Ivermectin: effectiveness in lymphatic filariasis

K. R. BROWN[1], F. M. RICCI[1] *and* E. A. OTTESEN[2]*

[1] *Merck Research Laboratories, Merck & Co., Inc., West Point, PA 19486, USA*
[2] *Lymphatic Filariasis Elimination (CPE/CEE/FIL), World Health Organization, CH-1211 Geneva 27, Switzerland*

SUMMARY

This detailed review of the published studies underlying ivermectin's recent registration for use in lymphatic filariasis (LF) demonstrates the drug's single-dose efficacy (over the range of 20–400 μg/kg) in clearing microfilaraemia associated with both *Wuchereria bancrofti* and *Brugia malayi* infections of humans. While doses as low as 20 μg/kg could effect transient microfilarial (mf) clearance, higher dosages induced greater and more sustained mf reduction. The single dose of 400 μg/kg yielded maximal responses, but a number of practical considerations suggest that either 400 μg/kg or 200 μg/kg doses would be acceptable for use in LF control programmes. Associated safety assessments indicate that adverse events, which occur commonly following treatment of microfilaraemic individuals, develop not because of drug toxicity but because of host inflammatory responses to dying microfilariae killed by the ivermectin treatment. Ivermectin is, therefore, a highly effective and generally well tolerated microfilaricide that may soon become an essential component of many public health initiatives to interrupt transmission of lymphatic filarial infection in an effort to eliminate LF globally.

Key words: Ivermectin, lymphatic filariasis, brugian filariasis, Wuchereria bancrofti, Brugia malayi, control of bancroftian filariasis, microfilaraemia.

IVERMECTIN USE IN LYMPHATIC FILARIASIS: BACKGROUND AND RATIONALE

Lymphatic filariasis, caused by either *Wuchereria bancrofti* or *Brugia malayi*, exhibits a variety of clinical manifestations that result primarily from lymphatic tract damage induced first by the parasite (either adult worms or microfilariae [mf]) and subsequently by bacterial complications of the lymphatic dysfunction. The symptoms and signs of infection include fever, lymphangitis, lymphadenopathy, subacute or chronic oedema, elephantiasis and genital damage, as well as a syndrome of tropical pulmonary eosinophilia (TPE). Patients usually go through a prolonged asymptomatic period (with or without microfilaraemia) before the onset of symptomatic disease (Ottesen, 1993).

Recent clinical studies have also recognized renal abnormalities as an additional clinical manifestation in microfilaraemic patients with bancroftian (*W. bancrofti*) filariasis (Dreyer *et al*. 1992). Indeed, it was found that more than half of the microfilaraemic men studied had either haematuria (generally microscopic) or proteinuria, or had both. Importantly, these renal abnormalities were reversible by treatment of the microfilaraemia (Dreyer *et al*. 1992).

Lymphatic filariasis is generally diagnosed by clinical examination and by the detection of microfilariae in the blood by direct microscopic examination. Recently, however, two different assays for circulating antigen have been developed for diagnosing *W. bancrofti* infections. The assays can detect microfilaraemic infections as well as amicrofilaraemic, cryptic infections (e.g. tropical pulmonary eosinophilia syndrome and certain cases of lymphoedema without microfilaraemia) (Faris *et al*. 1993; Turner *et al*. 1993). In addition, ultrasound techniques can now localise live adult worms of *W. bancrofti*. Nests of highly motile adult worms can be readily visualised in the scrotal lymphatics of most infected men who have microfilariae circulating in the blood, whether or not they are otherwise symptomatic (Amaral *et al*. 1994; Ottesen, 1994). In women and children these adult worms are found primarily in the lymphatics of the inguinal or axillary regions or even in lymphatics of the breast (Dreyer *et al*. 1996, 1999).

There has never been an ideal therapy (i.e. safe, effective, inexpensive, convenient, and well-tolerated) for filarial infections (Ottesen, 1987). For more than 40 years, diethylcarbamazine (DEC) was the sole chemotherapeutic agent used to treat most forms of filariasis, since it rapidly killed microfilariae of *W. bancrofti*, *B. malayi*, *Onchocerca volvulus*, *Loa loa* and *Mansonella streptocerca* (Ottesen, 1985). In addition, DEC has a recognized macrofilaricidal effect against some species (Ottesen, 1985; Noroes *et al*. 1997). However, the drug, whose typically recommended course had been 6–12 days, has significant disadvantages, as a number of post-treatment adverse-reaction syndromes are induced by the very rapid killing of microfilariae. These include the following: (1) General malaise with headache, weakness, joint pains, anorexia, nausea, and vomiting (Ottesen, 1987); (2) Dermal and

* Corresponding author: Tel: +41 22 791 3225. Fax: +41 22 791 4777. E-mail: ottesene@who.ch

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systemic effects (especially in patients with onchocerciasis, in which the response has been termed the Mazzotti reaction [Francis, Awadzi & Ottesen, 1985]) caused by an acute inflammatory response following clearing/killing of microfilariae and characterised by itching and swelling of the skin, fever, tachycardia, hypotension, adenitis, and severe inflammatory reactions in both the anterior and posterior segments of the eyes of patients with onchocerciasis who have ocular infection; and (3) Encephalopathy in patients being treated with DEC for *Loa loa* infection (Carme *et al*. 1991).

Ivermectin has, during the past decade, become universally accepted as a drug of choice both for individuals and for mass treatment programmes to control onchocerciasis (Ottesen, 1994); it was this fact, coupled with the demonstration of the excellent safety profile of ivermectin in onchocerciasis patients (Awadzi *et al*. 1995) and its simplicity of dosing (single dose), that led to the first studies of its potential effectiveness in lymphatic filariasis. The initial rationale to evaluate the use of ivermectin to treat lymphatic filariasis was based on: (1) The known risks associated with the use of DEC in patients with lymphatic filariasis who might also be infected with either *O. volvulus* or *L. loa*, conditions in which reactions to DEC treatment are severe and sometimes life-threatening; and (2) The expectation was that ivermectin might not induce the same degree of post-treatment complications commonly associated with the use of DEC in patients with lymphatic filariasis.

