Filaria Journal

BioMed Central

Review

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Possible pathogenic pathways in the adverse clinical events seen following ivermectin administration to onchocerciasis patients.

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from Report of a Scientific Working Group on Serious Adverse Events following Mectizan® treatment of onchocerciasis in Loa loa endemic areas Shrigley Hall Hotel, Manchester, UK, 28 – 30 May 2002

Published: 24 October 2003

Filaria Journal 2003, **2**(Suppl 1):S5

This article is available from: http://filariajournal.com/content/2/S1/S5

Abstract

Background: Reactions are commonly associated with the chemotherapy of onchocerciasis. However unmanageable reactions are uncommon when ivermectin (Mectizan®) is used for the treatment of this infection, and this drug has proved to be a great improvement over previously used agents. Serious adverse events (SAE) nevertheless have occurred, and there is considerable concern about the negative effect such events may have on mass drug administration programs.

This paper reviews the basic pathogenic mechanisms that can be involved in the destruction of microfilaria by chemotherapeutic agents. A central challenge to filarial chemotherapy is the need to remove parasites from biologically sensitive tissues, a more difficult medical challenge than eliminating nematodes from the gastrointestinal tract.

Explanations for the etiology of the serious adverse reactions occurring with ivermectin treatment in specific geographic areas where there is coincident heavy *Loa loa* infections are hampered by a lack of specific pathological case material. Ways to investigate these possibilities are reviewed. Possible pathogenic mechanisms include embolic vascular pathology accompanied by local inflammation, blood brain barrier mdr1 abnormalities, and genetic predisposition to excessive inflammatory responses.

Conclusion: It is important to keep ivermectin, and all its associated adverse clinical events, in perspective with the many other chemotherapeutic agents in general use – many of which produce serious adverse events even more frequently than does ivermectin. Currently available evidence indicates that the pathogenesis of the Loa-associated adverse reactions are probably related to inflammatory responses to microfilariae in specific tissues. However, the possibility of genetic predispositions to pathology should also be considered.

Background

Ivermectin is an extremely safe drug when used in humans and other animals for the treatment and control of nematode and ectoparasite infections [1–3]. The destruction of nematodes in tissues, with a comparatively large mass of foreign material to remove, is a challenge to the host's defense systems. One might reasonably expect this process to be accompanied by overt clinical reactions. Indeed, it has been known for decades that anti-filarial chemotherapy is associated with excessive and sometimes fatal host reactions, the severity and clinical consequences of which depend on the therapeutic agent used [1]. The use of ivermectin for the treatment and control of *Onchocerca volvulus* infections is highly advantageous in this context,

as this drug produces far fewer serious adverse reactions than the previous drug of choice, diethylcarbamazine (DEC) [1,4].

There is a need to better understand the SAEs associated with anti-filarial chemotherapy, in particular the fatalities that have occurred in a small number of individuals who had recently been administered a standard dose of ivermectin; these individuals had coincident high loads of circulating *Loa loa* microfilariae (Mf). These are people, for a large part, living in a specific region of Cameroon – and who died after falling into a coma within four days of treatment [5–7]. This unexpected and unprecedented situation has rightly caused much concern, both from the medical aspect and from a programmatic perspective. This drug has been a key to the success of the major global control program for onchocerciasis. The program has been in existence now for over fifteen years, and is now under threat of interruption in the many endemic areas because of this unexplained and extremely serious toxicity.

Any discussion of the pathogenesis of these SAEs must be prefaced by the fact that very little pathological material or data has been collected on these *L. loa*-ivermectin patients to date, and thus such a discussion must be made with a strong theoretical rather than factual basis. The presence of high loads of Loa microfilariae strongly suggests that there is a possibility that the SAEs are associated with the destruction of these parasites in sensitive tissues such as the central nervous system (CNS). It is pertinent therefore to first review what is known about the basic mechanisms of parasite death and removal of Mf from the human host by way of introduction to mechanisms that may be involved in these adverse reactions. It is also important to compare the clinical events seen in Cameroon with other medical events and conditions with a similar presentation or history; this may be the only practical way to develop plausible theories about the pathogenesis of these specific adverse reactions.

