IVERMECTIN TREATMENT OF ONCHOCERCAL SKIN LESIONS: OBSERVATIONS FROM A PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL IN MALAWI

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Abstract. To determine effects of ivermectin on skin lesions of onchocerciasis, a placebo-controlled, double-blind trial was carried out in the Thyolo highlands of Malawi involving 70 persons over a 32-month period. Assessment was made using both a clinical numeric grading system and sequential photographs. Among both ivermectin and placebo recipients, there was a significant reduction in both the severity and extent of papular skin lesions. Persons with edematous or lichenified skin lesions of onchocerciasis who received ivermectin showed significantly more improvement than those receiving placebo. Twelve months after the placebo group received ivermectin, their skin lesions were similar to those of the ivermectin group. Changes were most evident for those persons with more severe skin disease in both the ivermectin and placebo groups. Annual ivermectin treatment for onchocercal skin lesions is probably inadequate, and treatment three or four times a year may be required, although the optimum regimen has not been established.

Onchocerca volvulus is a major cause of skin disease in many tropical countries in which the disease is prevalent.¹ Destruction of microfilariae evokes inflammation in the skin, the eye, and probably elsewhere. Initial presentation is usually an itchy papular skin reaction. Lesions are often excoriated and secondarily infected. Edema and lichenification are frequently present. With time, continuing inflammation leads to destruction of elastic fibers and collagen causing atrophy that is manifest as shiny fine wrinkled skin, increased skin fragility and, in the extreme, hanging groin. Spotty depigmentation around the pelvic girdle and pretibial area occurs because there is a gradual loss of epidermal melanin from chronic inflammation.^{1,2}

The severity of skin lesions does not clearly correspond to the intensity of infection and it seems more related to the state of immunologic reactivity toward microfilariae.³ In the Thyolo highlands of Malawi, the prevalence of infection among adults may reach 60%, but most have less than 20 microfilariae per milligram of skin. In spite of the light microfilarial counts, skin manifestations of onchocerciasis are common, and many are quite severe. The prevalence of skin lesions may be a consequence of heightened immune reactivity to microfilariae which, in turn, may reflect the effects of seasonal transmission or little immune tolerance to *O. volvulus*.⁴ Although the ocular consequences of onchocerciasis have been extensively studied, much less attention has been given to onchocercal skin lesions or to their social and economic consequences.

Regular treatment with ivermectin not only can prevent blindness due to onchocerciasis, but offers the potential of reversing established skin lesions as well. To evaluate the effect of yearly ivermectin on various types of onchocercal skin lesions, this study was carried out as part of a larger ivermectin study that investigated the adverse effects occurring with mass treatment.⁵

SUBJECTS AND METHODS

Participants. Two communities were selected in areas in which more than 50% of the persons 15 years of age and older had been found to be infected with *O. volvulus*.⁶

The nature of the study was discussed with village leaders and their consent was obtained. Persons at least five years of age with skin lesions were asked to come forward for examination. Those with skin lesions typical of onchocerciasis were offered treatment after the nature of the study was explained. From those consenting to participate, two skin snips were taken bilaterally from the iliac crest area. Those not wishing to participate were referred to a hospital where ivermectin treatment was available.

Of the 106 persons identified with skin lesions and who accepted treatment, one-third received placebo and two-thirds received ivermectin using the same stratified randomization procedures as for participants in the adverse effects study.⁵ Ivermectin, 150 µg/kg, or placebo was given following registration (0 months), at 12 months, and at 20 months. Skin assessment was carried out at registration, then at six, 12, 20, and 32 months. Skin snips were taken only at the time of registration. At 20 months, placebo recipients were given ivermectin, and the entire community was enrolled in an ivermectin mass-distribution program.

Assessment. Skin lesions were assessed at each visit using both a clinical assessment scale and photographed for a later independent evaluation.

Clinical assessment scale. Lesions were graded clinically as to severity and distribution using a numeric scale adapted from Mackenzie and others⁷ and are detailed in Table 1. Five assessments were done by the author over a 32-month period. Since not all participants attended each follow-up visit, analysis was done comparing the skin lesions of those attending at a particular visit with their own pretreatment values on the assessment scale, using a paired *t*-test.

