Antifilarial compounds in the treatment and control of lymphatic filariasis

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Abstract. Diethylcarbamazine citrate (DEC) has been used for treatment and control of lymphatic filariasis since the 1950s. Although this remarkable drug is still useful and modified strategies in its usage have been developed, a number of newer antifilarial compounds are now available. Numerous field trials evaluating their efficacy in the control of lymphatic filariasis have been conducted. In particular, ivermectin (IVM), albendazole (ALB), and DEC have been tested singly and in combinations and the results of such field studies should be evaluated. While most of the studies were based on efficacy in the clearance of microfilaraemia, a few clinical trials evaluated the adulticidal activity of these compounds. Some antibiotics are effective in killing *Wolbachia* bacteria symbionts of filarial worms, but their role in the chemotherapy of lymphatic filariasis is still undefined. This review of randomised controlled field studies and randomised controlled clinical trials with these compounds will summarise the findings and give recommendations on their appropriate use for the control and treatment of lymphatic filariasis.

Randomised controlled studies have shown the superiority of the combination of single dose IVM at 200-400 µg/kg and ALB at 400 mg in clearing *Wuchereria bancrofti* microfilariaemia in children 4 months post-treatment compared to those given IVM or ALB alone. At 1 year post-treatment IVM and its combination with ALB were effective but the difference in efficacy between these two treatments was minimal. An interesting finding was that DEC at a single dose of 6 mg/kg was as effective as a total dosage of 72 mg/kg given over 12 days. Amicrofilaraemia achieved was only 40-42% at 1 year of follow-up. In one study it was also found that co-administration of IVM with DEC interfered with the macrofilaricidal action of DEC. This conclusion needs urgent confirmation as it will have serious implications in control programmes utilising both drugs.

Various combinations of DEC, IVM and ALB were found to be safe and well tolerated. The combination of a single dose of ALB 400 mg + DEC 6 mg/kg is safe and effective for the control of filariasis.

Randomised mass treatment studies with either DEC (6 mg/kg) alone or in combination with IVM (400 µg/kg) annually for four years resulted in reduction of microfilaria rates > 95%. With 5 single annual doses of DEC at 6 mg/kg, there was a total reduction of 90% in positive microfilaria rate from the initial level. However, in other studies, with single-dose DEC or IVM annually over 4 years, the microfilarial rate fell only by 49% and 60% for the DEC and IVM groups respectively, compared to an increase by 28% in the placebo group. Microfilarial levels were also significantly decreased from pre-treatment levels.

The combination of IVM 400 µg/kg + DEC 6 mg/kg or 3 mg/kg was superior to that of single dose treatment with DEC or IVM alone. A single or 6 doses of DEC 6 mg/kg were also equivalent in reducing the microfilaria prevalence rate and mean microfilarial densities significantly at 1 year post-treatment in brugian filariasis.

Microfilaraemic patients treated with DEC or the newer antifilarial compounds commonly experience mild to severe side reactions within a few to 24 hours after the start of treatment. *Wolbachia* symbionts have been implicated in the pathogenesis of filariasis and adverse reactions associated with chemotherapy. Antibiotics which are effective against these bacteria may have an important role in the treatment and control of lymphatic filariasis.

It is considered desirable to achieve death of the adult worms in the treatment of lymphatic filariasis. DEC is presumed to have both microfilaricidal as well as macrofilaricidal activities. A recent study on its macrofilaricidal action on *W. bancrofti* has raised some concerns. While the macrofilaricidal effect of DEC was confirmed, a significant proportion of the worms were not killed even at doses in excess of 6 mg/kg. Ivermectin, even at a single dose of 400 µg/kg had no macrofilaricidal effect on adult worms.

BACKGROUND

Diethylcarbamazine citrate (DEC), discovered in 1947, has been used for the treatment and control of lymphatic filariasis since the 1950s. This remarkable drug is still useful and newer strategies in its usage have now been developed. Ivermectin (IVM), a 22, 23-dihydro derivative of avermectin B_1, is a macrocyclic lactone having activity against a broad spectrum of nematode and arthropod parasites.

