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Report of a Scientific Working Group on Serious Adverse Events following Mectizan® treatment of onchocerciasis in *Loa loa* endemic areas

Scientific Working Group on Serious Adverse Events in Loa Loa endemic areas*

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Abstract

The occurrence of Serious Adverse Experiences (SAEs) following Mectizan® treatment of onchocerciasis in *Loa loa* endemic areas has been increasingly reported over the past decade. These SAEs include a severely disabling, and potentially fatal, encephalopathy, which appears to correlate with a high load of *L. loa* microfilariae (> 30,000 mf/ml).

Previous consultations organized by the Mectizan® Donation Program (MDP) in 1995 and 1999 have developed useful "case" definitions of encephalopathic SAEs following Mectizan® treatment and have summarized available evidence on its pathogenesis and optimal clinical management. At both meetings, the need for better understanding of the pathogenesis of the encephalopathy was emphasized, including the need for biological and autopsy specimens from the affected cases.

Following a recommendation at the Joint Action Forum of the African Programme for Onchocerciasis Control in December 2001, the MDP, on behalf of the Mectizan® Expert Committee, organized a Scientific Working Group on *L. loa* associated SAEs following Mectizan® treatment in May 2002. The present report includes the background, new evidence, conclusions and recommendations from that Scientific Working Group. The following points represent a **summary of the present status**:

1. Although there are more and better quality clinical and epidemiological data on *L. loa*, the pathogenesis of the Mectizan®-related *L. loa* encephalopathy remains obscure.

2. Very limited progress has been made in research on the pathogenesis of encephalopathy, because of the lack of specimens from cases, and the lack of animal models.

3. There has been no particular breakthrough in terms of the medical management of patients with *L. loa* encephalopathy; however, a favorable outcome usually results from prompt general nursing and nutritional care which remain the major interventions.

The **main recommendations for future actions** are as follows:

1. Validate and update the mapping of *L. loa* with a combination of remote sensing and RAPLOA techniques.

2. Conduct an expert analysis of the apparent clustering of encephalopathic SAEs reported so far.

3. Investigate a possible "pre-treatment" scheme with high-dose albendazole in *L. loa* endemic communities at high risk of encephalopathic SAEs if treated with Mectizan®; this study will be conducted in collaboration with WHO/TDR.

4. Establish a post of Loiasis Technical Advisor for research and operational support in Cameroon, to conduct population surveys and to facilitate better data collection from SAE cases, including postmortem studies as appropriate.

5. Investigate the possibility of developing an animal model of *L. loa* encephalopathy; this activity would be linked to the above-mentioned research agenda in Cameroon.

6. Investigate the best care model for encephalopathic SAEs, including identification of early warning signs and therapeutic interventions.

7. Develop further models for health education messages needed for community compliance with Mectizan® treatment, and family support for SAE cases.

8. Conduct research studies on the safety of combination therapy of Mectizan® and albendazole in areas co-endemic for *L. loa* and lymphatic filariasis (LF) with coordination from the relevant technical bodies that oversee these issues.

The above recommendations will be implemented through a continuing collaboration between the interested parties represented at the Scientific Working Group, involved in onchocerciasis control and/or the Global Programme to Eliminate Lymphatic Filariasis.

Introduction

After a brief welcome of participants by Professor David Molyneux and Dr Björn Thylefors, the meeting was opened by the Chairman, Professor Mamoun Homeida. The agenda (see Additional File 1) was adopted and participants briefly introduced themselves (see Additional File 2 for List of Participants). The terms of reference for the meeting (see Additional File 3) were reviewed.

Review Of Previous Consultations On *Loa Loa* Associated SAEs – Björn Thylefors

The outcome of the two previous consultations convened by the Mectizan® Donation Program (MDP) was briefly reviewed. In the first meeting, which took place in Paris, France in 1995 on the theme of "CNS Complications of Loiasis and Adverse CNS Events following Treatment" a case definition was worked out, which has since been usefully applied. These definitions allowed for the classification of "definite" or "probable" *Loa loa* related cases, as distinguished from "coma events" in *L. loa* endemic areas. It was noted that the case definition in 1995 retained a post-treatment microfilaremia of 1,000 mf/ml or more. Today, available data would place this level between 3,000 – 5,000 mf/ml. More information and evidence is available today in the field of epidemiology, including new tools such as remote sensing mapping for *L. loa* and the recently elaborated RAPLOA technique for community assessment of high risk for Serious Adverse Experiences (SAEs) following treatment with Mectizan®.

In contrast, there is still little progress being made in the field of pathogenesis of the encephalopathy that typically ensues in heavily infected loiasis cases treated with Mectizan®. The persistent lack of biological specimens from these cases is a particular obstacle to progress in this regard. The reporting of SAEs also leaves much to be desired; it is often delayed, incomplete and contains irrelevant information instead of focusing on the main clinical and laboratory data needed. As a follow-up to the 1995 consultation, a survey on the SAE reporting system is now being conducted by the MDP, with a view to improving reporting performance.

The 1999 consultation, convened in Tours, France, focused more on the clinical picture, and possible associated conditions. There were no formal recommendations adopted at that meeting but suggestions were made to heighten monitoring for the first round of Mectizan® treatment in *L. loa* endemic areas and to refine the borders of areas of meso- and hyper- endemic onchocerciasis endemicity in order to justify treatment of communities at risk of SAEs. Stricter medical supervision was also proposed as a means of reducing the risk of permanent sequelae of SAEs following Mectizan® treatment in *L. loa* endemic areas.

