TREATMENT OF ONCHOCERCIASIS WITH IVERMECTIN (PROVINCE OF BURURI, BURUNDI): PARASITOLOGIC AND CLINICAL EVALUATION OF DIFFERENT PERIODICITIES OF TREATMENT

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Abstract. To find out whether biannual treatments of onchocerciasis with ivermectin were necessary or whether annual treatments could suffice, parasitologic and clinical results in Burundi were compared at 12 months after a single treatment and after two treatments with an interval of six months. Adverse reactions were also compared at 12 months, after a second or third treatment, respectively. The biannual treatment resulted in a greater reduction of parasitologic parameters, had a longer-lasting effect on itching, and produced less side effects (especially itching, rash, and swellings) at 12 months than an annual treatment. Skin lesions were not significantly modified by any of the treatment schemes at 12 months. Notwithstanding this slight advantage of biannual treatment, operational constraints forced us to choose an annual distribution of ivermectin. With minimal resources, a distribution scheme was organized that was adapted to the different levels of endemicity of onchocerciasis. The results of this study may be of interest to policy makers and public health officials in areas where logistical and resource issues severely restrict the scope of treatment programs. In view of the planned activities of the African Programme of Onchocerciasis Control, the achievements in Burundi indicate that even with limited resources, an appropriate annual distribution scheme can give meaningful results. In spite of the persistence of skin lesions, their severity decreased and most patients considered that their condition had improved even after just one year.

After cases of onchocerciasis were first reported in Burundi in the 1970s, detailed surveys were performed to determine the extent of the endemic areas, as well as the parasitologic and clinical parameters of the disease. The existence of an endemic area in the province of Bururi was confirmed, with prevalences in the different collines (administrative units) reaching 75% in the hyperendemic zone.

By the time these surveys were completed, the drug ivermectin was registered and treatment of onchocerciasis became easier. Indeed, ivermectin has advantages over diethylcarbamazine because it reduces prevalence figures and intensity of infection more and over a longer period, and because adverse reactions are milder. Ivermectin can also be taken as a single dose. However, ivermectin in the prescribed dosage is mainly a microfilaricide and, like diethylcarbamazine, the treatment has to be repeated.

For operational reasons it seemed difficult to organize distributions biannually in Burundi. To find out whether biannual treatments had more advantages or whether annual treatments could suffice, we decided to compare parasitologic and clinical results at 12 months after a single treatment, and also at 12 months but after two biannual treatments. Adverse reactions after each treatment were also recorded, as well as the subjective findings of the treated people.

PATIENTS AND METHODS

Survey. This study was approved by the Ethics Committee of the University of Burundi. All persons who were examined and/or treated provided informed consent to participate in the study. For children in the study, consent was provided by their parents. The survey was organized in the colline of Muhanda, which is situated in the onchocerciasis hyperendemic area of the province of Bururi. Treatment with ivermectin had started in this hyperendemic area in November 1990. One colline was treated at a time, and the first treatment round in Muhanda was not planned until April 1991. According to the population census of 1990, Muhanda had 2,755 inhabitants. A random sample of 120 families was chosen from a list provided by the local authorities. One hundred eight families responded. A total of 471 persons four or more years of age were examined in April 1991 before the treatment with ivermectin started. The examination consisted of a questionnaire and a physical and parasitologic examination. Personal data (identification) and information about the perception of itching were recorded. Itching was registered as yes (frequently/troublesome) or no (exceptionally/never). The skin of patients was palpated for subcutaneous onchocercal nodules and swollen inguinal lymph nodes, and examined for skin lesions typical of onchocerciasis (altered pigmentation, papular dermatitis or crab craw, lichenoid change, atrophy, and late depigmentation) as described by Buck. Craw craw was considered as a form of severe papular dermatitis often involving edema of the skin. Onchocercal nodules were counted and inguinal lymph nodes and the different skin lesions were characterized as present or absent. Visual acuity (with both eyes, as defined by the World Health Organization Study Group on the Prevention of Blindness) was tested with Snellen’s illiterate E-test.

