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REPORT OF A MEETING OF THE TDR/OCP/OCT SUBCOMMITTEE FOR MONITORING OF COMMUNITY TRIALS OF IVERMECTIN

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ABSTRACT

Community-based studies on the use of ivermectin against onchocerciasis in over 70 000 people in 14 countries in Africa and Latin America showed that it is an effective and extremely safe microfilaricidal agent when given as a single oral dose.

Depending on the intensity of infection, 10-30% of people experienced certain adverse reactions (the Mazzotti reaction) at the time of first treatment. In most cases, these reactions resolved spontaneously. These side-effects were much less intense and occurred in fewer patients following subsequent re-treatment.

It was recommended that current exclusion criteria, mainly involving women of childbearing age and young children, should be retained until further information becomes available, and that an experienced health care worker should be available to onchocerciasis patients for at least 36 hours following the first administration of ivermectin.

The impact of ivermectin on disease morbidity in the treated population requires further detailed studies over a longer period, but early lesions in the anterior regions of the eye have already been known to be reversible. And, the substantial reduction of microfilariae from the skin (sustained for at least six months following treatment) gives relief from itching and facilitates improvement of superficial lesions.

Research priorities include determining 1) the frequency of retreatment required in areas of differing endemicity, 2) the necessity to retain currently applied exclusion criteria, and 3) optimization of drug delivery systems to provide cost-effective methods for identifying and treating those infected with onchocerciasis. To fully evaluate the impact of ivermectin on disease transmission it will be essential to apply new molecular identification techniques to differentiate animal Onchocerca species occurring in the blackfly vector, and to use computer modelling techniques to predict the long-term effects of widespread use of the drug.

1. INTRODUCTION

A meeting of the TDR/OCP/OCT Subcommittee for monitoring of community trials of ivermectin was held in Ouagadougou, Burkina Faso on 25-27 January 1989. The meeting was chaired by Professor J.F. Williams (Chairman of SC/TDR/FIL), and had two main objectives: (1) to review progress in the community-based trials; (2) to make recommendations for the use of ivermectin, and for further research.

Dr E.M. Samba, Director of the Onchocerciasis Control Programme (OCP), welcomed participants and expressed optimism about the potential of ivermectin in onchocerciasis control, noting the appreciation of OCP for the gift of ivermectin made by Merck and Company (Dr Roy Vagelos, President).

REPORTS FROM COMMUNITY TRIALS

2. REPORT FROM OCP

Dr B. Philippon (OCP) reviewed the status of larviciding activities, noting the recommendations of the Expert Advisory Committee (EAC) and JPC that these activities should continue. In the past year, aerial larviciding had been extended to the south of Togo and Benin and into western Mali, as well as selective and seasonal larviciding in eastern Guinea. In 1989, rivers in northern Sierra Leone, central Guinea, and Senegal will also be treated.

Recent developments in OCP vector control activities include the following:

- Development of temephos resistance affecting most of the Programme area; five larvicidal compounds are now used in rotation, and resistance is now under control. This has increased operational costs but has had no impact on the efficacy of transmission control.
- In 80% of the original area, Onchocerca transmission is virtually interrupted. In the remaining 20%, the major cause of residual transmission is reinvasion by savanna flies and local treatment failures.
- The southern extension was well-controlled in 1988 and reinvasion of the southeastern margin of the OCP area was controlled for the first time in the history of the Programme.
- The western extension is more complex, with very intense areas of transmission, especially in Guinea. The southern movement of savanna flies is particularly important in southern Sierra Leone.

Important questions to be considered are: (1) when to terminate larviciding in areas under control for 12-14 years, (2) what role ivermectin may play in preventing recrudescence when vector control is interrupted, and (3) how to proceed in the western extension area in which the nine years remaining to OCP are inadequate to achieve vector control. Professor J.F. Williams emphasized that the role of ivermectin in controlling transmission of onchocerciasis remains a major question.