Overall, it was felt that the two previous consultations had certainly been of use, but there was now a need to take advantage of some new openings, such as easier assessment of *L. loa* endemic areas, and to draw up an agenda for needed research in the immediate and mid-term perspective. This aim was reflected in the terms of reference for the present meeting (see Additional File 3).

Since working papers for the meeting had been previously distributed to participants, it was intended that presentations would be brief, focusing only on salient points, in order to facilitate maximum discussion and formulation of recommendations. The list of working papers submitted for the meeting is provided in Additional file 4.

Mapping Of *L. Loa*

Remote sensing – David Molyneux

Overview

A remote sensing map of *L. loa* has been developed by the Liverpool School of Tropical Medicine (see Additional File 5). Predicted prevalence was based on several environmental factors suggestive of the presence of *Chrysops spp*. while epidemiological surveys conducted by the Institut de Recherche pour le Développement (IRD) in Cameroon from 1991 to 2001, provided the observed prevalence data to determine the best predictive model. Mapping of other parts of Central Africa, Sudan and Ethiopia are ongoing.

RAPLOA Validation – Hans Remme

Overview

A rapid epidemiological assessment of community prevalence of high intensity *L. loa* microfilaremia, based on a simple questionnaire, has been developed by TDR and conducted in Cross River State in south-eastern Nigeria, and in the North West, South West and East provinces of Cameroon. Prevalence was found to be highly correlated with intensity of infection. The most sensitive and specific survey question was that which was restricted to individuals who responded positively to a past experience of an eye worm, confirmed by a representative photograph, and which lasted between 1 and 7 days (RAPLOA). Validation of the RAPLOA technique is ongoing. The sampling methodology and the threshold at which 'high-risk' communities are identified are yet to be determined.

Recommendations

1. TDR and Liverpool to continue their collaboration to validate these tools. Validation of remote sensing mapping should include predicted negative as well as predicted positive areas.

2. Develop a protocol to combine these tools for mapping of *L. loa* that assesses both presence of infection and risk of *L. loa* encephalopathy following treatment with Mectizan® (% of restricted eye worm defined as a proxy indicator).

3. Consider different thresholds of RAPLOA positivity before defining the threshold to be used in the field to minimize the risk of *L. loa* encephalopathy following treatment with Mectizan® in a given community.

Recent Advances In Knowledge About SAEs In *L. Loa* Endemic Areas

Review of reported cases – Nana Twum-Danso

Overview

1. The definitions of SAEs and important medical events which may be considered SAEs were provided:

A serious adverse event/experience is "an adverse experience occurring at any dose that results in any of the following outcomes:

- ***Death***

- ***Life-threatening adverse drug experience***

- ***Hospitalization or prolongation of existing hospitalization***

- ***Persistent or significant disability/incapacity***

- ***Congenital anomaly/birth defect***

- ***Cancer***

- ***Overdose (accidental or intentional)***

Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered an SAE when,

based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed above" (Merck & Co., Inc.).

2. As of May 10, 2002 a total of 204 SAE cases have been reported to the MDP as having occurred since the mass treatment program began in 1988 up to the end of 2001, giving rise to a cumulative incidence of approximately 1 reported SAE per 1 million treatments.

3. In light of research findings made available since the 1995 MDP consultation on *L. loa* encephalopathy, the case definitions have been modified by the MDP (see Additional File 6).

4. The majority of these SAE cases have been reported from Cameroon (n = 175; 86%). Ninety-six of the 175 cases from Cameroon (55%) were encephalopathic in nature; 61 had sufficient clinical and laboratory data to support a diagnosis of 'Probable' or 'Possible' *L. loa* Encephalopathy temporally Related to treatment with Mectizan® (PLERM) (see Additional File 6 for case definitions).

5. There appears to be a clustering of PLERM cases in the Central Province of Cameroon, from where 51 of the 61 PLERM cases have been reported. The neighboring districts of Monatélé and Okola reported the highest number (and highest incidence) of PLERM during the years 1994/95 and 1999 respectively when mass treatment programs were initially launched in those districts.

6. During 2001, there appears to have been over-reporting of SAEs that are not clinically important but fit the strict definition of an SAE, such as mild-Mazzotti reactions. The use of hemorrhages of the palpebral conjunctivae (HPC) as a screening tool for impending PLERM, though useful, may be exacerbating this problem since it lacks specificity and may be poorly differentiated by the community health volunteers.

7. Interpretation of these data are limited due to the overall poor quality and incomplete nature of SAE forms returned to the MDP and the lack of knowledge about incidence of SAEs in countries other than Cameroon.

8. In order to better understand the epidemiology of PLERM, the MDP is currently conducting a survey of onchocerciasis field staff at the national and peripheral health levels, to investigate the degree of under-reporting, if any, from countries other than Cameroon.

Recommendations

1. Determine spatial distribution of the encephalopathic cases at village level using GIS software to better understand the clustering phenomenon observed.

2. In spite of the limitations of clinical data submitted, determine case-fatality rates, trends over time, and effectiveness of supportive treatment of PLERM cases.

3. Continue to monitor aggregate numbers. It is important to include an assessment of number of cases per first-round treatments.

4. Where possible, correlate encephalopathic cases with *L. loa* aggregate mf (CMFL or RAPLOA results).

5. Accept modified case definitions of *L. loa* encephalopathy.

Clinical picture, epidemiology & outcome – Michel Boussinesq

Overview

1. The most common symptoms reported by SAE patients in *L. loa* endemic areas are fatigue, anorexia, headache, generalized arthralgia and severe lumbar pain; onset of symptoms is usually within the first 12–24 hours. For patients who develop encephalopathy, the above-listed symptoms are also associated with confusion, agitation, dysarthria, aphasia and incontinence which may begin as early as the first day following treatment with Mectizan®.