An early exploratory, dose-ranging study examined the efficacy and safety of ivermectin in 16 men with filariasis due to *W. bancrofti* (Diallo *et al*. 1987). Seven of the 16 men received 50 μg/kg of ivermectin, and 9 received 100 μg/kg. After treatment, patients were examined daily for 21 days, and follow-up examinations were performed at 3 and 6 months. Ivermectin, in a single oral dose of 50 or 100 μg/kg, cleared the blood microfilariae within 3 days. However, microfilariae subsequently reappeared, and most patients were positive again by the third month. The reduction in microfilarial density was greater after 100 μg/kg than after the lower dose. These preliminary data suggested that ivermectin might prove to be a useful microfilaricide in bancroftian filariasis and that 100 μg/kg might be more effective than 50 μg/kg. This finding led to a series of clinical studies in patients with lymphatic filariasis; the results of those studies are reviewed below.

METHODS AND STUDY POPULATION

Data available for assessment of efficacy

Publications through 1998 on the use of ivermectin, alone or in combination with other agents, for treating lymphatic filariasis (LF) caused by either *W. bancrofti* (bancroftian filariasis) or *B. malayi* (brugian filariasis) were selected for inclusion in this report (Table 1). The published studies have been categorised as 'dose-ranging', 'comparative', or 'open non-comparative' with respect to treatment with ivermectin. In addition, exploratory-type studies appearing in the literature that included the use of a 'clearing dose' of either ivermectin or DEC for treating lymphatic filariasis are also included in this report. The primary purpose of these 'clearing dose' investigations was to determine whether the use of an initial low dose of ivermectin or DEC (to reduce the density of microfilariae) could reduce the frequency and or intensity of side-reactions (i.e. fever, myalgias, etc.) following subsequent, larger (more effective) doses of the same drug given 5 days later.

In all cited studies where numeric values were not available in the publication itself (i.e. in cases where data were presented in figures and not in numeric-tabular form), estimates of mf densities were derived from the published figures. In cases where a particular study was presented in multiple publications, all relevant information from those publications was included in the review.

Criteria for evaluating efficacy

In treating microfilaraemic LF patients with agents such as ivermectin or DEC, not all microfilariae are eliminated. Indeed, the goal of such treatment in community settings is the long-term suppression of microfilaraemia that will result first in the reduction of transmission and ultimately in a decrease in both incidence and prevalence of the clinical disease itself. Therefore, in this report, efficacy refers to the ability to reduce microfilarial density in the blood. Baseline evaluation of the infection was established by determinations of blood microfilarial (mf) density in each subject prior to the initiation of specific drug therapy. These pre-treatment levels were then compared with determinations made at several post-treatment time points, typically within the first 2 weeks post-treatment and at 1, 3, 6, and 12 months. The principal efficacy consideration in this report is the post-treatment reduction of blood microfilarial density expressed as a percent of pre-treatment level.

Data available for safety assessment

The safety data reported in the individual studies cited in this evaluation varied with respect to both scope and detail. Some studies had to be excluded from the pooled presentation of the data because accurate and/or detailed information relating to the nature or frequency of adverse experiences could not be established. For studies that were comparative in

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Table 1. Published studies included in present analysis

Type of study	Studies	Country	Number of patients	
			Ivermectin	Comparator*
Efficacy				
Dose-ranging	Diallo *et al*. 1987; Kumaraswami *et al*. 1988; Roux *et al*. 1989; Cartel *et al*. 1990*a*, *b*; Kar *et al*. 1993; Coutinho *et al*. 1994; Ismail *et al*. 1991; Shenoy *et al*. 1992; Mak *et al*. 1993	Senegal, India, French Polynesia, Brazil, Sri Lanka, Malaysia	339[a]	NA
Comparative	Ottesen *et al*. 1990; Vijaysekaran *et al*. 1990; Zheng *et al*. 1991; Sabry *et al*. 1991; Cartel *et al*. 1991*a*, *b*, *c*, 1992*a*, 1992*b*, *c*; Youssef *et al*. 1997, 1993; Cummings & Youssef, 1994	India, China, Egypt French Polynesia, Malaysia	318	191[b]
Open, non-comparative	Cartel *et al*. 1992*d*, *e*, 1993; Nguyen *et al*. 1993; Moulia-Pelat *et al*. 1993;	India, China, French Polynesia, Egypt	205[c]	NA
Other (e.g. 'clearing dose' studies)	Addiss *et al*. 1991, 1993; Richards *et al*. 1991; Dreyer *et al*. 1995; Kazura *et al*. 1993*a*, *b*; Shenoy *et al*. 1993	Haiti, Brazil, Papua New Guinea, India	162[d]	114
Safety	Diallo *et al*. 1987; Kumaraswami *et al*. 1988; Roux *et al*. 1989; Cartel *et al*. 1990*a*, *b*, 1992*d*, *e*; Kar *et al*. 1993; Coutinho *et al*. 1994; Ismail *et al*. 1991; Shenoy *et al*. 1992, 1993; Ottesen *et al*. 1990; Zheng *et al*. 1991; Sabry *et al*. 1991; Youssef *et al*. 1997, 1993; Cummings & Youssef, 1994; Nguyen *et al*. 1993; Moulia-Pelat *et al*. 1993; Addiss *et al*. 1991, 1993; Richards *et al*. 1991; Weil *et al*. 1991; Eberhard *et al*. 1992; Dreyer *et al*. 1995; Kazura *et al*. 1993*a*, *b*; Mak *et al*. 1993	Senegal, India, French Polynesia, Brazil, Sri Lanka, China, Egypt, Haiti, Malaysia, Papua New Guinea.	1671[e]	NA

* Comparator is DEC except as otherwise noted.

[a] Includes 100 subjects with brugian filariasis (Shenoy *et al*. 1992; Mak *et al*. 1993) and 239 subjects with bancroftian filariasis (Diallo *et al*. 1987; Kumaraswami *et al*. 1988; Roux *et al*. 1989; Cartel *et al*. 1990*a*, *b*; Kar *et al*. 1993; Coutinho *et al*. 1994; Ismail *et al*. 1991).