3. REPORT FROM MERCK SHARP & DOHME

Dr K. Brown (Merck) reviewed ivermectin toxicity and pharmacology. The drug is fat-soluble but, due to lack of penetration of the blood-brain barrier, is not found in brain tissue to any great extent. The therapeutic index is high; for example, in dogs more than a 10-fold increase above therapeutic amounts can be given before mydriasis is seen as the first manifestation of toxicity. Average peak serum concentration in humans occurs at four hours; the half-life is 10 hours. Ivermectin appears in milk in lactating females and because of uncertain safety in newborns, should not be given to nursing mothers during the first three months after birth. The mechanism of action of ivermectin is unknown but may relate to its binding to GABA receptors and effect on chloride channels. Resistance to ivermectin in Haemonchus contortus occurred after four passages in sheep receiving ivermectin treatment in the field, and has also been produced in the laboratory. The potential relevance of this observation to Onchocerca volvulus is unknown. Non-responders in field trials may simply represent non-compliance or poor absorption, since retreatment of these patients is usually successful. However, measurement of serum levels has not been done in this setting. Idiosyncratic reactions relating to toxicity have been noted in dogs (collies), mice and cattle; any relationship to human responses is unknown.

4. COMMUNITY-BASED STUDIES

4.1 Liberia (reported by Dr H.R. Taylor)

A study of community-based mass treatment of onchocerciasis with ivermectin continues at the Liberian Agricultural Company (LAC) rubber plantation in the rain forest area of Liberia. The initial census and treatment of the population took place from September to December 1987 and this was repeated from September to December 1988.

The censused population of the area during the second treatment was 13 977. Altogether, 8062 people (97% of those eligible) were treated; 5629 people (40% of the population) were ineligible for treatment.

Data on adverse reactions were collected by four different methods. These included: (a) a systematic house-to-house, follow-up visit three days after treatment; (b) a year-round population surveillance system; (c) monitoring of the records of the plantation mobile clinic; and (d) monitoring of LAC hospital records. No severe adverse reactions were noted with retreatment, and no cases of postural hypotension, chest pain or haematoma were seen. With the second round of treatment, adverse reactions were even less common than during the first treatment. Only 37 people (0.3%) had a moderate reaction of the Mazzotti type, presumably related to the killing of microfilariae. No unusual or unexpected reactions were seen. No deaths could be related to ivermectin treatment.

Of the 61 people who had moderate reactions after treatment in 1987 and were retreated this year, none had reactions in 1988.

All 676 infants were examined who were born on the plantation since the first round of treatment. 159 of the mothers took ivermectin either during pregnancy or in the three months preceding pregnancy. 96 mothers had taken ivermectin during pregnancy, 83 of them during the first three months after conception. Only three infants with congenital malformations were seen and these could not be related to ivermectin treatment. In addition, 153 babies born in the hospital 9-11 months after the start of the first treatment round were examined at birth and showed no abnormalities.

To monitor the efficacy of the community-based distribution of ivermectin to reduce microfilarial densities, a sample consisting of the population of five camps had skin snips taken before treatment, and again six and 12 months later.

One year after the community-based distribution of ivermectin there was a 75% reduction of microfilarial density in those who were actually treated, and an overall 52% reduction in microfilarial load of the community in which treatment was distributed.

There was a 14.9% incidence of new infection (based on skin-snip positivity) in children 5-11 years of age during this year. In this age group, only children with positive skin snips were treated with ivermectin.

4.2 Mali (reported by Dr G. Soula)

In an open Phase IV clinical trial in non-hospitalized subjects living in separate valleys, 856 patients with onchocerciasis (Koba Valley) received an initial dose of 150 mcg/kg ivermectin in May 1987, while 607 (Dlaba Valley) were included as controls. This cohort was followed up seven and 12 months later. In June 1988, a second dose of ivermectin was administered to the 749 patients of the Koba Valley, while 511 patients of the Dlaba Valley received an initial dose.

The tolerance to treatment with ivermectin was good and has improved after the second dose given one year later: 15.2% of patients treated for the first time in May 1987 reported side-effects, which were mostly mild or moderate, appearing early and quickly resolving. Only eight cases were impeded from carrying out their normal daily activities. The second dose, given one year after the first, produced mild side-effects only in 3.7% of cases.