2. HPCs have been associated with pre-treatment *L. loa* microfilaremia of > 1000 mf/ml and may serve as an early screening tool, that could be easily applied at the village level, even though it would yield a high false-positive rate.

3. Treatment with Mectizan® has been associated with passage of *L. loa* mf into the cerebrospinal fluid (CSF) irrespective of pre-treatment *L. loa* mf levels. However there was an observed gradient in this phenomenon: a greater proportion of individuals with levels > 30,000 mf/ml compared to those with 15,000 to 30,000 mf/ml, and a greater proportion of individuals with 15,000 to 30,000 mf/ml compared to those with < 15,000 mf/ml. Not all individuals in whom this phenomenon was observed developed an encephalopathy.

4. Treatment with Mectizan® has also been associated with hematuria and microfilaruria, the level of which correlates with the pre-treament *L. loa* microfilarial load.

5. Eosinophil levels have been shown to decrease dramatically 24 hours after treatment with Mectizan®, and rise above pre-treatment levels 48 hours later.

6. Electroencephalographic and computed tomography studies have been of limited value in these cases, yielding no clearly identified patterns.

7. Based on the work of Boussinesq and colleagues, the single known risk factor for developing *L. loa* encephalopathy is pre-treatment *L. loa* microfilaremia > 50,000 mf/ml. Age and gender have not been definitely shown to be correlated with risk.

Recommendations

1. Additional work should be done to test the usefulness of possible predictors of high-density microfilaremia, *L. loa* encephalopathy, and chronic neurologic sequelae, including:

• Existence of local terminology for eye worm

• History of repeated eye worm passage on an individual level; possible sources of data include the RAPLOA study by TDR and unpublished studies conducted in Cameroon.

2. The usefulness of HPC as a predictor of impending neurologic involvement of *L. loa* associated adverse reactions should be immediately studied to determine, among others, whether this sign could be correctly recognized by

community-based distributors and health workers. If these studies appear promising, the MDP or African Programme for Onchocerciasis Control (APOC) should sponsor the development of laminated cards depicting HPCs and describing appropriate referral and management of patients with this condition.

Immunopathology & immunogenetics – Charles Mackenzie

Overview

1. Clinical and laboratory findings suggest that Mectizan®-associated *L. loa* encephalopathy:

• is consistent with an embolic process triggered by massive microfilarial death;

• may also involve circulating immune complexes or polymorphic inflammatory responses;

• differs from the acute neurologic reactions seen in some animals (e.g., collie dogs) following treatment with Mectizan®, which is associated with mutation of the multiple drug resistance (mdr1) gene and inadequate production of P glycoprotein.

2. Research on the pathogenesis and treatment of *L. loa* encephalopathy has been inhibited by the lack of an animal model and the paucity of:

• detailed epidemiological and clinical information;

• diagnostic specimens during the course of illness; and

• autopsies and post-mortem tissue specimens.

Recommendations

1. Consideration should be given to the development of a murine model of *L. loa* encephalopathy, preferably in an area endemic for loiasis.

2. Although it would be costly and perhaps difficult to obtain the necessary clearances, the feasibility of developing a primate model of *L. loa* encephalopathy should be explored.

3. When cases of *L. loa* encephalopathy occur, attempts should be made to collect and have tested:

• serial blood/serum specimens;

• conjunctival biopsies;

• tissue specimens on autopsy (e.g. via transphenoidal or transethmoidal route).

4. A position for a "Loiasis Technical Advisor" should be created and filled as soon as possible in Cameroon. The Technical Advisor would work closely and liaise with the Ministry of Health, the National Onchoceriasis Task Force (NOTF), and other partners involved in onchocerciasis control and lymphatic filariasis elimination, but would retain a certain independence in that he/she would not work "for" any one particular group. The responsibilities of this position would include, among others:

a. Responding quickly when cases of *L. loa* encephalopathy occur to collect detailed epidemiological and clinical information on each case;

b. Collecting necessary laboratory and tissue specimens;

c. Assisting the NOTF and others with adhering to guidelines for Mectizan® treatment strategies in *L. loa* endemic areas;

d. Assisting the NOTF and the Ministry of Health with epidemiological mapping and surveillance *of L. loa, Wuchereria bancrofti*, and *Onchocerca volvulus*;

e. Conducting operational research on risk factors for, and clinical management of, *L. loa* encephalopathy and its sequelae;

f. Conducting formative research on attitudes and beliefs regarding *Loa* encephalopathy;

g. Conducting ethnographic research on patterns of food and beverage consumption and use of traditional medicines that may increase risk of *L. loa* encephalopathy.

Pathogenic role of Wolbachia *– Mark Taylor*

Overview

The presentation provided a brief history of the events that led to the discovery of *Wolbachia* as intracellular endosymbiotic bacteria of filarial nematodes. Their association with systemic inflammatory reactions to anti-filarial chemotherapy and the possibility of exploiting these bacteria as novel targets for antibiotic therapy of filariasis were also discussed.