This drug is now used for the treatment of onchocerciasis as well as for lymphatic filariasis. Albendazole (ALB) developed as an anthelmintic for the treatment of gastrointestinal parasites since the late 1980s has recently been included for the treatment of lymphatic filariasis. DEC and IVM are used alone or in combination for the mass-treatment of lymphatic filariasis and recently ALB has also been added to DEC or IVM for the same purpose. The apparent reasons for the current use of drug combinations are firstly the desire for effective single dose drug regimens for mass-therapy, secondly to kill both adult worms and microfilariae, and finally to prevent the emergence of drug resistance.

The clinician is now faced with various alternatives for the treatment of lymphatic filariasis, but the choice of drugs and their combinations must be evidence-based. DEC was previously given in multiple doses (6 doses of 6 mg/kg totalling 36 mg/kg for brugian filariasis and 12 doses totalling 72 mg/kg for bancroftian filariasis) in mass treatment for the control of lymphatic filariasis. For the individual patient, DEC at 6 mg/kg/day for 12 and 21 days was used to treat brugian and bancroftian filariasis respectively.

Clinical evidence supported by experimental chemotherapeutic studies in non-human primates (Mak *et al.*, 1990) show that DEC has microfilaricidal and macrofilaricidal activities. Ultrasound studies show that DEC even when given at a single dose can kill adult worms. However, IVM even when given at high doses did not kill adult *W. bancrofti* worms (Dreyer *et al*., 1995). This is to be expected as Mak *et al.* (1988) found it to have poor adulticidal activity against *B. malayi* infection in the leaf monkey. ALB is believed to have filaricidal activity and experimental data in primates show it to have adulticidal but no microfilaricidal activity against subperiodic *Brugia malayi* (Mak *et al.*, 1984). However, a recent systematic review to assess the effects of ALB on lymphatic filariasis in patients and populations concluded that there is insufficient reliable research to confirm or refute whether ALB alone, or given together with DEC or IVM, has an effect on lymphatic filariasis (International Filariasis Review Group, 2004).

The purpose of this review is to examine randomised control studies of these three drugs either alone or in combinations for effectiveness in the treatment of lymphatic filariasis. Field studies will also be analysed for efficacy of these compounds when used for the mass-treatment of endemic

populations in the control of lymphatic filariasis. Another objective is to give recommendations, based on these systematic reviews, on the current approach in the treatment of the individual patient.

EFFICACY OF DRUGS USED IN THE TREATMENT OF LYMPHATIC FILARIASIS

Efficacy of albendazole (alb) and its combination with other filaricides

Efficacy of ALB

There were only two small placebo-controlled randomised studies on the efficacy of ALB in clearing microfilariae in bancroftian filariasis (Addiss *et al*., 1997; Dunyo *et al*., 2000a). In Haitian microfilaraemic children, a single dose of ALB at 400 mg was not statistically different from placebo in clearing microfilaraemia at follow-up 4 months after treatment (RR = 1.170, 95% CI = 0.595-2.300; Table 1). In the study by Dunyo *et al*. (2000a), there was also no significant difference in clearing microfilaraemia when ALB was compared with placebo in Ghanaians (Table 1). When these two studies were combined a similar conclusion is reached. There is no statistical difference between ALB at a single dose of 400 mg and placebo in clearing microfilaraemia (RR = 1.170; 95% CI = 0.595-2.300). This is to be expected as experimental studies of ALB against subperiodic *Brugia malayi* infection in primates do not indicate any microfilaricidal activity (Mak *et al*., 1984).

Table 1. Efficacy of albendazole (ALB) in clearing microfilaraemia in the treatment of lymphatic filariasis

Reference	Placebo	ALB	RR	95% CI
Addiss *et al.* (1997)[1]	9/29 (31.0%)	7/29 (24.1%)	0.777	0.335 – 1.806
Dunyo *et al.* (2000a)[2]	4/66 (6.1%)	9/71 (12.7%)	2.091	0.676 – 6.469
Combined	**13/95 (13.7%)**	**16/100 (16.0%)**	**1.170**	**0.595 – 2.300**

[1]ALB 400 mg x 1; in Haitian children 5-11 years old with bancroftian filariasis, follow-up 4 months post-treatment. [2]ALB 400 mg x 1; bancroftian filariasis in Ghana, follow-up 1 year.

