SINGLE DOSES OF IVERMECTIN 400 μg/kg^{-1}: THE MOST EFFECTIVE DOSAGE IN BANCROFTIAN FILARIASIS

JP Moulia-Pelat, P Glaziou, LN Nguyen and JL Cartel

Institut Territorial de Recherches Médicales Louis Malardé, BP 30 Papeete, Tahiti, French Polynesia

Abstract. Forty-three *Wuchereria bancrofti* carriers were given four successive semi-annual single doses of ivermectin 100 μg.kg^{-1} (IVER 100). The geometric mean microfilaremia (mf) recurrence percentage as compared to the pre-initial treatment mf level was 35%, 21%, 17% and 17% at 6, 12, 18 and 24 months, respectively. However, the recurrence of mf 6 months after the fourth treatment remained high in several individuals: 15 have been considered as 'bad responders' and 28 as 'good responders' individuals. At month 24 (M 24), they were randomly allocated into 2 groups. A first group was treated with a fifth and a sixth dose of IVER 100, at M24 and M30, respectively; the second one was treated, at the same time, with single doses of IVER 400 μg.kg^{-1} (IVER 400). At M 36, the mf recurrence percentage (mf M36/mf M0) was significantly higher in patients treated with IVER 100 than IVER 400 (11% vs 1%, $p < 10^{-4}$). From the group IVER 100, 6 out of the 8 'bad responders' remained 'bad responders' whereas there were none of the 7 in the group IVER 400. Moreover, there were only 2 more patients in the group IVER 100 showing sustained complete zero mf, whereas they were 13 in the group IVER 400. Single doses of IVER 400 were effective on 'bad responders'; IVER 400 must be recommended for semi-annual mass treatment in bancroftian filariasis.

INTRODUCTION

Over the past decade, several trials have indicated that single dose treatments with diethylcarbamazine (DEC) or ivermectin (IVER) were effective against lymphatic filariasis due to *Wuchereria bancrofti* (Diallo *et al,* 1987; Kumaraswami *et al,* 1988; Cartel *et al,* 1990; Cartel *et al,* 1992a,b; Kimura *et al,* 1992; Kar *et al,* 1993). But, at the dosage of 3 or 6 mg/kg DEC did not give a negativation of microfilaremia (mf) of the carriers. Conversely, ivermectin provoked a complete immediate negativation of mf at the dosage of 100 μgkg^{-1} (IVER 100). However 6 months after the drug intake, reapparance of mf at the same initial level was observed in several patients called 'fast repopulating or bad responders', whereas sustained reduction was observed in others called 'slow repopulating or good responders'; this reapparance of mf might be due, among other explanations, to insufficient drug dosage (Mahmud *et al,* 1992). Recently, a treatment with a total dosage of IVER 400 μgkg^{-1} (IVER 400) given in successive intakes resulted in excellent long-term reduction of mf (Richards *et al,* 1991; Eberhard *et al,* 1992). Moreover, IVER 400 as single dose was reported to be safe and effective against bancroftian filariasis (Cartel *et al,* 1992c). Just after, we tested the effect of IVER 400 on 'bad responders' and we compared the efficacy of IVER 100 *vs* IVER 400 in 43 carriers previously treated with 4 semi-annual doses of IVER 100. The aim of this paper is to report the results of this follow-up study with 2 successive semi-annual doses of IVER 400 and to consider the potent dosage of IVER for mass chemoprophylaxis treatment.

PATIENTS AND METHODS

In June 1990 (MO), a trial was implemented in Huahine, one of the Leeward islands close to Tahiti, to assess the efficacy of repeated doses of IVER 100 given every 6 months for the treatment of *W. bancrofti* var *pacifica*. Forty-six carriers between 18 and 53 years old, in whom microfilariae (mf) density was ≥ 20 mf/ml, were effectively given four successive single doses of ivermectin. During the study, 3 patients were withdrawn from the study: the first one had taken DEC prescribed by his physician for treatment of filariasis hydrocele and the two others had left Huahine.