Main Issues

In Central and West Africa, particularly in central-southern Cameroon, where onchocerciasis co-exists with *L. loa*, severe adverse reactions involving inflammatory encephalopathy and the presence of *L. loa* microfilariae in the CSF have been observed following ivermectin therapy. These observations prompted an examination of *L. loa* worms for the presence of *Wolbachia*. Previous studies using electron microscopy have failed to detect endosymbionts. Results from current studies using immuno-electron

microscopy show bacterial structures within host vacuoles labeled with antibodies to *Wolbachia* surface proteins in samples of infective larvae from Cameroon. Further, in PCR-based studies on adult worms, microfilariae and infective larvae have all been positive for the presence of *Wolbachia* DNA, with unique sequences. Of note, 10% of CSF samples from fatal cases of *L. loa* encephalopathy following treatment with Mectizan® were PCR-positive for *Wolbachia* but DNA sequencing demonstrated that these *Wolbachia* were derived from *O. volvulus* and not *L. loa*.

Cumulative results from these studies suggest that *L. loa* does harbor *Wolbachia* endosymbionts, albeit in very low numbers. Trials currently underway, in onchocerciasis and lymphatic filariasis patients and those planned in loiasis patients, are designed to determine whether antibiotic therapy can lead to adulticidal activity and long-term sterility of the adult worms.

Discussion

• Presence of *Wolbachia* in *L. loa* is uncertain, evidence from studies conducted by the Liverpool group indicates that they are present, but other laboratories have not obtained similar results.

• In its present form, antibiotic therapy is not suited to mass treatment, since children and pregnant women cannot receive doxycycline. Furthermore, the duration of treatment required is not practical for mass treatment programs.

Recommendations

1. Communicate with large pharmaceutical manufacturers to access antibiotics that have been developed but are not in general use and examine their effect on *Wolbachia*. This strategy is considered to be more productive than using antibiotics which are currently in use due to possibility of resistance developing to pathogens other than the target *Wolbachia.*

2. It would be informative to examine *Wolbachia* symbiosis in different strains of *O. volvulus* and *L. loa*.

3. Despite the controversy surrounding the presence of *Wolbachia* in *L. loa* it may be useful to examine the potential for using antibiotics for the treatment of loiasis given their potential for limiting pathological inflammation during routine therapy.

4. Continue studies aimed at reducing the period of antibiotic treatment.

Note: Additional analysis using immunohistochemistry and PCR have failed to corroborate initial findings of *Wolbachia* symbiosis in *Loa loa* (Evidence against Wolbachia symbiosis in *Loa loa*. McGarry et al., *Filaria Journal* 2003, 2:9 and Obligatory symbiotic Wolbachia endobacteria are absent from *Loa loa*. Büttner et al., Filaria Journal 2003, 2:10). We now conclude that *Loa loa* is free of *Wolbachia* symbiosis. It is therefore highly improbable that *Wolbachia* contributes to the neurological consequences of SAE following ivermectin treatment in individuals with infections of *L. loa* unaccompanied by other filarial species.

Onchocerciasis-Related SAEs – Kwablah Awadzi

Overview

With the exception of *L. loa* related SAEs, there have been very few serious or severe reactions to Mectizan® therapy, despite wide application of the drug for onchocerciasis control. In addition, because of their limited effect on microfilariae, the benzimidazoles such as albendazole that are currently being widely applied for lymphatic filariasis elimination in onchocerciasis endemic areas, do not predispose patients to adverse events related to parasite death. Therefore, the presentation concentrated mainly on the onchocerciasis-related adverse events which have been observed and recorded following therapy with pre-Mectizan® drugs – DEC and suramin – which are no longer employed as therapeutic agents in onchocerciasis endemic areas.

Main Issues

• Provided a definition of SAEs as defined in the 1996 International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice.

• Provided a very useful definition of causality, based on the WHO definition as follows:

- Not related
- Unlikely
- Possibly related
- Probably related
- Most probably related

• A very comprehensive account of SAEs which have been observed following therapy with the various drugs considered was presented. Events for which information was provided included:

- Mortality

➢ Collapse and therapeutic shock

➢ Severe Symptomatic Postural Hypotension (SSPH)

• An account of systemic reactions and the associated drugs was provided. The organ systems in which systemic reactions typically occur are dermatological, lymphatic, gastrointestinal, pulmonary, musculoskeletal, neurological and ocular.

The introduction of Mectizan® for the treatment and control of onchocerciasis has eliminated the use of either DEC or suramin. Although Mectizan® is generally well tolerated in patients with high *O. volvulus* microfilariae densities, the treatment of patients with intense *L. loa* infections has resulted in a number of SAEs including an acute encephalopathy that occasionally results in death. The pathogenesis of the encephalopathy is not well understood but does not appear to be related to the onchocercal post-treatment reactions.

Recommendations

1. During training, all health staff should be taught how to distinguish between reactions which are drug-patient related and those reactions which relate to the death of parasite following drug administration

2. Because Mazzotti reactions are relatively common there is still a great need to further study the immuno-pathogenesis of these reactions, with a view to more effective management.

Risk Factors For SAEs

Analysis of reported cases of PLERM – Nana Twum-Danso

Overview

1. Analysis of reported PLERM cases is very limited due to substantial amounts of missing and incomplete data. The only risk factors for development of PLERM that have been identified, with reasonable confidence, are the following:

• Age between 45 and 59;

• First-time treatment with Mectizan®;

• High *L. loa* microfilarial load – mean post-treatment level of 3600 mf/ml, which if extrapolated, is suggestive of a mean pre-treatment level of approximately 36,000 mf/ml.

2. Data were insufficient to determine the risk factors for poor clinical outcome (death or permanent neurologic sequelae once PLERM develops)

Recommendations

1. More complete and reliable demographic, clinical and laboratory data needs to be collected for the rare encephalopathic SAE cases that occur in the future (see above recommendation for the Loiasis Technical Advisor in Cameroon).

