Impact of annual dosing with ivermectin on progression of onchocercal visual field loss*

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Reported are the results of a randomized, double-masked, placebo-controlled trial of annual ivermectin dosing in 34 rural communities, Kaduna State, northern Nigeria, where guinea savanna onchocerciasis is mesoendemic. A total of 939 individuals underwent Friedmann field analysis at the first examination and saw at least 19 spots in at least one eye. Of these, 636 (68%) completed a subsequent Friedmann field analysis 2–3 years later. The adjusted incidence rate ratio for the ivermectin group versus the placebo group was 0.64 (95% confidence interval (CI): 0.42–0.98). There was some evidence that the impact of ivermectin was greatest among those who had received one dose of ivermectin. The majority of the deteriorations occurred in eyes that gave evidence of optic atrophy at the first examination. An analysis restricted to individuals with optic atrophy at baseline indicated a reduction of 45% in the incidence of visual field deterioration in the ivermectin group (95% CI: 8–67%). Previous findings have shown that ivermectin has an impact on the incidence of optic atrophy. Our results indicate, for the first time, that ivermectin has a substantial impact on the progression of visual field loss among those with pre-existing optic atrophy.

Introduction

Onchocerciasis is one of the major causes of blindness. Two commonly reported ocular sequelae of onchocercal infection are optic nerve disease and chorioretinitis (*1*), both of which can cause dramatic reductions in the peripheral visual field, leaving only a small island of central vision (*2*). In such cases visual acuity may be largely unaffected until a late stage of the disease process.

Ivermectin is now the drug of choice for the treatment of onchocerciasis, and annual dosing with it substantially reduces the incidence of optic nerve disease among infected individuals (*3*) and produces beneficial effects on other onchocercal eye lesions, including punctate keratitis (*4*) and iridocyclitis (*5*). Less is known, however, about the impact of ivermectin on visual function loss and, in particular, visual field loss. In this article we report the effect of annual dosing with the drug on the progressive deterioration of visual field loss in northern Nigeria.

Methods

The population studied and methods used in the trial have been described previously (*3*, *6*), Briefly, a randomized, double-masked, placebo-controlled trial of ivermectin was conducted in 34 rural communities that were mesoendemic for guinea savanna onchocerciasis, in Kaduna State, northern Nigeria. A census was carried out on the communities and demographic data and pertinent information, such as previous use of diethylcarbamazine (DEC), was collected.

Skin-snips were taken from villagers aged ≥5 years, who were then registered for inclusion in the trial and randomly assigned at the individual level using a blocked design to receive ivermectin or placebo. Annual dosing with ivermectin/placebo was performed over a 3-year period. At the fourth annual round, all villagers received ivermectin. Standard exclusion criteria were applied at each dosing.

The trial participants underwent ophthalmic examination prior to the first, third, and fourth annual dosings. At each examination all villages were visited, and registered individuals were asked to report to a central location in their village. Each patient was screened for signs of optic nerve disease by a team of ophthalmic nurses who had received intensive training from two ophthalmologists (*I.M.*, *O.E.B.*)

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before the start of the fieldwork. The screening examination consisted of a series of visual function tests (including visual acuity, peripheral visual field assessment by counting fingers in all four quadrants, paracentral visual field assessment using a variety of tests, colour vision, and a test for red desaturation), applanation tonometry, examination of pupillary light response, and undilated fundoscopy to assess optic disc colour and cup:disc ratio. Individuals who failed the screening examination were referred to an ophthalmologist; the referral criteria included reduced visual acuity that did not improve to 6/9 with pinhole, failure of any of the other visual function tests, and intraocular pressure ≥2.80 kPa (≥21 mmHg), an abnormal pupillary light response, suspicion of disc pallor or a cup:disc ratio >0.5. In addition, individuals belonging to a computer-generated random sample of the trial population were also referred to an ophthalmologist, regardless of the outcome of the screening examination.

The ophthalmologist examined the referred patients in a mobile clinic equipped with a slit-lamp biomicroscope, applanation tonometer, and retinal camera. After the patient's pupillary light response had been checked, the individual concerned returned to the ophthalmic nurse for pupillary dilation, dark adaptation, and Friedmann mark I visual field analysis. Topical mydriatics (cyclopentolate hydrochloride (1% (w/v)) and phenylephrine hydrochloride (10% (w/v)) were instilled until the pupils were maximally dilated and nonreactive to light.