[b] Includes 72 placebo controls (Vijaysekaran *et al*. 1990; Sabry *et al*. 1991; Youssef *et al*. 1992, 1993; Cummings & Youssef, 1994) and 119 DEC controls (Ottesen *et al*. 1990; Vijaysekaran *et al*. 1990; Zheng *et al*. 1991; Sabry *et al*. 1991; Cartel *et al*. 1991*a*, *b*, *c*, 1992*a*–*c*). Twenty-two of the 72 placebo subjects in one study (Sabry *et al*. 1991) received placebo on day 1 and after a one week assessment received ivermectin on day 9 of study. These 22 subjects are included in the safety summary but not in the efficacy summary for ivermectin.

[c] One study (Cartel *et al*. 1992*d*, Nguyen *et al*. 1993) included 864 subjects; however, only 122 of 864 were microfilaraemic. Only the 122 are included here.

[d] Includes 31 subjects with brugian filariasis (Shenoy *et al*. 1993) and 131 subjects with bancroftian filariasis (Addiss *et al*. 1991, 1993; Richards *et al*. 1991; Dreyer *et al*. 1995; Kazura *et al*. 1993*a*, *b*).

[e] Total number of subjects with safety data. When adjusted for the inclusion of only the 122 of 864 subjects with microfilaraemia in one study (Cartel *et al*. 1992*d*) then 929 microfilaraemic subjects are summarised in safety.

NA, not applicable.

nature, no attempt has been made to analyse the safety data from ivermectin-treated subjects as compared with subjects treated otherwise; however, comparisons by ivermectin dose were analysed statistically and are presented. Twenty-two studies (37 publications) overall were included in this review of safety (1748 ivermectin-treated subjects), but four of the 22 studies (10 publications) did not contain sufficiently detailed adverse experience information for inclusion in a safety summary (Vijaysekaran *et al*. 1990; Cartel *et al*. 1991*a*, *b*, *c*; 1992*a*, *b*, *c*, 1993; Addiss *et al*. 1993; Moulia-Pelat *et al*. 1994). Thus, there were 18 studies (1671 ivermectin-treated subjects) that were sufficiently detailed for inclusion in the safety analysis (Table 1).

All dosages of ivermectin were administered as a single oral dose with the exception of those studies that employed 'clearing doses' of ivermectin (9 studies: Addiss *et al*. 1991, 1993; Richards *et al*. 1991; Weil *et al*. 1991; Eberhard *et al*. 1992; Kazura *et al*. 1993*a*, *b*; Shenoy *et al*. 1993; Dreyer *et al*. 1995). For those studies employing a 'clearing dose', in general, the frequency and intensity of adverse experiences for the initial low 'clearing dose' (e.g. 20 μg/kg ivermectin administered on day 1) were greater than those reported for the larger subsequent

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Table 2. The effectiveness of single-dose ivermectin in decreasing microfilaraemia in patients with bancroftian filariasis: dose-ranging studies

Study	Ivermectin dose (μg/kg)	Percentage of pre-treatment microfilarial density* [number of subjects at post-treatment times] Time post treatment					
		1 day	1–2 weeks	1 month	3 months	6 months	12 months
Kumaraswami *et al*. 1988† Kar *et al*. 1993† Coutinho *et al*. 1994† Ismail *et al*. 1991†	20–25	4·2 (0–7) [38]	1·1 (0·3–5) [48]	1·9 (0–3) [48]	12·4 (1–24) [48]	32·7 (8–66) [48]	13·0 (SS) [11]
Diallo *et al*. 1987 Kumaraswami *et al*. 1988† Cartel *et al*. 1990*a*	50	2·7 (1–5) [44]	< 0·1 (0–0·2) [61]	2·4 (0·3–5) [61]	15·2 (3–30) [61]	35·6 (7–55) [61]	57·0 (54–60) [19]
Kar *et al*. 1993† Coutinho *et al*. 1994† Ismail *et al*. 1991†	100–150	1·0 (0–2) [57]	0·2 (0–1) [76]	0·6 (0–2) [76]	8·8 (3–18) [76]	24·6 (10–60) [76]	32·8 (18–51) [24]
Kumaraswami *et al*. 1988† Cartel *et al*. 1990*a* Kar *et al*. 1993† Coutinho *et al*. 1994† Ismail *et al*. 1991†	200	1·0 (0–2) [44]	0·1 (0–0·6) [54]	1·0 (0–3) [54]	8·7 (2–19) [54]	16·8 (3–32) [53]	23·2 (17–26) [15]

* Values are arithmetic means (and range) of the published results at each time point; these published results were geometric means of the individual patient data.
† Microfilarial densities from these studies were derived from the graphs presented in the publications.
SS, Single-site study.

standard dose of ivermectin (e.g. 200 or 400 μg/kg administered on day 5). This finding is consistent with the general consensus that adverse experiences are related to the presence and intensity of pre-treatment microfilaremia in such patients (Ottesen *et al*. 1990). Nevertheless, when 'clearing doses' of ivermectin were employed and adverse experiences were reported for individual subjects for both the initial 'clearing dose' and the standard dose, both adverse experiences are included in the accounting described below.

RESULTS

Efficacy assessments

A series of dose-ranging studies involving 339 subjects (single doses ranging from 20 to 200 μg/kg) demonstrated that oral administration of ivermectin for the treatment of bancroftian and brugian filariasis was effective in decreasing blood microfilarial density (Diallo *et al*. 1987; Kumaraswami *et al*. 1988; Roux *et al*. 1989; Cartel *et al*. 1990*a*, *b*; Ismail *et al*. 1991; Shenoy *et al*. 1992; Kar *et al*. 1993; Mak *et al*. 1993; Coutinho *et al*. 1994). Moreover a dose-response relationship was observed, with higher doses resulting in more sustained clearance of microfilariae (Table 2 for bancroftian filariasis [Diallo *et al*. 1987; Kumaraswami *et al*. 1988; Roux *et al*. 1989; Cartel *et al*. 1990*a*, *b*; Ismail *et al*. 1991; Kar *et al*. 1993; Coutinho *et al*. 1994]; Table 3 for brugian filariasis [Shenoy *et al*. 1992; Mak *et al*. 1993]). However, permanent clearance of microfilariae was not achieved, and, by inference, it does not appear that ivermectin is macrofilaricidal. At the doses of ivermectin studied (20 to 200 μg/kg) it appears that the reduction in mf density is more dramatic in bancroftian than in brugian filariasis.

