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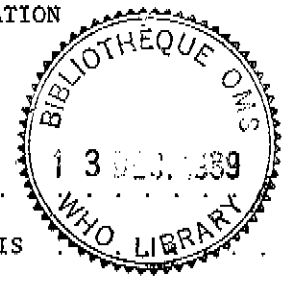


UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR
RESEARCH AND TRAINING IN TROPICAL DISEASES

Geneva, 24-26 May 1989

CLINICAL AND FIELD TRIALS OF IVERMECTIN FOR LYMPHATIC FILARIASIS
REPORT OF AN INFORMAL CONSULTATION

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This report contains the collective views of an international group of experts convened by the UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR RESEARCH AND TRAINING IN TROPICAL DISEASES (TDR). It does not necessarily reflect the views of TDR/WHO. In the interests of rapid communication it has been submitted to only minimal editorial revision. Moreover, any geographical designations used in the report do not imply the expression of any opinion whatsoever on the part of TDR or WHO concerning the legal status of any country, territory, city or area or of its authorities concerning the delimitation of its frontiers or boundaries.

Ce rapport exprime les vues collectives d'un groupe international d'experts réuni par le PROGRAMME SPECIAL PNUD/BANQUE MONDIALE/OMS DE RECHERCHE ET DE FORMATION CONCERNANT LES MALADIES TROPICALES (TDR). Il ne représente pas nécessairement les vues du TDR/OMS et, en vue d'une diffusion accélérée, il n'a pas été l'objet d'une mise en forme particulièrement soignée. En outre, les noms géographiques utilisés dans le présent rapport n'impliquent, de la part du TDR ou de l'OMS, aucune prise de position quant au statut juridique de tel ou tel pays, territoire, ville ou zone, ou de ses autorités, ni quant au tracé de ses frontières.

1. PURPOSE OF THE INFORMAL CONSULTATION

The objectives of the Informal Consultation were to review the information becoming available from the present Phase II trials and plan what further optimal dose finding and interval studies should be done; develop outline protocols for clinical trials of ivermectin for treatment of clinical disease; outline approaches for field trials of ivermectin for prevention of clinical disease; outline strategies for community trials for reduction of transmission; and examine the need for field site preparation and training needs for these trials.

2. EXPERIENCE WITH IVERMECTIN IN LYMPHATIC FILARIASIS

Numerous publications describe the pharmacological and general anti-parasitic effects of ivermectin (1,2) and its widespread use in onchocerciasis (e.g., 3-5). Only three trials have been completed in lymphatic filariasis (6,7); all three involved hospitalized patients with Wuchereria bancrofti infections. Two were in Madras, India and one was in Tahiti, French Polynesia. The major results were as follows:

(a) In Madras, the first trial involved 40 microfilaraemic men who were treated in groups of 10 with one of four ivermectin dosages (25, 50, 100 and 200 µg/kg) given as a single oral dose. While all dosages were found to be completely effective in clearing blood microfilariae (MF) within 5-12 days, in most patients microfilariae (MF) reappeared by 3 months; by 6 months, the levels averaged 14-32% of pretreatment values in all four study groups, with the efficacy of all groups being statistically equivalent given the small numbers in each group. Detailed monitoring identified side reactions in most patients; usually fever, headache, light-headedness, myalgia, pharyngitis, or cough that occurred most prominently 18-36 hours after treatment. These reactions correlated with patients' pretreatment blood MF levels in those treated with the higher dosages of ivermectin, but those receiving low-dose (25 µg/kg) ivermectin had significantly fewer side reactions than those in the other treatment groups.