Efficacy of diethylcarbamazine citrate (DEC) compared with albendazole (ALB) in clearing microfilaraemia

Pani *et al*. (2002) randomly assigned 54 *W. bancrofti* microfilaraemic volunteers (mean age 24.7 years, range 10-57 years) with pre-treatment microfilarial density between 22-606 per ml, into 3 single-dose treatment groups of DEC at 6 mg/kg, ALB at 400 mg, and combination of DEC 6 mg/kg + ALB 400 mg. They were followed up for 1 year post-treatment. This small study showed that of the 17 on DEC alone, 3 (17.6%) became amicrofilaraemic at 1 year compared to 5 out of 19 (26.3%) in the ALB group. Thus ALB appeared to be more effective in clearing microfilaraemia at 1 year post-treatment when compared with DEC (RR = 0.671; 95% CI = 1.944-2.395). A study with a longer follow-up period and a larger group of patients should be conducted to confirm this result.

Efficacy of albendazole (ALB) alone compared against its combination with diethylcarbamazine (DEC)

There were two small randomised controlled studies comparing ALB at 400-600 mg single dose against the combination with DEC at 6 mg/kg single dose. These studies carried out in Sri Lanka (Ismail *et al*., 1998) and in India (Pani *et al*., 2002a) showed no significant difference between these two regimes in the individual studies and when the results were combined (RR = 0.701; 95% CI = 0.277-1.776; Table 2).

Table 2. Efficacy of albendazole (ALB) compared with the combination diethylcarbamazine citrate (DEC) + ALB in clearing microfilaraemia in the treatment of lymphatic filariasis

Reference	ALB	DEC + ALB	RR	CI
Ismail *et al.* (1998) [1]	1/12 (8.3%)	3/11 (27.3%)	0.305	0.037 – 2.516
Pani *et al.* (2002)[2]	5/19 (26.3%)	5/18 (27.8%)	0.947	0.329 – 2.730
Combined	**6/31 (19.4%)**	**8/29 (27.6%)**	**0.701**	**0.277 – 1.776**

[1]ALB 600 mg x 1; Combination treatment = DEC 6 mg/kg x 1 + ALB 600 mg x 1; bancroftian filariasis in Sri Lankan, follow-up 15 months. [2]ALB 400 mg x 1; Combination treatment = DEC 6 mg/kg x 1 + ALB 400 mg x 1; bancroftian filariasis in Indians, follow-up 1 year.

Efficacy of diethylcarbamazine (DEC) and its combination with other filaricides

Efficacy of DEC

There was no placebo controlled study on the efficacy of DEC in clearing microfilaraemia. Andrade *et al*. (1995) in single-blind randomised study on the efficacy of DEC concluded that at 1 year after treatment a single dose of 6 mg/kg was as effective as a total dose of 72 mg/kg given over 12 days in a single daily or divided doses. Amicrofilaraemia achieved was 40-42% at 1 year of follow-up. In groups given daily single or divided doses of DEC 6 mg/kg/day for 12 days, and the group given 6 mg/kg single dose, those amicrofilaraemia were 30 out of 72 (41.7%) and 6 out of 15 (40%) respectively. There was no significant statistical difference between the results (RR = 1.042; 95% CI = 0.529-2.050).

Efficacy of DEC compared with DEC combined with ALB

There were two small randomised controlled studies comparing the efficacy of DEC alone against its combination with ALB in clearing bancroftian microfilaraemia in Indians (Kshirsagar *et al*., 2004; Pani *et al*., 2002). In both studies the difference in clearing microfilaraemia between the two treatment groups was not statistically significant at 1 year post-treatment. The combined results were similar, there being no statistical difference between the two treatment groups (RR = 0.994; 95% CI = 0.608-1.626; Table 3).

Table 3. Efficacy of diethylcarbamazine citrate (DEC) compared with the combination DEC + albendazole (ALB) in clearing microfilaraemia in the treatment of lymphatic filariasis

Reference	**DEC**	**DEC + ALB**	**RR**	**CI**
Kshirsagar *et al.* (2004)[1]	14/21 (70.0%)	13/22 (59.1%)	1.129	0.712 – 1.790
Pani *et al.* (2002)[2]	3/17 (17.6%)	5/18 (27.8%)	0.635	0.179 – 2.258
Combined	**17/38 (44.7%)**	**18/40 (45.0%)**	**0.994**	**0.608 – 1.626**

[1]DEC 6 mg/kg x 1; Combination treatment = DEC 6 mg/kg + ALB 400 mg x 1; mass-treatment of bancroftian filariasis in India, follow-up 1 year. [2]DEC 6 mg/kg x 1; Combination treatment = DEC 6 mg/kg + ALB 400 mg x 1; randomised control trial of bancroftian filariasis, India, follow-up 1 year.

