# River Blindness: An Old Disease on the Brink of Elimination and Control

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## ABSTRACT

For decades, onchocerciasis (or river blindness) was one of the most common infectious causes of blindness in the world. Primarily an infection of Africa, with limited distribution in the new world, disease due to the nematode *Onchocerca volvulus* is rapidly diminishing as a result of large public health campaigns targeting at risk populations in Africa and the Americas. Existing and newly-developed treatment strategies offer the chance to eliminate onchocercal ocular morbidity in some parts of the world. This article reviews these treatment strategies, current clinical and epidemiologic aspects of onchocerciasis, and the next steps toward elimination.

**Key words:** Doxycycline, Ivermectin, Onchocerciasis, *Onchocerca volvulus*, River blindness, *Wolbachia*

## ONCHOCERCIASIS EPIDEMIOLOGY AND TRANSMISSION

Onchocerciasis is the second leading infectious cause of blindness in the world, after trachoma.[1] For centuries, *Onchocerca volvulus* has infected humans causing severe skin and eye disease. Transmitted by the bite of the *Simulian* sp. black fly, the disease is prevalent in 19 African countries, and endemic in now just six American foci. In total, 37 million people are thought to have active disease, with nearly all such cases in Africa where over 100 million people live at risk of new infection.[2,3] This old world disease originated in Africa and spread to New World *via* the slave trade, where it formerly existed in 13 discrete geographic foci within Latin America.[4,5] Over 500,000 individuals live with a significant visual impairment from the disease, with an additional 270,000 individuals who have suffered from complete vision loss.[6]

*Onchocerca volvulus* lives only in humans, making it a good candidate for elimination. The *Simulian* vector is infected when biting infected humans, and after maturation of larva within the fly, can then re-infect others during subsequent blood-meals. These flies breed within and live around fast-flowing rivers (hence the name "river-blindness"), and generally only persons living in and around these areas are at risk for infection after repeated biting. Transmission efficiency of most *Simulian* species is quite low relative to other diseases (e.g., *Anopheles* mosquito with malaria), although variable between regions, such that travelers are generally not at risk for this infection unless living long-term in endemic areas.[7]

Once deposited within the skin, infective stage larvas maturate and trigger the development of fibrous subcutaneous nodule in which they will mate and reproduce. Annually, female adult worms can release hundreds of thousands of microfilariae (MF) that migrate freely through skin with the potential for reaching and invading the eye. In the skin, MF cause pruritis and dermatitis, and eventually can lead to skin atrophy and discoloration ("leopard skin"). In the eye, repeated MF insults can lead to significant intraocular inflammation and subsequent eye damage.

## THE OCULAR PATHOLOGY OF ONCHOCERCIASIS

The ocular pathology of this disease occurs in both anterior and posterior segments of the eye. Anteriorly, MF travel

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through scleral and subconjunctival tissues to reach the cornea whereby they attempt to penetrate and migrate through the cornea. Within the corneal stroma, MF can die and release *Wolbachia* sp. bacteria, an intracellular, rickettsia-like bacteria that lives symbiotically with MF and adult Onchocerca worms.[8,9] Interestingly, these organisms are extremely important to the lifecycle and reproduction of Onchocerca, and without them, female adult worms cannot reproduce.[10] Within the cornea, as with other tissues, release of *Wolbachia* elicits an immune response and inflammation.[11,12] This process clinically appears in the cornea as a punctate keratitis (PK), lesions that gradually resolve over 2–3 months as the MF are degraded by immune cells. The prevalence of PK has served as the cornerstone for evaluating the progress of mass ivermectin therapy during recent elimination campaigns in the Americas.[13] Repeated MF-associated corneal insults eventually lead to sclerosing keratitis (opacification and scarring of the cornea), a major cause of onchocercal-related visual loss. A large proportion of visual morbidity and blindness caused by this disease, however, is due to posterior pole lesions that persist even after ivermectin therapy.[14-16] In the posterior segment of the eye, MF invade retinal tissues causing chronic chorioretinitis, inflammation, scarring, and in some cases optic atrophy and glaucoma. It is likely that dying MF in these tissues trigger an inflammatory response there, one that is potentially promoted by cross reactivity between *O. volvulus* antigen (Ov39) and human retinal pathogen (hr44) found in the optic nerve and neural epithelial layers of the retina.[17-19] Interestingly, Onchocercal chorioretinitis continues despite ivermectin therapy and extermination of the parasite from the eye, potentially as a result of an autoimmune response provoked by the parasite.[14,20]

