Onchocerciasis – A potential revolution in its treatment

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Abstract

Onchocerciasis is a major blinding disease affecting at least 28 million people in Africa and Latin America. Although a large-scale vector control program has been highly successful in limiting transmission of infection in West Africa, there has not been a satisfactory form of treatment available for those already infected or those living in other areas. Despite the fact that two drugs, diethylcarbamazine and suramin, are active against the filarial parasite that causes onchocerciasis, their use is severely limited by their toxicity and the reaction they induce. A newly developed drug, ivermectin, appears to offer a major revolution in the treatment of onchocerciasis. In a series of clinical trials, ivermectin has been shown to be an extremely effective microfilaricide which induces only minimal side effects. Ivermectin is given as a single oral dose which can be repeated on an annual basis. In view of its safety and efficacy and its ease of administration, it seems likely that ivermectin will be suitable for use in mass chemotherapy programs against onchocerciasis.

In our busy practices, it is all too easy to become absorbed in the problems that confront us daily. All too often we shut out, or completely forget about, some of the major diseases that affect millions of people in less privileged areas. One of those diseases is ‘river blindness’, or onchocerciasis. Onchocerciasis is the blinding human disease caused by infection with the filarial worm Oncho-
cerca volvulus. It is transmitted by small, biting black flies that breed in rapids along the rivers of large areas of West and Central Africa and in smaller areas of Latin and South America. In areas in which it is endemic, onchocerciasis has a devastating impact. Almost everyone will be infected by adolescence, most will have some degree of the debilitating skin changes, two out of five people will become blind, and those that are blind have one-third the life expectancy of the sighted [8]. Villages of subsistance farmers along the fertile rivers are decimated and ultimately abandoned.

Until now there has not been a satisfactory way of treating onchocerciasis. For the last sixty years, two drugs have been in limited use for treating onchocerciasis – diethylcarbamazine (DEC) and Suramin. Both drugs cause dangerous and at times life-threatening side effects, and their use has been generally restricted to only those with the most severe sight-threatening disease and only then under close medical supervision [9]. For that reason, there has been essentially no way to reach the estimated 28 million people who continue to suffer from onchocerciasis or the 1 to 2 million people who have become blind.

An ambitious, large, long-term control program has operated in the worst affected areas of West Africa for the last decade. This program, the On-
chocerciasis Control Program (OCP), was established by the World Health Organization (WHO), the World Bank, and other United Nations agencies. The OCP has aimed at stopping the transmission of onchocerciasis by eliminating the black fly vectors [3]. It has done that by spraying the breeding sites of the black fly with a selective larvicide. This has been no mean task as the breeding sites are often relatively inaccessible. Also they must be sprayed by air – usually by helicopter – and constantly change as the water flow changes during the rainy and dry seasons. Despite many difficulties, it has been outstandingly effective and has essentially eliminated the transmission of infection in an area of over 700,000 square kilometers involving seven countries. It is now planned to extend this program and almost double the area it covers and include portions of four more countries.

The OCP has provided a protective umbrella for about one-quarter of those with onchocerciasis. But because of logistic and economic reasons, similar programs in other areas of onchocerciasis are not feasible, so the future for those living in these areas looked bleak.

Recently, however, there has been a major advance in the prospects for a safe and effective drug that can be used on a large scale to treat onchocerciasis. Ivermectin is a synthetic derivative of a fungal fermentation product [4]. It is effective against a wide range of animal parasites and is being used extensively in veterinary medicine. Recent trials (sponsored by WHO and Merck Sharp & Dohme) have evaluated ivermectin in patients infected with onchocerciasis [1, 2, 6]. These studies suggest that ivermectin is not only extremely effective in reducing the level of infection but that it is also much safer than the previously available drugs for treating onchocerciasis.

In man, the onchocerciasis parasite develops into male and female adult worms that reproduce sexually and the female worm releases millions of tiny worms or microfilariae. The microfilariae migrate throughout the body but especially to the skin and the eye. Much of the pathology that is seen in onchocerciasis is thought to be due to the severe reaction that forms around dead microfilariae. Drugs such as DEC kill microfilariae and cause a severe reaction known as the Mazzotti reaction. That reaction may lead to visual loss and seriously limits the usefulness of such drugs. Several controlled clinical trials of ivermectin have now been reported [6, 7]. They show that ivermectin is at least as effective as DEC in reducing the levels of microfilariae in the skin and the eye. However, unlike DEC, ivermectin does not precipitate a marked Mazzotti reaction nor does it cause untoward ocular changes [11]. Although the type of systemic reaction seen with ivermectin treatment is similar to that seen with DEC, it occurs much less frequently and is much less severe. The studies to date do not suggest any inherent toxicity of the drug at the doses studied. So far the mechanism of action of ivermectin against the microfilariae is unknown although its main pharmacological effect is that of a gabbag agonist.

Ivermectin does not kill the adult worms of *O. volvulus*, so a single course of ivermectin is not curative. It does, however, appear to have some effect on the uterus of the female worm so that the rate at which microfilariae can repopulate the skin and eye after ivermectin treatment is much slower than after DEC. A further benefit of ivermectin treatment is a reduction in the uptake of microfilariae by black flies [5]. Flies fed on patients treated with ivermectin took up fewer microfilariae than flies fed on patients treated with DEC. That suggests that ivermectin treatment could also significantly reduce transmission.

The most striking thing about ivermectin is that these outstanding results have followed a single oral dose of only 100 to 200 μg/kg. Long-term follow-up data is limited at present, but it seems reasonable to envisage the mass distribution of an annual single oral dose of 150 μg/kg of ivermectin possibly just before the start of the transmission season. Such a program could be based within the context of a country’s primary health care program. It should not only offer optimal treatment to those already infected but also provide protection to others by reducing transmission. Large community-based studies are now planned in several countries to test the safety and efficacy of ivermectin given as a mass treatment.

In the interim, it would seem to be wise to follow