(b) Since this first study had shown ivermectin to be very good, but not perfect, in eliminating MF from the blood and producing relatively minor adverse reactions, the next question was how ivermectin compared (in attributes and drawbacks) with the standard therapy, diethylcarbamazine (DEC). Thus, for the second study, an additional 40 men from South India, again with nocturnally periodic bancroftian filariasis manifested solely as asymptomatic microfilaraemia, were entered in a double-blind fashion into one of four treatment groups. On the first day patients received one of the following: 1 mg of ivermectin (approximately 20 µg/kg); 6 mg of ivermectin (approximately 120 µg/kg); DEC (at half strength, i.e., 150 mg (approximately 3 mg/kg)); or placebo. On the following 12 days, patients in the DEC group were given 300 mg DEC each morning; those in the ivermectin groups received placebo capsules. Because the placebo group was included only to control for side-reaction complaints, and since essentially all of these developed during the first 5 days, after 5 days these individuals were reassigned to one of the three active-drug groups by a clinical monitor not involved in patient care or evaluation. The results of this comparison were clear:

(i) With respect to efficacy, ivermectin cleared MF from the blood more rapidly than DEC; it was similar to DEC in decreasing MF for up to 3 months post-treatment but, by 6 months, did not sustain this decrease as well as DEC. Furthermore, the 20 µg/kg dose was as effective as the 120 µg/kg dose.

(ii) With respect to side reactions, findings were essentially identical (qualitatively and quantitatively) both for DEC and the lower ivermectin dosage regimen. For both drugs, the occurrence and severity of the side reactions generally correlated with patients' pretreatment MF levels--an observation implying that direct drug toxicity was in neither case the cause of the side reactions; the host inflammatory response to dying parasites appears to be the primary determinant of treatment side effects.

Since DEC and the low-dose ivermectin (20 µg/kg) showed generally similar efficacy and side reactions, and since in both studies the lowest dose of ivermectin tested was associated with fewer side reactions than were the higher doses, a third study has been initiated in Madras to compare the effectiveness and side reactions of a still lower ivermectin dose (10 µg/kg) with a 20 µg/kg dose, with DEC, and with placebo. This study is not yet complete.

(c) In French Polynesia, a four-dosage open trial of ivermectin, similar to the first study in Madras, was carried out on 40 microfilaraemic individuals who received single doses of ivermectin at 50, 100, 150 or 200 µg/kg. The results of this study showed clearly that doses ≥ 100 µg/kg were more effective than a lower one of 50 µg/kg in decreasing and sustaining the decrease in blood MF without inducing a greater number of side reactions. For example, 29/30 patients receiving ≥ 100 µg/kg cleared their blood MF within two weeks following ivermectin treatment, whereas only 2/10 receiving 50 µg/kg showed such clearance; similarly, MF levels in the 50 µg/kg group were almost 3 times higher at 90 days post treatment than in the other groups, and even by 6 months they remained twice as high.

These findings, were distinctly different from those in South India, where dosages of 20 - 25 µg/kg had been found to be just as effective as those up to 200 µg/kg in reducing MF, and importantly, had been associated with fewer side reactions than the higher ones. These discrepant findings suggested the possibility that different susceptibility to ivermectin will be found among W. bancrofti parasites in different regions of the world. To examine this possibility, hospital-based Phase II studies are currently underway (Brazil) or planned (Kenya, India, Malaysia, Sri Lanka and Indonesia) to evaluate the susceptibility both of W. bancrofti and Brugia malayi infections to a broad range of ivermectin dosages in endemic regions around the world.

3. THE TYPES OF STUDIES TO EVALUATE IVERMECTIN USEFULNESS IN LYMPHATIC FILARIASIS

3.1 Factors in the Pathogenesis of Lymphatic Filariasis Important to the Study Design

The pathogenesis of disease from the lymphatic filariases is not clear. Contributions to the disease process may be made by the host's reactions to any or all of the following: (1) the microfilariae, (2) the adult worms, (3) the inoculation of infective larvae by the vector and their subsequent moults. Of additional importance may be: (4) secondary factors such as bacterial superinfection, and (5) underlying host factors such as HLA type, nutritional status, and in utero exposure to MF and maternal response factors. At present our tools for understanding and measuring the process consist of the following: (1) quantitative MF counts (in a variety of ways), (2) clinical symptoms and signs, and (3) immunological/biochemical tests (a great variety of tests and antigens but no general agreement about their role or usefulness as indicators).

