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The effects of ivermectin on onchocercal skin disease and severe itching: results of a multicentre trial

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Summary

OBJECTIVE To determine the effects of ivermectin in annual, 3-monthly and 6-monthly doses on onchocercal skin disease (OSD) and severe itching.

METHOD A multicentre, double-blind placebo controlled trial was conducted among 4072 residents of rural communities in Ghana, Nigeria and Uganda. Baseline clinical examination categorized reactive skin lesions as acute papular onchodermatitis, chronic papular onchodermatitis and lichenified onchodermatitis. Presence and severity of itching was determined by open-ended and probing questions. Clinical examination and interview took place at baseline and each of 5 subsequent 3-monthly follow-up visits.

RESULTS While prevalence and severity of reactive lesions decreased for all 4 arms, those receiving ivermectin maintained a greater decrease in prevalence and severity over time. The difference between ivermectin and placebo groups was significant for prevalence at 9 months and for severity at 3 months. Differences between placebo and ivermectin groups were much more pronounced for itching. From 6 months onward, the prevalence of severe itching was reduced by 40–50% among those receiving ivermectin compared to the trend in the placebo group.

CONCLUSION This is an important effect on disease burden as severe itching is for the affected people the most troubling complication of onchocerciasis. The difference among regimens was not significant, and the recommended regimen of annual treatment for the control of ocular onchocerciasis appears also the most appropriate for onchocerciasis control in areas where the skin manifestations predominate. The final determination of the effect on skin lesions requires a longer period of study.

keywords onchocerciasis, ivermectin, onchodermatitis, itching

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Introduction

Onchocerciasis is known for both its ocular and dermatological effects. Until recently, the former has received more attention in terms of organized efforts to control the disease (Kim & Benton 1995). However, more than half of the 17 million affected persons in Africa live in forest areas where onchocercal skin disease (OSD) is common but where onchocercal blindness is rare (WHO 1995). Recent studies of the burden of onchocerciasis in forest areas have shown that OSD is a major public health problem associated with significant social stigma (Amazigo 1994; Pan African Study Group 1995; Brieger *et al*. 1998) and economic loss (Workneh *et al*. 1993; Oladepo *et al*. 1997). For the affected people the most severe complication of onchocerciasis infection is intense itching (Pan African Study Group 1995), while in terms of DALYs the estimated global burden of itching alone is greater than that of onchocercal blindness and visual impairment combined (Remme 1998).

The introduction of ivermectin and its provision free of charge by the manufacturer has provided an opportunity to control onchocerciasis in all endemic areas. Ivermectin is a highly effective and safe microfilaricide (WHO 1995), and annual ivermectin treatment significantly reduces the incidence and progression of ocular lesions and visual impairment (Dadzie *et al*. 1991; Abiose *et al*. 1993; Cousens *et al*. 1997). Annual ivermectin treatment has therefore become the principal control strategy for onchocercal eye disease and blindness.

In forest areas, the burden of onchocercal disease is linearly related to the level of onchocerciasis endemicity (Pan African Study Group 1995). Annual ivermectin treatment results in a significant reduction in transmission and incidence of infection (Remme *et al*. 1989; Taylor *et al*. 1990; Boussinesq *et al*. 1997), and it is predicted that in the long term large-scale annual ivermectin treatment will reduce onchocerciasis endemicity to levels at which the disease is no longer a public health problem. It is not yet known how many years this will take, but this reasoning was considered sufficient to justify large scale ivermectin-based control in forest areas in APOC countries. For the short and medium term, it is hoped that the reduction in microfilarial loads in treated individuals will reduce the incidence and progression of onchocercal skin lesions and the severity of itching.

Current evidence on the short-term effect of ivermectin on onchocercal skin disease (OSD) and related itching is conflicting and inconclusive. Although ivermectin reduces microfilarial loads in the skin, previous studies did not find a consistent and clear effect on OSD (Pacque *et al*. 1991; Whitworth *et al*. 1992b; Sumo *et al*. 1993; Burnham 1995) and itching (Sumo *et al*. 1993; Whitworth *et al*. 1992a, 1996; Burnham 1995).

Experiences from research noted above led to several suggestions for improved study design to include more frequent field observations and testing of quarterly administration of the drug (Burnham 1995), standardized clinical assessment (Murdoch *et al*. 1993) and larger number of participants (Whitworth *et al*. 1992a). In previous studies information about itching was gathered through direct questions, which may have introduced an over-reporting bias, and other interviewing techniques were indicated. Therefore, a double-blind, placebo controlled trial on the effect of 3-, 6-, and 12-monthly ivermectin treatment on OSD and severe itching was undertaken. The results of these efforts are reported here.