## DIAGNOSIS AND CLINICAL MANAGEMENT OF ONCHOCERCIASIS

Diagnosing onchocerciasis relies on demonstration of characteristic eye pathology (visible MF in the cornea or anterior chamber) or demonstration of MF within the skin. On the individual level, visible MF in the anterior segment are specific to onchocerciasis; however, it is often difficult to observe MF in the anterior chamber, and punctuate keratitis lesions are fleeting and can be nonspecific for onchocerciasis if the degraded MF is not visible within the lesion.[21] At lower levels of microfiladermia, ocular lesions are rare and are less likely to be present. Skin-snips, a superficial (dermal) biopsy of 1–3mg, examined microscopically for MF are invasive and suffer from poor sensitivity in patients with low levels of microfiladermia. PCR examination of skin snips improves this situation, although sensitivity is still low in such persons, making this tool less useful in endemic areas where ivermectin has been used to treat this disease for years.[22,23] Skin patch testing with diethylcarbamazine (DEC) has been shown as a good alternative to skin snip evaluations in Africa. This test relies upon DEC killing of MF within the dermis and subsequent provocation of a hypersensitivity reaction (i.e., localized Mazzoti reaction). Advantages over skin snip evaluation (noninvasive, better patient acceptance), although can be operationally difficult (patches can fall off, patients must return in 24 h for test reading). The sensitivity and specificity of the DEC patch test is not yet clear, although recent studies using newer formulations suggest its utility in monitoring for infection within mass onchocerciasis treatment programs in Africa.[1,24,25] Serologic antibody tests using recombinant antigens, such as the OV-16, can be useful, but cannot distinguish between past and active infection.[26-29] In addition, the sensitivity of this assay is questionable, with at least one study showing that a large percentage of those with active eye disease living in endemic areas have negative OV-16 results.[21] A highly specific antigen detection test capable of diagnosing active infection has been reported in the literature, but to date, has received little evaluation.[30] The development of a highly specific and sensitive test capable of determining active onchocercal infection remains an imperative for public health campaigns seeking to control and eliminate this parasite.

### Antifilarial therapy

The development of a safe and effective macrofilaricidal drug has been long sought for this disease. For years, ivermectin, a macrocyclic lactone, has been the mainstay of therapy; however, ivermectin kills only the MF.[31,32] In effect, ivermectin serves as a birth control device for adult worms, in that female worms are temporarily sterilized for an average of 6 months, preventing the release of MF during that time. Consequently, periodic single dose oral treatment prevents the onset of new ocular and dermal lesions and reduces transmission as the vector is less exposed to MF during its feeding on human skin.[33] Ivermectin is excluded from the eye by the blood–ocular barrier, thus avoiding intraocular killing of MF and subsequent intraocular damage due to inflammation. Newer lactones in development include moxidectin that has shown some potential as a macrofilaricide.[34,35] However, new therapies targeting the endosymbiotic *Wolbachia* within the adult worms have now been proven to be effective in causing long-term (and potentially permanent) sterilization of adult worms and early worm death. Doxycycline treatment (100mg/day) for 6 weeks with a single dose of ivermectin has become the treatment of choice for individuals based on recent clinical trial data,

although 4 week courses of doxycycline or rifampin are also effective [Table 1].[36,37] From a public health perspective, however, the mass treatment of affected populations with doxycycline is difficult given the length of necessary therapy and the potential for re-infection in endemic areas. However, these therapies may be of particular use in areas of co-endemicity with loiasis where mass distribution of ivermectin is complicated by potential adverse events in patients co-infected with loiasis.[38]