The distinction between infection and disease has been very useful in understanding basic disease processes in many viral, bacterial and protozoan

infections. For some helminthic infections quantification of the worm load has proven to be the key to understanding the relation of infection to disease. For example, egg counts in schistosomiasis and MF counts in onchocerciasis provide reasonable though imperfect indicators of infection, and the disease process in infected individuals very closely parallels their quantitative counts (with due allowance for time lags). For lymphatic filariasis, however, the MF counts do not seem to parallel the disease process and in individuals in endemic areas the absence of MF is not an indicator of absence of infection. At the community level, on the other hand, there is often quite a good relationship between the community MF load and the amount of clinical disease; further, when it has been possible to reduce the community MF load over time, new cases of clinical disease have also declined, sometimes to zero.

3.2 The Series of Studies

In order to evaluate the usefulness of ivermectin in lymphatic filariasis, the following types of studies will be needed. The study population size, duration, type and setting of these sets of studies will be quite different one from another. Though there may be some overlapping, these sets will generally follow in sequence.

- (1) The effect of ivermectin on MF levels in individuals. These studies will be an extension of the dose ranging studies and will generally involve 10-20 MF positive individuals in each study group.
- (2) The effect of ivermectin for treatment of acute clinical disease. These studies will be individually randomised clinical trials of ivermectin on patients with acute adenolymphangitis attacks or with tropical pulmonary eosinophilia (TPE); they will be carried out in a hospital or clinic setting.
- (3) The effect of ivermectin on prevention of clinical disease in individuals. These studies will involve large field trials of many thousands of persons who will be individually randomised and followed over several years. In addition, the effect of treatment on chronic manifestations can probably best be done in the context of these trials.
- (4) The effect of ivermectin on reduction of transmission in communities and the effect such reduction may have on the prevention of disease in the community. These studies will require the randomisation of many villages to receive one of the other treatment schedules for several years and will also require periodic entomological assessments.

The next four sections discuss and outline the approach and strategy for each of the above four types of studies. Draft protocols for the first two sets are available as indicated on p. 13, but more information from the outcomes of these studies and specific information related to the exact location will be required before detailed protocols for the third and fourth sets can be developed.

4. DRUG EFFECTS ON MF LEVELS IN INDIVIDUALS

The following are questions that remain to be resolved concerning ivermectin and/or DEC effects on MF levels in individuals:

- (a) What is the lowest single dose of ivermectin that will achieve maximum efficacy (defined as sustained clearance of MF from the blood)? Does this dose differ for different strains of W. bancrofti parasites and for B. malayi?
- (b) What is the optimum regimen of ivermectin to keep the level of blood MF close to zero?

- (c) Is there any effect of ivermectin on the adult stage?
- (d) Does some combination of ivermectin with DEC give a greater effect than either alone?

To date, all completed trials of ivermectin in lymphatic filariasis have focused on the decrease in microfilaraemia effected by a single ivermectin dose, sometimes in comparison to a 13-day course of DEC. We still do not know how a single oral dose of ivermectin compares to a single oral dose of DEC; nor is it known how frequently ivermectin (or DEC) must be given to bring down and maintain microfilaraemia to very low levels without inducing side reactions that significantly affect patient compliance. Furthermore, it is not clear just how low the levels of blood microfilariae must be in order to decrease significantly the infectivity of the blood to mosquitos.

Therefore, after completion of the current round of protocols to establish the lowest effective and well tolerated dose of ivermectin and to compare its efficacy with that of a "standard" course of DEC, a study following the first draft protocol as listed on p. 13 should be undertaken. That study would define the tolerability (in terms of adverse reactions) of repeated single doses of ivermectin or DEC given at two different intervals (for example, every 3 months or every 6 months) while at the same time determining the efficacy of such regimens in reducing blood microfilariae levels. In this regard, the trial would be similar to that soon to be initiated in French Polynesia where DEC or ivermectin is given as single oral doses every 6 or 12 months.

In addition to assessing efficacy and tolerability, such a study protocol would also permit evaluation of the effects of these regimens on transmissibility of the parasites from the blood of treated individuals to the vector mosquitos. In different areas of the world where there are facilities for studying the major vectors (Culex, Aedes, Anopheles, Mansonia), blood-feeding experiments could be considered, perhaps to be carried out serially in the same individuals as they undergo treatment with ivermectin or DEC given at different intervals. The results of such a study would answer many technical questions important for designing optimal strategies for mass-administration of the drugs and for assessing the likelihood that such administration would actually decrease transmission.