The Friedmann mark I Analyser is a form of static perimetry in which the central 25° of visual field is measured at a distance of 33 cm. A total of 46 illuminated targets (generated by electronic flash and modified by specified neutral density filters) are presented to the patient in patterns of two, three, or four at a time. The patient indicates how many points or "spots" were seen and localizes their position; the points are then recorded on a standard form with the corresponding filter value at which they were seen. This form of field analysis is less sensitive to some early visual field defects than some other methods, such as computer-assisted or Goldmann (*7*). The Friedmann Analyser performs relatively well at detecting visual fields with a central island or central defects (*8*). Since onchocercal defects essentially constrict the visual field with preservation of a central island (*2*), the Friedmann Analyser is suitable for use in onchocercal populations. The mark II Friedmann Analyser tests 98 rather than 46 points, but the small advantage that this would provide (*9*) was not considered sufficient to warrant the additional test time required, nor the increased potential for machine failure. Field loss, as measured by the Friedmann Analyser, may manifest itself as either a decrease in sensitivity or absolute loss of stimulus perception. In this article, we consider only absolute loss of stimulus perception.

The Friedmann field analyses were performed in rooms darkened with blackout material. The patient sat at the appropriate height and used the palm of one hand to occlude one eye. The nurse performing the analysis explained the test in Hausa, the most widely spoken language in the area, and the macular threshold was determined. Individuals were encouraged to maintain central fixation and were observed while the test was run at 0.4 dB below the macular threshold, at a further 0.4 dB below this value, and finally at maximum brightness, when necessary. The results of the test were noted on the standard Friedmann analysis form. At the first examination, the Friedmann test for each patient was performed by the ophthalmic nurse who had performed the screening examination; at the subsequent examinations, all Friedmann field tests were performed by one ophthalmic nurse.

Following Friedmann field analysis, the patient returned to the mobile clinic. At the second and third examinations the ophthalmologist compared the Friedmann field result with any previous results using a quadrant-by-quadrant summary. If there were major incongruities, the Friedmann analysis was repeated. Patients then underwent posterior segment examination with slit-lamp biomicroscopy, direct and indirect ophthalmoscopy, and fundus fluoroscein angiography. Upon completion of the examination, patients were dosed with ivermectin/placebo by a general physician or rural health officer.

In order to identify individuals with visual field deterioration during follow-up, an initial analysis of Friedmann field changes was performed. The number of individuals showing an improvement was compared with the number showing a deterioration for each designated cut-off point (e.g. ≥12 spots lost or gained). We assumed that most apparent improvements were probably due to measurement variations rather than true improvements, and in order to maintain as high a specificity as possible, we chose as cut-off point the minimum number of spots lost/gained that produced a ratio of deteriorations: improvements ≥10:1. The cut-off point thus identified was a change of ≥19 spots seen/not seen in one eye (92 individuals with deteriorations versus 8 with improvements, 4 of whom received ivermectin). Below, "visual field deterioration" refers to the absolute loss of ≥19 of the 46 Friedmann spots in one eye during the period of follow-up. Only changes between the first and last examination are considered here.

Data were double-entered on microcomputers and analysed using SAS/PC and EGRET software

packages. Poisson regression was used to estimate the incidence ratios using person-time of follow-up as the denominator. The homogeneity of the rate ratio (ivermectin versus placebo) across different values of other variables was tested by fitting an interaction term and examining the likelihood ratio statistic (*10*).