2. An epidemiologist with expertise in clustering should review the geographic distribution of cases in Cameroon to investigate other potential risk factors (e.g. environmental, dietary etc.).

Pharmacologic neurotoxicity – Geoffrey Edwards

Overview

1. Ivermectin, a lipophilic drug, does not normally cross the blood-brain barrier in vertebrates due to the action of the P-glycoprotein (PGP) efflux transporter.

2. Ivermectin is also a substrate of cytochrome P-450 (CYP) 3A4, which is widely distributed in humans and expressed in the liver and intestine.

3. Thus, drug-drug interactions at the level of PGP and/or CYP3A4, may increase the neurotoxicity of ivermectin.

4. Albendazole is a known substrate of CYP3A4 but it does not appear to be a substrate for human PGP.

5. Many foods, drinks and traditional medicines contain inhibitors of transport proteins such as PGP.

Discussion

1. The local foods, alcoholic brews, and the traditional and allopathic medicines vary from one region to another in Cameroon and may warrant further investigation as possible co-factors in PLERM cases through inhibition of PGP and CYP3A4.

2. Side effects noted in studies using high-dose ivermectin are mydriasis, nausea, vomiting and weakness. No neurotoxicity has ever been observed in these studies. Thus, it is unlikely that inhibition of PGP and possible increased levels of ivermectin in the brain, could result in the same clinical picture as has been observed in PLERM. Another mechanism needs to be sought.

Recommendations

1. Generate list of competitors of PGP and CYP3A4 that may be co-administered with Mectizan® in the field.

2. Determine if the local foods, brews, and traditional medicines used in the region of Cameroon where the encephalopathy cases appear to be clustered could be potential substrates of PGP and CYP3A4 (see above

recommendation for the Loiasis Technical Advisor in Cameroon).

Alcohol – Mamoun Homeida

Overview

Alcohol intake in conjunction with Mectizan® treatment has been implicated as a possible cause of SAEs, including encephalopathy in *L. loa* endemic areas. As alcohol consumption is very common in all known *L. loa* endemic areas, there is a need to study this matter, in order to make a clear recommendation about the possible harmful interaction with Mectizan®. There are, however, two issues which must be clarified:

(a) the possible interaction between ethanol and Mectizan® would refer to acute, high intake of alcoholic beverages;

(b) there are a great variety of local alcoholic brews in the communities concerned, with varying possible associated toxic compounds.

Main Issues

An ongoing cross-over study in Sudan where males are administered Mectizan® in a fasting state, with a sorghum-based meal (high in carbohydrates) or with a standard quantity of a local alcoholic brew, was briefly presented. Absorption of Mectizan® was not found to be significantly different between the 3 groups. Surprisingly, no ethanol was found in the local alcoholic brews in this study; rather they contained approximately 2% methanol and 11% propanol.

Recommendations

1. Local patterns of alcohol brewing and consumption and use of traditional medicines in the high-risk areas of Cameroon should be determined (see above recommendation for the Loiasis Technical Advisor in Cameroon).

2. Pending the outcome of the above study, a clear recommendation about alcohol intake at the time of Mectizan® administration in mass treatment programs should be formulated by the Mectizan® Expert Committee (MEC) and communicated to field programs.

Risk-Management Approaches To *L. Loa* Associated SAEs

Risk group identification approach – David Addiss

Overview

1. A decision analysis model for mass treatment strategies of onchocerciasis with Mectizan® in *L. loa* endemic areas was presented (see Additional File 7 for current MEC recommendations for treatment strategies in areas co-endemic for onchocerciasis and loiasis). The current approach of village-by-village REA was compared with RAPLOA alone, and RAPLOA in combination with REA. Two thresholds of prevalence of high intensity *L. loa* microfilaremia (20% and 40%) were illustrated.

2. Based on the preliminary assumptions in the model, excluding communities at high risk of *L. loa* encephalopathy using RAPLOA techniques, did not appear to decrease the expected cases of death or permanent neurologic sequelae following the encephalopathic event.

3. The current version of the model focused on the risks and benefits of Mectizan® treatment, training, surveillance, and supportive care for any SAEs that may occur.

4. Cost and feasibility factors have not yet been included in the model.

Recommendations

1. Refine the estimates used in developing model assumptions.

2. Work should continue on the model to include feasibility and cost of different strategies using REA, RAPLOA and their combinations; different thresholds of RAPLOA should be explored.

3. Consider the cost implications in carrying out effective treatment in communities that are hypo-endemic for onchocerciasis that will involve training of health staff, sensitization and education of the communities as well as monitoring and case management.

4. Develop the model further to allow its application to LF particularly a risk benefit analysis.

Pre-treatment with albendazole – John Horton & Mark Bradley

Overview

The presentation provided overviews of evidence of the effect that albendazole has, in both single and multiple dose regimens, on a wide variety of filarial species including *L. loa*. From the information available concerning the effect that albendazole has on *L. loa* microfilarial densities, a simple model of the effect of temporally spaced single dose administration of albendazole on *L. loa* microfilarial levels was presented.

Main issues

• In a number of different filarial infections, multiple and at least in some cases, single doses of albendazole leads to a reduction in mf counts

• The pattern of clearance is consistent with an effect on the adult (either a moderate macrofilaricidal effect or an effect on fertility/embryo production)

• The clearance is slow, and detection requires relatively prolonged follow up. Mazzotti reactions are not reported.

• The single dose effect seen with *L. loa* can be utilized to potentially prevent reactions, and is compatible with a public health approach

Discussion

1. Although one case of non-fatal encephalopathy has been observed following albendazole therapy, most studies conducted to date show that single dose albendazole does not result in an increase of adverse events during the treatment of patients with LF or loiasis.