Efficacy of DEC compared with DEC combined with ivermectin (IVM)

There were two randomised studies comparing the efficacy of DEC alone and its combination with IVM. Moulia-Pelat *et al.* (1995) carried out the study on bancroftian filariasis in Polynesia using a single dose regimen in mass-treatment and followed up the microfilaraemics over 1 year. Bockarie *et al*. (2002) used single annual doses in mass-treatment of endemic villages in Papua New Guinea over 4 years. Both studies showed a significant difference in microfilarial clearance with the combination regimen. The combined results using the data at a year's follow-up, also showed the combination treatment cleared 72.7% of the microfilaraemics compared to 62.9% in the DEC group (RR = 0.864; 95% CI = 0.816-0.915; Table 4). Thus significantly more patients in the combination group were amicrofilaraemic at a year post-treatment.

Table 4. Efficacy of diethylcarbamazine citrate (DEC) compared with the combination DEC + ivermectin (IVM) in clearing microfilaraemia in the treatment of lymphatic filariasis

Reference	DEC	DEC + IVM	RR	CI
Moulia-Pelat *et al*. (1995)[1]	16/86 (18.6%)	29/89 (32.6%)	0.571	0.335 – 0.972
Bockarie *et al*. (2002)[2]	671/1007 (66.6%)	817/1074 (76.1%)	0.087	0.069 – 0.110
Combined	**687/1093 (62.9%)**	**846/1163 (72.7%)**	**0.864**	**0.816 – 0.915**

[1]DEC 6 mg/kg x 1; DEC 3-6 mg/kg + IVM 400 µg/kg x 1; mass-treatment of bancroftian filariasis in Polynesia, follow-up 1 year. [2]DEC 6 mg/kg x 1; combination DEC 6 mg/kg + IVM 400 µg/kg x 1; annual doses x 4 years; randomised mass-treatment of bancroftian filariasis in Papua New Guinea; results at 1 year post-treatment given here

Efficacy of DEC and IVM given simultaneously and sequentially

Dreyer *et al*. (1998) carried out a randomised comparative study of a combination of DEC (6 mg/kg x 1) and IVM (200-400 µg/kg x 1) given either together or sequentially (IVM 200 µg/kg x 1 first followed by DEC 6 mg/kg on Day 5) in *W. bancrofti* microfilaraemic patients. End point measurements included clinical signs of nodular formation after treatment, microfilarial density and ultrasonography for 'filaria dance sign' to assess macrofilaricidal effect at 1 year after treatment.

None of the 30 worm nests in the simultaneous drug administration group showed worm death compared to 3 out of 19 (16%) in the sequential drug group. Scrotal nodules were seen in 24% (5/21) and 80% (8/10) simultaneous and sequential groups respectively (p = 0.01). It was concluded that co-administration of IVM with DEC interfered with the macrofilaricidal action of DEC. This finding will have to be confirmed in further studies as there are important implications for control programmes utilising both drugs.

When the groups given DEC + IVM simultaneously were combined and compared to the group given the two drugs sequentially, 20 out of 21 (95.2%) and 10 out of 10 (100%) were amicrofilaraemic at a year post-treatment. The difference is not statistically significant (RR = 0.9524; 95% CI = 0.866-1.048.

The above findings therefore show that similar amicrofilaraemia rates were achieved in spite of the statistical difference in the proportion of adult parasites killed. Thus amicrofilaraemia could be due to other mechanisms including long-term sterilisation of the worms.

Efficacy of ivermectin (IVM)

Efficacy of IVM compared with placebo

There were two small randomised placebo-controlled studies on the efficacy of IVM. Addiss *et al*. (1997) followed up Haitian children with bancroftian microfilaraemia who were treated with a single dose of IVM at 200-400 µg/kg, for 4 months post-treatment. The other study using single dose IVM at 150 µg/kg in Ghanaian bancrofti microfilaraemic patients had a follow-up period of a year. Both studies showed IVM to be significantly better in clearing microfilaraemia; the combined results show the IVM treated group to clear 29.6% compared to 13.7% of microfilaraemia at 1 year follow-up (RR = 2.163; 95% CI = 1.199-3.903; Table 5).

