Stemming the tide of river blindness: the early years of ivermectin

Hugh R Taylor

IN 1978, when I was a Fellow in Ophthalmology at the Johns Hopkins Hospital in Baltimore, I went to a seminar given by one of the senior faculty (Maurice Langham) about work he was doing on an unusual disease called onchocerciasis. Although I must have learnt about onchocerciasis at medical school and during my ophthalmology training, it was such an esoteric tropical disease in small print that it had made no perceptible impact on me.

Actually, onchocerciasis is a fascinating disease. It is also called river blindness, as those who are affected live along rivers and streams. It affects about 20 million people; 99% of these live in Africa, with a few in Latin America (see Box 1).[1] In endemic areas, half will become blind before they die and, at any one time, some half a million people with onchocerciasis are blind.

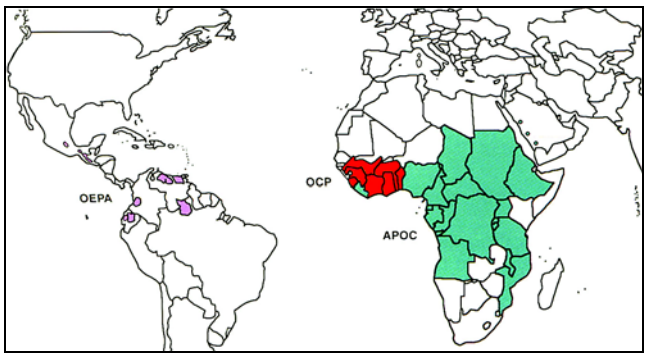
Onchocerciasis has had a devastating impact in Africa. All but the poorest of the poor have abandoned the endemic areas. In the worst affected villages, everyone is infected by the age of 14 or 15 years.[1] People go blind in their 20s and 30s, just when these subsistence-farming families are raising children. Once blind, parents often need to be led to their fields by their young children. This has a devastating effect on all aspects of the villagers' lives.

There have been various attempts to treat and control onchocerciasis. During the Second World War, tens of thousands of Australian and American soldiers fighting in the Pacific islands were afflicted with lymphatic filariasis. Wartime drug development led to the discovery of diethylcarbamazine (DEC) that would halt the progression of, and sometimes cure, filariasis. After the war, DEC was tried on some people with onchocerciasis and was found to have a temporary holding effect.[1,2] DEC was better than nothing, but its use was limited, as many infected people had a severe reaction to the treatment caused by the sudden death of billions of microfilariae, the so-called Mazzotti reaction.[3]

Sleeping sickness or trypanosomiasis is almost invariably fatal. During the First World War a drug called suramin was developed in Germany that could save some people with sleeping sickness, although it was very toxic. It was tested and found to be effective against onchocerciasis, but 2%–3% of those treated died and so it was not widely used.[4]

The World Health Organization had started a major program to control onchocerciasis by spraying breeding sites to control the black fly vectors. This program started in 1974 in 11 countries in West Africa. Breeding sites in rivers and streams were "bombed" each week with the aerial application of larvicide. This was an effective, if slow and expensive, method of controlling the disease in open savanna but, because of problems with aerial access, it could not be used in rainforest areas.

1: Onchocerciasis endemic areas



Two onchocerciasis control programs provide onchocerciasis control in 30 endemic countries in Africa. (OCP — Onchocerciasis Control Program — initial area of vector control; APOC — African Program for Onchocerciasis Control — World Bank and WHO supported ivermectin distribution; OPEA — Onchocerciasis Elimination Program for the Americas — ivermectin distribution in Latin America). Reprinted from Reference 19 with permission.

This was the state of play as I listened to Langham in Baltimore describe the human studies to treat onchocerciasis he had recently done in Africa. After the lecture, I suggested some clinical trials he could do. It seemed so simple to me then: get a small team of two or three people and a bit of equipment to examine people and do a prospective randomised trial. I had had great lab training at the Royal Melbourne Hospital under Peter Morris (later Professor Sir Peter Morris), and I had had an extraordinary experience of working in the field with Professor Fred Hollows when I travelled throughout outback Australia on the National Trachoma and Eye Health Programme. I little suspected how much I still had to learn, but Langham proposed that I should do the study and offered to help me put it together. Within a few months I was starting a study in Liberia and another in Guatemala. I teamed up with a young infectious diseases doctor, Bruce Greene, who was at Hopkins and later went to Case Western University in Cleveland. This was the start of a very successful collaboration.