The skin scarification technique was used for the parasitologic examination. This technique and its sensitivity and value compared with other techniques has already been described and evaluated. Briefly, four incisions 8 mm in length and 2 mm apart were made at the level of the iliac crest. After approximately 10 sec, the skin was squeezed until tissue fluid mixed with blood appears. A precleaned microscope slide was brought repeatedly into contact with the incisions, without pressure, so that the blood left imprints that should cover almost the whole slide. After drying and staining (with Giemsa stain for 40 min), the slide was examined at a magnification of 50× or more. Microfilariae were easily recognized and the number per slide was counted.

Together with the remainder of the population of Muhanda,
da, all eligible persons (n = 370) who had been examined were treated immediately with ivermectin. The following individuals were ineligible for treatment: children < five years old or weighing < 15 kg, pregnant women or mothers breast-feeding a child < three months old, and patients with severe hepatic, renal, or nervous diseases, including epilepsy. Ivermectin was administered as a single dose based on body weight (150 μg/kg). Information was given about possible side effects and the continuous presence of someone to treat them. Until four days after the last treatment day, one of us (FV) stayed in Muhanda to monitor and to treat the adverse reactions. These included (increased) itching, (increased) rash, painful conditions (headache, joint pain, muscle aches), fever (subjective information), painful or swollen lymph nodes, swelling of limbs or the face, and conjunctivitis.

In October 1991, six months after the first treatment, half of the sample (every second family), was invited to be re-examined and to be treated a second time: 203 persons were examined and treated three times at intervals of six months (named hereafter the six-month cohort) and another cohort of 148 persons who had been examined and treated three times at intervals of six months (named hereafter the six-month cohort). After the second and third treatments, respectively, the participants were questioned about any subjective improvement of itching and of the skin condition.

For statistical analysis of the results, the chi-square test or Fisher’s two-tailed exact test were used to compare proportions. For the comparison of means, the Student’s t-test was used (paired and unpaired comparisons).

### RESULTS

Table 1 shows the parasitologic and clinical findings, at the start and at 12 months, for the 12-month and six-month cohorts, respectively. There were no significant differences in age and sex distribution between the two cohorts, and no parasitologic or clinical parameters were different between the groups before treatment. Only three persons had a reduced visual acuity.

Twelve months after the first treatment there was a significant reduction (P < 0.001) in the prevalence and intensity of the infection and in the occurrence of itching in both groups. The presence of excoriations was also significantly reduced (P < 0.02). The overall prevalence of skin lesions increased in both groups, but this increase was only significant in the six-month cohort (P < 0.02). Individual skin lesions remained virtually the same after 12 months. However, there were no longer any severe cases of craw craw. In both groups the prevalence of lymphadenopathy increased, but this was only significant in the 12-month cohort (P < 0.05).

When comparing the results of both groups at 12 months, the prevalence and intensity of infection and the prevalence of pruritus were significantly lower in the six-month cohort. The other clinical findings were equally reduced or had equally increased in both groups.

Table 2 shows the prevalence of adverse reactions in both groups after the first treatment and at 12 months, respectively. After the second or third treatment. Adverse reactions after the first treatment occurred equally in both groups, except for a few cases of painful or swollen inguinal lymph nodes, which occurred only in the six-month group, and rashes, which were more frequent in the 12-month cohort. At 12...
months, adverse reactions were significantly reduced in both groups, especially itching (as a side effect of treatment; \( P < 0.01 \)) and painful conditions (\( P < 0.02 \)). Swollen limbs or faces occurred significantly less frequently (\( P < 0.001 \)) only in the six-month cohort (after the third treatment).

A comparison of both groups at 12 months showed that significantly fewer people had adverse reactions in the six-month group. Itching, rash, and swellings occurred less frequently in this group. Within the six-month cohort the lessening of adverse reactions was not significantly different at six months (second treatment) and at 12 months (third treatment). The side effects were also generally milder following the second or third treatment than after the first treatment. After the first treatment round, an average of 0.6 side effects were registered per treated person, of which 33% were mild and 67% were moderate. There were no severe adverse reactions. Forty-one percent of the side effects started on the same day as the treatment and 45% started on the next day. Only 14% appeared on the second day after treatment or later. Swellings (face and limbs) generally appeared later than the other adverse reactions. The fact that more people showed moderate adverse reactions might be because persons with mild reactions did not find it necessary to come back for their treatment. Dizziness and asthenia seldom occurred (2.7%) and were usually mild.