Pathological events in human onchocerciasis

General Aspects

Filarial parasites are relatively large organisms. It is a remarkable biological phenomenon that they can reside in tissues, or circulate in the blood and lymph in large numbers, whilst only causing minimal clinical response and little or no apparent pathology. Some filariae, such as *Mansonella perstans*, despite their considerable prevalence, cause no significant pathology in contrast to the filariae that cause onchocerciasis and lymphatic filariasis; the pathobiology underlying these differences remains poorly understood but nevertheless intriguing.

The central pathogenic event in the development of clinical disease in onchocerciasis is thought to be the destruction of Mf and the associated inflammatory events, such as local tissue damage and degradation of host structures (constitutive collagen fibers, pigmentary cells) [8]. The adult-containing nodules in themselves are usually more an aesthetic problem and cause no major or systemic clinical effects (although the presence of such large antigenic entities in the host in all likelihood has effects other than simply being the source of new Mf). Other phenomena, such as immune complex pathology, autoimmune disease and secondary infections, should be considered as possible factors in this disease complex [8]. For example, there is a direct correlation between anti-collagen antibody levels and the development of chronic disease, and these levels of antibodies exceed those seen in major autoimmune diseases such as system lupus erythematosus (Mackenzie, unpublished observations). The possibility that these pathogenic mechanisms may be involved cannot be ignored; obviously, much still remains to be understood.

Onchocerciasis patients are in a delicate immunological balance with their parasites, and host responses are clearly integral to the clinical outcome [8,9]. Many onchocerciasis patients carry >100 million Mf in the immunologically sensitive connective tissues of the skin, yet experience minimal discomfort or severe clinical effects, at least not in the short term; this same phenomenon apparently exist with *Loa* infections This phenomenon of tolerance contrasts with the situation occurring in onchocercal patients with "sowda" (reactive onchodermatitis) who appear to not be in this quiescent state and suffer tremendously from constant and extremely disquieting dermal pathology; these patients also react severely to treatment with filariacides [10].

Treatment with filariacides disturbs this balance. Furthermore, immune responses following administration of these drugs play a key role in parasite clearance (i.e., efficacy). The involvement of the immune system in the anti-filarial efficacy of ivermectin has been raised repeatedly [11–13]. This phenomenon occurs with other filarial parasites as well, although not always as strikingly as in onchocerciasis. Differences in the contribution of immune responses to chemotherapeutic success among the filariases may reflect the tissue or organs involved in the parasitism (and the ability of that tissue to handle dying Mf), or perhaps a more complicated phenomenon involving the degree of adaptation of the parasite species to the host. The fundamental phenomenon of a balance between the host and the parasite maintained by parasite-derived immunosuppression and other mechanisms is central to the persistence of these infections in the untreated state.

Recently, it has also been proposed that endosymbiotic bacteria (*Wolbachia spp.*) infecting filariae exacerbate the

Table 1: The types of reactions seen in the treatment of onchocerciasis with oral diethylcarbamazine, ivermectin* and others

EXPECTED ("ACCEPTABLE") REACTIONS
• "Classical Mazzotti reactions"
Pruritus
Papular dermal response
Dermal edema
Headache
Nausea
Lethargy
EXCESSIVE ("UNACCEPTABLE") REACTIONS
• Excessive forms of the normally expected Mazzotti reactions
Temporal association with treatment
Lethargy
Papular, pruritic, and edematous dermal responses
Severe headache
Bone ache
Inability to work
Prostration (e.g. Sowda patients)
• Major neurological changes
Coma
Epilepsy
• Specific (non-Mazzotti) dermal responses
Drug-related allergic responses (dermal plaques etc.)
• Other responses
Unsubstantiated reports (bleeding, etc.)