In studies comparing ivermectin to DEC and/or placebo, single-dose regimens of ivermectin between 20 and 126 μg/kg were shown to be consistently more effective, within the first month post-treatment, than either single- or multiple-dose (13 days) regimens of either 3 or 6 mg/kg DEC (Table 4; [Ottesen *et al*. 1990; Vijaysekaran *et al*. 1990; Zheng *et al*. 1991; Sabry *et al*. 1991; Cartel *et al*. 1991*a*, *b*, *c*, 1992*a*, *b*, *c*; Youssef *et al*. 1993, 1997; Cummings & Youssef, 1994]). However, the efficacy of multiple-dose DEC was comparable to single-dose ivermectin from months 1 to 6 post-treatment and then favoured DEC at 12 months. The number of subjects at time points after 6 months post-treatment was too small for meaningful comparisons of single-dose ivermectin versus single-dose DEC (either 3 mg/kg or 6 mg/kg). In the 3 studies employing placebo there was no substantive change of mf density in the placebo groups after dosing (Vijaysekaran *et al*. 1990; Sabry *et al*. 1991; Youssef *et al*. 1993, 1997; Cummings & Youssef, 1994).

Studies exploring the effectiveness of various dose levels of ivermectin given at different frequencies indicated that ivermectin, given in three successive doses of 100 μg/kg at intervals of 6 months, provided

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Table 3. The effectiveness of single-dose ivermectin in decreasing microfilaraemia in patients with brugian filariasis: dose-ranging studies[1]

Ivermectin dose (μg/kg)	Percentage of pre-treatment microfilarial density* [number of subjects at post-treatment times] Time post treatment				
	1 day	1–2 weeks	1 month	3 months	6 months
20	56·5 (38–75) [24]	13·1 (9·5–18) [24]	12·5 (7–18) [24]	18·5 (7–30) [24]	32·5 (25–40) [24]
50	37·0 (34–40) [26]	9·0 (9–9) [26]	7·5 (6–9) [26]	23·0 (20–26) [26]	33·5 (29–38) [26]
100	32·0 (32–32) [25]	8·5 (7–10) [25]	6·5 (6–7) [25]	12·5 (7–18) [25]	18·0 (18–18) [25]
200	39·0 (28–50) [25]	10·0 (9–11) [25]	9·0 (5–13) [25]	13·5 (13–14) [25]	24·0 (22–26) [25]

[1] Data from Shenoy *et al*. (1992) and Mak *et al*. (1993).
* Values are arithmetic means (and range) of the published results at each time point; these published results were geometric means of the individual patient data; microfilarial densities from these studies were derived from the graphs presented in the publications.

sustained lowering of microfilarial density, but it did not alter the prevalence of microfilaraemia (Cartel *et al*. 1992*d*, *e*, 1993; Nguyen *et al*. 1993; Moulia-Pelat *et al*. 1993, 1994). Indeed, it took a dose of 400 μg/kg ivermectin to significantly reduce both microfilarial density and microfilaraemia prevalence in that same endemic population. With more frequent dosing, however, even 100 μg/kg ivermectin given at 3 month intervals was effective in inducing long-term clearance (9 months) of microfilaraemia in almost 50% of patients, and only low-level microfilarial density (< 10% of pre-treatment levels) persisted in the others (Youssef *et al*. 1993, 1997; Cummings & Youssef, 1994). These studies also demonstrated clearly, however, that single doses of 400 μg/kg ivermectin were generally more effective than single doses of 100 μg/kg ivermectin (Table 5) (400 μg/kg: Moulia-Pelat *et al*. 1993; Cartel *et al*. 1992*e* *vs*. 100 μg/kg: Cartel *et al*. 1992*d*, 1993; Nguyen *et al*. 1993).

Studies evaluating the potential usefulness of a 'clearing dose' (see Methods, above) of either ivermectin or DEC indicated that the effectiveness of these regimens (20 μg/kg ivermectin followed by a larger dose 5 days later, or 1 mg/kg DEC followed by a 6 mg/kg dose 5 days later) did not differ from that of the larger single dose given alone (Chodakewitz, 1995). The results confirmed the earlier findings that ivermectin caused a more rapid reduction in microfilaraemia than DEC in the immediate post-treatment period. In addition, the results confirmed the earlier findings for brugian filariasis of a less dramatic reduction in mf density than for bancroftian filariasis in the ivermectin dose range of 20 to 200 μg/kg (Shenoy et *al*. 1992; Mak *et al*. 1993). However, at the higher ivermectin dose (400 μg/kg), reductions in mf density for brugian filariasis were comparable to those achieved for bancroftian filariasis (Tables 6 and 7, respectively, for bancroftian filariasis [Richards *et al*. 1991; Addiss *et al*. 1993; Kazura *et al*. 1993*a*; Dreyer *et al*. 1995] and brugian filariasis [Shenoy *et al*. 1993]). Recipients of DEC had a gradual reduction in microfilarial density at successive post-treatment times, whereas recipients of ivermectin had a rapid, sharp reduction in microfilarial density followed by a gradual rise at successive post-treatment times. At 12 months post-treatment subjects given ~ 400 μg/kg ivermectin had lower microfilarial densities than those given ~ 200 μg/kg for both bancroftian (Richards *et al*. 1991; Addiss *et al*. 1993; Kazura *et al*. 1993*a*; Dreyer *et al*. 1995) and brugian filariasis (Shenoy *et al*. 1993) and were comparable to those given ~ 6 mg/kg DEC. These findings are consistent with earlier findings in open studies involving 400 μg/kg ivermectin for bancroftian filariasis in which long-term suppression of microfilaraemia was achieved by this dose and host-to-host variation in response was lessened (Moulia-Pelat *et al*. 1993; Cartel *et al*. 1992*e*).