5. DRUG EFFECTS ON TREATMENT OF ACUTE CLINICAL DISEASE

5.1 Acute Adenolymphangitis

The second draft protocol listed on p. 13 is that of a clinical trial based on careful monitoring of about 120 patients selected because they have frequent acute adenolymphangitis attacks: these patients will be randomly assigned to one of three groups receiving therapy with DEC, ivermectin, or placebo (in addition to antibiotics as required per clinical diagnosis and analgesics received by all). In some locations those with acute genital diseases (funiculitis and/or epididymitis-orchitis) could be included in the same protocol. In addition to assessing the response of the acute episode itself and to monitoring the frequency and characteristics of the recurrent acute adenolymphangitis attacks, careful measurements of the affected limbs of each individual would be obtained at intervals throughout the study to record the development or progression of lymphoedematose changes.

5.2 Tropical Pulmonary Eosinophilia (TPE)

The filarial syndrome most dramatically reversible by antifilarial chemotherapy is the TPE syndrome. Within 3-4 days of beginning treatment with DEC patients show dramatic improvement in their pulmonary symptoms as well as a

marked fall in their peripheral blood eosinophil count. Over the course of subsequent weeks the eosinophil count returns almost to normal, chest x-ray findings improve dramatically or resolve completely, and total IgE and anti-filarial antibody levels in the serum decrease markedly. Thus, there are many potential end-points to be assessed in treatment trials of patients with this syndrome. The major problem, however, is that TPE is relatively rare, no more than 10-20 patients per year being diagnosed even in areas where the syndrome is reasonably frequent (e.g., Madras, India, or Recife, Brazil).

The study design for initial evaluation of ivermectin's efficacy in treating TPE would be an open trial (see third draft protocol, p. 13) in which individuals with this syndrome are treated in a very high but safe dose of ivermectin (e.g., 200 or 400 µg/kg) and then followed serially with measurement of the various rapidly changing clinical and laboratory parameters. If improvement did occur, then subsequent studies to compare ivermectin's effectiveness with that of DEC could be carried out, as well as studies to optimize the dose of ivermectin to be used in patients with this syndrome. As indicated in the draft protocol, however, because the triggering of asthmatic attacks in people with a history of asthma has been an occasional side effect of ivermectin treatment of onchocerciasis and because mild obstructive pulmonary airway changes have been noted in some bancroftian filariasis patients treated with ivermectin, for the first TPE patients being treated with ivermectin, an initial very small dose (e.g., 10 µg/kg) will be given one day prior to the larger "trial" dose of 200 or 400 µg/kg. If neither dose causes an exacerbation of the patient's symptoms, the initial small dose will be dropped for the subsequent patients in the protocol.

6. DRUG EFFECTS ON PREVENTION OF CLINICAL DISEASE IN INDIVIDUALS

These studies are to determine the effects of the alternative drug regimens on each of the following:

- (a) the incidence of acute disease among those who have not yet suffered any acute episodes of filarial lymphangitis or lymphadenitis (who may or may not have MF);
- (b) the recurrence of acute disease among those who already have a history of one or more acute episodes of filarial lymphangitis or lymphadenitis (who may or may not have MF);
- (c) the incidence of lymphoedema including hydrocoele among those who do not yet have this condition (who may or may not already have a history of acute lymphangitis/lymphadenitis or of microfilaraemia);
- (d) the progression (or regression) of lymphoedema and hydrocoele among those who already are affected (methods of measuring and criteria for grading to be standardized).

In addition, the following may also be determined:

- (e) the incidence of symptomatic disease caused by other organisms (e.g., Strongyloides, Ascaris, ectoparasites, etc.) that might be at least partially controlled by ivermectin;
- (f) the incidence of any other diseases that might cause people to seek medical attention as a check for unexpected benefits or side-effects.