Photographs. Sequential photos were taken of the same sites at each visit. After the fourth examination (20 months), the photographs were evaluated by a dermatologist experienced with onchocerciasis in Malawi. Papular or lichenified lesions were separately graded using a four-point scale based on severity as follows: 0 = no lesions present; + = scattered papules with or without excoriation/mild lichenification; ++ = marked or extensive papules

mild papular lesions

mild lichenified lesions

moderate or severe papular lesions

moderate or severe lichenification

FIGURE 1. Photographic assessment of changes in skin lesions among ivermectin recipients who were examined at six, 12, and 20 months. Change is assessed in comparison with the appearance of lesions upon entry into the study. The clinical scale used to assess severity and distribution of skin lesions was adapted from Mackenzie and others.⁷ ■ = worse; ▨ = little or no change; □ = better; ▩ = much better/cleared.

with excoriation/marked or extensive lichenification; and +++ = severe or widespread papular lesions, excoriated, and maybe confluent or secondarily infected/severe lichenification with or without secondary pigmentary changes (sowda), atrophy, and lymphedema. Changes in the severity of lesions over time in ivermectin and placebo recipients were analyzed by chi-square test.

RESULTS

Of the 106 persons who initially registered, 70 were seen two or more times and only these 70 were included in the analysis. Of these 70, 47 received ivermectin and 23 received placebo. Thirty persons were seen at all four follow-up visits; 27 persons missed one follow-up visit, 17 persons missed two follow-up visits, and two persons missed three follow-up visits. Population migration, as a result of severe drought that occurred during the course of this study, may have contributed to both placebo and ivermectin recipients

missing visits. Placebo recipients were lost to follow-up in the same proportion as were the ivermectin recipients.

Of the 70 persons, microfilariae were present in 39 (range 1–113 mf/mg). The arithmetic mean microfilarial count (mf/mg) was 15.4 mf/mg for ivermectin recipients and 15.0 mf/mg for the placebo group. In those participants who were skin snip-negative, the diagnosis of onchocerciasis was made by the presence of palpable nodules in five and by the characteristics of skin lesions in 26.

Improvement in the severity and distribution of onchocercal skin lesions occurred in both ivermectin and placebo recipients when compared with baseline values. Among persons with papular lesions, both ivermectin and placebo recipients showed statistically significant improvement when compared with baseline status. This was true both for the severity as well as the extent of papular lesions by clinical assessment. Persons with edema, as well as those with lichenified lesions, who received ivermectin had significantly more improvement in skin lesions than those who

TABLE 1

*Clinical scale used to assess the severity and distribution of skin lesions**

Characteristic	Score
Papular lesions (type)	
No papules present	0
Discrete papules localized to one area of the body	1
Discrete papules in multiple areas of the body	2
Confluent papules localized in one area of the body	3
Confluent papules in multiple areas of the body	4
Localized areas of excoriated and infected papules	5
Multiple areas of excoriated and infected papules	6
Papular lesions (extent)	
No lesions	0
Confined to one area of the body	1
Present in several areas of the body	2
Generalized	3
Edema	
No edema present	0
Edema barely detectable	1
Easily detectable edema	2
Edema present that restricts physical activity	3
Lichenification	
No lichenification	0
Barely detectable skin thickening	1
Easily detectable skin thickening in one or more areas	2
Skin thickening associated with scaling or hyperpigmentation	3
Depigmentation	
No depigmentation	0
Occasional spots (<5)	1
Confluent spots	2
Large areas free of pigment	3

* Adapted from Mackenzie and others.⁷

FIGURE 2. Photographs of the same person A, before and B, six months after treatment with ivermectin.

TABLE 2

*Pretreatment clinical scores and percentage changes in these scores at six, 12, 20, and 32 months for ivermectin and placebo recipients, using the clinical scale in Table 1**