Safety assessments

The methods of assessing and reporting adverse experiences (AEs) varied from study to study. Adverse experiences were reported in some studies at frequencies as low as 3·8% (Cartel *et al*. 1992*d*) while in other studies the frequency was as high as 100% (Shenoy *et al*. 1992; Ottesen *et al*. 1990). Analysis of the study with the lowest frequency of adverse experiences (3·8%; Cartel *et al*. 1992*d*) is instructive, however, since it involved a mass distribution programme in which a total of 864 subjects received ivermectin. Pre-treatment microfilaraemia status was evaluated in 577 subjects; 122 were found to be microfilaraemic while 455 were

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Table 4. Effectiveness of single-dose ivermectin vs. single- or multiple-dose DEC in decreasing microfilaraemia in patients with bancroftian filariasis

Studies	Treatment regimen	Percentage of pre-treatment microfilarial density* [number of subjects at post-treatment times] Time post treatment					
		1 day	1–2 weeks	1 month	3 months	6 months	12 months
Ottesen *et al*. 1990†§	Ivermectin single dose 21·3 μg/kg	1 (SS) [13]	0 (SS) [12]	2 (SS) [13]	10 (SS) [13]	22 (SS) [13]	NA
Ottesen *et al*. 1990†‡; Zheng *et al*. 1991†; Sabry *et al*. 1991; Cartel *et al*. 1991*a*, *b*, *c*, 1992*a*, *b*, *c*; Youssef *et al*. 1993, 1997; Cummings & Youssef, 1994	Ivermectin single dose 100 to 126 μg/kg	15 (0–30) [62]	< 0·1 (0–0·1) [85]	3·3 (0–8) [85]	6·4 (4–21) [196]	25·1 (20–33) [66]	35·5 (25–56) [41]
Cartel *et al*. 1991*a*, *b*, *c*, 1992*a*, *b*, *c*	DEC single dose 3 mg/kg	NA	12·2 (1–13) [24]	17·7 (15–21) [24]	23·6 (15–32) [24]	18·9 (15–23) [24]	52·8 (SS) [12]
Cartel *et al*. 1991*a*, *b*, *c*, 1992*a*, *b*, *c*	DEC single dose 6 mg/kg	NA	9·4 (SS) [11]	10·2 (SS) [11]	10·4 (SS) [11]	8·0 (SS) [11]	33·4 (SS) [11]
Ottesen *et al*. 1990†; Zheng *et al*. 1991†; Sabry *et al*. 1991	DEC × 13 days (3 mg/kg × 1 day; 6 mg/kg × 12 days)	28 (5–50) [74]	2·5 (0–5) [74]	2·7 (2–10) [74]	9·0 (2–18) [74]	16·5 (9–20) [44]	19·0 (SS) [30]

* Values are arithmetic means (and range) of the published results at each time, these published results were geometric means of the individual patient data.
SS, Single-site study; NA, Not available.
† Microfilarial densities from these studies were derived from the graphs presented in the publications.
§ A dose of 1 mg ivermectin was administered, resulting in a mean ± S.E. of 21·3 ± 0·7 μg/kg.
‡ A dose of 6 mg ivermectin was administered, resulting in a mean ± S.E. of 126·2 ± 3·7 μg/kg.

Table 5. The effectiveness of single-dose ivermectin in decreasing microfilaraemia in patients with bancroftian filariasis: open non-comparative studies

Studies	Ivermectin dose (μg/kg)	Percentage of pre-treatment microfilarial density† [number of subjects at post-treatment times] Time post-treatment					
		1 day	1–2 weeks	1 month	3 months	6 months	12 months
Cartel *et al.* 1992*d*; Nguyen *et al.* 1993; Cartel *et al.* 1993	100	0·3 (SS) [46]	NA	NA	NA	33·7 (31–39) [163]	NA
Moulia-Pelat *et al.* 1993; Cartel *et al.* 1992*e*	400	0·6 (SS) [37]	NA	NA	2·4 (SS) [37]	3·2 (SS) [37]	13·5 (SS) [37]

† Values are arithmetic means (and range) of the published results at each time; these published results were geometric means of the individual patient data.
SS, Single-site study; NA, Not Available.

Table 6. Comparative effectiveness of ivermectin vs. DEC in decreasing microfilaraemia in patients with bancroftian filariasis§

Studies	Treatment regimen	Percentage of pre-treatment microfilarial density* [number of subjects at post-treatment times] Time post treatment				
		1–2 weeks	1 month	3 months	6 months	12 months
	Ivermectin dose (μg/kg)					
Richards *et al.* 1991 Dreyer *et al.* 1995 Kazura *et al.* 1993*a*	200–220	3·5 (3–4) [20]	1·7 (0–4) [42]	8·8 (8–9) [42]	11·0 (2–23) [61]	9·7 (3–23) [51]
Addiss *et al.* 1993	400–420	2·0 (SS) [10]	1·0 (0–2) [21]	7·6 (6–9) [21]	5·7 (0·3–8) [30]	4·1 (0·4–10) [30]
	DEC dose (mg/kg)					
Dreyer *et al.* 1995 Kazura *et al.* 1993*a* Addiss *et al.* 1993	6–7	21·1 (3–42) [40]	21·3 (1–30) [42]	15·0 (3–20) [42]	12·6 (1–25) [62]	6·5 (0·3–11) [42]

§ Data derived from 'clearing-dose' studies in 4 references cited (see text).
* Values are arithmetic means (and range) of the published results at each time; these published results were geometric means of the individual patient data.