Results

Follow-up

At the first examination and dosing, 939 individuals registered in the trial underwent Friedmann field analysis and saw ≥19 spots in at least one eye (and thus were at risk of deterioration according to the definition chosen). Of these individuals, 636 (68%) completed a Friedmann field analysis at one or more of the follow-up examinations. The mean period of follow-up was 28.3 months (range, 17.0–38.0 months). Follow-up was similar in the two treatment groups (ivermectin = 314 individuals (66%), mean = 28.3 months; placebo = 322 individuals (69%), mean = 28.2 months). The rate of follow-up was not associated with age ($P = 0.19$), sex ($P = 0.18$), or microfilarial load at baseline ($P = 0.18$). Rates of follow-up were higher among individuals in the random sample (75% versus 63%, $P < 0.001$) and those who had reported having taken DEC (77% versus 60%, $P < 0.001$). Follow-up also varied according to the individual's Friedmann field status at baseline, being highest among those who had missed some, but not all spots in their worse eye (75%), compared with 64% among those who had seen all 46 spots and 68% among those who had missed them all ($P = 0.04$).

Baseline characteristics of the treatment groups

Table 1 shows the distribution of individuals and follow-up time by treatment group according to age at census, sex, microfilarial load at baseline, reported history of DEC consumption, membership of the random sample, and the results of the Friedmann field analysis at baseline. There were no major differences between the two treatment groups with regard to any of these variables. All age groups were represented, though the number of individuals aged over 64 years was comparatively small. There were more males (55%) than females. The majority of individuals (71%) were skin-snip positive at baseline, 31% having loads >10 microfilarae (mf) per mg; very few, however, had loads >50 mf per mg (6%). About half (52%) reported having used DEC. A total of 270 individuals (42%) were from the random sample; 348 individuals (55%) saw all Friedmann spots in both eyes at baseline, while 67 individuals (11%) missed all 46 spots in one eye.

Treatment with ivermectin/placebo

Of the 636 individuals who completed follow-up, 255 (40%) underwent Friedmann field analysis only twice (at the start and end of follow-up), 286 (45%) three times, and 95 (15%) on four occasions. The mean number of analyses performed was similar in the two treatment groups (ivermectin = 2.73; placebo = 2.76). Over the period of follow-up, 273 individuals (43%) received three doses of ivermectin/placebo between their first and final examinations, 287 (45%) two doses, 60 (9%) one dose, and 16 (3%) were excluded at each dosing round and thus were never dosed during the period of follow-up. The distribution of the number of doses received by individuals with follow-up in the two treatment groups was similar (Table 1).

Visual field deteriorations

A total of 92 individuals (14%) had "lost" at least 19 spots in one eye between the baseline and follow-up examinations. Of these individuals 19 had suffered bilateral deteriorations, while the other 73 had deteriorated unilaterally. Of these 92 individuals, 34 (37%) were in the ivermectin group and 58 (63%) in the placebo group (Table 1), giving an incidence ratio of 0.60 (95% confidence interval (CI) = 0.39–0.92; $P = 0.02$) in the ivermectin group relative to the placebo group.

The incidence of deteriorations tended to increase with age ($P < 0.001$), although there were relatively few instances among those aged 55–64 years, and was higher among males than females ($P = 0.02$) in both treatment groups (Table 1). Deteriorations appeared to be commoner among the skin-snip positive, particularly in the placebo group ($P = 0.03$). There was no evidence that reported DEC consumption prior to the initial examination was associated with the incidence of visual field deteriorations during the period of follow-up ($P = 0.15$). Deteriorations among members of the random sample (who had not necessarily failed the screening examination) were much less likely than among those who were not members of this sample (and who had failed the screening examination; $P < 0.001$). Visual field status at baseline was associated with rate of deterioration ($P < 0.001$), deteriorations tending to be more frequent among individuals who had missed spots at baseline. Although the incidence of deteriorations appeared to increase with the num-

Table 1: **Baseline characteristics, number of Friedmann field analyses undergone, number of doses of ivermectin/placebo received, and incidence of deteriorations in Friedmann visual field analysis, by treatment group, among the study subjects**[a]