To answer these questions sufficiently reliably for public health purposes, large individually-randomized trials are needed in areas where filariasis is endemic. Such trials should include a substantial proportion of

symptomatic individuals (although the ratio of symptomatic to asymptomatic individuals need not be the same in the trial as in the community in which the trial takes place). At least three options - placebo, intermittent ivermectin and intermittent DEC, and, if evidence can be found that the combination of ivermectin with DEC might be better than either alone then the trial should be extended to include, as a fourth option, a combination of the two drugs. Details of dose and frequency of ivermectin and DEC to be used will be based upon the studies outlined above. To resolve some of the important issues the trials are likely to require populations of at least 20,000 followed for at least 3 years.

In the Madras studies the MF levels returned to about 20% of their former levels within 3 months, and to about 30-40% within 6 months. Hence, to obtain a substantial (e.g., about 80-90%) degree of control of microfilaraemia, treatment will probably have to be repeated at least every few months; conversely, to facilitate compliance, and for the schedule to be of practical relevance, it should not involve more than a few doses per year, e.g., every 3-4 months. Longer intervals might be more practical in terms of costs and logistics, but if a higher MF buildup is allowed then the rate of adverse reactions would be higher and could reduce compliance. Studies on tolerability as outlined in the final draft protocol (see p. 13) may be needed for each trial area.

Criteria will have to be established for exclusions including pregnancy and lactation; arrangements for treatment of those excluded will have to be worked out as soon as possible after the period for exclusion has ended; and provision must be made for follow-up of all births amongst those who may have inadvertently received a drug/placebo during pregnancy.

7. DRUG EFFECTS ON REDUCTION OF TRANSMISSION IN COMMUNITIES

7.1 Community Randomised Trials

The trials described in the previous section, in which individuals were randomized to receive periodically ivermectin, DEC or a placebo, were designed to determine if ivermectin or DEC, when taken regularly, will reduce clinical disease in those individuals in a situation in which the transmission is not reduced substantially. However, if the development of disease is primarily due to adult worms, whereas the drug being used affects only microfilariae, then it is possible that these studies will demonstrate that disease incidence is no greater amongst those receiving the placebo than amongst those receiving either ivermectin or DEC (depending upon which, if either, affects adult worms). Additionally, if acute attacks are precipitated by the inoculation of larvae by the vector into a sensitized host, then these studies would show no difference. Nevertheless, if a sufficient proportion of the affected community is treated regularly, it is possible that regular drug therapy may reduce disease incidence and progression through an impact on the transmission of filariasis.

In order to investigate the effect of chemotherapy on transmission it is necessary to consider the community as the unit of study; the ideal study design would involve the randomization of a number of communities to receive one or another of the different intervention strategies under consideration and then measuring disease incidence in each. Although it would be of interest to compare a number of possible control strategies (e.g., various kinds of vector control, adding DEC to salt, different DEC treatment schedules, and various combinations), the focus of this document is on studies of ivermectin as compared with DEC. The exact regimens to be compared will depend upon results of the studies outlined above.

The specific objectives of such community intervention trials is to evaluate the impact that different control measures applied in a community have

on filariasis, as measured by changes in: the community microfilarial load, the incidence of acute filarial attacks and the incidence and progression of chronic filarial disease. The impact of the intervention on transmission may be assessed by measuring the community microfilarial load and the incidence of microfilaraemia among those not targeted for the drug intervention (e.g., young children); it may also be assessed through entomological studies.

The "community", as the unit of randomization, ideally should correspond to the "transmission zone" for filarial infection that is locally appropriate, i.e., the area over which both humans and mosquitoes range to acquire their infections. In practice, such a zone may be difficult to define, especially with respect to the range of human movements. Study units should be chosen to be sufficiently large, or with sufficient "buffer" zones, such that there would not be substantial "contamination" due to infections acquired (by mosquitoes or man) from adjacent areas.

Community randomized trials are likely to be large and ideally should be planned such that each intervention is applied to not less than 6 communities, and preferably more. Communities should be selected for inclusion in a trial in which the microfilarial loads are relatively high. The duration of such trials will be of the order of 3-5 years initially. The identity of the interventions applied to the different communities should be kept "blind" both to the participants and the study investigators to the extent possible to avoid bias in the assessment of effects. With measures such as vector control this may be difficult or impossible, but if the intervention strategy involves the use of drugs then identical looking comparison drugs, possibly including a placebo, should be employed.