Methods

The trial was undertaken in areas in the forest belt in West and East Africa where onchocercal blindness is rare. Villages were selected for study based on ivermectin treatment criteria described by Ngoumou & Walsh (1993), i.e. 'highly desirable' with a nodule prevalence rate of 20–39% in males over 20 years, or 'urgent' where the prevalence is 40% or higher. Community residents who had attained the age of 20 years were recruited and followed over a 15-month period. Following guidelines for distribution of ivermectin at the community level (WHO 1991), the researchers used interview and examination to exclude pregnant women and severely ill persons. Informed consent was sought through village leaders and during village meetings, and at the first examination from each recruited individual. A stopping rule for the placebo arm was adopted should substantial improvements be observed at the 3-month follow-up by analysis based in Geneva. The placebo arm was to be suspended if at the first intermediate examination at 3 months there was an improvement of 50% or more in the prevalence of troublesome itching or of 66% or more in the prevalence of reactive skin lesions in any of the ivermectin treatment groups compared to the placebo group.

Study sites

The study took place in rural, endemic communities in Ghana, Nigeria (Oyo and Anambra States) and Uganda. In Ghana, Jomoro, Asantekrom, Jema and Assemkrom villages in Aowin-Suaman District of the Western Region were the focus of study. The district is drained by a number of fast-flowing tributaries of the Tano River. Rapid assessment procedures found a nodule rate of 75–80%. The Ibarapa District of Oyo State in south-western Nigeria is transversed by four rivers that are known breeding grounds for *Simulium damnosum* (Wyatt 1971). Rapid assessment procedures found a 30% prevalence of nodules in adults. The district has seven main towns, but 20% of the population live in over 400 farm hamlets where the onchocerciasis problem is greatest. Forty-six hamlets along the Ofiki and Oyan Rivers were included.

Villages near the Nkisi River in Anambra State in south-eastern Nigeria were chosen because this river is a known black fly breeding site (Iwuala & Ezike 1980). Rapid assessment found a nodule rate of 40%. The Ugandan site was located in Kibaale District in the mid-west of the country. The area is characterized by hills, valleys and many streams. The nodule rate for that area was 35%.

Procedures

The presence of OSD was determined by physical examination and presence of troublesome itching through interview. An initial survey included physical examination for skins lesions using the procedures developed by Murdoch *et al*. (1993) The primary focus was on reactive skin lesions, that is acute papular onchodermatitis (APOD), consisting of

small, widely scattered pruritic papules, which progress into vesicles and pustules in more severe cases; chronic papular onchodermatitis (CPOD), where the skin lesions are scattered, flat-topped papules which vary greatly in size and height above the skin surface and where itching occurs in some lesions, but is not a constant feature; with increasing severity the plaques become more confluent LOD lesions, pruritic hyperpigmented hyperkeratotic plaques. Examinations were conducted by trained physicians and nurses who had worked in the endemic communities for several years. Interviewers were mature local residents who had completed secondary school and were fluent in both English and their indigenous languages.

The severity of reactive lesions (APOD, CPOD, LOD) was scored as follows: 0, absent; 1, lesion without scratch marks; 2, lesion with scratch marks; 3, excoriation; 4, excoriation with superinfection. Five general sites of the body were considered when recording the findings: the head, the upper limbs, the front of the trunk, the back of the trunk and the lower limbs. Each site was scored and a total reactive lesion score was compiled as the sum of the maximum score for each of the three reactive skin lesions. Depigmentation was noted, but used primarily for allocation of participants to treatment groups as explained below.

Information about itching was obtained in two ways. First, during initial open-ended interviewing, participants were asked how they had been feeling since the last visit of the team. Spontaneous responses were recorded. Follow-up probes were then made asking specifically about itching and other conditions as described below. Responses to the open-ended question were coded as: 0 – not mentioned; 1 – mentioned; 2 – mentioned with emphasis. Responses to the follow-up probe were coded as: 0 – no itching; 1 – present; 2 – troublesome; 3 – severe. An itching score was constructed by multiplying the code for the initial open-ended response by two (i.e. giving it more weight) and adding it to the coded response for the follow-up probe. Secondly, severe itching was defined as mentioning itching with emphasis to the open-ended question or indicating that itching was either troublesome or severe during the follow-up probe.

