The Promise of Wolbachia-Targeted Chemotherapy as a Public Health Intervention for Lymphatic Filariasis and Onchocerciasis

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(See the article by Turner et al. on pages 1081–9)

Great fleas have little fleas upon their backs to bite 'em
And little fleas have lesser fleas, and so ad infinitum.

—Augustus de Morgan

After the initial observations by Kozek [1] and McLaren et al. [2] that filarial parasites are themselves host to endosymbiotic bacteria, nearly 20 years passed before the discovery that tetracycline and other drugs that target Wolbachia species interfere with worm molting and fertility [3]. This rediscovery led to an explosion of interest in the contribution of these bacteria to the pathogenesis of filarial disease, as well as interest in the potential utility of antibiotics for chemotherapy of filariasis [4]. Initial trials of doxycycline for the treatment of onchocerciasis and lymphatic filariasis (LF) have shown that 6–8-week courses of doxycycline treatment reduce levels of both microfilaria and Wolbachia species [5–8]. More important, there is evidence that adult worm fertility is compromised and that viability also is reduced. The existence of an intervention that permanently reduces the reproductive potential of adult worms would represent a significant development for the global program to eliminate LF.

The global program to eliminate LF is an ambitious public health initiative that aims to interrupt transmission of filariasis by reducing levels of circulating microfilariae through annual mass treatment with albendazole plus either ivermectin or diethylcarbamazine. Fueled by what are arguably the largest drug donations ever for a public health program, the LF elimination effort has seen rapid growth in the number of persons treated and the number of participating countries [9]. Early results are promising: the programs are delivering important public health benefits, both through a reduction in transmission of LF and through dramatic decreases in the prevalence of hookworm and other intestinal helminths [10–13]. Mathematical models predict that the success of the elimination effort is a function of the initial infection prevalence, population coverage, and the effect of the drugs on the viability of adult worms [14, 15]. Unfortunately, only diethylcarbamazine shows any substantial adulticidal effect at the dosages used in the global program. The need for an adulticidal drug is even more acute in the onchocerciasis-control programs in which ivermectin is used, because adult worms can live for 10+ years. A new drug that kills or sterilizes adult worms would accelerate the pace of both programs and, in principle, could decrease their operational costs.

In this issue of Clinical Infectious Diseases, Turner et al. [16] report the results of a placebo-controlled trial of doxycycline for the treatment of Wuchereria bancrofti infection. Patients were treated for 3 weeks with doxycycline or placebo and were then administered ivermectin plus albendazole 4 months later. Outcomes analyzed included the effect of treatment on microfilarialaemia and on the occurrence of adverse events after standard treatment with ivermectin plus albendazole. The results show that 3 weeks of treatment with doxycycline is sufficient to reduce the microfilarialaemia...
level significantly in patients with W. bancrofti infection. It was equally important that no persons in the doxycycline arm of the study experienced moderate adverse events after receipt of treatment with ivermectin and albendazole, compared with 3 of 17 subjects in the placebo group. Although this difference was not statistically significant, it is an important observation that merits follow-up. Systemic adverse events, including headache, fever, and nausea, occur after treatment with ivermectin or diethlcarbamazine and have been attributed to the release of Wolbachia species from microfilariae [17, 18]. Although these adverse events are typically well tolerated and have a short duration, they tend to discourage compliance in large drug-administration programs. Because elimination of LF requires several years of high population coverage, adverse events are a potential threat to the program.

That a shorter course of chemotherapy may reduce the microfilaria level and the occurrence of adverse events is encouraging and provides an additional proof of the concept that Wolbachia species are an attractive target for drug interventions. Unfortunately, the length of treatment with doxycycline is still a stumbling block, especially from the public health perspective. Even a mere 3-week course of doxycycline is not a realistic public health intervention. Public health workers considering such an effort are faced with a difficult dilemma: whether to accept the increased distribution costs associated with multiple days of supervised chemotherapy or to accept the lower compliance that inevitably accompanies unsupervised treatment of more than a few days. It is worth bearing in mind that a 12-day course of diethlcarbamazine, the standard treatment for LF before the advent of single-dose therapeutic regimens for mass treatment, was not considered to represent a practical public health intervention for the same reason. Longer courses of treatment with any drug also raise the risk of adverse events. In addition, the potential effect of mass treatment with antibiotics on the development of drug resistance by nontargeted bacteria must also be considered.

Research is needed to develop additional drug interventions for the global LF program. Either sterilization or killing of adult worms would accelerate the success of the elimination program for LF and could make elimination of onchocerciasis in Africa feasible. Although developing drugs that kill adult worms directly would seem to be the better research strategy, there is a significant advantage to targeting Wolbachia species. From the biological perspective, sterilization of adult worms is as useful as killing them. In addition, because of the preferential location of adult W. bancrofti worms in lymphatic vessels of the spermatic cord of adult men, drugs with macrofilaricidal activity are associated with scrotal reactions that can be painful and can reduce compliance with mass drug administration [19]. In experimental models of filariasis, both intermittent therapy (i.e., monthly) and liposomal formulations of antibiotics have met with some success [20, 21]. Adaptation of such approaches for human filarial infections is a topic for future study.

Additional research on the mechanism of action of doxycycline and related drugs is also warranted. It is interesting that the effect of antibiotics on the filarial parasite may go beyond its effect on Wolbachia species. Rajan [22] has shown that chemically modified tetracyclines that lack chemo-therapeutic activity, nonetheless, interfere with the L3 to L4 molt in vitro. The implications of this observation for antifilarial chemotherapy are not clear.

Where could a multiple-week regimen of doxycycline be considered? As pointed out by Turner et al. [16], an extended course of curative treatment with doxycycline offers significant advantages for the treatment of individual patients—especially for patients with onchocerciasis for whom long-term reductions in the microfilariae level will prevent skin and ocular pathology. In addition, doxycycline may be useful as an adjunct to diethlcarbamazine therapy for patients with tropical pulmonary eosinophilia. Beyond these limited uses, we are anxiously awaiting the development of shorter-course treatment regimens that can be applied in field settings.

Acknowledgments

Potential conflicts of interest. P.J.L.: no conflicts.

References