The intensity of the microfilarial infection constitutes a risk factor for side-effects to ivermectin. The likelihood of side-effects also increases with age. Neither sex nor dosage varying from 100 to 200 mcg/kg seems to be related to the frequency of side-reactions, after controlling for the effects of age and dermal microfilarial load.

The microfilaricidal effect of treatment appears to be more long-lasting on the ocular involvement than on dermal involvement. For example, there was 58% and 60% reduction in numbers of microfilariae in the anterior chamber at seven and 12 months post-treatment. After the decline in skin microfilariae observed at seven months after treatment (of the order of 80% of the initial load), the microfilarial count had a tendency to rise again one year later. Thus, one might expect that the improvement in the reversible ocular lesions may persist longer than any effect on transmission.

4.3 OCP (reported by Drs G. De Sole, K. Awadzi, J.H. Remme, R.H.A. Baker and Y. Dadzie)

Ivermectin has been distributed in eight sites throughout the OCP area, each with specific epidemiological or disease control characteristics. 49 874 people (60% of a population of 86 422) were treated with ivermectin, and more than half of those had already received a second treatment.

There was a correlation between the incidence of all recorded reactions to treatment and intensity of infection (with the exception of skin reactions). Adverse reactions did not correlate with dosage of ivermectin. Maximum reactions were recorded on the first day after treatment. Delayed reactions (swelling, abscess) seen at first treatment, were not seen with retreatment.

Several people who had severe hypotension (see report of this Sub-committee from the meeting held on 20 March 1988) after the first treatment were retreated and did not report such a reaction with retreatment. However, a significant number of people experiencing such severe reactions refused treatment on the second occasion.

There were cases in the OCP area (and two cases in Malawi) in which administration of ivermectin appeared to precipitate a severe asthma attack in persons with pre-existing asthma. There were two deaths in the OCP trials during the time of ivermectin administration. One occurred at second treatment in a one-year old epileptic whose family withheld the history of epilepsy, and a second in a person with pneumococcal meningitis. Neither could be attributed causally to ivermectin treatment.

Effects of ivermectin on microfilarial counts were documented at 2, 4, 12 and 14 months post-treatment at Asubende -- an area of very high intensity of transmission. Following an initial fall in skin microfilariae, there was a major increase in microfilarial counts within 12 months (to over 40% of pretreatment levels). Sixteen people with a poor response to first treatment were retreated. Twelve of these had a good response to the second treatment.

The effect of ivermectin treatment in the OCP area on transmission was examined in detail at six out of the eight trials. A substantial reduction (70-75%) in transmission was observed during the first three months after treatment at Asubende. A year later, when vector control was again suspended

and before the second treatment, transmission returned to 50-60% of the pre-treatment level. This second treatment brought transmission down to a level similar to that observed after the first treatment. These observed changes in transmission levels correspond well with predictions based on observed changes in the microfilarial reservoir in the total human population and on estimates of the infective potential of the human hosts in relation to their microfilarial load.

Analysis was complicated in other trials, either by high and indistinguishable animal onchocerciasis transmission (Mali and Senegal), vector control (Bui), differences in vector population dynamics between pre- and post-ivermectin study periods (Comoe and Dienkoa), or rapid recrudescence in the microfilarial loads (Dienkoa). Nevertheless, on the Bui River all transmission indices were reduced by 50-70% and on the Dienkoa, L3 indices were reduced by 50-60% and L1/L2 indices by 20-30%.

Xenodiagnostics have been carried out to examine the relationship between microfilarial load in the skin and the number of infective larvae in the fly, and experiments are under way to examine the quantitative effect of ivermectin treatment on transmission. These data will be used in computer modelling to predict frequency of treatment required to control transmission in the OCP area.