## CONTROL AND ELIMINATION OF ONCHOCERCIASIS

Two large public health campaigns currently operate worldwide with goals of either elimination or control of this parasite. The cornerstone of these campaigns is the mass distribution of ivermectin, delivered semi-annually or annually, and donated in perpetuity for this cause by Merck.[39] When ivermectin is delivered as such in the long-term, sustained fashion to large percentages of at risk populations (e.g., >85% is the goal in Latin America), dermal MF levels fall such that new eye lesions and transmission are prevented.[7,40,41] The African Programme for Onchocerciasis Control (APOC) currently strives to eliminate onchocerciasis as a "public health concern" by delivering ivermectin to populations where dermal MF prevalence of ≥40%.[39,42] Recent studies in Mali and Senegal indicate a tremendous reduction in microfilaridermia and a profound reduction in the prevalence of black fly infection indicating that elimination is feasible in at least some African foci.[24]

**Table 1: Studies evaluating the efficacy of antibiotic therapy directed at onchocercal endosymbiotic *Wolbachia* bacteria**

| Authors | Year published | Country | Sample size | Setting | Outcomes |
|---|---|---|---|---|---|
| Turner *et al.*[46] | 2010 | Cameroon | 104 subjects | Doxycycline 200mg/day for 6 weeks alone, *vs.* Doxycycline 200mg/day for 6 weeks + Ivermectin 150 µg/kg (4 months after Doxycyclin); *vs.* Ivermectin alone | 1 year of follow up: Doxycycline + ivermectin had lower skin microfiliaria prevalence (23.9%) than doxycycline (61.9%) and ivermectin only (78.4%), *P*<0.005. 21 months of follow-up: skin microfiliaria prevalence was smaller in the Doxycycline + ivermectin (10.9%) and doxycycline alone (33.3%) than the ivermectin group (78.4%), *P*<0.05. |
| Hoerauf *et al.*[47] | 2009 | Ghana | 30 subjects | Doxycycline 100mg/day for 5 or 6 weeks *vs.* control (untreated) | (A) Worms: Doxycycline group had more dead female (49% *vs.* 16%, *P*<0.0001) and male (27% *vs.* 5%, *P*<0.034) worms than untreated group. (B) *Wolbachia*: Doxycycline group had 24% female and 38% male worms containing *Wolbachia*, while the untreated group had 98% and 86%, respectively (*P*<0.0001). * The authors considered that worms containing several *Wolbachia* acquired the bacteria after Doxycycline treatment. |
| Specht *et al.*[48] | 2009 | Ghana | 72 subjects | Doxycycline 100–200mg/day for 4, 5 or 6 weeks *vs.* control (untreated), followed by ivermectin | Only worms acquired after Doxycycline treatment showed microfiliaria production; only newly acquired *O. volvulus* were classified as having several live *Wolbachia* |
| Hoerauf *et al.*[37] | 2008 | Ghana | 67 subjects | Doxycycline 200mg/day for 4 or 6 weeks (*vs.* placebo only), followed by Ivermectin (150 µg/kg) 6 months later | Skin nodules: (A) Quantitative PCR: Reduction on *Wolbachia* load in worm tissue in both Doxycycline groups compared to placebo (*P*<0.05). (B) Immunology: At both treatment groups, higher proportion of dead female worms compared to the placebo group (*P*<0.05) |
| Specht *et al.*[49] | 2008 | Ghana | 26 subjects | Three groups: Rifampicin for 2 weeks, Rifampicin for 4 weeks, and control (untreated) | Reduction of *Wolbachia*-colonized female *O. volvulus* after 2 weeks (66%) and 4 weeks of Rifampicin (21%) compared to control (92%, *P*<0.0002) |
| Richards *et al.*[50,51] | 2007 | Guatemala | 73 subjects | Four groups: rifampin, azithromycin, rifampin + azithromycin, and control (vitamins). Drugs taken for 5 days, followed by Ivermectin (single dose). Patients evaluated 9 months later | No significant differences in the percentage of live females with *Wolbachia* and live females reproductively active (*P*>0.05) |
| Hoerauf *et al.*[52] | 2008 | Ghana | 40 patients | Azithromycin for 6 weeks (250mg daily, or 1200mg once a week), nodules examined after 6 and 12 months | After 1 year, the group that received 250mg daily presented a reduction of the number of female worms containing elevated number of *Wolbachia* compared to untreated patients (65% *vs.* 92%, *P*<0.0001) |
| Debrah *et al.*[53] | 2006 | Ghana | 60 subjects | Doxycycline 200mg/day for 2, 4 or 6 weeks; control (untreated). Some subjects received Ivermectin 150 µg/kg 8 months after first Doxycycline dose | Compared to controls, reduction in skin microfiliaria load seen in the 4-week group (*P* = 0.0039) after 1.5 years of first dose. |
| Hoerauf *et al.*[54] | 2003 | Ghana | 99 subjects | Doxycycline 100mg/day for 6 weeks or control (no treated), followed by ivermectin 2 or 6 months later | Reduction of live female worms with numerous *Wolbachia* compared to the control group (88% *vs.* 0–2%, *P*<0.0008); reduction of number of female worms with microfilariae production compared to controls (56% *vs.* 1–4%, *P*<0.0001); reduction of number of male worms containing sperm after 11 months of first dose of doxycycline, compared to control (89% *vs.* 63%, *P*<0.002) and number of female worms containing sperm in their uterus (56% *vs.* 15%, *P*<0.002) after 11 months of first dose of doxycycline. |
| Hoerauf *et al.*[36] | 2001 | Ghana | 88 subjects | Doxycycline 100mg/day for 6 weeks; Ivermectin 150 µg/kg | Group that received ivermectin + doxycycline had a smaller microfilaridermia than ivermectin only, after 1 year of initial treatment (0.22 *vs.* 1.89 microfiliaria/mg skin, *P*<0.0001) |
| Hoerauf *et al.*[10] | 2000 | Ghana | 35 subjects | Doxycycline 100mg/day for 6 weeks *vs.* control (untreated) | Skin nodules: Treatment group had fewer female worms (*P*<0.03), fewer live females containing *Wolbachia* (*P*<0.0001), fewer live females with intact embryogenesis (*P*<0.0001) than control group and fewer nodules with live microfilariae (*P*<0.0001) |