	Ivermectin group			Placebo group		
	n	No. with deterioration	Incidence (per 100 person-years)	*n*	No. with deterioration	Incidence (per 100 person-years)
Age (years)						
5–14	24	1	1.80	23	0	0
15–24	45	1	0.96	38	0	0
25–34	67	4	2.52	68	14	8.88
35–44	76	9	4.92	88	18	8.76
45–54	57	11	8.28	53	13	10.20
55–64	29	3	4.56	36	3	3.60
⩾65	16	5	12.60	16	10	25.20
Sex						
Male	172	24	5.88	176	38	9.12
Female	142	10	3.00	146	20	5.88
Microfilarial load						
Negative	94	7	3.24	89	8	3.72
0.1–10.0	119	16	5.64	131	31	9.96
10.1–50.0	73	8	4.68	82	17	9.00
50.1–100.0	20	3	6.12	12	2	6.72
>100	2	0	0	4	0	0
Unknown	6	0	0	4	0	0
DEC[b] taken in past						
No	156	14	3.96	149	22	6.48
Yes	155	20	5.40	173	36	8.64
Unknown	3	0	0	0	0	Undefined
Random sample						
No	174	31	7.56	192	48	10.56
Yes	140	3	0.96	130	10	3.36
No. of spots missed in better eye at baseline						
0	229	17	3.12	245	37	6.48
1–10	43	12	11.64	36	14	16.56
11–20	24	4	7.32	28	6	9.12
⩾21	18	1	2.16	10	1	4.32
No. of spots missed in worse eye at baseline						
0	169	6	1.56	179	17	4.08
1–10	38	10	10.92	51	16	13.44
11–20	28	5	7.44	21	4	7.68
21–45	43	6	5.76	40	9	9.60
All	36	7	7.92	31	12	16.20
No. of Friedmann analyses performed						
2	133	10	3.64	122	16	6.55
3	132	15	4.48	154	31	7.91
4	49	9	6.89	46	11	9.00
No. of doses of ivermectin/placebo received						
0	7	1	6.72	9	1	5.28
1	36	1	1.32	24	8	15.00
2	137	9	3.12	150	23	7.44
3	134	23	6.36	139	26	6.96
Total	314	34	4.56	322	58	7.68

[a] A subsample was also examined 7–14 days after first dosing, so that some individuals underwent four Friedmann field analyses.
[b] DEC: diethylcarbamazine.

ber of Friedmann analyses performed, this trend was not statistically significant ($P = 0.12$). None of these factors appeared to confound the association between treatment group and incidence of visual field deterioration.

When each variable was entered individually into a Poisson regression model containing a term for treatment group, the rate ratio for ivermectin versus placebo varied between 0.59 (number of spots missed by worse eye at baseline) and 0.63 (membership of random sample). The impact of ivermectin could vary with age (rate ratio = 0.47, <45 years; rate ratio = 0.93, 45–64 years; rate ratio = 0.50, >65 years), but this variation was not statistically significant ($P = 0.35$). Also, there was no evidence that the impact of ivermectin on the incidence of visual field deteriorations varied with any of the following: sex ($P = 0.50$); microfilarial load ($P = 0.84$); DEC ($P = 0.92$); random sample membership ($P = 0.14$); visual field status at baseline ($P = 0.70$); and number of Friedmann field analyses performed ($P = 0.84$).

The incidence of visual field deterioration was not associated with the number of doses of ivermectin/placebo received ($P > 0.50$; Table 1). However, when individuals who had not received any doses of ivermectin/placebo were excluded there was some evidence that the impact of ivermectin varied according to the number of doses received, the impact appearing to be greater among those receiving one or two doses of ivermectin/placebo than among those receiving three doses (rate ratios: 0.09, 0.42 and 0.92, resp.; $P = 0.02$).

A Poisson regression model was fitted to estimate the impact of ivermectin on the incidence of visual field deteriorations, adjusting for age, sex, microfilarial load, reported use of DEC, membership of the random sample, visual field status at baseline (worse eye), number of Friedmann field analyses performed, and number of doses of ivermectin placebo received. Treatment with ivermectin was associated with a 36% reduction in the incidence of visual field deterioration (incidence rate ratio = 0.64; 95% CI = 0.42–0.98; $P = 0.04$).

To investigate the etiology of the observed deteriorations, we reviewed the records of all 92 individuals with visual field loss to determine the prevalence among them of media opacities, chorioretinal, and optic nerve pathologies at the end of follow-up. A total of 24 individuals had evidence of media opacities, mostly in the lens, that could have restricted visual function (13 ivermectin, 11 placebo). Of those individuals, 21 also had evidence of optic nerve and/or chorioretinal pathology.