During the first visit the recruited participants were randomly allocated to four treatment arms: ivermectin given at 3-month, 6-month, and 12-month intervals as well as a placebo group. Each arm was given a letter code, the corresponding regimen of which was not revealed to the researchers until the end of the final data analysis workshop. At subsequent visits each subject was given doses appropriate to their treatment arm. Allocation of subjects to treatment arm was stratified by their main type of skin lesions (APOD, CPOD, LOD, Depigmentation, or None) to ensure equal distribution of the various lesions in the four treatment arms. The manufacturer provided ivermectin and placebo in identical white capsules. Those that contained ivermectin were equivalent to half of the standard ivermectin tablet.

At 3-month intervals, five follow-up visits to the study communities were conducted by the teams to conduct interviews on the participants, perceived health condition, to repeat the clinical examinations and to distribute the capsules. Data were entered at each site using standard EPI INFO computer programmes and later cleaned, combined and analysed using the SPSS statistical package at a workshop in Ghana. The Pearson χ^2-test was used to test the significance of differences in prevalences and ANOVA to test the difference in scores. To test the significance of differences between treatment groups in the reduction in prevalence and scores after treatment, as reported in Tables 3 and 5, the difference in score between the post-treatment and pretreatment score was calculated for each individual (for prevalence data a score of 0 for negative and 1 for positive was used). ANOVA was applied to these individual score differences to test the statistical significance of differences between groups.

As will be described below, defaulting was an important problem at follow-up. In-depth investigations were therefore undertaken by the social scientists of each team between the first and second follow-up examination to identify the reasons. Furthermore, at each follow-up visit, at least a second effort was made to trace all defaulters.

Results

A total of 4070 people were enrolled and Table 1 shows the participation rate at each site at each follow-up period. On average, 73% of recruited persons attended each follow-up, but not all of these participants were able to attend each examination. A total of 1530 (38%) persons were examined and treated at baseline and at all five follow-up visits. Information on itching during follow-up visits was not collected in Uganda due to a communication problem with the field, and therefore, analysis of that variable is based on 1314 (43%) of the initial participants who attended each subsequent treatment and examination in the two Nigerian sites and Ghana.

Teams in Ghana and Nigeria studied reasons for missing a follow-up treatment and identified that physical absence from the village was the main reason (70%) for defaulting. Such absences were due to trading, other business activities, visiting relatives, farming at a distance, and resettlement in another village. Another 7% of defaulters were sick at the time of a follow-up visit. Pregnancy (9%) and death (1%) were other reasons for not receiving a follow-up treatment. Only 5% specifically refused to be treated because of side-effects of their treatment. The remainder were physically absent at the time of the visit and a reason for their absence

Table 1 Characteristics of population recruited and number examined at each follow-up examination

	Project sites				
	Ghana, Western Region	Nigeria, Anambra State	Nigeria, Oyo State	Uganda, Kibaale District	Total
Date started	7/9/1995	4/9/1995	15/11/1995	10/9/1995	
Number of persons recruited	974	1075	1032	989	4070
Pre-treatment prevalence in population recruited					
Reactive skin lesions	30.8	29.5	42.5	15.3	
Severe itching	30.8	24.5	11.2	72.3	
Number of persons examined (% of number recruited) at					
3 months	737(75.7)	833(77.5)	787(76.3)	610(61.7)	2967(72.9)
6 months	730(74.9)	992(92.3)	763(73.9)	511(51.7)	2996(73.6)
9 months	764(78.4)	952(88.6)	667(64.6)	585(59.2)	2968(72.9)
12 months	789(81.0)	954(88.7)	677(65.6)	568(57.4)	2988(73.4)
15 months	753(77.3)	944(87.8)	723(70.1)	562(56.8)	2982(73.3)

could not be ascertained from co-villagers. The Ugandan team indicated that the foregoing reasons for missing follow-up visits were similar to their own experiences.

Those who were not available for all treatments were younger; 28% of those less than 40 years old completed all treatments compared to 44% of older participants. A similar proportion of male (38%) and female (34%) participants took all treatments. Differences in defaulting rate among the treatment arms were not significant.

Table 2 shows that the prevalence of severe itching and reactive skin lesions was similar for those who attended all treatments and examinations and those who missed some of them. The main difference concerned the prevalence of severe itching in the placebo group, but this was not statistically significant.

Itching

At baseline, 35.1% of 1314 respondents indicated during open-ended questioning that they experienced itching. An additional 14.8% of respondents, when prompted, indicated that they had experienced itching. Severe itching was indicated by 21.7% of all respondents at baseline. An average baseline itching score of 1.56 was obtained.