* Ivermectin produces reactions significantly less in severity and duration.

Table 2: The major components associated with microfilarial destruction.

NATURAL SITUATIONS
DERMAL RESPONSES
• Clinical
Pruritus
Self-destruction of the skin (mechanical)
Development of dermal microabscesses
• Histopathological
Vascular endothelial activation
Mast cell increase
Blood and tissue eosinophilia
Eosinophil adherence to the surface of the microfilariae
Macrophage accumulation
Fragmentation of microfilariae
Local tissue damage (destruction of collagen, etc.)
SYSTEMIC EFFECTS
• Antigen release
• Organ dysfunction
• Cytokine circulation
DRUG INDUCED SITUATIONS (additional activities):
GENERAL (in addition to those activities in Natural Situations)
• Clinical
Migration of microfilariae
Increased rate of Mf destruction,
More rapid and severe development of the events
Progressive movement of the papular response over different parts the body (with low dose DEC)
• Histopathological
Macrophage ingestion of excess eosinophil-derived material
Evidence of immunostimulation

pathology of onchocerciasis [14]. The literature concerning most human filariae, including *O. volvulus*, is replete with reports and details of anaphylactoid reactions – known as Mazzotti reactions (after the Mexican Luis Mazzotti, who first described them) – associated with chemotherapy. It is now thought possible that these reactions may be directed, at least in part, to bacterial rather than nematode antigens.

It must be emphasized that it is the rule rather than the exception for a treated individual infected with onchocerciasis to experience some form of clinical discomfort or systemic change after treatment with antifilarial drugs (Table 1). The frequency and severity of such reactions differ with the chemotherapeutic agent used, but all cause at least some undesirable effect. It is the degree of these effects that are of interest here, with special attention paid to the severe, sometimes fatal reactions that have occurred in one *L. loa* endemic area (Cameroon). A key question is whether the pathogenesis of the severe cases simply reflects an unusual enhancement of commonly encountered processes, or involves new processes that are not seen in the vast majority of onchocerciasis patients.

Specific events associated with microfilarial destruction

Events surrounding the death and removal of Mf are of primary importance in any discussion of the pathogenesis of SAEs encountered during the treatment of filarial infections. Much of the information to date related to this phenomenon is taken from data collected with the treatment of *O. volvulus* and *L. loa* with older agents such as DEC [15]. Events associated with Mf destruction are noted in Table 2. Many of the events following treatment with ivermectin are similar to those seen with DEC although to lesser in intensity and rate.

The body in most cases can, although with some discomfort, handle the events related to Mf destruction and removal, and return to a state of relative normality within 24–48 hr after anti-filarial drug administration. However, these reactions can exceed the capacity of the individual to manage them, for example, when topical DEC is used [15]. This latter treatment can lead to overwhelming local dermal reactions and associated systemic effects that are too severe for the patient to tolerate. This is an example of excessive and severe reactions in a tissue that is unable to absorb the changes and return to relative normality. In other words, there are situations in chemotherapy when

the body cannot easily handle the reactions that develop associated with the degenerating microfilariae.

Inflammation associated with Mf destruction and removal probably includes all of the basic inflammatory phenomena, including cytokine release, immune complex formation, autoimmune responses and various physical events, all often resulting in tissue damage. High levels of immune responses are found in onchocerciasis patients, reflecting the heavy antigenic burden and very active antibody responses that are hallmarks of this infection; their pathological significance remains unclear. Neither peripheral lymphoid tissues, nor the liver or kidney (or other organs that might process such complexes) are notably compromised in these patients. Thus, there is no definitive evidence for a central involvement of immune complexes in the pathogenesis of ivermectin-associated adverse reactions. That anti-inflammatory drugs (e.g. cortisone, antihistamines) cannot completely suppress the immunological events associated with Mf destruction emphasizes the complex balance among the various pathways activated.