It would be highly desirable to choose control strategies that would be realistic to apply on a widespread basis. An important determinant in the choice of a control strategy for a public health programme would be the cost-effectiveness of the strategy as compared to alternatives; community-based studies should include careful study of this aspect for each intervention strategy.

Research is also required on the most effective, sustainable way to deliver drugs for the control of filariasis. Thus community randomized trials might compare "vertical" with "horizontal" strategies. For example, the use of special teams to deliver the drugs to all in a community several times a year might be compared to distribution methods through the primary health care system.

An idealized plan for such a community-randomized trial is given below:

- | | | |
|---|--------------------------|--|
| 8 | communities - ivermectin | - 4 "vertical" distribution |
| | | - 4 "primary health care" distribution. |
| 8 | communities - DEC | - 4 "vertical" distribution. |
| | | - DEC in salt. |
| 8 | "control" communities | - no intervention except to the existing disease control policy. |

The frequency with which DEC or ivermectin is distributed will need to be determined as outlined in the earlier studies. This may have to be a compromise between that frequency which is optimal for maintaining low microfilarial counts and the frequency which is sustainable in a public health programme, which is likely to be, at most, 2 or 3 times a year. The DEC strategy includes DEC in salt because previous studies have demonstrated that this may be a feasible way of maintaining low microfilarial counts over a long

period and this approach would seem worthy of further evaluation. The other communities receiving DEC would be allocated to a "vertical" strategy to provide a direct comparison with the corresponding ivermectin arm.

At least for communities receiving ivermectin, it will be necessary to exclude from treatment pregnant and lactating women and young children, as well as persons with evidence of neurological disease or any other serious illness. As with the earlier studies, criteria will have to be established for exclusion, arrangements for future treatment, and provision for follow-up of all births of those who may have inadvertently received drugs/placebo during pregnancy.

7.2 Possible Demonstration Areas where Elimination of Transmission may be Possible

Studies designed to decrease the transmission of bancroftian filariasis by treating affected populations with ivermectin must take into account the very different patterns of transmission dynamics found in different areas of the world. Some situations would be much more amenable to reduction or elimination of transmission based on ivermectin mass-treatment than others. For example:

- (i) In Africa, where W. bancrofti is transmitted by anopheline mosquitos (An. funestus and An. gambiae and An. arabiensis), the affected human populations are clustered in relatively isolated small villages that could be treated in their entirety with ivermectin. The anopheline vectors have a relatively limited flight range, and it is most likely that in situations such as these, good treatment coverage of the human population with ivermectin would result in markedly diminished transmission by the vector mosquitoes. These remarks also apply to Papua New Guinea where An. farauti and An. punctulatus are important vectors.
- (ii) In the South Pacific Islands, where Aedes polynesiensis is one of the most widely distributed vectors of bancroftian filariasis, the mosquito population tends to be over-dispersed (i.e. with a clumped or aggregated distribution) with high breeding activity and many micro-niches that are difficult to control. If the human population in such a situation is relatively small and confined (for example, on a small atoll), good treatment coverage of the population should be possible and would be predicted to decrease transmission significantly, despite the over-dispersed mosquito population; however, on larger islands, where the populations are such that near-complete coverage with ivermectin treatment is unlikely, the residual reservoir of MF in the untreated individuals, coupled with the over-dispersed mosquito population, would make effective transmission control by ivermectin treatment much less likely.
- (iii) Culex quinquefasciatus, the vector of urban and peri-urban bancroftian filariasis, also has high breeding activity and, because complete treatment coverage of such populations is unlikely, the remaining reservoir of MF is likely to result in persistent transmission despite aggressive ivermectin chemotherapy.

Since the interruption of transmission requires bringing the parasite contact with susceptible vectors down below a threshold level (requiring very high coverage of the population for at least 6 years), it is important to select appropriate trial sites if one wants to demonstrate the effectiveness of chemotherapy (e.g., ivermectin) alone to block transmission. Other trial designs would be required to study the effectiveness of chemotherapy in combination with other interventions such as vector control.