Table 5. Effect of ivermectin (IVM) in clearing microfilaraemia in the treatment of lymphatic filariasis

Reference	Placebo	IVM	RR	CI
Addiss *et al.* (1997)[1]	9/29 (31.0%)	11/28 (39.3%)	1.266	0.621 – 2.579
Dunyo *et al.* (2000a)[2]	4/66 (6.1%)	18/70 (25.7%)	4.243	1.515 – 11.884
Combined	**13/95 (13.7%)**	**29/98 (29.6%)**	**2.163**	**1.199 – 3.903**

[1]IVM 200-400 µg/kg x 1; in Haitian children 5-11 years old with bancroftian filariasis, follow-up 4 months post-treatment.

[2]IVM 150 µg/kg x 1; bancroftian filariasis in Ghana, follow-up 1 year.

Efficacy of IVM combined with ALB

Addis *et al*. (1997) found the combination of a single dose IVM at 200-400 µg/kg and ALB at 400 mg to be superior in clearing *W. bancrofti* microfilaraemic in children 4 months post-treatment compared to those given IVM or ALB alone or in placebo group (p = 0.004). In the placebo group, ALB alone, IVM alone, and the combination treatment group of IVM + ALB, 9 out of 11 (31%), 7 out of 29 (24.1%), 11 out of 28 (39.3%), and 20 out of 24 (83.3%) were amicrofilaraemic 4 months post-treatment respectively. Although this is a small study, the results show the drug combination to be superior to the IVM group (RR = 0.4715; 95% CI = 0.288-0.773) and the ALB group (RR = 0.290; 95% CI = 0.148-0.566). Systemic side reactions were similar in all 4 groups.

Dunyo *et al*. (2000a) carried out a double-blind randomised placebo controlled field-trial to assess the efficacy of IVM and ALB given alone and in combination. End point measurements at a year post-treatment included the number amicrofilaraemic and geometric mean microfilarial count (GMC). The combination as well as the IVM regimes induced the largest percentage of amicrofilaraemia after treatment. Although the differences between the IVM and combination groups were significantly different from that of the placebo group (p = 0.007) they were not significantly different from the albendazole group nor between themselves. The GMCs at 12 months post-treatment were significantly lower in groups with IVM in the regimen when compared to the placebo group. The authors concluded that the IVM and combination of IVM + ALB were effective but the difference in

efficacy between these two treatments was minimal. Side reactions were few and mostly mild, and occurred in 25.8% and 36.3% of patients respectively (Dunyo *et al*., 2000).

Ismail *et al*. (1998) compared single dose ALB (400 mg) against the combination of ALB (600 mg) + IVM (400 µg/kg) over a 1.5 year follow-up.

Both studies show the combination of IVM + ALB to be superior to ALB alone in clearing microfilaraemia. The combined data is similar there being a statistically significant difference in the clearing of microfilariae with the combination of IVM + ALB compared to ALB alone (RR = 2.157; 95% CI = 1.115-4.175; Table 6).

Table 6. Efficacy of albendazole (ALB) compared to IVM + ALB in clearing microfilaraemia in the treatment of lymphatic filariasis

Reference	**ALB**	**ALB + IVM**	**RR**	**CI**
Ismail *et al.* (1998) [1]	1/12 (8.3%)	9/13 (69.2%)	8.308	1.228 – 56.165
Dunyo *et al.* (2000a)[2]	9/71 (12.7%)	17/75 (22.7%)	1.788	0.853 – 3.747
Combined	**10/73 (13.7%)**	**26/88 (29.5%)**	**2.157**	**1.115 – 4.175**

[1]ALB 600 mg x 1; IVM 400 µg/kg x 1 in bancroftian filariasis in Sri Lankan; follow-up 1.5 years. [2]ALB 400 mg x 1; IVM 150-200 µg/kg x 1 in bancroftian filariasis in Ghana; follow-up 1 year.