These microfilarial reactions have been investigated and described in most detail with DEC treatment, but in all likelihood similar phenomena occur with reactions to other Mf such as *Loa loa*.

Clinical problems encountered in the chemotherapy of onchocerciasis patients

Non-Serious

Remarkably few serious reactions are reported with the use of ivermectin in humans or in most animals. In general, the signs and symptoms, which vary in duration (usually no longer than four days), include nausea, headache, minor fever and dermatological responses associated with the presence of dying MF in the skin; pruritic injection of the conjunctiva has also been reported. These Mazzotti-type reactions are similar in many respects to those seen with other microfilariacidal agents, such as DEC [15], although lesser in extent and intensity than with the latter drug.

The unacceptability of these reactions with DEC, especially as associated with an adverse effect on ocular tissues (inducing loss of vision), and the severity of these dermal reactions in many people, drove the search for new and safer agents. Ivermectin filled many of the requirements, including a lack of pathology in the ocular tissues, high microfilaricidal efficacy, long lasting Mf suppression and much reduced severity of associated dermal reactions. It was thus adopted as the drug of choice for the treatment of onchocerciasis.

Serious

General

Most adverse reactions to treatment with antifilarial drugs occur in the period shortly after the administration of the drug, i.e. usually "discomforting" and are short lived. Only when they persist, or are of severe intensity, do they become matters of medical concern. There have been one or two anecdotal reports of serious clinical responses that are consistent with classic allergic reactions to the drug itself. Given the number of doses (tens of millions) that have been administered in the Control Programs as a whole, true ivermectin drug hypersensitivity cases are extremely rare. The serious drug reactions are summarized in Table 1.

The situation in Cameroon: Associated with Loa loa co-infection?

An apparent exception to the ivermectin success story has been the situation involving the exceptionally serious CNS reactions observed in a small number of people, and proposed to be related to the presence of concurrent high burdens of *Loa loa* Mf. In 1996, cases of coma and death began to appear in Cameroon [5–7,16,17]. To date, 46 cases of this syndrome have been recorded, with 22 fatalities. The condition has probably been under-reported, with possibly up to 80 fatalities out of ~300 cases of the syndrome actually having occurred in Cameroon (Boussinesq, personal communication). Limited medical information is available on most of the cases due to the rural location in which the cases occurred and the understandably minimal local medical support system at hand. The fatalities in Cameroon occurred with patients who had high loads of circulating *L. loa* Mf, and this association has raised great concern among local medical officials, program directors and the scientific community alike. These cases have been defined as "*Loa loa*-associated adverse reactions" and have the characteristics of a gradually developing encephalopathy (Table 3). It is important to note that co-infection with *O. volvulus* and *L. loa* is found in many other regions, and that these kinds of very severe reaction have only been reported from Cameroon. The apparent geographic restriction of the phenomenon must be incorporated into any analysis of the pathology of this condition.

Serious CNS pathology has been previously reported with DEC treatment of patients with *Loa loa* infection; these have some clinical similarities as the current Loa-associated cases treated with ivermectin. Ducorps and colleagues [18] reported significant adverse reactions in patients with loiasis, particularly those with >30,000 mf/ml in their circulation; these changes included fever, pruritus, headache, arthralgia, disturbed consciousness (obnubilation), as well as the more significant coma and renal impairment. The symptoms in these cases occurred a little earlier than those with ivermectin (i.e. within 24–

Table 3: Major clinical characteristics of patients with loa-associated adverse reaction syndrome – "loa encephalopathy" *