The geometric mean microfilaremia recurrence percentage for the 43 carriers, as compared to the pre-initial treatment mf level was 35%, 21%, 17% and 17% at month 6 (M6), 12 (M12), 18 (M18) and

24 (M24) respectively. However, the mf recurrence (MFR) 6 months after the fourth treatment remained high in some individuals (similar to or higher than the initial pretreatment mf level in 13 of them). When considering the arithmetic mean value of the 43 MFR at M24, 40%, and using this value as a threshold, it was possible to classify the carriers into 2 groups: 15 in whom the MFR was higher than 40% who were considered as 'bad responders' individuals, and the remaining 28 who were considered as 'good responders' individuals. The MFR, 6 months after each of the 4 treatment, were respectively 23%, 9%, 7% and 4% in the group of 'good responders', while they were 81%, 94%, 100% and 100% in the group of 'bad responders' (Cartel *et al,* 1993; Moulia-Pelat *et al,* 1993a).

At M24, the 43 carriers were randomly allocated into 2 groups. The first group (n = 22, '8 bad responders' and 14 'good responders' individuals) was treated with IVER 100 while the second one (n = 21, 7 'bad responders' and 14 'good responders' individuals) was treated with IVER 400.

At M30, the 2 groups were treated with the same treatment IVER 100 (n = 22) or IVER 400 (n = 21) than at m24. Determination of mf, performed by the membrane filtration technique on venous blood samples was carried out at M24, M30 and M36 just before drug intake. The physician in charge of the patients as well as the microscopy technician remained 'blind' throughout the study.

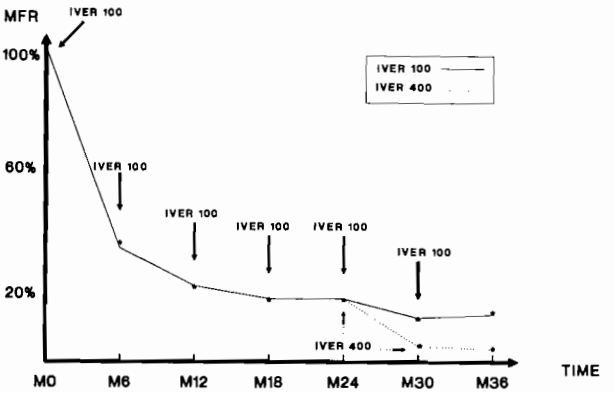

Fig 1–Evolution of geometric mean microfilariae recurrence (MFR) percentages in 43 carriers according to the time (M0-M36) and the treatments (IVER100- IVER400).

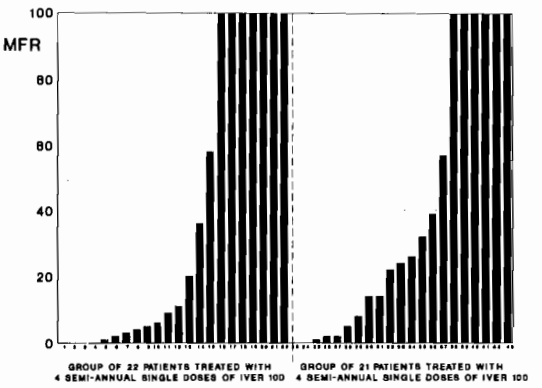

Fig 2–Microfilariae recurrence (MFR) percentages at M24 in 43 carriers randomly allocated in 2 groups.

RESULTS

The fig 1 shows the evolution of mf in the 43 carriers throughout this follow-up study, particulary in the 2 groups between M24 and M36 when treatments were different. At M30, 6 months after the first dose of IVER 400, the mf recurrence percentage was significantly higher in the group IVER 100 (8%) than in the group IVER 400 (2%) ($p < 0.05$). At M36, 6 months after the second dose of IVER 400 or after the sixth dose of IVER 100, the mf recurrence was significantly higher in the group IVER 100 (9%) than in the group IVER 400 (1%) ($p < 10^{-4}$).

The fig 2 represents for each patient the MFR percentages after 4 doses (mf M24/mf M0). The patients of each group are sorted according to ascendant MFR values. At M24, the two groups were comparable, 4 patients showed a complete negativation in the group IVER 100, 2 in the group IVER 400; 8 individuals were 'bad responders' in the group IVER 100, 7 in the group IVER 400.