Efficacy of combination of DEC + ALB compared with combination of IVM + ALB

Ismail *et al.* (2001) in a randomised controlled study on the efficacy of various combinations of DEC, IVM and ALB, followed patients up for 2 years post-treatment and found all the combinations used to be safe and well tolerated. They concluded that the combination of a single dose of ALB 400 mg + DEC 6 mg/kg is a safe and effective combination for the control of filariasis. The GMCs at 24 months post-treatment were 0.4%, 2.9%, and 2.3% of pre-treatment levels for the DEC+ALB 400mg, ALB 400mg+IVM 200 µg/kg, and the ALB 600 mg+IVM 400 µg/kg groups respectively. Based on these and because of the greater macrofilaricidal effect shown by the decline in filarial antigenaemia, they recommended a single dose of the combination of DEC 6 mg/kg + ALB 400 mg.

When the drug combination DEC + ALB was compared to that of ALB + IVM, 6 out of 13 (46.2%) and 7 out of 29 (24.1%) were amicrofilaraemic at 2 years post-treatment. However, the difference in inducing amicrofilaraemia is not significant (RR = 1.912; 95% CI = 0.799-4.575).

Randomised mass treatment studies

Mass treatment with single dose DEC at 6 mg/kg

Mataika *et al.* (1998) mass-treated 4,686 people in 32 villages in Fiji with single annual dose of 6 mg/kg and followed them up for 5 years. The microfilaria rate was reduced by about 90% from the initial level of 6.9% (Table 7). The initial microfilaria GMC/60 µl ranged from 1.0 – 67.6.

Das *et al.* (2001) carried out a randomised placebo-controlled mass-treatment field trial on *Wuchereria bancrofti* infection in India with single-dose DEC or IVM or placebo annually over 4 years. Coverage was 54-77% of eligible people. End point measurements included reduction in prevalence rates and changes in microfilarial GMC/60 µl. The microfilarial rate fell by 49% and 60% for the DEC and IVM groups respectively, compared to an increase by 28% in the placebo group. GMC levels fell by 65.2%, 80.7%, and 34.5% in the DEC, IVM, and placebo groups respectively.

Bockarie *et al*. (2002) evaluated annual single mass treatment with either DEC (6 mg/kg) alone or in combination with IVM (400 µg/kg) for four years. Coverage was 77-86 % of the population aged ≥ 5 years old. The microfilaria rate decreased by 86 – 98%, greater reduction being obtained in areas with moderate rate of transmission than in those with higher rate of transmission. At the end of the 4 annual treatments, 96.5% and 97.9% were amicrofilaraemic after four doses of DEC and the combination of DEC+IVM respectively. Geometric mean microfilaria count (GMC) was reduced from 9.6-49.8/ml to 0.5-0.3/ml for the combination treatment group, and from 8.8-55.2/ml to 0.5/ml in the DEC group. Hydrocoele and leg lymphoedema were eliminated in 87% and 69% respectively of those with these initial lesions. There was no severe reaction and minor side reactions were less frequent in the DEC group (11%) compared to the DEC+IVM group (20%), the difference being significant ($p = 0.01$).

Moulia-Pelat *et al*. (1995) mass-treated bancroftian filariasis in Polynesia with a single dose of DEC, IVM or their combinations and found the combination of IVM 400 µg/kg + DEC 6 mg/kg or 3

mg/kg to be superior to that of single dose treatment with DEC or IVM alone. Reductions of microfilaria prevalence rates were 35% for both combinations and 11% and 14% for single dose IVM and DEC respectively. Microfilarial density was reduced by 96%, 80%, 82% and 95% for IVM + DEC 6 mg/kg, IVM alone, DEC alone, IVM + DEC 3 mg/kg respectively.

Lokman-Hakim *et al*. (1995) treated mass-treated a periodic *Brugia malayi* endemic population with either a single or 6 doses of DEC 6 mg/kg. At a year post-treatment the microfilaria prevalence rate was reduced by 40.9% and 57.9% of initial rates respectively ($p = 0.001$). The mean microfilarial densities were significantly reduced by 79.7% and 83.1% ($p = 0.001$). The difference in reduction between the single and multiple doses was not significant ($p = 0.178$) (Table 8).