2. Effects of albendazole are slow to manifest: *Wuchereria bancrofti* microfilarial densities decline to around 20% of pre-treatment levels in LF patients over an 8–9 month period. In loiasis patients the decline is less pronounced, declining to around 50–70% of pre-treatment density over a period of 6 months.

3. Observed patterns of microfilarial decay are consistent with an effect on embryo-genesis rather than a direct effect on the microfilariae

Recommendations

1. Research on the feasibility of albendazole as a pre-treatment drug for Mectizan® in the onchocerciasis control and LF elimination programs in *L. loa* endemic areas is urgently needed. These studies should examine the effect of temporally spaced dosing with single 400 mg and 800 mg dose albendazole in *L. loa* patients with high-risk mf densities (> 30,000 mf/ml). A second intervention would be administered after 2–3 months. The proposed studies must show consistency of albendazole absorption.

Pre-treatment with low dose Mectizan® – Michel Boussinesq

Overview

In a recent study, the kinetics of decline in *L. loa* microfilaremia was no different for patients receiving a standard dose of ivermectin than it was for those receiving a low dose (3 mg).

Recommendation

Further research to identify a low dose of ivermectin that could clear *L. loa* microfilaremia without provoking SAEs should not be pursued further at this time since it does not seem possible to identify a therapeutic minimum dose for this effective microfilaricide.

Update On Management Of *L. Loa* Encephalopathy – Kenneth Brown

Overview

1. A limited amount of reliable information exists on *L. loa* encephalopathy and its management, including treatment guidelines by Gardon *et al*., reports of previous workshops, and the published literature. However, this information is not always readily available, especially outside Cameroon.

2. As no substantially new clinical data have been generated or published since the 1999 workshop in Tours, recommendations for clinical management have not changed substantially.

Recommendations

1. Endorse the current *L. loa* encephalopathy treatment manual by Gardon (Bull Liais doc OCEAC 1999; 32 pg 37-51), with modifications (i.e. no massage of coma patients).

2. Corticosteriods are not recommended for treatment of *L. loa* encephalopathy. (rationale: no evidence of efficacy for this condition and they may be harmful)

3. Antihistamines are contraindicated for treatment of *L. loa* encephalopathy. (rationale: no evidence of efficacy for this condition and they sedate a patient with a neurologic condition, interfering with diagnosis and neurologic assessment)

4. Hydration is an important component of supportive care. Hypotonic intravenous solutions should be avoided if there is any evidence of increased intracranial pressure.

5. For village-level care, a simple algorithm card for recognition, referral and care of *L. loa* encephalopathy should be developed, pre-tested, and distributed.

6. Additional 'deliverables' for patient education, training of medical personnel, establishment of best practices for nursing and rehabilitation, counseling of patients and families, and dissemination of treatment guidelines, should be promulgated.

7. Efforts should be made to collect detailed clinical information on every case of *L. loa* encephalopathy (see above recommendation for Loiasis Technical Advisor in Cameroon).

Health Educational Issues In Relation To SAEs – Nancy Haselow

Overview

1. The goal of Information, Education and Communication (IEC) strategies for Community-Directed Treatment

with Invermectin (CDTI) in Cameroon has primarily been that of increasing treatment coverage. In the past, IEC activities have placed little emphasis on adverse events (AEs), both mild and severe, even though recent surveys have shown that both types of AEs affect treatment coverage.

2. A "Vicious Cycle" between SAEs and low treatment coverage was presented; fear of, and rumors about, SAEs increase reticence of the population to take Mectizan® in subsequent years which ultimately increases their risk of SAEs that are associated with high *L. loa* microfilarial loads since the microfilarial loads are increasingly restored to pre-treatment levels with the passage of time.

3. Increased human and financial resources are required to plan and implement CDTI in *L. loa* endemic areas due to the need for enhanced IEC activities, increase in the content and duration of training for CDDs and health staff, additional supervision of community activities, and provision of medical supplies to health facilities for management of any SAEs that may occur. In addition, because of the need for strict monitoring of drug inventory and close supervision of community activities, Mectizan® distribution in these areas by definition, does not and can not, fit into the classic CDTI approach.

4. Great efforts have been made in the past year to include Adverse Event (AE) occurrence, referral and management in the IEC plans of mass treatment programs in Cameroon.

5. There is a need for emphasis on community-based research in the design of IEC tools with greater importance placed on pre-testing these tools before producing them *en masse* for the entire country. In addition, given the linguistic, cultural and religious differences in the country, IEC tools must be tailored for the specific audience.

6. Effective management of SAE cases, with early and appropriate feedback to affected families and communities (including counseling), is a critical component of the IEC strategy. This has not yet been fully employed.

Recommendations

1. Health education and communication materials should be developed based on research carried out in the communities. Subsequently, the product should be tested and refined before widespread application.

2. Counseling methods need to be developed to support those who suffer serious adverse event. Two aspects of counseling should be considered:

(a) Medical counseling carried out by medical staff to explain the condition to the affected family; and

(b) Social support that should be carried out by a prominent person in the community. Regarding the latter it was suggested that the religious leader would be apt to provide such support.

3. Training materials need to be developed further to enhance the efficiency at all levels. In this regard it was also pointed out that selection of subjects from communities for carrying out REA is not always random. It is recommended that training of health staff on this subject should stress the importance of random selection of subjects to give an accurate estimate of endemicity.

4. In order to encourage early management of SAEs, families should be educated to seek treatment as early as possible for even mild AEs. Cost should not be a barrier to seeking medical care for AEs.