The distribution of optic nerve and chorioretinal disease among the 92 individuals with visual field loss is shown in Table 2. More than 90% had clinical evidence of optic nerve pathology, while just over half had clinical evidence of chorioretinal pathology. More than 40% had optic nerve pathology in the absence of chorioretinal pathology, while only one individual had chorioretinal pathology in the absence of optic nerve pathology.

Table 2: **Distribution of optic nerve and retinal pathologies at the end of follow-up among 92 individuals with visual field deteriorations, by treatment group**

Pathology	No. of individuals		
	Ivermectin group	Placebo group	Total
Optic nerve only	15 (44)[a]	24 (41)	39 (42)
Retina only	1 (3)	0 (0)	1 (1)
Optic nerve and retina	14 (41)	33 (57)	47 (51)
Neither pathology	4 (11)	1 (2)	5 (5)
Total	34 (100)	58 (100)	92 (100)

[a] Figures in parentheses are percentages.

Discussion

Our results suggest that annual dosing with ivermectin reduces by 36% the occurrence of visual field deterioration, which is similar to our previous finding that such dosing reduces the incidence of optic nerve disease by about 35% (*3*).

This similarity is, perhaps, not surprising since optic nerve disease typically results in visual field loss. Our definition of an incident case of optic nerve disease was an individual with one or both eyes having onset of optic disc pallor associated with a deterioration in visual function and/or pupillary light response (these cases therefore constitute cases of optic atrophy). One approach to identifying visual function deterioration is Friedmann field analysis. Thus, it is therefore plausible that both of these outcome measures reflect the same deteriorations, in the same eyes, in the same individuals. This was, however, not the case. Of the 92 individuals we identified with visual field deterioration, only 14 (15%) were considered to have suffered onset of optic nerve disease (optic atrophy) during the follow-up period. Furthermore, among these 92 individuals, 111 eyes were identified as having suffered visual field deterioration, and of the latter eyes, only 7 (6%) had developed optic nerve disease as defined above. The apparent inconsistency between the data for individuals and those for eyes arises because some individuals experienced onset of optic atrophy in one eye and visual field deterioration in the other.

The majority of the 111 eyes with visual field deterioration (75%) already had evidence of optic atrophy at the baseline examination. Of the 13 random sample individuals with deteriorations, 12 (92%) failed the nurse's screening examination at baseline. The one individual who was not identified at baseline suffered a traumatic cataract during follow-up. Thus, while our previous findings (*3*) revealed that ivermectin had an impact on the incidence of optic atrophy, our present results suggest that it has also an impact on the progression of pre-existing disease.

An analysis restricted to individuals with optic atrophy at baseline confirms the above impression (Table 3). Among such individuals ivermectin was associated with a 52% reduction in the incidence of visual field deteriorations ($P = 0.004$). There was no strong evidence to suggest that the impact varied with the number of doses received (1 dose, rate ratio = 0.27; 2 doses, rate ratio = 0.38; 3 doses, rate ratio = 0.63; $P = 0.24$). After adjustment for age, sex, microfilarial load at baseline, and visual field in the worse eye, the estimated reduction in the incidence of visual field loss in those receiving ivermectin was 45% (95% CI = 8–67%).

Our data indicate that optic nerve pathology, alone or in combination with chorioretinal pathology, is an important cause of visual field loss in the study population; chorioretinal pathology in the absence of optic nerve pathology does not appear to be important in this respect. This finding should, however, be interpreted with caution. The original ophthalmic nurses' screening examination, which identified individuals (other than those in the random sample) for Friedmann field analysis, was designed to identify those with optic nerve disease rather than chorioretinal pathology. Individuals with the latter pathology, in the absence of visual function defects at first examination, will in general have been excluded from our sample; however, those with chorioretinal pathology and visual function defects were included.