Table 3 shows that the four study arms did not differ in prevalence of severe itching at baseline, nor at the 3-month follow-up visit, although all groups reported some drop in severe itching. During subsequent examinations there was a significantly greater drop in prevalence of severe itching in all ivermectin groups compared to placebo (Figure 1). Between 6 and 15 months the prevalence of severe itching ranged from 52 to 56% of the baseline prevalence values for those receiving ivermectin compared to 85–105% for the placebo group. After correction for the trend in the placebo group, the reduction in the prevalence of severe itching was 39% at 9 months, 47% at 12 months and 38% at 15 months. The greatest reduction in the prevalence of severe itching was observed among those receiving treatment every 6 months with a corrected reduction of 46% – 53% between 9 and 15 months follow-up. However, the differences among the three ivermectin groups were not statistically significant.

The change in itching score is also seen in Table 3. Again, there were no differences among treatment arms at baseline or at 3 months, but from 6 to 15 months the score was significantly lower among those receiving ivermectin compared to the placebo group. As with the prevalence of severe itching, participants in the 6-monthly treatment group maintained the greatest reduction in itching score, but again, the differences among the 3 ivermectin groups were not statistically significant.

Further analysis was done to discern and compare the effect of treatment among those who reported itching at baseline and those who did not. The results in Table 4 show a different pattern of response for those who reported no severe itching at baseline compared to those who did. From the 6th month (3rd follow-up visit) onward, those who did not report itching at baseline and also received ivermectin were significantly less likely to have developed severe itching than

Table 2 Pre-treatment levels of itching and skin lesions in the cohort of persons who received all 5 treatments and attended all 6 examinations as compared to pre-treatment levels in persons who missed some treatments or examinations.

	Severe itching (excluding Uganda)		Reactive skin lesions (all sites)	
	No. of persons examined	Prevalence (as %)	No. of persons examined	Prevalence (%)
Placebo				
All treatment/exams (cohort)	309	18.8	367	27.5
Some treatments/exams missed	464	23.9	652	30.5
Statistical significance of difference		$P=0.09$		$P=0.31$
Annual ivermectin				
All treatments and all exams	329	21.6	368	28.8
Some treatments/exams missed	432	21.1	29.4	29.4
Statistical significance of difference		$P=0.86$		$P=0.83$
6-monthly ivermectin				
All treatments and all exams	355	25.9	413	29.1
Some treatments/exams missed	424	22.4	624	30.8
Statistical significance of difference		$P=0.25$		$P=0.56$
3-monthly ivermectin				
All treatments and all exams	321	19.9	381	27.8
Some treatments/exams missed	447	21.7	630	31.1
Statistical significance of difference		$P=0.59$		$P=0.29$

those in the placebo group who did not have severe itching at enrolment. No significant effect on itching was observed among those who did report itching at enrolment.

Changes in lesions

The baseline prevalence of reactive lesions among those 1529 persons who attended all sessions was 8.0% for APOD, 15.8% for CPOD, and 12.3% for LOD. Overall, 28.3% had one or more reactive skin lesions. In Table 5, one can see that the groups had similar prevalences at baseline. The prevalence of any reactive lesion subsequently dropped for all groups and remained consistently lower for those receiving ivermectin than the placebo group throughout the period of study (Figure 2). The difference between placebo and ivermectin groups was statistically significant only at the 9-month examination ($P = 0.012$).

The prevalence of APOD in the placebo group actually rose to 107% of baseline value at 3 months compared to 70% for those receiving ivermectin. As with reactive lesions overall, APOD specifically experienced a consistently lower value among ivermectin than placebo group members through the 15-month visit. After correction for the trend in the placebo group, there was a reduction of 26% − 41% in the prevalence of APOD among those who received ivermectin. However, the difference was not statistically significant. The prevalence of CPOD lesions was also lower among the ivermectin group but the difference with the placebo group was less pronounced than for APOD. The results concerning LOD were inconsistent. At 9 months the ivermectin group had a significantly greater reduction in lesions than did the placebo group, but by 12 months the observed values had reversed, though this was not significant.

The reactive lesion score was not significantly different among groups at baseline. Thereafter, while it generally decreased in all groups, the decrease remained greater for the ivermectin group members than for those receiving placebo. The difference among groups was statistically significant at 3 months (Table 5). The placebo group members actually experienced an increase in their lesion score at 3 months. During the final three observations, the 6-monthly treatment group maintained the greatest decrease in their score compared to baseline.