As there were only a few ophthalmologists working on onchocerciasis, I was soon appointed to a WHO Scientific Working Group on Filariasis that included onchocerciasis. In the 1970s, WHO had started a drug-screening program under their Special Programs for Training and Research in Tropical Diseases. Pharmaceutical companies could send interesting compounds to be tested in WHO-supported laboratories in selected universities to see if their new drug had an

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2: Onchocerciasis fact file

Simulum damnosum

Cause

Onchocerca volvulus, a filarial worm.

Transmission

Various biting black flies. Main African vector is *Simulum damnosum*. The flies breed along the river banks and in the rapids and fast-flowing streams. A female fly bites an infected person to take a blood meal, and becomes infected with a tiny microscopic worm – a microfilaria – that is less than a third of a millimetre long. Over a week or so, these microfilariae develop into infective larvae and can be transmitted when the fly bites another person.

Life stages

A partially dissected nodule showing a densely coiled adult female worm with a small adult male worm emerging in the upper right quadrant.

After entering the body, the infective larvae grow to become adult male or female worms. The males are only 5 cm or so long, but the females may be up to a metre long. The adult worms are wrapped together in a nodule like a ball of string. The worms reproduce sexually and the female releases tens of thousands of microfilariae every day. As the female can live for 10 years or so, she literally releases millions and millions of microfilariae.

The microfilariae migrate throughout the host's body, especially to the skin and the eye. In the skin they wait to be taken up by another black fly to continue the life cycle. If this does not occur within 18 months or so, the microfilariae die. There is no inflammatory response to live microfilariae, but dead or dying microfilariae provoke an intense local response.

Disease manifestations

- Subcutaneous nodules (adult worms often attach to bones or joints)
- Skin changes: severe pruritus and rash, maculopustular reaction, pigmentary changes, atrophy
- Eye changes: microfilaria in cornea, anterior chamber and retina; uveitis; sclerosing keratitis; chorioretinal atrophy

Liberian rubber tappers from one of the early onchocerciasis drug studies. Bruce Green (left) and Hugh Taylor standing at the back.

effect against some of the targeted tropical diseases. In 1983, I was asked to chair a new WHO Scientific Working Group on Onchocerciasis Chemotherapy.

Since the Second World War, major drug companies have scoured the world looking for new antibiotics, many of which came from fungi. In 1978, a Japanese scientist collected a fungus species that was to revolutionise the treatment of onchocerciasis from beside a golf course in Kawano, Japan — I have been told it was from beside the fifth fairway. This fungus made a compound that was called in the lab MK 933. Later, it was called ivermectin. It was not good as an antibiotic, but it was a very potent killer of parasites. It went to a WHO test laboratory where it created some interest, but then it disappeared.

It was the pharmaceutical firm Merck and Co. that developed ivermectin and started to market it for veterinary use. It is now a worldwide product used to treat heartworm in dogs, and a whole range of parasites in sheep, cattle, horses, pigs and other animals.[5]

Dr Mohammed Aziz worked for Merck. He was originally from Bangladesh, and had worked in Africa with WHO where he learned about onchocerciasis. He insisted that MK 933 be tried in onchocerciasis. Once the veterinary product was successfully launched, he got his way, and he did a small pilot study in Senegal.[6] The results were published in the *Lancet* and picked up by the *New York Times*, *Le Monde* and other newspapers. This was the first time that I, and others in the field, had heard of this drug.

The study was somewhat unusual. The results seemed to be too good to be true. How could any drug kill the microfilaria without producing the intense Mazzotti reaction we saw with every other drug that killed microfilaria? This did not fit with any conceivable clinical, laboratory or theoretical explanation at the time. Besides, the study patients were only lightly infected, the investigators had not worked on "oncho" before, the study was funded by a drug company, and it was published simultaneously in the newspapers and the scientific literature. Maybe it was just wishful thinking, or artefact.