5. Appropriate information on adverse reactions to Mectizan® treatment needs to be communicated to the communities to avoid development of reticence to continue subsequent treatments.

Review Of Present Recommendations For Mectizan® Treatment In *L. Loa* Endemic Areas (See Additional File 7)

Recommendations

1. Introductory text needs to be updated to reflect knowledge gained since 1999 including the new RAPLOA technique once it has been validated.

2. Recommendations for program areas where there has been no previous treatment, or fewer than 2 rounds of annual treatment, or less than 60% coverage during 2 or more rounds of annual treatment, or have had cases of encephalopathic SAEs following treatment, needs to be reworded to reflect the following:

• recommended strategy should be made on a community-by-community basis rather than for entire program areas since there is often great variability in treatment coverage within different communities in a given program area.

• recommended strategy for communities found to be hypo-endemic by REA, particularly if previously believed to be hyper- or meso- endemic by REMO, should be made more flexible.

3. Recommendations for follow-up care after clinic-based treatment should be more clearly written.

4. Consideration should be given to moving the section on "the ultimate decision on how to proceed ... should be made by the National Onchocerciasis Task Force (NOTF) and the Ministry of Health" to the top of the guidelines so that program managers more fully appreciate their role and authority in implementing the recommendations.

The MEC and TCC (please see the Glossary of Abbreviations) should clarify whether the above-referenced recommendations should be viewed as 'strict' recommendations or 'flexible' guidelines.

Reporting Of SAEs – Amy Klion

Overview

The different and overlapping goals and responsibilities of AE reporting were reviewed for different categories of institutions and professionals (Food and Drug Administration (FDA) of the U.S., manufacturer/distributor, health professionals and clinical researchers).

The limitations of AE reporting were also presented:

Spontaneous reporting (FDA and similar agencies)

• AE recognition is subjective

• Underreporting is systemic

• Biases (length of time a product has been on the market, country, quality of data) can affect reporting

• Estimation of population exposure is imprecise

Active surveillance (Research studies; Prescription-Event Monitoring)

• Adverse event recognition is subjective

• Costly (in time and money)

Main issues

With regard to the MDP, the presumed goals of AE reporting are:

• to obtain information pertaining to the incidence, pathogenesis and treatment of *L. loa*-related encephalopathy following Mectizan® administration,

• to identify other severe adverse events that may lead to decreased coverage.

The responsibility of the MDP with regards to AE reporting is the transmittal of SAE reports to manufacturer and/or FDA. However, it faces numerous limitations:

• Quality and quantity of information,

• Logistics (information not available),

• Form (information not recorded),

• Variability in reporting,

• Subjective nature of adverse event recognition (perception of what is to be reported).

The possibilities for improvement of AE reporting of the MDP are:

• Encourage reporting of severe or unexpected AEs instead of "serious" AEs,

• Consider two-step form:

➢ Step 1: check box/short text form to collect research data on **all reported AEs**

➢ Step 2: additional (free-text) information required by FDA for **reported SAEs,**

• Institution of a "rapid response team" to augment and standardize acute and follow-up information collected on cases of *L. loa*-induced encephalopathy,

Recommendations

1. MDP needs to clearly define the reasons why SAE reports are required and these messages must be conveyed to health staff working in program areas

2. MDP needs to clearly differentiate between expected reactions to therapy and what could constitute an unexpected event. This difference needs to be communicated to health staff in program areas. It is anticipated that this understanding should reduce the number of reports for expected events.

3. The current SAE reporting form may be too complex and therefore it is not being adequately completed with subsequent loss of vital information. It is recommended that the form is examined and possible revised. The alternative is to have a 2-step reporting system as suggested above.

4. The MDP should examine its current database and compile a list of data which need to be captured to better understand and track the occurrence of *L. loa* related encephalopathic events following Mectizan® treatment. Feedback on the SAE reporting survey that the MDP is conducting will be available in July 2002. It is hoped that this will provide useful input for the re-design of the SAE

Table 1: Recommended Action Items

ACTION ITEM	RELATIVE COST	RELATIVE IMPORTANCE
1. Mapping		
Updating country maps	***High/Moderate***	***High***
RAPLOA implementation	***Low***	***High***
2. Pathogenesis and Clinical Aspects		
Field case studies		
Serial sampling (blood, CSF)	***Moderate***	***High***
Quick response (telephone system)	***Moderate***	***High***
Better clinical definition	***Low***	***High***
Improve data forms etc.	***Low***	***High***
Analysis of evolution of clinical picture to identify potential early warning signs	***Low***	***High***
Research on HPCs		
Pathological specimens (with blood/serological correlates)	***Moderate***	***High***
Utility as early warning sign for PLERM	***Moderate***	***High***
Reliability of application by CDDs & community health workers	***Low***	***High***
Support Local Loiasis Technical Advisor	***High***	***High***
Hospital studies (more sophisticated sampling/testing)	***Moderate***	***High***
Population studies		
Mdr1 and other genetic studies	***High***	***Low***
Food and alcohol toxicity surveys	***Moderate***	***Moderate***
Post-mortem studies		
Core samples	***Low***	***High***
Immunohistology etc on AFIP/Marc Wéry samples	***Low***	***High***
Conjunctival samples	***Moderate***	***Moderate***
3. Epidemiologic Aspects		
Use of GIS software to map SAE cases	***Low***	***High***
Support epidemiologist specialized in cluster phenomena	***High***	***High***
Research on RAPLOA techniques applied at individual level	***Low***	***High***
4. Pre-Treatment Approaches for *L. loa* endemic areas		
Explore existing drugs with potential efficacy against *L. loa*	***Moderate***	***High***
Albendazole – repeated doses	***Moderate***	***Moderate***
Wolbachia (follow developments and respond where appropriate)	***(Low)***	***(High)***
Steroids (hospital study)	***Moderate***	***Moderate***
List of co-substrates for PGP and CYP3A4 potentially used locally	***Low***	***Moderate***
5. Animal Models		
Primates in Cameroon		
To eventually lead to new therapies	***High***	***(Pending))***
To study pathogenesis	***High***	***Low***
Mouse (should be secondary to primate studies)	***Moderate***	***(Controversial)***
Dog (unlikely to be comparable)	***High***	***Low***
In vitro studies (already being done at NIH)	***(High)***	***(Medium)***
6. SAE management improvement / best care methodology		
Improve SAE surveillance & reporting system	***Low***	***High***
Validation of activities, training, surveillance system	***Low***	***High***
Development & assessment of risk management models (incl. for LF)	***Low***	***High***
Education & counseling materials guided by community-based research	***Low***	***High***
Simple algorithm card for recognition, referral & management	***Low***	***High***
7. Support research addressing expansion of programs to LF areas	***Low***	***High***

