Importance of ivermectin to human onchocerciasis: past, present, and future

Cupp EW, Mackenzie CD, Unnasch T. *Research and reports in Tropical Medicine* 2011,2:81-92

Introduction

Ivermectin (IVM), donated as Mectizan® by Merck &Co Inc, is safe and highly effective in killing *Onchocerca volvulus* (Ov) microfilaria (mf), the causal agent of onchocerciasis or river blindeness. IVM has been used for more than 22 years for mass treatment to control or eliminate onchocerciasis in endemic countries which culminated to more than 800 million doses administered to over 80 million people. Consequently onchocerciasis has been significantly reduced in over 25 countries, transmission interrupted in foci in at least 10 countries and no new infection seen in children in many countries. However, concerns were raised on IVM efficacy after several reports from Ghana, describing suboptimal responses to IVM alluding possible resistance. The authors of this paper reviewed the peer-reviewed scientific articles with the recent findings from the technical consultative committee of the African Program for Onchocerciasis Control (APOC) to provide alternative explanations to the phenomenon and to suggest treatment strategies to prevent resistance.

Suboptimal response-Is it resistance?

Different explanations for the reported suboptimal responses: A) A small proportion of adult female worms may intrinsically be insensitive or tolerant to the paralyzing effect of IVM, which can show "a higher than normal rate of skin repopulation by Ov mf". This phenomenon was occasionally observed in IVM-naive individuals. B) It was suggested that IVM resistance was developing on the basis of doubling of the nonresponders between 2000-05. However, the annual transmission potential found in the areas was ≥45 L3s, which suggested that many of the suboptimal responders lived in areas where transmission was at least five times higher than necessary level (8 L3s per person per year) to maintain Ov population. This might have been due simply to failure to achieve adequate drug coverage or that young, highly fecund worms recovered more quickly from treatment. The former was confirmed by an APOC evaluation that the treatment coverage had been a major issue, either not treated or inconsistent in those villages before the original studies. C) The variation of immune response to mf killing in human individuals may be another contributor to the suboptimal response. This phenomenon was observed in other places.

Conflation of resistance in veterinary parasites with Ov

Resistance to IVM developed by *Haemonchus contortus* a parasite of small ruminants is often wrongly cited as basis for comparison. *H. contortus* has a direct life-cycle and completes development in about 30 days while Ov has a long life-cycle 12-16 months and requires a vector for development. The low infected vector survivor rate would limit the flow of Ov resistant alleles. Ov has at least 12 times slower gene flow in a much larger geographical area with a much low gene selection pressure.

What vector-transmitted parasites might be harbingers for IVM-resistance in Ov?

The genus *Dirifilaria* is a sister group phylogenetically related to *Onchocerca*. Controlled laboratory trials suggest that the IVM efficacy to prevent *D. immitis* (dog heartworm) infection has diminished after over 30 years of use. However there are several important dissimilarities between the two species: different hosts (canine *vs* human), different life spans with different pre-patent times (6 months for *D. immitis vs* 12-16 months for Ov), different sensitive stages to IVM (L3 and L4 for *D. immitis vs* mf and adults for

Ov), and most importantly, different dosing schedules hence exposure rates (monthly for *D. immitis* vs annually for Ov). Other close indicator species (exclusively veterinary parasites) to Ov include *O. lienalis*, *O. gutturosa*, *O. Gibson* and *O. cervicalis*, but no IVM resistance has been reported after over 25 years of use in these species.

Genetic evidence for resistance selection

There are absence of a clearly defined phenotype for IVM resistance, lack of a convenient laboratory host for Ov, and lack of tools to genetically manipulate Ov, which make it impossible to study association of specific parasite genotypes with resistance directly. Most studies on IVM resistance in Ov have thus focused on allelic frequency changes in certain genes hypothesized to confer resistance. However, the significance of these changes in the development of resistance remains unclear, and may result at least in part from genetic bottlenecks resulting from mass drug treatment and disruption of the normal mating behavior of the parasite. Studies also suggested host genetic differences as an important component in the variable drug response to IVM.