Table 7. Comparative effectiveness of ivermectin vs. DEC in decreasing microfilaraemia in patients with brugian filariasis: report of a single study

Treatment regimen	Percentage of pre-treatment microfilarial density* [number of subjects at post-treatment times] Time post treatment				
	1–2 weeks	1 month	3 months	6 months	12 months
Ivermectin dose (μg/kg)					
200–220	14·0 [20]	6·0 [20]	6·0 [20]	8·3 [20]	13·0 [20]
400–420	10·0 [11]	2·6 [11]	1·0 [11]	5·2 [11]	4·6 [11]
DEC dose (mg/kg)					
6**	17·6 [19]	11·6 [19]	7·3 [19]	11·0 [19]	4·5 [19]

§ Data derived from 'clearing-dose' study (Shenoy *et al.* 1993; see text).
* Values are the geometric means of the individual patient data.
** Includes subjects with and without clearing dose of 1 mg/kg DEC.

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Table 8. Relationship between pre-treatment microfilaraemia status and the development of clinical adverse experiences (AE) after ivermectin treatment[1]

Pre-treatment microfilaraemia status	Number of subjects with AE reported	Number of subjects without AE reported	Total
With microfilaraemia	29	93	122
Without microfilaraemia	4	451	455
Total	33	544	577

[1] Source: Cartel *et al.* (1992*d*); $P < 0{\cdot}001$, Fisher's exact test.

Table 9. Most common clinical adverse experiences reported for ivermectin-treated, microfilaraemic subjects with bancroftian ($n = 798$) or brugian ($n = 131$)

	Number (%) of microfilaraemic subjects ($n = 929$) with clinical adverse experiences*
Systemic	
Fever	398 (42·8)
Chills	89 (9·6)
Asthenia/Weakness	210 (22·6)
Neurologic and Eye	
Headache	384 (37·5)
Musculoskeletal	
Myalgia	219 (23·6)
Gastrointestinal	
Anorexia	103 (11·1)
Respiratory	
Cough	102 (11·0)

* The counts represent the number of individual subjects with the AE indicated, except in rare cases where a subject might have reported the same adverse experience for two separate doses (as could have happened in the studies using a 'clearing dose' [Addiss *et al.* 1991; Richards *et al.* 1991; Weil *et al.* 1991; Eberhard *et al.* 1992; Kazura *et al.* 1993*a*, *b*; Shenoy *et al.* 1993; Dreyer *et al.* 1995]. These publications do not allow one to identify individual subjects who might have had the same AEs reported for each of two doses. In such cases, there will be a slight overestimate of the true number of adverse experiences occurring.

amicrofilaraemic (Table 8). Twenty-nine of the 33 subjects (87·9%) who reported adverse experiences were microfilaraemic; of the 455 amicrofilaraemic subjects who received ivermectin, only 4 (0·9%) reported an adverse experience. In this study, the frequency of adverse experiences in subjects who were amicrofilaraemic was significantly less than in subjects with microfilaraemia ($P < 0{\cdot}001$, Fisher's exact test).

The time-course of adverse experiences reported in all studies was similar, with reactions usually beginning about 12–24 h post-treatment, peaking in frequency and intensity at 24 to 48 h, and then subsiding by 48–72 h. Even at their peak intensities, adverse experiences were generally mild to moderate and were not serious in nature. Typically the adverse experiences were well tolerated and easily managed with simple medications such as acetaminophen. The most serious adverse experience, transient hypotension/postural hypotension, occurred in seven studies and involved 20 patients (2·0% of the microfilaraemic subjects [Kumaraswami *et al.* 1988; Ottesen *et al.* 1990; Addiss *et al.* 1991; Ismail *et al.* 1991; Sabry *et al.* 1991; Kar *et al.* 1993; Coutinho *et al.* 1994]).

As indicated clearly in Table 8, clinical adverse reactions occur only rarely in amicrofilaraemic subjects; since all of the other reported studies treated only microfilaraemic patients, Table 9 summarises the most common clinical adverse experiences (i.e. those that occurred in at least 10% of the 929 microfilaraemic individuals with safety data [798 with *W. bancrofti* infection and 131 with *B. malayi* infection]). The less commonly reported AEs (all of either mild or moderate severity) included lethargy, arthralgia, nausea, diaphoresis, sore throat, abdominal pain, light-headedness, malaise, epigastric pain, postural hypotension, lung function alterations, dizziness, body pain, chest pain, fatigue, testicular tenderness, faecal expulsion/elimination of *Ascaris* worms and 'others' that were not specified.

DISCUSSION

Dosage selection for the use of ivermectin in lymphatic filariasis

Tables 10 and 11 summarise all of the observations on the changes in microfilarial densities following ivermectin treatment for bancroftian and brugian filariasis respectively, that were made in the various studies presented above. As shown in Tables 6 and 7, because a multi-centre trial had demonstrated that a 'clearing dose' of 20 μg/kg ivermectin did not affect the efficacy of a subsequent larger dose (Chodakewitz, 1995), both patients who received a 'clearing dose' and those who did not are considered as one group for each therapeutic dose level (200 or 400 μg/kg) of ivermectin in this summation.

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Table 10. Effectiveness of single-dose ivermectin in decreasing microfilaraemia in patients with bancroftian filariasis