Subjectively, most people were satisfied with the treatment because they subsequently had less itching. More people experienced an improvement in itching that lasted until the next treatment in the six-month cohort (88 of 148) than in the 12-month group (53 of 189). Of the people who subjectively declared that they had skin lesions at the start of the study (65 of 148 in the six-month cohort and 47 of 189 in the 12-month group) 54 and 36, respectively, judged that the condition of their skin had improved.

**DISCUSSION**

There have not been many community trials conducted that compared the efficacy of ivermectin on the parasitologic changes and/or the adverse reactions after annual or biannual treatments.\(^8,^{10-12}\) These studies reported that a six-month therapy regimen had a slight advantage in terms of an antiparasitic effect compared with an annual treatment. Adverse reactions were milder after second or third treatments, whether these were given annually or biannually.

Our study was the first to compare different intervals of treatment in east Africa. It confirmed the important diminution of prevalence and intensity of infection after both a single or two biannual treatments. At 12 months, however, the reduction was greater after two biannual treatments than after a single dose. Side effects at six and 12 months after a second or third treatment were generally milder and less frequent, except for edema of the face or limbs, the frequency of which was not reduced in the 12-month cohort. Adverse reactions in general, especially itching, rash, and swelling, were much less frequent after a third biannual treatment than after a second annual treatment.

The influence of different periodicities of ivermectin therapy on clinical aspects of the disease has been examined only in Cameroon and Sierra Leone.\(^{10,11}\) Except for pruritus and serious hyperkeratosis, onchocercal skin lesions were not significantly modified by ivermectin treatment in these studies. In Burundi, the diminution of both itching and scratch marks was very pronounced, even more so in the group with biannual treatments. The prevalence of skin lesions, however, had increased at 12 months in both treatment groups (to a significant degree in the six-month cohort). This was due mainly to an increase in the frequency of papular dermatitis. The severity of this dermatitis, however, had diminished and severe cases of craw craw were no longer seen at 12 months. Subjectively, the majority of treated patients with skin symptoms or who experienced itching believed that their condition had improved. The improvement in itching, however, was less long-lasting and this was an important reason why some patients requested to be re-treated before one year had elapsed.

Although biannual treatment reduced parasitologic parameters more, had a longer-lasting effect on itching, and produced lesser side effects at 12 months than an annual treatment, operational constraints made us choose an annual distribution of ivermectin. Shortage of staff (for medical follow-up of side effects and supervision), transport problems (insufficient vehicles and drivers), and difficulties of access made it impossible to organize treatment every six months.
in this mountainous area of 625 km² and with a population of 130,000. As a result, the distribution of ivermectin was organized in such a way that two medical assistants moved from colline to colline in the hyperendemic zone, staying a few weeks in every colline, treating as many people as possible. In this way, the 12 collines of the hyperendemic zone were covered in seven months. Next, the same two medical assistants moved to the health centers in the mesoendemic zone to assist the staff with an actively promoted distribution campaign, which lasted a few weeks in every health center. This active distribution of ivermectin in the health centers took five months. This organization allowed the annual distribution of ivermectin with only two medical assistants, one 4 × 4 vehicle, and one supervisor, who was also responsible for the supply system. In this way, an average of 37,250 persons were treated with ivermectin every year between 1991 and 1994 (four annual treatment rounds) in both the hyperendemic and mesoendemic zones.

In conclusion, although six-month treatments proved slightly more beneficial, a 12-month interval may be adequate to reduce morbidity. These results may be of interest to policy makers and public health officials in areas in which logistical and resource issues severely restrict the scope of treatment programs. In view of the planned activities of the African Programme of Onchocerciasis Control, which aim to clear 16 endemic countries of the worst ocular and cutaneous effects of onchocerciasis, the achievements in Burundi indicate that even with limited resources, an appropriate annual distribution scheme can give meaningful results. In spite of the persistence of skin lesions, their severity decreased and most patients were satisfied with the improvements, even after just one year.

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