Table 6 shows the changes in skin lesions by pretreatment status. The only significant difference between ivermectin and placebo is observed at 9 months among those who had reactive skin lesions at the pretreatment examination.

Discussion

A major reason for conducting a double-blind, placebo-controlled trial was to ensure that the differences between the

Table 3 Effect of ivermectin treatment on severe itching

	Number	Pre-treatment prevalence of severe itching (%)	Prevalence of severe itching as percentage of pre-treatment prevalence				
			3 months	6 months	9 months	12 months	15 months
Prevalence of severe itching							
Placebo	309	18.8	89.4	84.6	85.6	104.8	87.8
Annual ivermectin	329	21.6	94.4	55.1	53.7	50.5	69.0
6-monthly ivermectin	355	25.9	78.4	49.0	40.2	56.4	43.6
3-monthly ivermectin	322	19.9	87.4	60.8	68.8	60.8	54.8
Ivermectin groups combined	1006	22.6	85.8	54.0	52.2	55.8	54.4
Significance of difference (*P*)							
Among 4 treatment groups		0.116	0.690	0.043	0.007	0.008	0.014
Ivermectin versus placebo		0.090	0.712	0.014	0.010	0.001	0.014
		Pre-treatment itching score	Itching score as percentage of pre-treatment score				
			3 months	6 months	9 months	12 months	15 months
Itching score							
Placebo	309	1.50	90.0	75.5	77.5	72.1	68.2
Annual ivermectin	329	1.54	106.3	54.1	51.8	48.8	60.5
6-monthly ivermectin	355	1.72	93.3	54.1	46.2	44.1	37.7
3-monthly ivermectin	322	1.50	92.1	59.5	55.2	45.6	46.9
Ivermectin groups combined	1006	1.59	97.1	55.7	50.7	46.1	47.7
Significance of difference (*P*)							
Among 4 treatment groups		0.338	0.563	0.067	0.008	0.022	0.004
Ivermectin versus placebo		0.441	0.527	0.013	0.002	0.003	0.015

natural course of OSD, wherein the prevalence and severity of onchocercal skin lesions and itching is known to change considerably over time (Whitworth *et al*. 1992; Burnham 1995), and the effect of ivermectin treatment could be observed. The results for this study confirm the variable nature of reactive skin lesions and severe itching over time, and the importance of a placebo group.

The major finding of this study is the 40–50% reduction in the prevalence of reported severe itching after ivermectin treatment. It was not possible to determine the level of background itching due to other causes which would not be affected by ivermectin treatment. However, a previous study which used the same interviewing methodology showed a prevalence of troublesome itching of around 50% in hyper-endemic villages and around 10% in hypo-endemic or non-endemic villages (Pan African Study Group 1995). Taking this into account, one may suggest that ivermectin treatment has reduced severe itching due to onchocerciasis infection by 50 to 60%. This is an important effect on community disease burden since severe itching is for the affected people the worst complication of the disease (Pan African Study Group 1995).

At the first follow-up examination at 3 months, the itching scores were higher among the ivermectin groups than in the placebo group. This is likely to derive from the inclusion of transient itching, arising from Mazzotti reactions, in reported severe itching for the 3-month period between examinations. After the first treatment round, microfilarial loads were low and Mazotti reactions no longer important. Hence, from the second follow-up examination at 6-months onward, the effect of treatment on severe itching could be properly measured. It is likely, however, that treatment had already reduced severe itching several days after the first treatment. The relatively high prevalence of severe itching at 15 months in the annual