We have previously reported that the impact of ivermectin on the incidence of optic nerve disease appears to be largely confined to individuals with microfilarial loads >10 mf per mg. The incidence of visual field deterioration by microfilarial load shown in Table 1 suggests that ivermectin has little or no impact on such deterioration among skin-snip-negative individuals (rate ratio = 0.85), but may do so among those with loads <10 mf per mg. In Sierra Leone this threshold density had previously been suggested as being necessary for the occurrence of acute skin changes (*11*). Among individuals with loads ≤10 mf per mg or >10 mf per mg, ivermectin reduced by 43% the rate of visual field deterioration. Such an interpretation of the data should be treated very cautiously, however, since small changes in the values could radically alter the observed pattern; had we, for example, observed two fewer deteriorations in skin-snip-negative individuals receiving ivermectin, the rate ratio among such individuals would have been 0.61. There was no statistically significant interaction between the impact of ivermectin and microfilarial load.

Table 3: **Incidence of visual field deterioration in individuals with optic nerve disease at baseline**

	Ivermectin group	Placebo group
No. of individuals	118	109
Person–months of follow-up	3421	3100
No. of deteriorations	24	45
Rate ratio for ivermectin versus placebo	0.48 (0.29, 0.79)[a]	

[a] Figures in parentheses are the 95% confidence interval.

Our results contain two apparent anomalies which may be related. First, we detected only six individuals aged 55–64 years with visual field deteriorations; in view of the pattern of deteriorations in the other age groups, three or four times as many might have been expected. We have no explanation for this shortfall. Second, the impact of a single dose of ivermectin appears to be greater than that of two or three doses.

The number of doses of ivermectin/placebo received was associated with age and sex — older individuals tending to receive more doses ($P < 0.001$) and 51% of males receiving all three doses compared with only 32% of women ($P < 0.001$). The number of doses received did not appear to vary with initial microfilarial load — 89% of skin-snip-negative individuals receiving two or three doses of ivermectin/placebo compared with 88% of skin-snip positives. The more doses of ivermectin/placebo received, the more likely the individual reported having used DEC ($P < 0.0001$), the less likely the individual was included in the random sample ($P = 0.001$), and the less likely the individual was to have seen all spots at baseline ($P = 0.005$).

We did not skin-snip all individuals annually, since this procedure appeared to reduce participation in the trial, and we aimed to achieve the highest level of ophthalmic follow-up possible. It is highly probable, however, that the first dose of ivermectin produced the greatest reduction in microfilarial load, with subsequent doses producing smaller reductions, as observed in other trials (*12–15*). In addition, Alley et al. (*15*) have reported that microfilarial loads can remain at around half their pre-treatment level for up to 4 years after a single dose of ivermectin. If the

rate of visual field deterioration is associated with microfilarial load, over a 3-year period a single dose might be almost as effective as annual doses. Such a mechanism does not, however, explain why a single dose should appear more effective than two or three doses.

A possible explanation for the observed interaction is that number of doses acts as a proxy for another variable. If, for example, older individuals are more likely than younger individuals to suffer non-onchocercal visual field loss (e.g. because of glaucoma or dense cataract), ivermectin would be expected to have less overall impact among older age groups — the very groups that received more doses of ivermectin/placebo. The plausibility of such an explanation is weakened, however, by our failure to demonstrate any direct interaction between ivermectin and age, sex, or any of the other variables considered. A total of 21 of the individuals with visual field deteriorations had cataracts at the end of follow-up (12 in the ivermectin group and 9 in the placebo group). Excluding such individuals from the analysis gives an estimated rate ratio of 0.49 (95% CI = 0.29, 0.81) for ivermectin versus placebo. The interaction between ivermectin and number of doses of ivermectin/placebo received is then no longer statistically significant ($P = 0.10$). The estimated rate ratios for one, two, and three doses, respectively, are 0.11, 0.35, and 0.74. Similarly, if only individuals with optic atrophy at baseline are considered, there is no strong evidence that the impact of ivermectin varies with the number of doses ($P = 0.23$).