The fig 3 represent for each patient, in the same order that in M24, the MFR percentages (mf M30/ mf M0) after 5 doses of IVER 100, or, after 4 doses of IVER 100 and a first dose of IVER 400. Concerning the group treated with only IVER 100, the number of 'bad responders', 8 patients, were the same after 4 or 5 doses. Six came from the group of 8 initial 'bad responders' individuals; and, 2 'good responders' individuals became 'bad responders'. A sustained complete negativation was observed in 3 more patients. Concerning the group treated with IVER 400, of the 7 'bad responders' individuals, only 2 remained 'bad responders'. Nine more patients

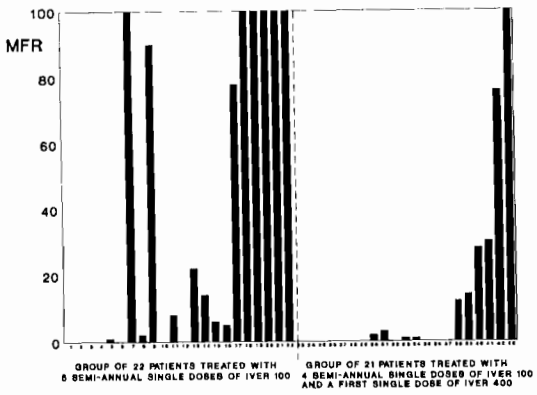

Fig 3–Microfilariae recurrency (MFR) percentages at M30 in 43 carriers randomly allocated in 2 groups.

showed a complete negativation and none reverted to 'bad responder status' during the same period.

The fig 4 represents for each patient the MFR percentages (mf M36/mf M0) after 6 doses of IVER 100 or after 2 additional doses of IVER 400. At M36, concerning the group treated with IVER 100, the number of 'bad responders', 8 patients, was dramatically the same after 4, 5 or 6 doses of IVER 100. Six patients showed a complete negativation, one less than at M30. Concerning the group treated with IVER 400, none of them remained 'bad responders' at M36. In contrast with the group IVER 100, there were four more patients who showed a complete negativation; altogether, there were 15 patients with a complete negativation in the group IVER 400.

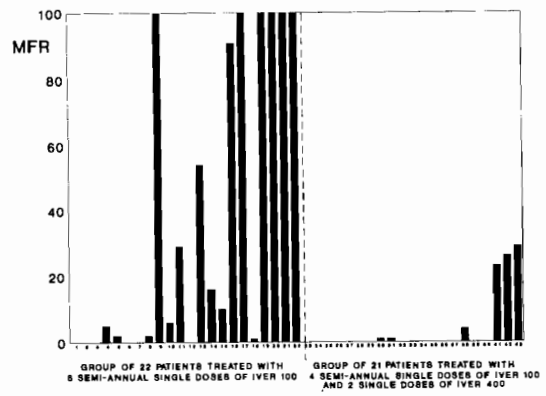

Fig 4–Microfilariae recurrence (MFR) percentages at M36 in 43 carriers randomly allocated in 2 groups.

DISCUSSION

Our results demonstrated the better efficacy of IVER 400 on 'bad responders' and suggest a macrofilarial effect of this dosage. After only 2 single doses of IVER 400, all the 7 'bad responders' at M24 had a recurrence percentage lower than 30% and 15 out of the 19 mf patients showed a sustained complete absence of mf. It is possible to speculate that after 3 or more doses of IVER 400 all the patients will show a complete cure. Indeed, during the 6 months after the intake of IVER 400, adult worms were in physical impossibility to produce microfilariae, due probably to a sterilizing effect of the drug (Bennet *et al,* 1992). Conversely, a high mf recurrence, 6 months after the intake of IVER 100, is related to the non effect of the drug at this dosage on adult worms.

The phenomenon of 'bad responders' may be explained by the under dosage of IVER, in addition to the variability of the drug absorption (Mahmud *et al,* 1992). This dose effect of IVER on macrofilaria is very important: the overall clearance of mf during 6 months will interrupt transmission and could have a strong effect on the reservoir of parasites.

IVER 100 must not be used for mass chemoprophylaxis treatment in bancroftian filariasis. After six doses, 'bad responders' individuals who remain potential transmitters, were numerous even if the MFR percentage was lower than 10%. With IVER 100, the program of mass treatment will be continue all the life. With IVER 400 a short or a middle term, between 5 and 10 years, is the case under consideration. A last point must be discussed, a twice yearly treatment is a possible strategy with single doses of IVER 400 in 1993; but the difficulties, individuals will be less persevering with 2 drug intakes per year than with only one periodicity per year, and costs of 2 organizations per year are more expensive, are the reasons why a yearly strategy is searched through other trials with IVER 400 plus DEC. A yearly intake of IVER 400 might not be sufficient for mass chemoprophylaxis treatment, the effect on macrofilariae is not enough longer (Moulia-Pelat *et al,* 1993b).