The refugium and resistance selection in Ov

It is believed that by maintaining a sufficient quantity of susceptible alleles to pair with resistant ones, robust selection for drug resistance can be prevented or decelerated. The refugium is the parasite population not exposed to the control measure and is composed of various stages of parasites not affected by the treatment or residing in untreated hosts and free-living environment. Thus the larger the refugium is, the more it would offset resistance. In the Ghana situation, with low coverage one would expect a large refugium which would hinder the development of resistance.

Recommendations for further actions:

Studies in chimpanzees: To date, there is no direct proof that resistance to IVM by Ov exists. Chimpanzees can develop patent Ov infection and simple methods are available to infect them. The model can be used in a controlled environment free from confounding effects to confirm or refute the existence of resistance.

Entomological monitoring and genetics of IVM resistance: To explore genetic changes, monitoring L3 to assess should be conducted for allele frequency and Hardy-Weinber equilibria of potential resistance loci as L3 is most likely to show genotypic evidence of resistance soon after mass treatment. Studies using free living nematode *C. elegans* suggested that resistance to IVM had been linked to specific peptides encoded by avr-14 and avr-15 genes. The homologs are also present in Ov genomes. Studies are recommended to determine if such resistance alleles confirmed in *C. elegans* exist in Ov after long-term IVM exposure.

Search for a macrofilaricide: Given IVM's sole drug status and complication with *Loa loa*, continued search for new drugs and "reposition" of old drugs are needed. Moxidectin is a promising drug in Phase III trials, but structural similarity to IVM makes it vulnerable to similar resistance if it does occur. Its registration for public health use and prospect for donation are uncertain. Safe formulation of flubendazole is also under development. The old drug Closantel has been shown to prevent the L3 molting to L4 which has a limited window for action and range of activities, thus the usefulness for mass drug treatment is limited.

New strategies: Twice a year treatment has been proven to be effective with high coverage and has interrupted transmission in the Americas and in certain foci in Mali and Senegal in Africa. The strategy also has a macrofilariacidal effect. Such strategy with coverage of 85% or more could resolve the problem of suboptimal responders. However, proper guidelines for treatment frequency should be established based on epidemiological, biological, and empirical facts.

Conclusion

IVM has made groundbreaking contribution to public health programs in developing countries, but monotherapy for Ov carries the risk of resistance. Therefore effort should be made to monitor any resistance, to develop strategies to minimize the risk, and to search for new drugs.

Editor's Comments

The unprecedented Mectizan® donation and the distribution system for onchocerciasis control has set a model for health care in many rural areas in developing countries and changed the face of tropical disease control. Elimination of onchocerciasis has been the goal in the Americas since 1991 with IVM mass distribution. As of today, 7 out of the 13 foci have stopped treatment and are under surveillance. Onchocerciasis is also a major public health problem in Africa where 99% of the world population at risk of onchocerciasis lives. The goal of onchocerciasis control in the African region is now also shifted to elimination building on the success of the last decades. As IVM is currently the only drug for onchocerciasis control, some published studies have raised concerns about potential drug resistance. However, as the authors explored in this paper, it is vital for the scientific community to address such an issue of potential IVM resistance with great care, make the best assessment and develop strategies to address resistance should the resistance does happen.

According to the current scientific evidence as discussed in the paper, the emergence of resistance is still not certain. However there is indeed a potential risk of resistance in the long-term given the sole drug status and as shown in other disease models. To prevent or delay this from happening, strict monitoring of drug efficacy should be conducted while search for new drugs is going on. As the treatment coverage is one of the key determinants of a successful mass treatment program to control and eliminate onchocerciasis, the program managers in endemic countries need to make sure the good coverage achieved and correctly reported. New WHO guidelines for treatment strategies may also be needed to minimize the risk of resistance.

Recommended readings

African Programme for Onchocerciasis Control (APOC): Fifteen Session of the Joint Action Forum-Tunis, Tunisia, 8-10 December 2009; Final communiqué (http://www.who.int/apoc/about/structure/jaf/JAF15_Final_Communique.pdf)

Gustavsen K, Hopkins A, Sauerbry M. Onchocerciasis in the Americas: from arrival to (near) elimination. Parasites & Vector 2011, 4:205

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