In the Americas, the Onchocerciasis Elimination Program for the Americas (OEPA) strives to completely eliminate the disease by treating ≥85% of at risk persons with ivermectin every 6 months.[4] As of 2010, 7 of the 13 endemic foci have been declared free of onchocerciasis, treatment with ivermectin therapy has stopped, and surveillance for disease recrudescence will continue for 3 years prior to a declaration of disease elimination in these foci. Currently, active eye disease only exists within several foci within Venezuela and Brazil, where treatment coverage has been more recently increased and it is anticipated that elimination of eye disease in these areas will follow in subsequent years.[2]

As anti-*Wolbachia* therapy has been shown to be effective in clinical trials, its optimal use within these public health campaigns is not yet clear. Within Latin America, conceivably, anti-*Wolbachia* therapy could be used in limited circumstances either to "mop-up" or "catch-up" in regions that continue to have active disease or where ivermectin coverage has been less than complete. As elimination with ivermectin looms near in Latin America, however, it is not clear that such alternative therapies will ever be needed.[43] Within Africa, at least one large scale community directed treatment program using doxycycline has been reported.[38] As with Latin America, a role for mass doxycycline therapy there has not yet been clearly defined, and might differ by region based on vector competence, parasite pathogenicity, public health capacity, and the ability to deliver 4–6 weeks of such therapy in mass fashion. Lastly, anti-*Wolbachia* would theoretically become very important in either region should the parasite develop resistance to ivermectin. Although ivermectin resistance has not definitively been reported, it remains a concern and anti-*Wolbachia* therapy offers an alternative should such an event occur.[16,44,45]

## FUTURE EFFORTS

In Latin America, OEPA has declared the year 2015 as a goal for the final year of mass treatment with ivermectin for onchocerciasis,[55] and in Africa great reductions in disease have been documented with mass ivermectin therapy. Although current progress with these mass ivermectin drug campaigns is encouraging, improved diagnostics and further development and evaluation of anti-*Wolbachia* and other drug therapies will improve the chances that these large regional public health initiatives will achieve long-term success.

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