Studies	Ivermectin dose (μg/kg)	Percentage of pre-treatment microfilarial density* [number of subjects at post-treatment times] Time post treatment				
		1–2 weeks post	1 month post	3 months post	6 months post	12 months post
Kumaraswami *et al*. 1988†; Ottesen *et al*. 1990†; Kar *et al*. 1993†; Coutinho *et al*. 1994†; Ismail *et al*. 1991†	20–25	0·9 (0–5) [60]	1·9 (0–2) [61]	11·9 (1–24) [61]	30·4 (8–66) [61]	13·0 (SS) [11]
Diallo *et al*. 1987; Kumaraswami *et al*. 1988†; Cartel *et al*. 1990*a*; Kar *et al*. 1993†; Coutinho *et al*. 1994†; Ismail *et al*. 1991†	50	< 0·1 (0–0·2) [61]	2·4 (0·3–5) [61]	15·2 (3–30) [61]	35·6 (7–55) [61]	57·0 (54–60) [19]
Diallo *et al*. 1987; Kumaraswami *et al*. 1988†; Cartel *et al*. 1990*a*; Kar *et al*. 1993†; Coutinho *et al*. 1994†; Ismail *et al*. 1991†; Ottesen *et al*. 1990†; Zheng *et al*. 1991†; Sabry *et al*. 1991; Cartel *et al*. 1991*a*, *b*, *c*, 1992*a*, *b*, *c*, *d*, 1993; Youssef *et al*. 1993, 1997; Cummings & Youssef, 1994; Nguyen *et al*. 1993; Moulia-Pelat *et al*. 1994	100–150	0·1 (0–1) [161]	2·0 (0–8) [161]	7·1 (3–21) [272]	29·6 (10–33) [305]	34·5 (18–56) [65]
Kumaraswami *et al*. 1988†; Cartel *et al*. 1990*a*; Kar *et al*. 1993†; Coutinho *et al*. 1994†; Ismail *et al*. 1991†; Richards *et al*. 1991; Dreyer *et al*. 1995; Kazura *et al*. 1993*a*; Addiss *et al*. 1993	200–220	1·0 (0–4) [74]	1·3 (0–4) [96]	8·7 (2–19) [96]	8·3 (1–32) [114]	12·8 (3–32) [66]
Moulia-Pelat *et al*. 1993; Richards *et al*. 1991; Dreyer *et al*. 1995; Kazura *et al*. 1993*a*; Addiss *et al*. 1993	400–420	2 (SS) [10]	1 (0–2) [21]	4·3 (2–9) [58]	2·1 (0·3–8) [67]	9·3 (0·4–14) [67]

* Values are arithmetic means (and range) of the published results at each time point; these published results were geometric means of the individual patient data.
† Microfilarial densities from these studies were derived from the graphs presented in the publications.
SS, Single-site study.

Table 11. Effectiveness of single-dose ivermectin in decreasing microfilaraemia in patients with brugian filariasis

Studies	Ivermectin dose (μg/kg)	Percentage of pre-treatment microfilarial density* [number of subjects at post-treatment times] Time post treatment				
		1–2 weeks post	1 month post	3 months post	6 months post	12 months post
Shenoy *et al*. 1992 Mak *et al*. 1993	20	13·1 (9·5–18) [24]	12·5 (7–18) [24]	18·5 (7–30) [24]	32·5 (25–40) [24]	NA†
Shenoy *et al*. 1992 Mak *et al*. 1993	50	9·0 (9–9) [26]	7·5 (6–9) [26]	23·0 (20–26) [26]	33·5 (29–38) [26]	NA
Shenoy *et al*. 1992 Mak *et al*. 1993	100	8·5 (7–10) [25]	6·5 (6–7) [25]	12·5 (7–18) [25]	18·0 (18–18) [25]	NA
Shenoy *et al*. 1992 Shenoy *et al*. 1993 Mak *et al*. 1993	200–220	11·7 (9–18) [45]	7·2 (2–13) [45]	10·2 (2–14) [45]	15·8 (2–26) [45]	14·5 (9–20) [20]
Shenoy *et al*. 1993	400	10·0 (SS) [11]	1·0 (SS) [11]	1·0 (SS) [11]	2·0 (SS) [11]	5·0 (SS) [11]

* Values are arithmetic means (and range) of the published results at each time; these published results were geometric means of the individual patient data; Microfilarial densities from these studies were derived from the graphs presented in the publications.
† NA, Not Available; SS, Single site.

For each ivermectin dose level there was a rapid decline in microfilarial densities, and within 2 weeks post-treatment, microfilariae had almost completely disappeared from the blood. This change was more dramatic in subjects with bancroftian filariasis than in subjects with brugian filariasis at doses $< 400\ \mu$g/kg; but, at the higher dose level of ivermectin (i.e. 400 μg/kg) results were similar in both groups. One month after treatment, microfilaraemia began to recur, and the microfilarial density gradually began to increase. This increase continued progressively, and at 1 year post-treatment the geometric mean microfilarial densities ranged from 9·3 % to 57 % of pre-treatment values in subjects with bancroftian filariasis who received, respectively $\sim 400\ \mu$g/kg and 50 μg/kg. It should be noted that too few subjects accrued at the 20–25 μg/kg dose range to be used for meaningful comparisons.

The pool of information is more limited in subjects with brugian filariasis; however, a clear dose-response is evident, and at 1 year post-treatment mf densities ranged from 5·0 % to 14·5 % of pre-treatment values for the $\sim 400\ \mu$g/kg and $\sim 200\ \mu$g/kg dose levels of ivermectin, respectively.

Fig. 1 displays the information for bancroftian filariasis appearing in Table 10 (a similar profile would be evident for brugian filariasis) and clearly emphasises the dose-response relationship for ivermectin, with the 400 μg/kg dose achieving more sustained reductions in microfilarial densities than the lower doses. Furthermore, the data support the previously demonstrated findings that use of the lower-dose regimens of ivermectin (100–200 μg/kg) in areas where mass distribution of the drug can be carried out on a more frequent (i.e. 3–6 months) basis might be adequate to reduce microfilaraemia to very low or zero levels and thereby control lymphatic filariasis, both in terms of preventing microfilaraemia in the individual patient and in terms of decreasing transmission within an endemic area. However, if a dosing interval as long as approximately 12 months is most practicable, a higher dose of 400 μg/kg ivermctin could be considered in order to minimise host-to-host variation and maximise effectiveness in individuals' responses.