	Papular lesion, severity				Papular lesions, extent				Edema				Lichenification			
	Ivermectin		Placebo		Ivermectin		Placebo		Ivermectin		Placebo		Ivermectin		Placebo	
	No.	% pre-treatment	No.	% pre-treatment	No.	% pre-treatment	No.	% pre-treatment	No.	% pre-treatment	No.	% pre-treatment	No.	% pre-treatment	No.	% pre-treatment
Pretreatment (0 months)																
All persons seen at one or more follow-up visits (treatment given)	47	8.3†	23	8.3†	47	14.2†	23	13.6†	22	3.9†	15	2.8†	27	4.5†	13	5.9†
Six months																
All persons seen	32	16.2	15	45.8	32	20.8	15	41.9	12	18.5	11	77.4	27	10.0	10	56.4
Group paired with own pretreatment values		18.4‡		41.0§		22.9‡		42.3§		10.0§		66.7		17.9§		47.8
12 months																
All persons seen	36	24.2	17	26.7	35	28.8	17	24.6	18	35.5	10	64.2	21	27.3	10	97.4
Group paired with own pretreatment values (treatment given)		29.0‡		20.8§		21.4‡		22.6§		30.0§		66.7		24.0§		82.6
20 months																
All persons seen	36	27.4	17	30.5	36	21.7	17	29.4	16	21.6	11	46.4	21	21.1	10	25.6
Group paired with own pretreatment values (treatment given)¶		28.4‡		28.6§		25.4‡		33.0§		25.3§		48.5§		26.5‡		73.8
32 months																
All persons seen	30	10.3	18	14.5	30	7.3	18	25.4	17	7.3	12	8.0	18	11.5	11	15.7
Group paired with own pretreatment values (treatment given)¶		15.4‡		19.1‡		14.7‡		14.3‡		10.7‡		9.3‡		25.8§		35.8§

* Values are the percentage of the pretreatment score at registration. Not all recipients were present for all follow-up visits. For each of the follow-up visits, the first column compares the means for all ivermectin- and placebo-treated recipients returning at that visit, with the mean scores for all ivermectin- and placebo-treated recipients at registration. In the second column, for each follow-up visit the mean scores of the group returning are compared with their own scores at registration. † Mean pretreatment values. ‡ $P < 0.001$. § $P < 0.05$. ¶ Placebo group received ivermectin at 20 and 32 months.

FIGURE 3. Photographs of the same person **A**, before and **B**, six months after treatment with ivermectin.

received placebo. By photographic assessment, improvement in skin lesions among ivermectin recipients was not statistically greater than among the placebo group. The pretreatment clinical scores for ivermectin and placebo recipients using the scale presented in Table 1 and the percentage change from these pretreatment scores following treatment are shown in Table 2. Photographic assessments are shown in Figure 1. Photographs of skin lesions before treatment and six months after receiving ivermectin are shown in Figures 2 and 3. Photographs showing spontaneous improvement in skin lesions in placebo recipients are shown in Figures 4 and 5.

Variations in the intensity and distribution of skin lesions from one visit to another were observed among placebo recipients, and to a lesser extent among those taking ivermectin. This was particularly true for papular lesions, although much less so for lichenified lesions.

Persons presenting severe and extensive papular lesions attended follow-up sessions as faithfully as those with less extensive lesions. However, there was an attrition with time in the numbers of persons with severe lichenification or edema attending, both among placebo and ivermectin groups. The mean score for severity and extent of papular lesions at 20 months among those who received ivermectin

at 12 months was less than those who missed treatment two, although the differences are not significant.

There was no noticeable difference in the response to ivermectin between those who had microfilariae in skin snips or nodules present and those who did not. There was no correlation between microfilarial counts and changes in skin lesions over time in either ivermectin or placebo recipients. Neither was the response in those more than 45 years old any different from younger persons. No differences in response were noted by sex.

Pruritus was specifically queried at each visit, and it was almost universally reported by both ivermectin and placebo recipients. A general impression from ivermectin recipients was that treatment brought a relief from itching that lasted only a few months, and symptoms had returned within six months. Excoriation marks were recorded when present, but there was no clear pattern.

Common adverse reactions to ivermectin were itching, aggravation of skin lesions, and edema, usually of the face or limbs. These reactions seldom lasted more than 2–3 days. No life-threatening reactions occurred. Symptomatic treatment with antihistamine and analgesics was provided to those complaining of adverse reactions.

Photographic interpretation showed that pigmented pre-

FIGURE 4. Photographs showing spontaneous improvement of skin lesions and skin edema of the arm and back over a seven-month period in a recipient receiving placebo.

tibial skin lesions progressed in one person who received ivermectin, and repigmentation occurred in three. In all four, the changes were very small.