The effect of community-based treatment on ocular onchocerciasis was studied. 376 people were examined pre-treatment, and at four and 12 months after treatment, and the results compared to a non-treated group of 49. Numbers of microfilariae in the anterior chamber and cornea decreased by about 80% at four months followed by a slight increase by 12 months post-treatment. Twelve months after treatment, half the people with early sclerosing keratitis showed resolution, whereas advanced sclerosing keratitis was minimally responsive. Early iridocyclitis was even more responsive over a one-year period. In contrast, choroidoretinitis showed no significant change. Similarly, ivermectin had no effect on visual acuity.

4.4 Cameroon (reported by Dr J. Prod'hon)

Of 11 371 inhabitants of villages between Touboro and Vongna, 7780 were treated. Of these, 5753 received their first treatment with ivermectin, while 2027 received a second dose six months after original treatment. 20% of inhabitants of a hyperendemic zone and 12% from a meso-endemic zone showed a Mazzotti-type reaction with first treatment. Only 9% of those treated for a second time showed any adverse reaction. Six months after treatment, there was a greater than 90% reduction in skin microfilarial counts. In addition, in a subgroup of 1120 people aged 15-35, there was a 33%, 53% and 39% decrease in numbers with punctate keratitis, iritis and optic nerve pallor, respectively. The number of microfilariae in the anterior chamber fell sharply. Two people had hypotension below 100 mm systolic; this appeared the first day after treatment, was asymptomatic, did not require therapy and resolved before the second day after treatment.

The Cameroon study examined effects of treatment on fly infection. There was a 30% reduction in infective larvae/1000 flies. The parous rates were virtually the same before and after treatment.

4.4.1 Cameroon (reported by Dr R. Moyou)

Four villages were selected for a second study in Cameroon, conducted in the Rumpi hills forest reserve. 1761 of 3092 inhabitants were treated. The geometric mean microfilarial count before treatment was 5.29 (arithmetic mean 140) with a prevalence rate of 93%. Fifty-five percent of persons had microfilariae in the anterior chamber, 42% choroidoretinitis, 40% punctate keratitis, 4% sclerosing keratitis, and 8% optic atrophy. Following treatment,

fever occurred in 13.5% (much more frequently than in the study in the Cameroon savanna) and pruritus in 8.5%. Temporary incapacitation occurred in seven people (0.4%) due to Mazzotti-type reaction. Follow-up clinical, ophthalmological, and parasitological results are pending.

4.5 Malawi (reported by Dr G. Burnham)

This community-based trial in the Thyolo highlands has two main objectives: (1) to assess, in a placebo-control trial, the frequency of adverse reactions to ivermectin; and (2) to examine the effect of ivermectin on skin lesions. Registration of subjects commenced during summer 1988 and ivermectin was distributed to 2741 people in September. Adverse reactions have been recorded and entered for computer analysis. 60% of people had some reaction, but it will not be known if these were related to the drug until the treatment code is broken. 18% of people had some type of cutaneous swelling. One 19-year old boy had vesicular, bullous lesions on the forearm requiring steroid therapy. Two asthmatics had exacerbations following ivermectin therapy that responded to aminophylline. Overall, therapy was well tolerated and well accepted. Seventy pre-existing epileptics were inadvertently treated with no apparent side effects.

4.6 Guatemala (reported by Dr E.W. Cupp)

Five villages in Guatemala are under study. Four of these will receive ivermectin and continue to have nodulectomies performed. One village will have nodulectomy only. Prevalence of infection ranged from 42 to 80% and geometric mean microfilarial counts from 7.3 to 26.1. Ivermectin was given to 1045 persons in May 1988, and to 1018 in November 1988. In one village, many refused treatment so that coverage was very poor (20% of censused population). One 40-year old woman with light infection developed headache eight days after treatment, which did not resolve and was associated with diplopia and ataxia; cerebral pseudotumour was diagnosed. Overall, 25.9% of treated persons developed Mazzotti-type reactions following first treatment, and 9.9% after second treatment.

The possible effect of ivermectin treatment on transmission is being examined. Preliminary evidence suggests a downward trend in percentage of parous flies with larvae.

In Guatemala, resistance to nodulectomy may adversely influence the ivermectin distribution programme. It may be necessary to dissociate ivermectin treatment from nodulectomy.