Soon a series of parallel, randomised clinical trials were planned to more fully evaluate this very exciting new drug. These studies started after some further patients were treated in an open dose-ranging study.

Bruce Greene and I undertook a study in Liberia. We treated men who had become heavily infected with onchocerciasis while working as rubber tappers on a plantation. In this controlled trial, 10 men received ivermectin, 10 received DEC, and 10 took placebos. We were very anxious for the first few days, as we expected to see similar reactions to those seen in patients treated with DEC. Some animal studies suggested even worse reactions were possible with ivermectin. Maybe some people would even die. We were elated six months later when our results showed that ivermectin was at least as effective as DEC, but safer.[7] The two other parallel studies came up with similar results.[8,9] Subsequently, one partial answer emerged for the lack of a Mazzotti reaction. It seems that, rather than killing the microfilariae in the tissues, the microfilariae are paralysed and then pass through the lymphatic system and die in the lymph nodes.

We went back to Liberia and this time treated 300 people, men and women, to test different doses. We followed this group for 2 years. A tiny tablet of ivermectin cleared the microfilariae almost completely and people's skin and eye signs improved dramatically.[10,11] The adult worms were not affected, so ivermectin needed to be given once every year.

By August 1987, Merck had enough data to register ivermectin for use in onchocerciasis. The chairman of Merck, Dr Roy Vagalos, announced that his company would provide the drug at no cost to treat anyone with onchocer-

ciasis, anywhere in the world, for as long as it was needed.[12] This was an unprecedented and extraordinarily generous and courageous decision. Although Merck was selling huge amounts of ivermectin to treat animals, there were some 20 million people with onchocerciasis, and maybe 40 million who would need treatment. Treatment had to be continued for at least 10 years. This was a huge commitment when each pill was worth US$3. However, Vagalos knew that if Merck did not do something, this breakthrough treatment could never be afforded by those who lived beyond the end of the road, the poorest of the poor.

Ivermectin was now freely available. But how could it be distributed to the millions who needed it? There were other questions to be answered: for example, would ivermectin have rare but serious side effects? And what would happen if pregnant women inadvertently took a tablet?

We then started another study of 30 000 people in Liberia to assess the community acceptance and safety, and to work out distribution strategies. We monitored every person, every month, investigating and documenting all births and deaths. We kept track of people as they moved, we caught and examined the biting black flies, and we thoroughly examined all the children. This huge study was very successful and confirmed the safety of ivermectin: it could be distributed to nearly everybody in the community.[13,14] We showed that by treating the whole community we could reduce transmission and the incidence of new infection in children.[15]

Initially, the dose of ivermectin was adjusted for each individual's weight, so everyone had to be weighed, but later work showed that height could be used instead.[16] If children could walk under the stick, they got one pill; if they were too tall, they got two.

By 1989, when our last Liberian study was finishing, several government and non-government organisations coordinated by WHO had started delivering ivermectin in pilot projects. Although Merck would deliver boxes of ivermectin to the national port, it still cost between 5 cents and $5 a tablet to get the ivermectin up-country and into people's mouths. A lot of work was done to develop cost-efficient ways of community-based distribution.

To supervise the distribution of the donated ivermectin, Merck created the Mectizan Expert Committee.[1,17] This joint committee was based at the Jimmy Carter Presidential Centre in Atlanta and included representatives from WHO and Merck, and other experts. I had the privilege to serve on this committee in the early 1990s.

In 1990, a Houston software developer, John Moores, read an article about ivermectin in the *Houston Chronicle*. He was so taken by this story that he started a foundation to support this work. I was also fortunate to be on the Board of the River Blindness Foundation and eventually John Moores gave US$25 million to the Foundation. It became clear that a lot more money would be needed to distribute ivermectin in the 28 African endemic countries. The River Blindness Foundation, the Carter Centre and other non-government organisations convinced the World Bank to start a special program to distribute ivermectin in Africa, worth about $300 million.[18] Another smaller program was set up for the six endemic countries in Latin America.