Evaluation of lesions using the clinical grading of lesions and photographic assessment produced similar results. The dermatologist noted slightly more lichenification than did the clinical examiner and less change with time than the clinical assessment, especially with lichenified lesions. The clinical assessment had the advantage of detecting distribution of lesions and the presence of edema more readily.

DISCUSSION

Over a 32-month period, the severity and distribution of papular skin lesions improved significantly among both ivermectin and placebo recipients compared with baseline values. Among persons with edema and lichenified lesions, persons receiving ivermectin did significantly better than the placebo group, although both groups improved. The treatment proved to be well-tolerated and without serious adverse reactions.

Some ivermectin recipients with papular or lichenified lesions said their lesions had improved immediately after treatment, but had begun to worsen 4–6 months later. This

suggests that for persons with moderate or severe skin disease, ivermectin every three or four months might be more effective. A similar conclusion has also been made by Pacque and others during the evaluation of the response to ivermectin of onchocercal skin lesions in Liberia.⁸

Complaints of itching among ivermectin recipients were not significantly less than placebo recipients, a finding similar to that of Whitworth and others.⁹ The Malawi ivermectin trial drew a similar conclusion.⁵ Availability of free medications and attention from field staff may have increased the frequency with which participants reported itching. Excoriations were noted in some participants during clinical examinations, but there was no clear pattern.

Some variation in skin lesions with time due to intermittent episodes of immune-mediated microfilarial destruction had been anticipated.^{8, 10} The substantial improvement seen among many placebo recipients, particularly with papular lesions, was unexpected, and not considered in the study design. Some placebo recipients may have entered the trial during a phase of immune hyperactivity that would have been responsible for an episode of acute skin lesions. If this hyperactivity subsequently abated, skin lesions could have lessened in severity or cleared altogether.¹¹

In this study, a numerical grading scheme was found to

FIGURE 5. Photographs showing spontaneous improvement of skin lesions of the legs and thighs over a 20-month period in a placebo recipient.

be useful in evaluating the nature and the extent of onchocercal skin lesions and their changes with time. The classification recommended by Murdoch and others,¹² which was similar to that used in this study, could help document the prevalence of skin disease and response to treatment across foci. Although photographic assessment of lesions had the advantage of producing a permanent record that could be subsequently examined by others, there was difficulty with lighting, recording the extent of disease, and film processing. Nonetheless, photographic assessment was a valuable adjunct.

The availability of effective onchocerciasis treatment has awakened interest in the control of nonocular morbidity. Persons infected with *O. volvulus* weigh less and have more symptomatic complaints than the uninfected.¹³ In Uganda, onchocerciasis has been associated with a six-fold increase in the risk for epilepsy.¹⁴ The social consequences of skin disease has been studied in Nigeria.¹⁵ In Enugu State, Nigeria, Amazigo noted that the presence of onchodermatitis could prevent adolescent girls from marrying.¹⁶ Onchocerciasis probably plays a role in reduced productivity through mechanisms other than blindness, although this has received little attention.^{17, 18}

This trial has shown that ivermectin has potential for the

improvement of at least some skin lesions of onchocerciasis. Further work is needed to confirm these findings and explore the effects of ivermectin on papular skin lesions. Design of further trials should consider the changing patterns of onchocercal skin changes, particularly papular lesions, which appear to be part of the natural history of this disease. The six monthly observations used in this study were clearly too infrequent to detect these changes. It also seems evident that annual ivermectin treatment at a dose of 150 $\mu\text{g/kg}$ is suboptimal for treatment of onchocercal skin lesions. Ivermectin every three months, an interval that corresponds to the gestation period of microfilariae, would seem to be a reasonable basis for a further study.¹⁹ With effective treatment available, an understanding of the natural history of onchocercal skin lesions may now be harder to obtain.

Acknowledgments: Appreciation is expressed to Dr. Vincent Gooskins for evaluations of skin photographs, to Fedson Nkhoma, Laxton Manyika, and Kennix Makina for assistance with the field work, and to the residents of Amosi and Walani villages in Thyolo district for cooperation and good humor.

Financial support: This work was supported by was provided by World Health Organization/TDR grant no. 870069.