8. PROPOSED TIME LINE

MK-933 Lymphatic Filariasis Trials
Progressed Time Line

| # | Program/Study | N | Issues | 1989 | | 1990 | | 1991 | | 1992 | | 1993 | | 1994 | |
|----|---|-----|--|------|-------|------|-------|------|-------|------|-------|------|-------|------|-------|
| | | | | 1Q | 2Q | 3Q | 4Q | 1Q | 2Q | 3Q | 4Q | 1Q | 2Q | 3Q | 4Q |
| 1) | Dose-Ranging Studies {W. Bancrofti/ B. Malayi | 280 | (1) Determine Single Oral Optimal Dose for Microfilaria Clearance (20/50/100/200 mcg/kg) | | ----- | | ----- | | ----- | | ----- | | ----- | | ----- |
| 2) | Ivermectin/DEC (SD) Comparative Study in Microfilaremia (W. Bancrofti var. Pacifica)/French- Polynesia | 20 | (1) Pilot Study to Determine Comparative Efficacy & Safety of Single Oral Dose (100 mcg/kg) of Ivermectin vs. DEC Single Dose at 6 & 12 months | | ----- | | ----- | | ----- | | ----- | | ----- | | ----- |
| 3) | Ivermectin/DEC Comparative Study in Microfilaremia W. Bancrofti/Haiti | 60 | (1) Pilot Study to Compare Safety & Efficacy of SD Ivermectin 200 mcg/ kg & 400 mcg/kg with DEC at 3.6 Months | | ----- | | ----- | | ----- | | ----- | | ----- | | ----- |
| 4) | Ivermectin/DEC Comparative Study in Microfilaremia W. Bancrofti/Egypt | 60 | (1) Pilot Study to Compare Safety & Efficacy of SD Ivermectin 100 mcg/ kg with DEC at 3.6 Months | | ----- | | ----- | | ----- | | ----- | | ----- | | ----- |
| 5) | Ivermectin/DEC Comparative Study in Microfilaremia W. Bancrofti/India | 40 | (1) Pilot Study to Compare Safety & Efficacy of SD Ivermectin 10 mcg/ kg & 20 mcg/kg with DEC at 3.6 months | | ----- | | ----- | | ----- | | ----- | | ----- | | ----- |

(A) GO/NO-GO Decision: Lack of efficacy in B. malayi infection would exclude it from further study.

8. PROPOSED TIME LINE (continued)

MK-933 Lymphatic Filariasis Trials
Proposed Time Line

| # | Program/Study | n | Issues | 1989 | | | | 1990 | | | | 1991 | | | | 1992 | | | | 1993 | | | | 1994 | | | |
|----|---|----|--|------|----|----|----|------|----|----|----|------|----|----|----|------|----|----|----|------|----|----|----|------|----|----|----|
| | | | | 1Q | 2Q | 3Q | 4Q | 1Q | 2Q | 3Q | 4Q | 1Q | 2Q | 3Q | 4Q | 1Q | 2Q | 3Q | 4Q | 1Q | 2Q | 3Q | 4Q | 1Q | 2Q | 3Q | 4Q |
| 6) | Tropical Pulmonary Eosinophilia Study | 20 | (1)Pilot Open Study to Determine Safety, Tolerability, and Efficacy | | | | | | | | | | | | | | | | | | | | | | | | |
| 7) | Ivermectin/DEC Comparative Studies in Microfilaremia (W. Bancrofti/ B. Malayi) | — | (1)Determine Comparative Efficacy & Safety of Optimal Ivermectin Single Dose with Standard DEC Dose and at 3, 6, & 12 Months | | | | | | | | | | | | | | | | | | | | | | | | |
| 8) | Ivermectin/DEC Comparative Studies in Acute Lymphangitis due to (W. Bancrofti) | — | (1)Determine Comparative Safety & Efficacy in Hospital/Clinic Based Studies at 3, 6, 12, 18, & 24 Months | | | | | | | | | | | | | | | | | | | | | | | | |
| 9) | Ivermectin/DEC Comparative Studies in Preventing Acute Lymphangitis & Progression of Lymphedema due to (W. Bancrofti) | — | (1)Determine Comparative Safety & Efficacy in Community-Based Studies with 2-3 year follow-up | | | | | | | | | | | | | | | | | | | | | | | | |