Gyapong (2000) followed up microfilaraemic subjects in Ghana who were mass treated 2 years previously with ivermectin at 200 µg/kg single dose. More than 90% of the population were covered in the two surveys, the numbers included in the survey being 664 and 605 in 1997 and 1999 respectively. The reduction in microfilaria prevalence rate was 25.5% while the reduction in geometric mean count/20µl was 39.5%.

Table 7. Efficacy of diethylcarbamazine citrate (DEC) in mass treatment of lymphatic filariasis at 6 mg/kg yearly x 4 years

Reference	**Pre-treatment +ve/examined (%)**	**Post-treatment +ve/examined (%)**	**% decline in Mf rate**	**c^2; P value**
Mataika *et al*. (1998)[1]	324/4686 (6.9)	38/2830 (1.3)	81.2	127.6; < 0.001
Das *et al*. (2001)[2]	94/711 (13.2)	47/692 (6.8)	48.5	16.0; < 0.001
Bockarie *et al*. (2002)[3]	566/1146 (49.4)	28/804 (3.5)	92.9	470.1; < 0.001
Combined	**984/6543 (15.0)**	**113/4326 (2.6)**	**82.7**	**443.2; < 0.001**

[1]Study in 32 villages in Fiji endemic for bancroftian filariasis; 100% coverage in pre-treatment survey; blood exam by 60µl thick blood film; single yearly dose treatment x 5 years; data after 4 doses analysed. [2]Study in 5 Indian villages as part of a placebo-controlled trial in 15 villages with single dose DEC (6 mg/kg), IVM (400 µg/kg) or placebo; treatment initially at 6 monthly cycle x 2 cycles then yearly x 2 cycles. [3]Open-label study among 14 villages in Papua New Guinea comparing single annual dose of DEC (6 mg/kg) or the combination o DEC + IVM (400 µg/kg x 1) in reducing transmission of bancroftian filariasis; 77-86% of population treated; data for both moderate and high transmission areas combined; initial GMC/ml at moderate and high transmission 8.8 and 55.2 and at post-treatment 0.5 and 0.5 respectively.

Table 8. Comparison of diethylcarbamazine citrate (DEC) versus ivermectin (IVM) in reducing microfilaria prevalence rates and geometric mean counts in mass treatment of lymphatic filariasis

Reference	**IVM**		**DEC**	
	Reduction in MF rate	**Reduction in GMC**	**Reduction in MF rate**	**Reduction in GMC**
Das *et al*. (2001)[1]	60.0% (614, 603)	80.6% (614, 603)	48.5% (711, 692)	65.2% (711, 692)
Moulia-Pelat *et al*. (1995)[2]	10.7% (412, 412)	80.5% (412, 412)	14.0% (352, 352)	82.3% (352, 352)
Lokman-Hakim *et al*. (1995)[3]			72.5%	79.7%
Mataika *et al*. (1998)[4]			89.9% (4686, 2611)	

[1]DEC at 6 mg/kg x 4 cycles or IVM 400 µg/kg x 4 cycles over 3 years for bancroftian filariasis in Tamil Nadu, India; beginning and final no. examined in parenthesis. [2]DEC 6 mg/kg x 1 or IVM 400 µg/kg x 1 in bancroftian filariasis in French Polynesia; follow-up 1 year after treatment; beginning and final no. examined in parentheses. [3]DEC 6 mg/kg x 1 against periodic brugian filariasis in Malaysia; follow-up 19 months after treatment; mean no of subjects studied = 131. [4]DEC 6 mg/kg single annual dose x 5 doses against bancroftian filariasis in Fiji.

Macrofilaricidal drugs

It is currently believed that it is desirable to achieve death of the adult worms in the treatment of lymphatic filariasis. DEC is presumed to have both microfilaricidal as well as macrofilaricidal activities. A recent study by Noroes *et al*. (1997) on the adult worm killing activity of DEC on *W. bancrofti* has raised some concerns. In the study, 31 infected men were randomly assigned to three DEC treatment groups. Treatment groups started with an initial 1 mg/kg (Group 1), 6 mg/kg (Group 2), and 12 mg/kg (Group 3). After 7 days the dosage and duration were progressively increased to 12 mg/kg for 7-10 weeks. Evaluation of efficacy was based on clinical and ultrasound monitoring of adult worm activity termed as the 'filaria dance sign' (Amaral *et al*., 1994; Dreyer *et al*., 1994). The macrofilaricidal effect of DEC on *W. bancrofti* was confirmed, the response of the worms to treatment was detected within 1 week after the initial dose. Only 2 (14.3%) of the 14 worm nests in those given

the initial 1 mg/kg had sensitive response compared to 20 (51.3%) of 39 nests in those given the initial 6 or 12 mg/kg ($p = 0.04$). A significant proportion of the worms were not sensitive even to doses given in excess of 6 mg/kg.