In 2002, nearly 50 million doses of ivermectin were given away free: over four million doses a month, treating about 100 people every minute. Despite local disturbances and civil war, ivermectin distribution programs are active in 25 of the 27 endemic countries and currently reach 45% of the "Ultimate Treatment Goal", the total number of people required to be treated (see www.mectizan.org). The number treated each year continues to increase at an almost exponential rate, and progress is closely monitored by the Mectizan Expert Committee, WHO and non-government organisations. The commitment and strategies are in place to reach everyone who needs treatment and to eliminate onchocerciasis by the year 2020.

Success has many parents, and failure only one. Obviously, many people were involved in the ivermectin story, but it has been a great thrill to be one of them and to have been a part of what must be one of the most significant breakthroughs in tropical medicine in the past 25 years.

References

1. Onchocerciasis and its control. Report of a WHO Expert Committee on Onchocerciasis Control. *World Health Organ Tech Rep Ser* 1995; 852: 1-104.
2. Hewitt RI, White DE, Jushner S, et al. Piperazines in the treatment of filariasis. *Ann N Y Acad Sci* 1948; 50: 128-140.
3. Mazzotti L. Possibility of using the allergic reactions due to the administration of Hetrazan as an auxiliary diagnostic test for onchocerciasis. *Revista del Instituto del Salubridad y Enfermedades Tropicales* 1948; 9: 235-237.
4. Hawking F. Suramin: with special reference to onchocerciasis. *Adv Pharm Chemother* 1978; 15: 289-322.
5. Campbell WC. Invermectin and abamectin. New York: Springer-Verlag, 1989.
6. Aziz MA, Diallo S, Diop IM, et al. Efficacy and tolerance of ivermectin in human onchocerciasis. *Lancet* 1982; 2: 70-78.
7. Greene BM, Taylor HR, Cupp EW, et al. Comparison of ivermectin and diethylcarbamazine in the treatment of onchocerciasis. *N Engl J Med* 1985; 313: 133-138.
8. Lariviere M, Vingtain P, Aziz M, et al. Double-blind study of ivermectin and diethylcarbamazine in African onchocerciasis patients with ocular involvement. *Lancet* 1985; 2: 174-177.
9. Awadzi K, Dadzie KY, Schulz-Key H, et al. The chemotherapy of onchocerciasis. XI: a double-blind comparative study of ivermectin, diethylcarbamazine and placebo in human onchocerciasis in northern Ghana. *Ann Trop Med Parasitol* 1986; 80: 433-442.
10. White AT, Newland HS, Taylor HR, et al. Controlled trial and dose-finding study of ivermectin for treatment of onchocerciasis. *J Infect Dis* 1987; 156: 463-470.
11. Newlands HS, White AT, Green BM, et al. Effect of single-dose ivermectin therapy on human *Onchocerca volvulus* infection with onchocercal ocular involvement. *Br J Ophthalmol* 1988; 72: 561-569.
12. Lindley D. Merck's new drug free to WHO for river blindness programme. *Nature* 1987; 329: 752.
13. Pacque MC, Dukuly Z, Greene BM, et al. Community-based treatment of onchocerciasis with ivermectin: acceptability and early adverse reactions. *Bull World Health Organ* 1989; 67: 721-730.
14. Pacque M, Munoz B, Poetschke G, et al. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. *Lancet* 1990; 336: 1486-1489.
15. Taylor HR, Pacque M, Munoz B, Greene BM. Impact of mass treatment of onchocerciasis with ivermectin on the transmission of infection. *Science* 1990; 250: 116-118.
16. Taylor HR, Gonzalas C, Duke B. Simplified dose schedule of ivermectin. *Lancet* 1993; 341: 50-51.
17. Dull HB, Meredith SEP. The Mectizan Donation Programme — a 10-year report. *Ann Trop Med Parasitol* 1998; 92 Suppl 1: S69-S71.
18. Richards R. Programmatic goals and approaches to onchocerciasis. *Lancet* 2000; 355: 1663-1664.
19. Dadzie KY, VanNewkirk MR, Taylor HR. Onchocerciasis. In: Denny M, Wallach RS, Dondrea CL, editors. International ophthalmology 2002-2003. San Francisco: American Academy of Ophthalmology, 2002: 231-246.

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