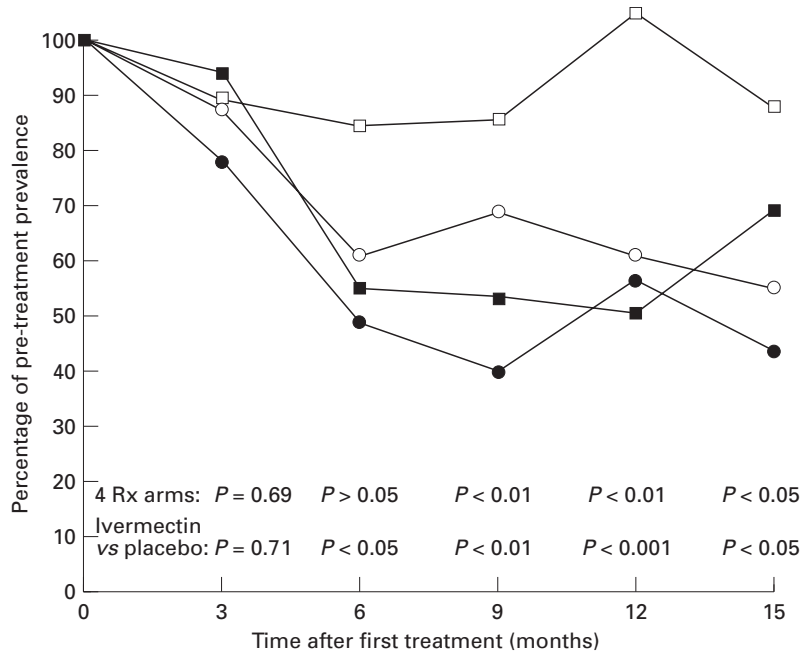

Figure 1 Effect of ivermectin on severe itching. ■ annual, ● 6 monthly, ○ 3 monthly ivermectin treatment and □ placebo.

ivermectin treatment group might also be due to a Mazotti reaction to treatment after an interval of 12 months when the microfilarial loads had again risen to substantial levels (Alley *et al*. 1994).

The study showed also a statistically significant effect of ivermectin treatment on reactive skin lesions. The effect was much more limited than for severe itching but that is not surprising given the short period of observation. Skin lesions

Table 4 Effect of ivermectin treatment on severe itching by pre-treatment itching status

		Prevalence of severe itching at				
	Number	3 months	6 months	9 months	12 months	15 months
Persons without severe itching at first examination						
Placebo	251	12.7	13.1	13.9	18.7	16.3
Annual ivermectin	258	16.7	7.4	8.1	8.9	12.0
6-monthly ivermectin	263	16.3	8.0	8.0	9.9	7.2
3-monthly ivermectin	258	15.1	8.5	12.4	10.9	8.9
Ivermectin groups combined	779	16.0	8.0	9.5	9.9	9.4
Significance of difference *(P)*						
Among 4 treatment groups		0.601	0.097	0.060	0.002	0.006
Ivermectin versus placebo		0.121	0.011	0.033	<0.001	0.002
Persons with severe itching at first examination						
Placebo	58	34.5	27.6	25.9	24.1	17.2
Annual ivermectin	71	33.8	28.2	23.9	18.3	25.4
6-monthly ivermectin	92	31.5	26.1	17.4	28.3	22.8
3-monthly ivermectin	64	26.6	26.6	18.8	17.2	18.8
Ivermectin groups combined	227	30.8	26.9	19.8	22.0	22.5
Significance of difference *(P)*						
Among 4 treatment groups		0.769	0.991	0.550	0.309	0.652
Ivermectin versus placebo		0.350	0.516	0.202	0.426	0.250