4.7 Nigeria (reported by Drs A. Abiose and C. Vajime)

The study in Kaduna State involves two areas: Saminaka (east of Kaduna) and Birnin-Gwari (west of Kaduna). Mapping, census, registration and skin snipping started in August 1988. Field teams were trained in ophthalmic and skin examinations during October-November and treatment began in December 1988.

Alternate subjects receive ivermectin or placebo, allowing concurrent control for side effects of ivermectin and the effect of ivermectin on optic nerve disease. The total population is 12 702, with a total eligible population over age five of approximately 8000. Prevalence of infection is 41% and 45% in the two areas, with 1.2 and 1.6 microfilariae per mg (geometric mean). In the 34 communities to receive ivermectin, parasite density is 10.9 microfilariae per snip in persons over 20 years old.

Ocular examination will include visual acuity, fields and basic eye examination by ophthalmic nurses, followed by referral to an ophthalmologist for people with significant abnormalities. Detailed ophthalmic examination

will include fluorescein angiography. In addition to those referred, a random sample of 400 persons will receive complete examination.

The effect on transmission will be monitored at a site that supports transmission year-round, where preliminary data are available. This is located on Galma River, 5 km northeast of Kaduna.

It is anticipated that this study will form the basis for future national programmes of ivermectin distribution.

4.8 Sierra Leone (reported by Dr J. Whitworth)

A double-blind, placebo-controlled trial of ivermectin treatment is being undertaken in southern Sierra Leone. The population of 1625 had a prevalence of 72% with a density of 4.4 microfilariae per mg skin; 630 received ivermectin and 622 placebo treatment. Some side effects were demonstrated by 23.4% of ivermectin recipients and by 9.8% of placebo recipients; 4.2% of ivermectin recipients were disabled by side effects compared to 0.9% of placebo subjects. Six months after treatment, microfilarial counts fell from 4.6 to 0.8 microfilariae per mg. There was a tendency towards improvement in visual status in the ivermectin recipients when compared to placebo recipients. Six-monthly treatments will continue until March 1990. Seventeen people had no significant response to treatment; this included nine with low microfilarial counts, men as well as women.

CONCLUSIONS AND RECOMMENDATIONS

5. SUMMARY: ADVERSE REACTIONS

At this point, more than 70 000 people have been treated with ivermectin, many with more than one dose, giving a total of over 120 000 treatments (Table 1). There are few, if any, drugs at present in use for the treatment of tropical diseases, that have undergone the scrutiny that ivermectin has had. The drug is extremely safe, and is without known pharmacological side-effects in humans. At present dosages, no deaths attributable to ivermectin have been reported.

TABLE 1.

TOTAL IVERMECTIN TREATMENTS AS OF 27 JANUARY 1989

OCP	-	85 000
Mali	-	1 800
Liberia	-	16 912
Cameroon	-	9 767
Malawi	-	2 741
Nigeria	-	425
Guatemala	-	2 213
Sierra Leone	-	1 400
Other	-	1 300
TOTAL		121 558

Treatment of Onchocerca volvulus infection is associated with a mild (Mazzotti-type) reaction in approximately 10-30% of persons. This occurs within the first 2-3 days in most cases and resolves spontaneously. The major components of this reaction include pruritus, fever, rash, oedema, lymph-node swelling and pain, muscle pain and headache.

More severe side-effects have occurred during ivermectin therapy, with a frequency of less than 1 in 1000. These include orthostatic hypotension and asthma attacks (in known asthmatics), both occurring within 36 hours of ingestion of ivermectin. In addition, bullous skin lesions occurring 1-2 weeks post-therapy have been observed.

5.1 Exclusion Criteria

At present, the following exclusion criteria apply to ivermectin distribution:

- Pregnancy (further data forthcoming in the next 1-2 years may render this exclusion unnecessary).
- Breastfeeding a child less than three months old.
- Age less than five, or weight less than 15 kg (unless there is a clear indication for therapy).
- Central nervous system disorders, especially meningitis and trypanosomiasis. Peak prevalence months for meningococcal meningitis should be avoided.)
- Severe concurrent illness.

