied annual ivermectin treatment doses to be attributed to sub-optimal responses. Elsewhere, inability to clear mf from skin after multiple treatments has been documented (29). It is worth mentioning that the low prevalence and skin mf density especially among inhabitants of Bomjock which had only received one treatment proved the long term efficacy of single dose ivermectin. Whether this could be attributed to reduce turnover of microfilaria production and release, or increased and sustained microfilaria elimination on the part of the host as suggested by Schulz-key and Karam (30) remained subjective. Another possibility is to suspect the role of partial drug-facilitated cell mediated immunity may play in preventing microfilariae from repopulating the skin on a long-term basis. Should that be the case, it will be an added advantage previously not anticipated when ivermectin treatment of onchocerciasis was approved for field use.

Earlier reports have documented delay in repopulation between 9-12 months (31). Due to lack of suitable model host for laboratory study, the high cost and ethical consideration for subjecting humans to placebo trial for up to ten years have precluded determination of the outcome of a single treatment. It has been documented by Pacque et al. (32) that up to 33% of patients in non-endemic areas were cured with only 1 dose of ivermectin. Thus, the study of treatment compliance rate after a decade of intervention and the observed impact of single dose treatment on skin mf load and nodule rates clearly support the efficacy of single-dose treatment.

It was feared that non-compliance to regular annual treatment will seriously jeopardize the attainment of the set target or objective (33,34). An astonishing finding that despite receiving only

one and few treatment doses, onchocerciasis prevalence was drastically reduced from 72% to 9% in Bomjock and overall. The same applies to the infection intensity. The precarious public health situation of river blindness in these villages within the Gurara river basin was being mitigated. Moreover, black fly uptake of mf has been shown not to be associated with the level of skin mf density (8). Therefore, the surrounding villages need to be enlisted for treatment to avert few pockets of few infected individuals serving as reservoir of infection.Yet, a panacea for effective control based on ComDTI is to attain 100% geographic coverage and at least 50% individual treatment compliance. The mechanism of sustained elimination of parasite reservoir may be accomplished if compliance rate is improved (35). It will require advocacy visits to mobilize the people to comply with annual treatment.

The outcome of this study has confirmed that repopulation of skin with mf may just be a transient features observed immediately after treatment. The long term impact of treatment could have resulted in clearing skin mf and remission of nodules as observed in this study. It has been reported by Pion *et al*. and Basáñez *et al*. (36,37) that *O. volvulus* microfilaria density measured after a first treatment with ivermectin, and thus probably the rate of skin repopulation by microfilariae (mf) varies according to several host factors. A mathematical model (38) had predicted reduction in microfilaridermia by 98–99% after 1–2 months treatment, which corresponds to the time when the fraction of females harbouring live microfilariae were at the lowest (reduced by around 70% from its original value).

The isolated mf positive case that was recorded in Rami Kura in a 35-year-old man who had taken 2 doses of Mectizan calls for concern. Whether this was a case of non-responder as observed (29) or resistance to ivermectin as suggested by Osei-Atweneboana *et al*. (39) remained unknown. This study has confirmed that the adjoining villages do not pose any threat of serving as reservoir of infection for re-invasion of endemic areas after post control. Interestingly, the case of the young boy with 9 nodules but without skin mf is a typical example. He took treatment that year before the screening exercise.

Inference drawn from this study holds a contrary opinion to the predicted duration required to attain elimination of mf, as suggested via mathematical model EPIONCHO, which proposed that it will only be achievable within 25 years for the setting with 51% baseline mf prevalence (40). Annual ivermectin mass treatment strategy may not require longer continuation to achieve the pOTTIS as averse in some quarters.

ACKNOWLEDGMENTS

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