In conclusion, single doses of IVER 400 were effective on 'bad responders' and have an effect on adult worms. IVER 400 is the most effective dosage and must be recommended for semi-annual mass treatment in bancroftian filariasis.

ACKNOWLEDGEMENTS

This study received financial support from Merck Sharp and Dohme Research Laboratories (MSDRL Pensylvania USA). The drugs used in the trial were provided by Merck Sharp and Dohme (BP 62, 78170. La Celle Saint-Cloud, France).

REFERENCES

Bennet JL, William JF, Dave V. Pharmacology of ivermectin. *Parasitol Today* 1992; 4 : 226-8.

Cartel JL, Séchan Y, Boutin JP, Célérier PH, Plichart R, Roux JF. Ivermectin for treatment of bancroftian filariasis in French Polynesia: efficacy in man, effect of transmission by vector *Aedes polynesiensis*. *Trop Med Parasitol* 1990; 41 : 241-4.

Cartel JL, Spiegel A, Nguyen L, *et al.* Compared efficacy of repeated annual and semi-annual doses of ivermectin and diethylcarbamazine for prevention of *Wuchereria bancrofti* filariasis in French Polynesia. Final evaluation. *Trop Med Parasitol* 1992a; 43 : 91-4.

Cartel JL, Nguyen L, Moulia-Pelat JP, Plichart R, Martin PMV, Spiegel A. Mass chemoprophylaxis of lymphatic filariasis with a single dose of ivermectin in a Polynesian community with high *Wuchereria bancrofti* infection rate. *Trans R Soc Trop Med Hyg* 1992b; 86 : 537-40.

Cartel JL, Moulia-Pelat JP, Glaziou P, Nguyen LN, Chanteau S, Roux JF. Results of a safety trial on single dose treatments with 400 $\mu g.kg^{-1}$ of ivermectin in bancroftian filariasis. *Trop Med Parasitol* 1992c; 43 : 263-6.

Cartel JL, Moulia-Pelat JP, Glaziou P, *et al.* Microfilariae recurrence in Polynesian *Wuchereria bancrofti* carriers treated with repeated single doses of 100 $\mu g.kg^{-1}$ of ivermectin. *Trans R Soc Trop Med* 1993 (in press).

Diallo S, Aziz MA, Ndir O, Badiane S, Bah IB, Gay O. Dose ranging-study of ivermectin in treatment of filariasis due to *Wuchereria bancrofti*. *Lancet* 1987; 1 : 1030.

Eberhard ML, Hightower AW, Mc Neeley DF, Lammie PJ. Long-term suppression of microfilaraemia following ivermectin treatment. *Trans R Soc Trop Med Hyg* 1992; 86 : 287-8.

Kar SK, Patnaik S, Mania J, Kumaraswami V. Ivermectin in the treatment of bancroftian filarial infection in Orissa, India. *Southeast Asean J Trop Med Public Health* 1993; 24 : 80-6.

Kimura E, Spears GFS, Singh KI, *et al.* The long-term efficacy of single-dose mass treatment with diethylcarbamazine citrate against diurnally subperiodic *Wuchereria bancrofti* : Eight-year experience in Samoa of three rounds at 6 $mgkg^{-1}$. *Bull WHO* 1992; 70 : 769-76.

Kumaraswami V, Ottesen EA, Vijayasekara V, *et al.* Ivermectin for the treatment of *Wuchereria bancrofti* filariasis. *Am J Med Assoc* 1988; 259 : 3150-3.

Mahmud R, Grewal JS, Mak JW, Mansor SM, Navaratnam V, Wernsdorfer WH. Ivermectin in lymphatic filariasis : a pharmacokinetic study. Oral presentation in XIIIth ICTM, Pattaya Thailand, December 1992.

Moulia-Pelat JP, Glaziou PH, Nguyen LN, *et al.* Ivermectin 400 mcg/kg: long term suppression of microfilaremia in bancroftian filariasis. *Trans R Soc Trop Med Hyg* 1993a; (in press).

Moulia-Pelat JP, Glaziou P, Nguyen LN, Chanteau S, Martin PMV, Cartel JL. Long term efficacy of single dose treatment with 400 μgkg^{-1} of ivermectin in bancroftian filariasis: results at one year. *Trop Med Parasitol* 1993b (submitted).

Richards Jr FO, Eberhard ML, Bryan RT, *et al.* Comparison of high dose ivermectin and diethylcarbamazine for activity against bancroftian filariasis in Haïti. *Am J Trop Med Hyg* 1991; 44 : 3-10.