PRESENT:
• Comatose condition with 4 days of treatment with ivermectin
• Microfilariae blood levels > 8000 Mf/ml
• Resident in an onchocerciasis meso- or hyper-endemic area
• Early fever
• Developing neurological symptoms and signs
• Gradual worsening (to coma) (basal ganglia)
• Retinal or conjunctival hemorrhages +/-
• Renal damage +/-
• Drop in Mf load
• Movement of Mf into CSF and urine (extra vascular)
OUTCOMES
• Coma – encephalopathy
• Death
• Secondary infections (poor nursing)
• Hypoglycaemia
• Persistent fever, sepsis
• Dehydration
• Abdominal pain
• Urinary complications
OTHER SIGNIFICANT OBSERVATIONS:
• No dermal reactions
• No acute Mazzotti reactions
• No allergic phenomenon (obvious non-parasitic, lung wheezing etc.)
• No cardiac complications
• No hepatic involvement (?)
• No bleeding
• No cerebral edema
• No fundal edema
• No convulsions

* Adapted from Reference [17].

36 hr of dosing) but did show progressing neurological severity. Other reports such as that of Carme *et al*., [19], which presents 5 cases showing fever and coma 9–18 days after DEC treatment (with one at day 3) have distinct similarities to the present cases. Downie [20] has also reviewed cases of complications after DEC treatment in loiasis patients. Thus there may be a similar etiologies in the pathology induced by these two drugs, i.e. the effects being primarily related to the death of microfilariae in CNS tissue and ensuing inflammation.

Eye lesions have been reported after DEC treatment of loiasis patients, as is seen in the current ivermectin cases in Cameroon. Toissant and Danis [21] found retinal hemorrhages and saccular microaneurysms associated with the degeneration of the associated cells such as pericytes. Mf were associated with at least 25% of these lesions. Likewise, hemorrhages have been seen in the conjunctiva and the retinal fundus of the current ivermectin treated Loa patients [22]. Importantly, these vascular lesions closely resemble ocular findings in malaria where it is believed that parasitic micro-emboli are an integral component of their pathogenesis. These, therefore, may represent the results of microemboli of *Loa loa* Mf. Interestingly, *Mansonella perstans* Mf were seen to be associated with the presence of the lesions [23] in the DEC cases, but this observation requires substantiation.

Other records of CNS and ocular pathology exist in relationship to the presence and treatment of loiasis. Of special interest is the report by Langois et al., [24], who showed obstruction to the central retinal artery in loiasis. Other reports describe various forms of neuropathology, including encephalitis, cerebral destruction with clinical hemiplegia, meningitis, and peripheral neuritis [25,26]. In the current cases reactions in the cranial cavity to drug-damaged adult parasites should not be ruled out, as severe and fatal outcomes occur in other CNS nematodiases, such as infections with *Angiostrongylus cantonensis*. There is, however, little evidence for a short-term adulticidal activity for ivermectin.

The similarities between these DEC-induced microfilariae-related pathologies and those that are appearing in the patients with the present Loa-associated syndrome support the hypothesis that the SAE in the latter group involve pathology associated with microfilarial death and destruction.

Possible pathogenic bases for adverse reactions seen after chemotherapy

In general the possible causes of the adverse reactions associated with antifilarial drugs can be considered in two major groups: pathological events and mechanisms involving a) the drug having a direct toxic effect on the host, and those involving b) the parasite-drug interaction effecting the host (Table 4).

Ivermectin and its structural analogs have been given to tens of millions of people and hundreds of millions of animals, with remarkably few severe reactions. Toxic consequences of administration of standard doses of a drug generally have two primary explanations:

1) The toxicity represents natural variation in sensitivity to any chemical compound, and represents a linear scale from trivial to serious [27].

2) Alternatively, toxicity is unrelated to more common untoward effects, and reflects a unique pharmacological action of the drug that could not be anticipated as simply the outer fringe of the normal distribution of responses (either therapeutic or toxic). In such a case, the toxic consequence represents an idiosyncratic response.