Table 5 Effect of ivermectin treatment on reactive skin lesions

	Number	Pre-treatment prevalence (%)	Prevalence at follow-up examination as percentage of pre-treatment prevalence				
			3 months	6 months	9 months	12 months	15 months
Reactive skin lesion							
Placebo	367	27.5	95.3	70.2	70.2	76.4	61.5
Annual ivermectin	368	28.8	76.4	55.6	47.2	67.0	57.6
6-monthly ivermectin	413	29.1	73.2	65.6	45.0	63.2	45.7
3-monthly ivermectin	381	27.7	87.0	52.0	52.0	70.0	43.3
Ivermectin groups combined	1162	28.5	78.6	58.2	48.1	66.7	48.8
Significance of difference (*P*)							
Among 4 treatment groups		0.954	0.184	0.337	0.074	0.654	0.360
Ivermectin versus placebo		0.378	0.078	0.156	0.012	0.281	0.169
APOD							
Placebo	367	7.1	107.0	64.8	69.0	91.5	62.0
Annual ivermectin	368	6.8	60.3	48.5	44.1	55.9	63.2
6-monthly ivermectin	413	9.4	67.0	43.6	33.0	48.9	25.5
3-monthly ivermectin	381	9.6	70.8	40.6	43.8	57.3	35.4
Ivermectin groups combined	1162	8.3	69.9	45.8	41.0	55.4	41.0
Significance of difference (*P*)							
Among 4 treatment groups		0.473	0.106	0.476	0.276	0.252	0.397
Ivermectin versus placebo		0.257	0.094	0.206	0.319	0.106	0.152
CPOD							
Placebo	367	15.5	96.8	52.9	45.8	67.1	45.8
Annual ivermectin	368	16.8	72.6	35.7	33.9	50.0	48.8
6-monthly ivermectin	413	17.4	63.8	55.7	26.4	50.0	32.2
3-monthly ivermectin	381	13.4	76.1	35.1	38.8	60.4	35.1
Ivermectin groups combined	1162	15.9	70.4	43.4	32.7	52.8	38.4
Significance of difference (*P*)							
Among 4 treatment groups		0.412	0.712	0.360	0.058	0.323	0.301
Ivermectin versus placebo		0.468	0.597	0.337	0.307	0.385	0.226
LOD							
Placebo	367	12.3	86.2	79.7	84.6	64.2	64.3
Annual ivermectin	368	14.9	69.1	61.7	56.4	67.8	51.0
6-monthly ivermectin	413	10.2	73.5	73.5	66.7	85.3	61.8
3-monthly ivermectin	381	12.0	82.5	63.3	52.5	70.0	48.3
Ivermectin groups combined	1162	12.3	74.8	65.9	57.7	73.2	52.8
Significance of difference (*P*)							
Among 4 treatment groups		0.245	0.442	0.323	0.165	0.560	0.321
Ivermectin versus placebo		0.534	0.132	0.070	0.038	0.340	0.182
		Pre-treatment Skin lesion score	Skin lesion score at follow-up examination as percentage of pre-treatment score				
			3 months	6 months	9 months	12 months	15 months
Skin lesion score							
Placebo	367	0.65	111.2	58.7	50.6	70.8	51.9
Annual ivermectin	368	0.79	63.5	38.6	38.3	53.8	46.9
6-monthly ivermectin	413	0.74	65.2	47.2	32.8	52.8	31.8
3-monthly ivermectin	381	0.66	81.0	39.5	43.5	62.4	32.9
Ivermectin groups combined	1162	0.73	69.3	42.0	37.9	56.0	37.3
Significance of difference (*P*)							
Among 4 treatment groups		0.580	0.003	0.236	0.234	0.322	0.396
Ivermectin versus placebo		0.412	0.001	0.071	0.107	0.143	0.129

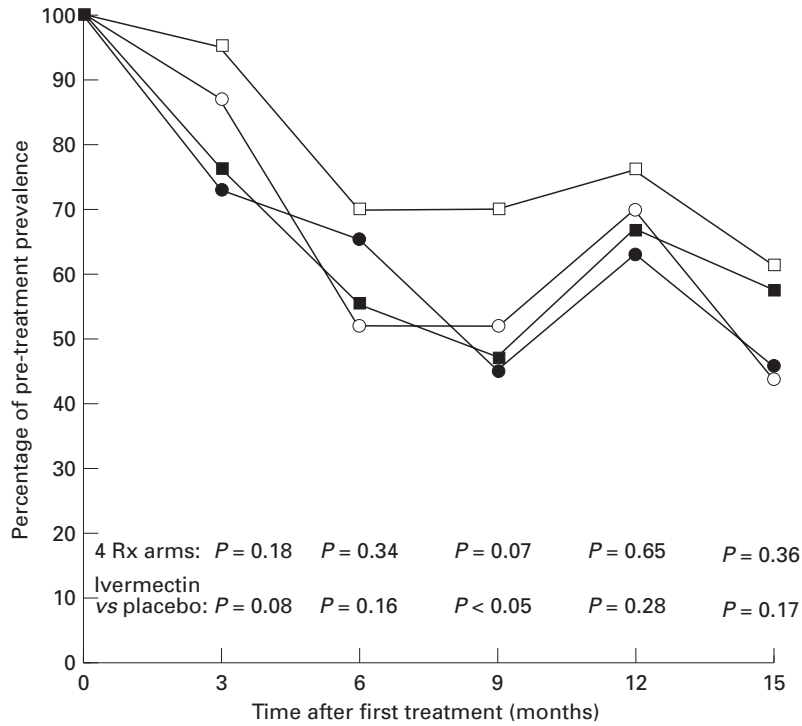

Figure 2 Effect of ivermectin on reactive skin lesions. ■ annual, ● 6 monthly, ○ 3 monthly ivermectin treatment and □ placebo.