5.2 Monitoring

Although ivermectin appears an extremely safe drug, some of the possible adverse side-effects (e.g. hypotension, asthma) seen in onchocerciasis patients are readily managed with appropriate medical advice and simple treatment. Most cases of hypotension will resolve with bed rest and oral fluids, and the asthma attacks have responded to aminophylline. Adverse reactions are more commonly seen with heavy infection. Furthermore, the most severe adverse events have occurred after the first dose of ivermectin. Reactions are less common and less severe with retreatment, presumably due to reduced microfilarial loads. Therefore, the following recommendations are made for monitoring after ivermectin treatment:

- With initial treatment, an experienced health-care worker (e.g. nurse or physician) should be readily available within the community for at least the first 36 hours following therapy.
- The level of monitoring for successive treatment can be determined based on the previous experience in the area.

5.3 Research Priorities

Although ivermectin has been thoroughly investigated for use in onchocerciasis and is suitable for mass administration, certain important questions remain unanswered. These include the following, which have been separated into questions that are necessary for effective mass distribution of ivermectin, and those that are desirable to know, although not essential in the near future.

Necessary

- Effect of ivermectin when taken during pregnancy, and with breastfeeding in children less than three months of age.

- Optimal drug delivery systems including strategies to optimize acceptability.

Desirable

- Causes of post-treatment fever and possible relationship to coexistent malaria.
- Interactions of ivermectin with other commonly used drugs (e.g. anti-malarials, compounds interacting with GABA receptors, and ethanol).
- Effect of coexistent Wuchereria bancrofti infection and implications for ivermectin dosage (note: ivermectin appears safe in Loa loa and Mansonella perstans infections).
- Safety of ivermectin in children less than five years of age.
- Safety of ivermectin in persons with epilepsy.
- Cause of asthma attacks seen following ivermectin, and means of prevention.
- Lack of apparent antiparasitic effect of ivermectin in some persons, bioavailability and pharmacokinetics in various groups and effect of food intake.
- General health effect of ivermectin treatment of onchocerciasis.

6. SUMMARY: EFFECT OF IVERMECTIN ON MICROFILARIAL LOADS AND TRANSMISSION

6.1 The Effect on Microfilarial Loads

Immediate dramatic reductions in skin microfilarial loads in patients were observed in all cases, but the repopulation dynamics in at least three of the community trials were faster than in the clinical trials (see Table 2). This was observed at six and especially 12 months after ivermectin delivery. There were indications that the rate of microfilarial repopulation was influenced by the intensity of transmission and was more marked where the infection was recrudescing.

As a result, the frequency of ivermectin delivery may have to be examined in certain areas.

Recommendation

Taking into account the increases in skin and ocular micofilarial loads with time since treatment, and the need to determine the optimal interval between drug deliveries in different areas, all trials should report uniformly on the dynamics of repopulation using standard age cohorts, as far as possible, both at six and 12 months after ivermectin treatment.

6.2 Transmission

Results from 10 detailed studies were available of the effect of ivermectin on vector transmission. Five different studies (Asubende in Ghana, Dienkoa in Burkina Faso, Guatemala, northern and western Cameroon) support the conclusion that community-based ivermectin treatment has reduced transmission. The maximum likely effect was that observed at Asubende with 70-75% reduction for the first three months after treatment in two consecutive years. However,

TABLE 2.

TREND IN GEOMETRIC MEAN MICROFILARIAL LOAD AFTER IVERMECTIN TREATMENT IN DIFFERENT COMMUNITY TRIALS

Study Area	Age cohort	Percentage of pre-treatment mean		
		4 months	6 months	12 months
Liberia	All ages	----	----	25.0
	Adults	----	----	21.0
Mali	All ages	----	21.0	33.0
	Adults	----	15.0	21.0
Asubende	All ages	7.0	----	43.0
	Adults	4.5	----	30.0
Dienkoa	All ages	----	33.0	----
	Adults	----	21.0	----
Milo	All ages	----	9.0	----
	Adults	----	4.0	----
Cameroon	All ages	----	7.0	----
	Adults	----	4.5	----
Guatemala	Cross-sectional data for 3 villages	----	17.0	----
Sierra Leone	All ages	----	18.0	----

the transmission potential was still over 10 times the tolerable level. Accurate estimates of transmission reduction were frequently difficult to make due to the presence of indistinguishable animal Onchocerca, differences in the vector population dynamics before and after treatment, and vector invasion. Population coverage with ivermectin was also critical. At Asubende, there was a good relationship between transmission reduction and the change in microfilarial densities in the human population, but a poor relationship with disease prevalence.