Table 4: The parasite and host mechanisms possibly involved in loa-associated encephalopathy

PARASITE RELATED MECHANISMS
• Massive movement and death of parasite clumps in vessels → embolic blockage → local vascular inflammation and subsequent tissue damage in sensitive tissues (similarities to malaria)
• Reactions against dying adult worms or wandering larvae?
• Due to two or more parasite species being present
PATIENT RELATED MECHANISMS
PATHOLOGICAL
• Effects of alcohol (co-administration and/or chronic changes)
• Effects of food (co-administration)
• Gut disease (increasing uptake)
• Altered processing (liver damage)
• Other co-existent infections or disease processes
• CNS Toxicity (overdose)
• Allergic drug sensitivity (rare)
GENETIC
• Blood Brain Barrier Alterations
Mdr1 mutation – homozygous
Human equivalent to dogs, mice, knockout mice and cattle
• Polymorphism to inflammation
Pro- versus anti-inflammatory cytokine expression
• Genetic predisposition to microfilariaemia

The serious clinical events observed in this Cameroonian group represent a tiny percentage of the total treated population. The most striking consequence is the onset of coma. This response could not have been easily anticipated since adverse neurological effects have not been described in treated populations. That is, we see no evidence for an escalating incidence of side effects, progressing from mild sleepiness or dizziness through slurred speech and ataxia to frank coma, in any population treated with ivermectin. Therefore occurrence of coma in these patients likely reflects an idiosyncratic response, one that could not be anticipated from the more common side effects seen in other patients in this same population or in populations treated for similar infections (e.g., lymphatic filariasis).

Given that the mechanism of microfilaricidal activity of ivermectin requires the intervention of immune effectors, there are two possible explanations for an idiosyncratic response to the drug in dually infected patients:

1) The response has nothing whatsoever to do with parasitism, and would be observed in these patients even if they were free of filariae, or

2) The response reflects an atypical outcome of the immune response to Mf in the presence of ivermectin. These possibilities must be evaluated in light of clinical experience obtained with ivermectin in veterinary and human medicine.

The target for the antiparasitic effects of ivermectin is a group of glutamate-gated Cl^- channels unique to invertebrates [28], which this drug profoundly and persistently opens. This action disrupts the regulation of transmembrane potential in invertebrate neuromuscular systems, leading to paralysis of critical muscles and the consequent demise of the organism. However, the drug also potently opens structurally related Cl^- channels that are gated by GABA [29], which are broadly expressed in the mammalian CNS. The remarkable therapeutic index of these compounds in mammals is due only in part because mammals completely lack glutamate-gated Cl^- channels. Instead, mammals are protected from ivermectin toxicity not by the absence of the molecular target, but by the presence of an effective blood-brain barrier that prevents access of the drug to a susceptible protein target in the CNS [30–33].

Work done in knock-out mice revealed (inadvertently) that exclusion of ivermectin from the CNS is due solely to the function of a specific subtype of P-glycoprotein, a protein family that translocates hydrophobic compounds across cell membranes (associated in the past with resistance of tumor cells to anticancer drugs). Disruption of the *mdr*1a locus in mice rendered them highly sensitive to ivermectin toxicity when the drug was given to control an outbreak of parasitism in the transgenic colony [34]. The primary toxicity was coma. That a small percentage of certain breeds of dogs (some collies and shepherds) also became comatose when dosed with ivermectin for heartworm prevention had also been long known [35]. Recently, it has been shown conclusively that susceptible dogs have inactivating mutations in the *mdr*1a gene [36,37]. The consequence of allowing ivermectin accumulation in the brain is a prolonged and progressive CNS intoxication in both dogs and mice, resulting in coma.

Could a similar phenomenon explain the apparent idiosyncratic toxic reactions observed in Cameroon? It would not be surprising to find that loss-of-function *mdr*1a mutations exist in humans, as they do in dogs. There is no evident phenotype for the mutation in dogs other than acute sensitivity to ivermectin and a few other drugs. It would also not be surprising to find that such a mutation would be geographically restricted [40], found perhaps at a detectable frequency in one or a few populations exposed to ivermectin (a rare event in wealthy countries). Indeed, one might almost predict the eventual appearance of ivermectin toxicity in a human population from an analysis of the situation observed in canines.