Table 6 Effect of ivermectin treatment on reactive skin lesions by pre-treatment skin lesions status

	No. of persons	Prevalence of reactive skin lesions at 3 months	6 months	9 months	12 months	15 months
Persons without reactive skin lesion at first examination						
Placebo	266	12.4	9.0	8.3	12.0	9.4
Annual ivermectin	262	9.2	4.2	3.4	6.5	10.3
6-monthly ivermectin	293	10.6	9.2	5.5	10.6	7.8
3-monthly ivermectin	276	11.2	5.4	6.9	9.1	5.4
Ivermectin groups combined	831	10.3	6.4	5.3	8.8	7.8
Significance of difference *(P)*						
Among 4 treatment groups		0.682	0.045	0.111	0.160	0.179
Ivermectin versus placebo		0.203	0.094	0.055	0.076	0.243
Persons with reactive skin lesion at first examination						
Placebo	101	62.4	46.5	48.5	44.6	36.6
Annual ivermectin	106	53.8	45.3	38.7	50.9	32.1
6-monthly ivermectin	120	47.5	43.3	31.7	37.5	26.7
3-monthly ivermectin	106	57.5	37.7	34.0	46.2	29.2
Ivermectin groups combined	332	52.7	42.2	34.6	44.6	29.2
Significance of difference *(P)*						
Among 4 treatment groups		0.152	0.586	0.056	0.232	0.429
Ivermectin versus placebo		0.055	0.254	0.009	0.545	0.100

evolve over time in the natural history of OSD. The relatively large decrease in APOD, which is regarded as an early stage skin lesion (Murdoch 1992; Pan African Study Group 1995), suggests that ivermectin may prevent, halt or reverse the development of early stage lesions. The preventive effect on severe itching, coupled with the reduction in APOD, are

promising with respect to a preventive effect on skin lesions in the long term. It may take a longer study period before the preventive effect on skin lesions can be detected.

The main limitation of the study is the high defaulter rate at follow-up examinations. Detailed investigations as to the reasons indicated that this was due to the high level of mobility among the rural agricultural populations in the study sites. The overall compliance rate did not decline over time and there was no statistically significant difference in the pretreatment prevalence of itching and reactive skin lesions between those who attended all examinations and those who were not included in the analysis because they had missed some examinations or treatments. Therefore there was no evidence that defaulting had introduced a bias in the results on the effectiveness of treatment. The problem of mobility-related defaulting was also observed by Burnham (1995), and possibly implies the need to recruit larger baseline populations. While stronger follow-up efforts have been suggested, these would likely require a strong and expensive incentive system to counteract the high level of mobility between rural and urban areas, most of which is economic based (Ososanya & Brieger 1994).

There was no significant difference between the effects of the 3-monthly, 6-monthly and annual ivermectin treatment regimens. All regimens showed a similar response pattern with a drop at 3 months in the prevalence of reactive skin lesions, at 6 months in the prevalence of severe itching, and little change from then onward. Surprisingly, the administration of ivermectin at 3-monthly intervals did not appear to give any additional benefit. The reasons for this are not clear. One explanation might be that severe itching in endemic populations is related to the microfilarial load in the skin and that the microfilarial loads in those treated were already so low that any further reduction through additional treatment had little effect. But that does not explain why there remained a substantial amount of reported severe itching after treatment. It is clear from the study that, in relation to OSD, some degree of itching persists for an as yet undetermined period of time after reduction in microfilarial load.

The 6-monthly regimen had the greatest effect on severe itching but the difference with the other treatment regimens was not statistically significant. Given the logistical constraints of more frequent treatments, the results of the present study would suggest that the currently recommended regimen of annual treatment for the control of ocular onchocerciasis is also the most appropriate for onchocerciasis control in areas where the skin manifestations of the disease predominate. We recommend, however, that further studies are undertaken to compare the effectiveness of the 6-monthly and the annual treatment regimens over a period of several years.

Implications for community-based control efforts are several. The short-term benefit in reducing and preventing severe itching was demonstrated and should be an important justification for starting community directed control efforts. In fact, such control efforts have already started in many countries under the auspices of the African Programme for Onchocerciasis Control (APOC). It is in the context of these large-scale control operations that longer-term effect on skin lesions can be observed, and APOC will document at 4-year intervals the effect of large-scale annual ivermectin treatment on ocular and skin disease in sentinel sites in 13 endemic countries. In the short term, educational efforts will be needed to guide community expectations about the benefits of treatment

Generally, community members have found mass ivermectin treatment quite acceptable, as evidenced by a higher return rate among those receiving ivermectin compared with a placebo group in Sierra Leone (Whitworth *et al*. 1991) and by the interest generated by the concomitant expulsion of *Ascaris lumbricoides* (Sumo *et al*. 1993) as well as the reported popularity of ivermectin and the sustained high treatment coverage after many years in control programs (Committee of Sponsoring Agencies 1996). Now the specific disease-related effect of reduction in severe itching can be added to the documented reasons for justifying mass ivermectin treatment in communities within the forest zone of Africa.

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