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REFERENCES

1. Connor DH, Palmieri JR, 1985. Blackfly bites, onchocerciasis and leopard skin. *Trans R Soc Trop Med Hyg* 79: 415-417.
2. Maizels RM, Lawrence RA, 1991. Immunological tolerance: the key feature in human filariasis? *Parasitol Today* 7: 271-276.
3. Ghalib HW, Mackenzie CD, Kron MA, Williams JF, El Khalifa M, El Sheikh H, 1987. Severe onchocercal dermatitis in the Ethiopian border region of Sudan. *Ann Trop Med Parasitol* 81: 405-419.
4. Prod'hon J, Ambroise-Thomas P, Lardeux F, 1982. Etude serologique et parasitologique comparative de deux villages d'hyperendemie onchocerquienne au Mali (zone de savane) et en cote d'Ivoire (zone pre-forestiere). Relation avec la gravite de la maladie. *Ann Soc Belg Med Trop* 62: 343-352.
5. Burnham GM, 1993. Adverse reactions to ivermectin. Results of a placebo-controlled, double-blind trial in Malawi. *Trans R Soc Trop Med Hyg* 87: 313-317.
6. Burnham GM, 1991. Onchocerciasis in Malawi. 1. Prevalence, intensity and geographical distribution of *Onchocerca volvulus* infection in the Thyolo highlands. *Trans R Soc Trop Med Hyg* 85: 493-496.
7. Mackenzie CD, Williams JF, Sisley BM, Steward MW, O'Day J, 1985. Variations in host responses and the pathogenesis of human onchocerciasis. *Rev Infect Dis* 7: 802-808.
8. Pacque M, Elmets C, Dukuly ZD, Munoz B, White AT, Taylor HR, Greene BM, 1991. Improvement in severe onchocercal skin disease after a single dose of ivermectin. *Am J Med* 90: 590-594.
9. Whitworth JAG, Luty AJF, Maude GH, Morgan D, Downham MD, Taylor DW, 1992. Ivermectin does not reduce the burden of itching in an onchocerciasis endemic community. *Trans R Soc Trop Med Hyg* 86: 281-283.
10. Mackenzie CD, Williams JF, 1985. Variations in the clinical presentation of onchocerciasis and their relationship to host-parasite interaction. *Sudan Med J* 21 (suppl): 41-48.
11. Mackenzie CD, Williams JF, Guderian RH, O'Day J, 1987. Clinical responses in human onchocerciasis: pathological and immunological implications. Evered D, Clark S, eds. *CIBA Symposium on Filariasis*. Chichester, UK: John Wiley & Sons, 46-67.
12. Murdoch ME, Hay RJ, Mackenzie CD, Williams JF, Ghalib HW, Cousens S, Abiose A, Jones BR, 1993. A clinical classification and grading system of the cutaneous changes in onchocerciasis. *Br J Dermatol* 129: 260-269.
13. Burnham G, 1991. Onchocerciasis in Malawi. 2. Subjective complaints and decreased weight in persons infected with *Onchocerca volvulus* in the Thyolo highlands. *Trans R Soc Trop Med Hyg* 85: 493-496.
14. Kipp W, Kosoro S, Burnham G, 1994. Onchocerciasis and epilepsy in Uganda (letter). *Lancet* 343: 183-184.
15. Nwoke BEB, 1990. The socio-economic aspects of human onchocerciasis in Africa: present appraisal. *J Hyg Epidemiol Microbiol Immun* 34: 37-44.
16. Amazigo U, 1993. Onchocerciasis and women's reproductive health: indigenous and biomedical concepts. *Trop Doct* 23: 149-151.
17. Thomson IG, 1971. Onchocerciasis in an oil palm estate. *Trans R Soc Trop Med Hyg* 65: 484-489.
18. Workneh W, Fletcher M, Olwit G, 1993. Onchocerciasis in field workers at Baya farm, Teppi coffee plantation project, southwestern Ethiopia: prevalence and impact on productivity. *Acta Trop (Basel)* 54: 89-97.
19. Duke BOL, Zea-Flores G, Castro J, Cupp E, Munoz B, 1992. Effects of three-month doses of ivermectin on adult *Onchocerca volvulus*. *Am J Trop Med Hyg* 46: 189-194.