(*) MAA-Target Date: 2092 for Microfilaremia

9. PREPARATIONS FOR FIELD TRIALS

9.1 Criteria for Site Selection

1. High endemicity for lymphatic filariasis
2. Well qualified and experienced epidemiological field team
3. High quality clinical and laboratory facilities suitable for field trials against lymphatic filariasis (and/or other diseases)
4. Entomological, behavioural science and other disciplinary expertise with interest and experience in lymphatic filariasis field research
5. Good community and governmental cooperation and participation, with lymphatic filariasis considered as an important problem.
6. A diversity of geographical-ecological situations should be selected, but not all studies are likely to be needed in all areas.

9.2 Possible Sites

Endemic areas near to current clinical trials should be given first consideration because they have the necessary clinical and laboratory expertise. However, not all of these have appreciable field research expertise or experience in field trials. In every case it should be expected that many if not all team members will require training, and most principal investigators will need specific preparation in epidemiological field trial design and implementation issues. Each study team will need a high level of expertise in mapping and census techniques, record keeping, data entry and analysis with the use of microcomputers, and competence in all aspects of quality control.

9.3 Training Needs/Baseline Studies

Principle investigators need to be identified as soon as possible. In most cases it must be expected that sites and field teams will have to be prepared from scratch and a period of 1 to 2 years may well be required for the training and preparation of the field teams. Consideration should be given to developing a special training course in field trial methods.

Clinical trials are unlikely to require baseline data, but for field and community trials, baseline data would include mapping, complete census and sufficient data on MF levels and clinical disease to have a good understanding of the distribution of these factors by age, sex and geographical area in the study region. Entomological data and knowledge of human activity patterns would be highly desirable additions.

9.4 Checklist for Minimum Requirements for Field Trials of Ivermectin for Lymphatic Filariasis

1. Field teams require:

Principal Investigator - generally will be an epidemiologist/clinician with experience with field work, field trial study design expertise, and large-scale data handling.

Demographical expertise
Computer and data handling expertise. Necessary equipment.
Clinical and parasitological expertise for lymphatic filariasis
and suitably equipped laboratory.
Entomological expertise and suitably equipped laboratory.
Base laboratories for the above, and freezer capacity.

2. Suggested functions for 2 sets of teams, but many variations possible.

- (a) Field teams for mapping, census, health questionnaires and physical examination

Driver, interviewer, clinician
1 team for 10-20 households per day. 50 to 100 individuals.

1000 to 2000 persons per month = 10 to 20 team months per survey.

- (b) Field teams for night examination

Driver, interviewer, technician for fingerstick.
1 team for 10-20 households, per night. 50 to 100 individuals,

1000 to 2000 persons per month = 10 to 20 team months per survey.

- (c) Field team for entomological studies

To be worked out.

3. Baseline data

Mapping and Census - 20,000 population at least

MF quantitative counts for total population with sufficient duplicates in various age and sex strata at differing MF levels to determine variability of counts. Ideally, two such surveys about a year apart to determine both mf count stability and extent of human population movement.

Clinical examinations - history of acute episodes and physical findings for chronic manifestations. Again, should be done at least twice to get some idea of incidence. (For acute episodes more frequent monitoring may be needed.)

Basic entomological baselines over at least a one year period.

10. DRAFT PROTOCOLS AVAILABLE ON REQUEST

Copies of the following draft protocols are available on request from Dr R.H. Morrow, WHO/Special Programme for Research and Training in Tropical Diseases, 1211 Geneva 27, Switzerland.

1. Double-blind study of tolerability and effectiveness of two single doses of ivermectin or DEC given at intervals of 3 or 6 months
2. Double-blind study of effectiveness of repeated doses of ivermectin or DEC in the management of adenolymphangitis
3. Ivermectin in treatment of TPE Syndrome Bancroftian Filariasis

11. LIST OF PARTICIPANTS

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