form to make it better suited for field use. After July, a data capture tool should be prepared which will be administered by a technical support person based in Cameroon (see above recommendation for Loiasis Technical Advisor in Cameroon).

Other Matters

Global Programme to Eliminate Lymphatic Filariasis (GPELF)

Discussion

The importance and urgency of addressing safety issues related to treatment in areas of onchocerciasis and/or LF co-endemicity with *L. loa* was stressed. Various potential

treatment strategies using Mectizan® alone, pre-treatment with albendazole followed by Mectizan®, and pre-treatment with Mectizan® followed by albendazole were discussed.

Recommendations

1. Well-designed research studies need to be conducted to address, as much as possible, safety issues in relation to combination treatment regimens with Mectizan® and albendazole in areas where LF is co-endemic with loiasis.

2. The relevant technical bodies that oversee these issues (TDR, MECAC, TAG, RPRG for AFRO - please see the Glossary of Abbreviations) should coordinate their input into this issue.

Conclusions & Recommendations

In addition to the conclusions and recommendations formulated under each section of this report, an overview of the plan of action and follow-up for future work, highlighting the cost and relative importance of each recommendation was agreed upon and is presented in Table 1.

Closure

The meeting closed at 18^{00} hours on 30 May. The participants expressed their appreciation to Merck and GSK for sponsoring the meeting, to Professor Mamoun Homeida for chairing the meeting, and to Professor David Molyneux and his team for hosting the meeting and for making such pleasant and practical arrangements for the working group.

Glossary of Abbreviations

AE Adverse Experience/Event

AFIP US Armed Forces Institute of Pathology

CDC US Centers for Disease Control and Prevention

CDD Community Drug Distributor

CDTI Community-Directed Treatment with Ivermectin

CMFL Community Microfilarial Load

CNS Central Nervous System

CSF Cerebrospinal Fluid

CYP Cytochrome P450

DEC Diethlycarbamazine

FDA US Food and Drug Administration

HKI Hellen Keller International

HPC Hemorrhages of the Palpebral Conjunctiva

IEC Information, Education & Communication

MDP Mectizan® Donation Program

mdr1 gene that encodes the Multiple Drug Resistance Associated Protein in humans

MEC Mectizan® Expert Committee

MECAC Mectizan® Expert Committee/Albendazole Coordination

NIH US National Institutes of Health

NOTF National Onchocerciasis Task Force

PCR Polymerase Chain Reaction

PGP p-Glycoprotein

PLERM Probable/Possible *Loa loa* Encephalopathy temporally Related to treatment with Mectizan®

RAPLOA Rapid Assessment Procedure for Loiasis based on restricted definition of history of eye worm passage

REA Rapid Epidemiologic Assessment (of onchocerciasis)

REMO Rapid Epidemiologic Mapping of Onchocerciasis

RPRG Regional Programme Review Group (for the Elimination of Lymphatic Filariasis)

SAE Serious Adverse Experience/Event

SSI Sight Savers International

SSPH Severe Symptomatic Postural Hypotension

TAG Technical Advisory Group (for the Global Programme to Eliminate Lymphatic Filariasis)

TDR UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases

TCC Technical Consultative Committee for the African Program for Onchocerciasis Control

Additional material

Additional File 1
Meeting agenda
Click here for file
[http://www.biomedcentral.com/content/supplementary/1475-2883-2-S1-S2-S1.pdf]

Additional File 2
List of Participants
Click here for file
[http://www.biomedcentral.com/content/supplementary/1475-2883-2-S1-S2-S2.pdf]

Additional File 3
Terms of reference
Click here for file
[http://www.biomedcentral.com/content/supplementary/1475-2883-2-S1-S2-S3.pdf]

Additional File 4
List of working papers
Click here for file
[http://www.biomedcentral.com/content/supplementary/1475-2883-2-S1-S2-S4.pdf]

Additional File 5
Remote sensing map
Click here for file
[http://www.biomedcentral.com/content/supplementary/1475-2883-2-S1-S2-S5.pdf]

Additional File 6
Case definitions
Click here for file
[http://www.biomedcentral.com/content/supplementary/1475-2883-2-S1-S2-S6.pdf]

Additional File 7
MEC/TCC Recommendations
Click here for file
[http://www.biomedcentral.com/content/supplementary/1475-2883-2-S1-S2-S7.pdf]