Histological evidence of macrofilaricidal activity was provided through the examination of biopsied nodules in patients treated with various doses of DEC (6 mg/kg x 1 - 12 mg/kg/d x 30 days. It was concluded that all doses including low doses of DEC resulted in damage and degeneration of adult worms (Figueredo-Silva *et al*., 1996). Another interesting observation was that apparently intact and degenerating worms can be seen in the same tissues.

Ivermectin at a single dose of 400 µg/kg had no macrofilaricidal effect on *W. bancrofti* adult worms based on ultrasonographic evaluation of the 'filaria dance sign' for 3-9 months and recovery of live adult worms eight months post-treatment (Dreyer *et al*., 1995).

Wolbachia endosymbionts in filarial worms and treatment implications

Microfilaraemic patients treated with DEC commonly experience side reactions ranging from mild to severe. Adverse reaction normally occurs within a few hours to 24 hours after the start of treatment. The severity of the reaction correlates with the microfilarial density at treatment, with severe reactions (fever >38.5ºC severe headache, body aches) being as high as 15% present in those with a GMC of 306/ml and moderate reaction (fever 37.8ºC to 38.5ºC) in 19.2% of those with a GMC of 126.8/ml , and 65.4% no or mild reactions (body temperature ≤ 37.7ºC) in those with a GMC of 0.6/ml (Haarbrink *et al*., 1999).

A recent review of the role of *Wolbachia* symbionts in the pathogenesis of filariasis, adverse reactions associated with chemotherapy, and the opportunities to target these organisms in the treatment and control of lymphatic filariasis is available (Taylor, 2000).

Conclusion

There are inadequate randomised controlled clinical and field studies on the use of these antifilarial compounds for the treatment of lymphatic filariasis. The recent Cochrane Review on Albendazole for Lymphatic Filariasis (International Filariasis Review Group, 2004) concluded that there is insufficient

evidence to confirm or refute whether ALB alone or given together with DEC or IVM, has an effect on lymphatic filariasis. DEC is an effective microfilaricide, a single dose of 6 mg/kg being as effective as the total dose of 72 mg/kg given over 12 days in clearing microfilaraemia. It is also effective against adult worms, killing > 50% adult worms even at a single dose of 6 mg/kg. However, half the worms are not sensitive to DEC even after multiple doses. IVM is an effective microfilaricide, a single dose of 150-400 µg/kg being effective in clearing the microfilaraemia in ~30% of patients at 1 year post-treatment. However, it does not kill the adult worms at these dosages. DEC 6 mg/kg when combined with IVM 400 µg/kg is superior to DEC alone in clearing microfilaraemia.

For mass treatment, a single dose of DEC 6 mg/kg annually for 4 cycles is effective in reducing the microfilarial rate and the microfilarial density by > 80% of the initial values. Four annual cycles of IVM 400 µg/kg achieved a reduction of microfilarial rate of 60% and the microfilarial density of > 80%. When the two drugs are combined the clearance of microfilaraemia is superior to the two drugs given alone. Side reactions encountered in the use of the antifialrial drugs when used alone or in combination are similar.

We need a better drug to kill adult worms than the currently available DEC. In view of experimental animal studies showing the possible adulticidal activity of ALB, the combination of DEC 6 mg/kg with ALB 600 mg should be further evaluated. The combination of DEC and doxycycline which can kill *Wolbachia* symbionts should be evaluated. While we await the results of these studies the following can be recommended:

(a) In mass chemotherapy for control of lymphatic filariasis, an annual dose of DEC 6 mg/kg alone or together with IVM at 400 µg/kg should given for at least 4-5 cycles.

(b) For treatment of lymphatic filariasis in the individual patient, a single dose of DEC 6 mg/kg should be used. If the adult worms are not sensitive to the DEC, ALB 600 mg single dose can be added on to DEC in the next course of treatment.

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