The evidence is not yet sufficient to define optimal strategies for transmission control. The long-term impact of ivermectin on transmission is as yet uncertain. It is clear, however, that the best strategy to be adopted will depend on the objectives of the control programme. Any attempt to control transmission with ivermectin will require far greater resources and much more time than a programme designed only to alleviate the ocular and skin manifestations of the disease.

Recommendations

Several additional studies are likely to yield good results during 1989 and, to facilitate comparisons, the following entomological transmission indices should be provided as standard: period of sampling, number of days collection, numbers of flies caught, numbers dissected, numbers parous, the MBR, MTP, number of flies with each parasite stage per 1000 parous and the number of each parasite stage per 1000 parous. The L1 and L2 data can be

lumped together but head and body L3s should be distinguished in the calculations.

Where infection rates (especially L3 rates) are low or where vector populations are subject to substantial variations in parous rate, flies should be stained with Mayers Acid Haemalum to maximize the detection of L1s and L2s.

Future studies of the effect of ivermectin on transmission should include accurate quantitative assessments of transmission reduction which can be related to the change in the microfilarial reservoir of the human population. Monitoring changing incidences in children may give an indirect measure of transmission reduction and should be included wherever appropriate.

6.3 Research Priorities

It is virtually impossible by entomological methods to assess the impact of ivermectin on transmission in areas where animal Onchocerca are transmitted by human onchocerciasis vectors, because many species are morphologically indistinguishable. New molecular identification techniques should now be applied to field studies to assist identification.

In order to predict the long-term impact of ivermectin delivery on microfilarial loads and transmission, mathematical models should be constructed and tested against the trial data.

7. SUMMARY: IVERMECTIN AND ITS IMPACT ON MORBIDITY AND THE PREVENTION OF MORBIDITY IN ONCHOCERCIASIS

Morbidity in onchocerciasis is usually a cumulative effect of the parasite and of parasite death in the eye, skin and elsewhere. Though morbidity may be associated with acute manifestations such as itching, the most severe effects such as poor vision, blindness and gross skin pathology, evolve over a period of many years.

Monitoring the impact of ivermectin on morbidity therefore requires assessment of skin and ocular pathology before, soon after, and for many years after ivermectin administration. The prevention of morbidity will require the monitoring of new lesions or symptoms that are associated with it.

Data from Phase II and III trials provide compelling evidence that ivermectin treatment will ameliorate reversible onchocercal ocular disease. Preliminary results from the Phase IV community-based trials, though uncontrolled, indicate improvement in reversible ocular and skin lesions. However, the data presented so far from the community-based studies do not yet provide sufficient detailed evidence on which to base firm conclusions on the effect of ivermectin on morbidity. This is either because the studies were not designed to address this question or because the follow-up has not proceeded long enough. Indirect evidence from the elimination of most of the skin and ocular microfilariae following single or repeated doses without any serious reactions clearly suggests that a beneficial effect on lesions and morbidity will be achieved.

Ongoing studies, especially the placebo-controlled studies, which are designed to investigate the impact of ivermectin on morbidity, should be encouraged to do this critically. The OCP studies, which include an ophthalmological monitoring element, will permit comparison of the effects of ivermectin treatment with information accumulated from areas with and without vector control. It is probably not necessary to design any further placebo-controlled studies to investigate this aspect.