In defining visual field deterioration, we chose a largely arbitrary cut-off point (≥19 spots lost in one eye). The corresponds to a major change in visual function. A strict cut-off point was chosen to ensure a high specificity for our outcome measure. Indirectly, the specificity can be assessed by examining the incidence of deteriorations according to the number of Friedmann field analyses undergone by individuals. If the outcome lacked specificity, the number of deteriorations might have been expected to decrease with the number of investigations as the patient's performance improved. There was no evidence that the incidence of visual field deteriorations was lower among individuals who underwent four analyses rather than only two (Table 1). An alternative indirect means of assessing specificity is to examine the effect of cut-off point, and for this purpose we examined the following: ≥11 spots lost; ≥16 spots lost; and ≥21 spots lost. At these cut-offs the ratio of deterioration in the ivermectin group to that in the placebo group was 0.87, 0.72, and 0.49, respectively (at ≥19 spots the ratio was 0.59). These ratios indicate that the specificity increased with the cut-off point. Crude analysis of these cut-off points indicate that the statistical significance of the impact of ivermectin increased as the cut-off criterion became stricter ($P = 0.38$, $P = 0.07$, $P = 0.01$, $P = 0.002$).

In summary, our findings indicate that annual dosing with ivermectin substantially reduces the rate of visual field loss in guinea savanna communities that are mesoendemic for onchocerciasis. As far as we are aware, this is the first report that ivermectin has an impact on visual function, rather than eye lesions; we have previously found that it has an impact on the onset of onchocercal optic atrophy. In the current study, the majority of cases of visual field loss that were identified occurred in eyes with optic atrophy at baseline. Thus, ivermectin appears to prevent or delay the onset of optic atrophy and subsequently slow the progression of the disease, as measured by visual field loss.

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Résumé

Impact de l'administration annuelle d'ivermectine sur l'évolution de la perte de champ visuel due à l'onchocercose

Cet article décrit l'impact de l'ivermectine en traitement annuel sur la perte de champ visuel, déterminé lors d'un essai randomisé en double aveugle contre placebo. L'essai a été réalisé dans 34 communautés rurales de l'Etat de Kaduna, dans le nord du Nigéria, où l'onchocercose de savane guinéenne est mésoendémique. L'exploration du champ visuel paracentral a été réalisée à l'aide d'un appareil de Friedmann mark I au début de l'essai puis au bout de 2 et 3 ans de suivi. Une perte

absolue de ≥19 points sur un œil pendant la période de suivi a été prise comme seuil de détérioration du champ visuel. Lors de l'examen initial, 939 personnes ont vu ≥19 points avec au moins un œil et ont pu être incluses dans l'étude; l'examen du champ visuel a été répété pendant le suivi chez 636 d'entre elles (68%). Les taux de suivi ont été similaires dans le groupe traité par l'ivermectine et dans le groupe placebo (durée moyenne = 28,3 mois), ces groupes étant bien appariés en ce qui concerne l'âge, le sexe, la charge microfilarienne et l'état initial du champ visuel. Au total, 92 personnes (34 dans le groupe ivermectine et 58 dans le groupe placebo) ont présenté une détérioration du champ visuel. Le rapport d'incidence corrigé du groupe placebo était de 0,64 (intervalle de confiance à 95% = 0,42–0,98). Il semble que l'impact de l'ivermectine soit plus grand chez les personnes qui ont reçu une seule dose que chez celles qui ont reçu trois doses. Une pathologie du nerf optique, seule ou associée à une pathologie chorio-rétinienne, a été observée chez plus de 90% des sujets ayant une détérioration du champ visuel. Alors que l'association de ces deux pathologies était courante chez ces sujets (51%), une pathologie chorio-rétinienne isolée n'a été observée que chez un seul sujet. La plupart des détériorations (75%) ont été observées chez des sujets ayant déjà une atrophie optique au premier examen. Une analyse limitée à ces cas a indiqué une diminution de 45% de l'incidence de la détérioration du champ visuel après administration d'ivermectine (intervalle de confiance à 95% = 8–67%). Nous avions déjà rapporté un impact de l'ivermectine sur l'incidence de l'atrophie optique dans cette même population. Les résultats de la présente étude montrent que ce composé a aussi un impact sensible sur la progression de la perte de champ visuel chez les sujets déjà atteints d'une atrophie optique. Il semble donc que l'ivermectine empêche ou retarde l'apparition d'une telle atrophie et ralentisse l'évolution de la maladie, mesurable par examen du champ visuel. A notre connaissance, c'est la première fois qu'un impact de l'ivermectine sur la fonction visuelle et non sur les lésions oculaires est rapporté.

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