Collectively these results confirm the earlier meta-analysis by Cao *et al*. (1997), and imply an advantage for the higher dose levels of ivermectin based on statistical evaluation of the levels of microfilaraemia at 12 months (Tables 6 and 10). However, there are at least four very practical considerations which should be taken into account when deciding on how to apply this research observation of greater efficacy for the 400 μg/kg (*vis-à-vis* that for the 200 μg/kg) dose in real public health programmes. First, no vector or transmission studies have been carried out that demonstrate a 'biologically meaningful' (as opposed to 'statistically significant') difference between the levels of microfilaraemia at 12 months in recipients of 200–220 μg/kg or 400–420 μg/kg, though it is intuitive that control is more likely with the lowest achievable levels of microfilaraemia. Second, from the results of the recently published studies of ivermectin-plus-DEC or ivermectin-plus-albendazole (Ismail *et al*. 1998; Beach *et al*. 1999), it is clear that either of those 'co-administration regimens' used in patients with microfilaraemia

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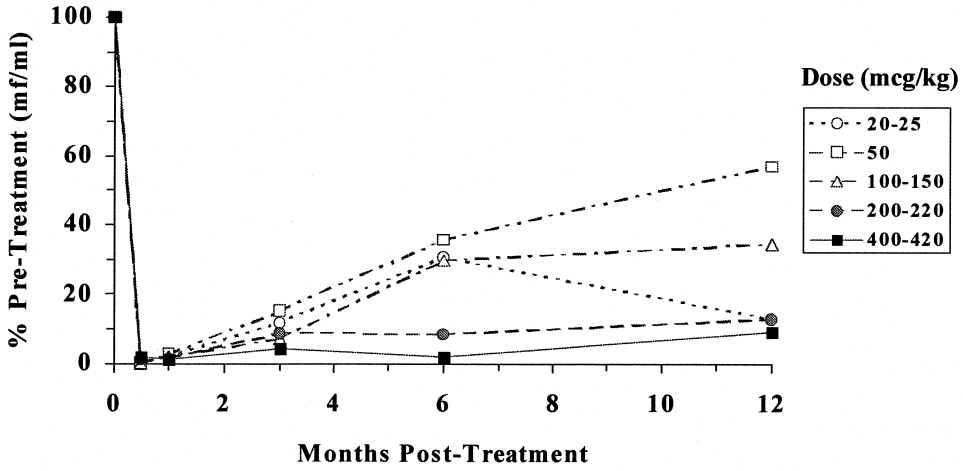

Fig. 1. Ivermectin: single-dose effectiveness in bancroftian filariasis. Dose response relationship for the ivermectin (20–400 μg/kg) effect on microfilaraemia. See text for details.

causes profound and sustained decreases in microfilaraemia that are generally greater than those that can be achieved with either drug alone. Third, in consideration of the recent announcement by Merck & Co Inc to provide ivermectin for use in lymphatic filariasis in countries where onchocerciasis is co-endemic, and the earlier announcement by Smith-Kline Beecham to provide albendazole needed for programmes seeking to eliminate lymphatic filariasis, it appears that all patients in Africa will indeed have access to appropriate two-drug treatment for lymphatic filariasis (Ottesen, Ismail & Horton 1999). Finally, on a very practical level, when treating co-endemic infections, it would be unreasonable to attempt to use an ivermectin regimen for lymphatic filariasis patients which is different from that for onchocerciasis (150–200 μg/kg once-yearly; Ottesen & Campbell, 1994) unless there were very compelling reasons for doing so.

Safety of ivermectin in lymphatic filariasis

There is general consensus that the occurrence and severity of adverse experiences following either ivermectin or DEC treatment in lymphatic filariasis are primarily the results of host inflammatory responses to dying microfilariae killed by the drugs (and not to drug toxicity itself); indeed, the degree and severity of reactions are in direct proportion to the pre-treatment microfilarial density rather than to the dosage of ivermectin or DEC (Ottesen, 1987, 1993; Roux *et al.* 1989; Cartel *et al.* 1990*a*, 1991*a*; Ottesen *et al.* 1990; Addiss *et al.* 1991; Ismail *et al.* 1991; Sabry *et al.* 1991; Shenoy *et al.* 1992; Kar *et al.* 1993; Coutinho *et al.* 1994). The observations made in all of the studies reviewed above add support to this notion that any adverse experiences to treatment are determined by clearance of microfilaraemia (regardless of the dose of ivermectin, throughout the dosage range tested) and not to any direct drug toxicity. Interesting new support for this conclusion was seen in the observations from those studies employing a small 'clearing dose' of ivermectin followed by a larger dose, since the major constitutional symptoms occurred more frequently after the initial, lower dose of ivermectin (20 μg/kg) when microfilarial density was highest, rather than after the second, larger standard doses of ivermectin 200 to 400 μg/kg (Richards *et al.* 1991; Weil *et al.* 1991). Such differences were statistically significant for chills, sweating, fever, headache, myalgia and cough (though transient pretibial oedema occurred in a small number of patients after the standard dose of ivermectin but not after the earlier 'clearing-dose'). Further confirmation was provided in the study by Cartel *et al.* (1992*d*) showing that the frequency of adverse experiences in subjects who were amicrofilaraemic was significantly less than in subjects with microfilaraemia (Table 8).

Because, however, the incidence of adverse experiences in relation to pre-treatment microfilarial density was not routinely reported in all of the studies reviewed here, because many of the publications cited did not attempt to establish a specific relationship between an adverse experience and the corresponding ivermectin dosage, and because the detail with which adverse experiences were monitored varied among the published studies, it is not possible to 'pool' all of this data quantitatively; rather, one can infer only qualitatively the lack of any significant relation between the incidence or severity of side effects and the dosage of ivermectin taken.

CONCLUSION

Ivermectin is a highly effective and generally well-tolerated drug for the treatment of lymphatic filariasis. Moreover, its simplicity of dosing, which improves compliance and is consistent with the dosing strategies currently being used for mass

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distribution campaigns for onchocerciasis, adds to its potential benefit. The rationale for the use of ivermectin in community treatment programmes targeting lymphatic filariasis is therefore clear.

Though 400 μg/kg appears to be a somewhat more effective dose than either 200 μg/kg or 100–150 μg/kg, choice of the dosage level and the dosing frequency of ivermectin for use in public health programmes against LF in Africa should be guided largely by the existing schedules for onchocerciasis control mass distribution programmes, where it is appropriate to coordinate these efforts. If mass distribution programmes for onchocerciasis control utilize a dosage of 150 to 200 μg/kg ivermectin, then the same should be adopted for patients with concurrent lymphatic filariasis, especially since these individuals will most likely be receiving a second anthelminthic drug, albendazole, concurrently as well (Ottesen *et al*. 1999).

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