7.1 Features that Contribute to Morbidity in Onchocerciasis, and Their Monitoring

Skin

(Acute)	itching	(Chronic)	lichenification
	papules		atrophy
	pustules		hanging groin
	infection		

Ocular

intraocular microfilariae
sclerosing keratitis
iridocyclitis
choroidoretinitis
optic nerve disease
defective ocular function, including blindness

7.2 Assessment of Impact on Morbidity

7.2.1 Skin manifestations

Itching is a major cause of morbidity in onchocerciasis and any drug that can offer relief is of substantial benefit. Although severe manifestations can be dramatic, lesser grades of itching are difficult to assess. To determine the impact of ivermectin on this symptom, it will be necessary to conduct a simple survey before and at intervals after treatment.

Monitoring of lesions may include records such as serial photographs or diagrams. It is expected that acute lesions such as papules, excoriations and pustules will improve while chronic lesions such as lichenification, atrophy and hanging groin may not show any change.

7.2.2 Ocular lesions

It is essential to monitor eye lesions before and after treatment with ivermectin on a long-term basis in some studies, both for existing lesions and the occurrence of new ones.

As noted above, some of the OCP studies and other studies of the community-based distribution of ivermectin have shown a trend for regression in the anterior segment lesions within one year of treatment. These findings are consistent with the ocular findings of the controlled clinical trials. However, it will be necessary to monitor eye lesions and intraocular microfilariae over longer periods using standardized methods, and giving due consideration to the factors of intra- and inter-observer variations. Such techniques as fundus photography and fluorescein angiography may be used to demonstrate changes which may occur in lesions of the posterior segment of the eye.

Where specialized facilities are unavailable, long-term tests of ocular function such as the visual acuity test need to be carried out, and particularly the incidence of blindness should be monitored.

7.2.3 Improvement in general health

As part of the general improvement in health due to the elimination of microfilariae, it would be useful to monitor general health such as weight and height, especially in the younger generation and also in women of child-bearing age.

7.2.4 The role of the primary health care worker in monitoring the impact on morbidity

It is envisaged that ivermectin could be distributed and monitored by the physician, assistant nurses and primary health care workers. It would be useful to train personnel to recognize and record simple skin manifestations such as itching, papules and excoriations, and to determine visual acuity and assess the presence of blindness both at the initial stage and on a long-term basis.

7.3 Research Priorities

Although data are available upon which one can devise rational regimens for dosing with ivermectin, many questions remain unanswered that may be necessary for optimal mass distribution to various populations with different patterns of intensity of infection, disease manifestations, primary health care systems, etc. Therefore, for optimal control of morbidity, research will be necessary in two major areas: (1) retreatment frequency, and (2) operational aspects of distribution. While these questions may be outside the mandate of this subcommittee, they will have to be addressed by those who propose to undertake mass distribution.

7.3.1 What is the optimal retreatment interval for each particular endemic focus? The interval may vary with level of endemicity. In some cases, yearly retreatment may be unnecessary and may not be cost-effective, while in others, twice-yearly treatment may be necessary for control of morbidity. The answer to these questions may require large-scale studies in the context of national control programmes.

7.3.2 In situations in which only some communities are at risk of onchocerciasis morbidity, how are those communities to be most cost-effectively identified? Are there simple ways to find such communities (e.g. surveys of skin signs or blindness)? Are parasite studies necessary and, if so, how are they best done?

7.3.3 What is the most cost-effective method of delivering ivermectin to communities at risk of onchocerciasis morbidity? How should delivery be incorporated into primary health care? Should community mobilization for treatment be stimulated through schemes such as "national treatment days", as has been done successfully for child immunizations in some countries? Should delivery be through a "vertical" or "horizontal" organization?

7.3.4 What are the most cost-effective means to motivate communities for treatment with ivermectin and to ensure high compliance? What are the factors associated with non-compliance and how can these be overcome most effectively?

7.3.5 What is the economic and social impact of ivermectin mass therapy? Control of the morbidity associated with onchocerciasis will have both social and economic impacts (e.g. repopulation of endemic areas, elimination or reduction of onchocercal blindness with associated social and economic effects). Studies should be conducted to assess the nature and magnitude of such effects in order to evaluate the overall consequences of community-based distribution of ivermectin.

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