It would be relatively simple to rule out the possibility that loss-of-function mutations in the human *mdr*1a gene underlie ivermectin toxicity. The sequence of this gene is known and it could be cloned from peripheral lym-

phocytes obtained from survivors of ivermectin-induced coma or relatives of victims (the phenotype is probably recessive, so heterozygotes may be unaffected and would be more common in the local population). Analysis of this locus will reveal whether lessons learned from dogs can be usefully applied to humans. Given the background and overall resemblance of the syndrome in dogs and affected humans, the conservative approach is to first determine whether a common molecular basis exists.

If this hypothesis proved to be correct, treatment programs could be continued without regard to coincident infections with *L. loa*. There is no simple and cheap diagnostic test that could pre-screen local populations that had not yet been dosed with ivermectin for evidence of *mdr*1a mutations. However, the phenotype is, on the evidence, exceedingly rare, and treatment could resume as long as the incidence of CNS sequelae following treatment was closely monitored. It is conceivable that a cost-effective PCR-based diagnostic test could be implemented to identify individuals in villages where serious adverse reactions were observed who should be excluded from treatment.

The possibility of the adverse reactions being directly related to microfilarial events, such as their death and destruction, has been proposed. In all likelihood antimicrofilarial agents such as DEC and ivermectin function either in conjunction with, or at least enhanced by, host immunological or inflammatory components. It is important to note that neither DEC nor ivermectin have detectable effects on microfilarial motility or viability in culture at pharmacologically relevant concentrations. Understanding how these drugs work to stimulate immune-dependent killing of Mf is an important step in clearly understanding the clinical reactions associated with them. Conversely we should also understand how these relatively large parasites manage to survive in large numbers without attracting attention from the host immune system. The mechanisms by which these parasites suppress recognition and destruction by the host must be the targets for DEC and ivermectin. Unfortunately these questions are difficult to address.

The clinical presentation of these patients and a consideration of the literature points clearly to the involvement of an inflammatory process, this probably leading to the coma and possibly hepatic dysfunction. One line of investigation would be to determine if the individuals suffering from the adverse effects have a perturbed cytokine response that predisposes them to an excessive inflammation. These individuals could be typed for cytokine profiles; this could be done retrospectively on survivors of adverse incidents. If predisposition was found to be the case then it might be possible to screen high *Loa loa* microfilariae carriers to determine those at greatest risk; however, this may not be practical in the field situation. The possibility exists that gene-controlled variation in specific immune response lies at the base of these idiosyncratic reactions to ivermectin [38]. There are many factors that contribute to an individual's response at a particular point in time: including the parasite load, the state of immune system (its immunosuppressive or stimulatory state), as well as the ability or inability to efficiently clear killed parasite material. However, a major factor that may be at play in these cases is the individual's own genetic predisposition towards either TH1 or TH2 responses [39] when challenged by stimuli, i.e. an individual responds with a predictable profile influenced or guided by their genetics. It could be important to determine which of the polymorphic alleles of several cytokine genes governs this phenomenon. Individual genetic variation could therefore be important to understanding this clinical phenomenon. It may be that the affected individuals in these cases have a predisposition to drive inflammatory responses to dying Mf to clinically unacceptable levels in such sensitive target organs such as the CNS. The fact that not all of the individuals with high microfilarial loads are affected by the encephalopathy is interesting in this light.

Approaches to the Problem

There is a medical and moral need to move quickly to the next step of proposing actions regarding these SAEs. These actions include managerial and political activities, but there are also scientific questions that must be answered to provide a more rational approach to this problem. To put this problem in perspective it should be noted that in the drug industry, this level of adverse reactions (1 case in 12,000,000 administrations) would be regarded as being comparatively low. Nevertheless, it is important consider the ramifications of the toxicity from the perspective of the state or community in which they occurred, and their immediate implications for onchocerciasis control programs there and elsewhere. There is an urgent need to proceed to a policy based on practical action to moves us ahead. What this action should be is open for discussion, but there a number of options and possibilities. The authors believe they must include research to better understand the scientific basis of the phenomenon, as well as steps that lead to responding to the field situation with appropriate levels of assessment and monitoring.

It is important to discriminate among the possible explanations for the pathogenesis of the *L. loa* associated syndrome, whether or not further fatalities unfortunately occur. It would be straightforward to examine the possibility of genetic polymorphisms in *mdr*1a genes or inflammatory responses in a population sample obtained from the geographic locale of the main cluster of cases. Careful prospective monitoring of the geographic distribution of

the occurrence of CNS reactions after ivermectin treatment in loiasis patients across the endemic areas will confirm or disprove the geographic restriction of the SAEs, pointing to human genetic variation as a key explanation of the syndrome. Further work to characterize the possibility of a micro-embolic pathology similar to that seen in malaria is also important. Direct examination of CNS tissues will reveal crucial data; core sampling of brain tissues after death, which requires minimal invasion of the body, is arguably the best approach. CSF fluid should be monitored for cellular content, glucose content and proteins such C-reactive proteins. Other potentially useful laboratory parameters include ivermectin concentration in CSF, eosinophil products and indicators of fibrin deposition, fibrin degradation products (FDPs), endothelial and platelet activation and hemorrhage.

What is the most likely pathogenesis?

Two major explanations for the fatal SAEs associated with *L. loa* infections in Cameroon currently seem the most feasible. Firstly, that the condition is directly related to *Loa* microfilariae and the development of a CNS centered micro-embolic vascular pathology with associated inflammatory reactions due to the parasite death and the intravascular clumping (supported by the clinical evidence of retinal and conjunctival hemorrhages); this has parallels with the micro-embolic events seen in malaria. Such events may be more severe in patients with a predisposition to excessive inflammatory responses occurring with microfilarial death. There may be predisposition for *L. loa* Mf to be trapped specifically in the CNS vasculature, promoting problems in this organ when chemotherapy begins to destroy the parasites. Increased migration of Mf appears also to be an important event after therapy and this may enhance the formation of embolic inflammatory foci of the dying parasites. The timing of clinical manifestations of the ensuing inflammatory and anoxic pathology after the 3rd and 4th days of treatment supports this theory.

Secondly, there may be a genetic susceptibility in the affected patients that allows ivermectin to accumulate in the CNS, causing a toxicity similar to that seen in dogs and mice. The apparent geographic clustering supports this hypothesis of a genetic predisposition and one cannot help but wonder if the human equivalent of the mdr-1 abnormality described in animals has now been found in humans. A genetically influenced inability to handle and absorb parasite induced-inflammation might also be in play.

Other mechanisms could very well be at play, but much more detailed clinical and pathological analyses is needed before definitive statements can be made about the cause of these fatal SAEs. Confounding circumstances appear unlikely. No association with locally common infections (such as malaria) has been seen. The only parasitic infection so far correlated with the occurrence of the serious reactions is loiasis; nonetheless, it would be wise to keep open the possibility of other co-infections. It has been suggested that alcohol intake may play a role in predisposing individuals to develop severe reactions to ivermectin by changing its pharmacokinetic behavior. However, this does not appear to be the case, as locally produced alcoholic beverages do not increase blood levels of ivermectin (Homeida et al., unpublished).

Any research-oriented approaches to addressing this problem should be matched with actions at the community level. These should include the establishment of clear medical guidelines for the responding medical and support staff, improving procedures to screen for high Mf load carriers, and developing better messages for the people living in the endemic areas where these fatalities occur. It is essential to address the medical, public and political challenges that the ivermectin-associated serious adverse reactions present, and to thus ensure the continuation of a medically sound chemotherapy program.

Competing interests

None declared

Author's contributions

Author 1 (CDM) led the authorship of the manuscript. Author 2 (JG) and 3 (TGG) both contributed text and ideas.

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