ONCHOCHERCIASIS (RIVER BLINDNESS): A REVOLUTION IN THERAPY

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ABSTRACT
In Abakaliki, Ebonyi State, we have recently completed clinical trials of a new drug, ivermectin (mectizan) that promises to revolutionize the treatment of river blindness or onchocerciasis. In a recent study of 100 patients, with skin biopsies, which were positive for microfilariae; we showed that ivermectin was at least as effective as the previously available standard drug diethylcarbamazine (DEC), but that ivermectin was much safer. In a larger study of 300 patients we have just completed we have confirmed both the safety and efficacy of ivermectin. These results are in agreement with other several trails following a standard protocol. There had not been the remotest possibility of realistically treating millions of people who have Onchocerciasis prior to the advent of ivermectin. This was because the previous drugs were too dangerous to use on a mass scale. Ivermectin is safe and effective. It is given in a single oral dose of as little as 6mg (for a 65kg. Weight human) that may be repeated on an annual basis. It seems to be so safe that it can be given on a mass scale within the primary health care delivery system.

INTRODUCTION
Onchocerciasis is caused by the filarial nematode Onchocerca volvulus, which is transmitted by Simulium sp. black flies, intermediate hosts that require fast-flowing water for their breeding and development; the disease is thus restricted to areas adjacent to river systems. An estimated 37 million people in 34 countries in sub-Saharan Africa and South America are infected with the disease. The large adult female worms are contained within fibrous nodules or onchocercomas in subcutaneous or deeper tissues. Males migrate between nodules to inseminate the females, which when fertilized give birth to 1,000 to 3,000 microfilariae per day that migrate into the skin to be transmitted to their black fly vectors. In communities where the infection is highly endemic, disease prevalence increases with age up to the 30-
40-year age group and is accompanied by an increasing prevalence of troublesome itching and chronic papular onchodermatitis. Older age groups then begin to acquire skin depigmentation, impaired vision, and blindness. In some areas two out of five people will become blind, and those that are blind have one-third the life expectancy of the sighted. Villages of subsistence farmers along the fertile rivers are decimated and ultimately abandoned.

Abakaliki is an important food producing area in Nigeria. The principal zones are Ikwo, Ezza, and Izzi which lie in typical rain- forest zone and are watered by Ebonyi, Esu, etc rivers which flow fast into the Cross River.

Because of the high oxygen content of these rivers, the vector of Onchocerciasis-simulium damnosum breeds in these areas in large numbers. This results in endemicity of River Blindness, which calls for urgent medical attention.

As agriculture is the main stay of the economy of these areas, the people engage in intensive agriculture with the result that Rice, Yam and Palm produce are abundant in these localities all the year round. During farming, they weed in ponds infected with the black fly, which predisposes them to Onchocerciasis.

**DISEASE MANIFESTATIONS**

The socioeconomic and public health importance of visual impairment, blindness, and the more widespread dermatitis are profound. The spectrum of disease manifestations ranges from asymptomatic/paucisymptomatic infection, or generalized onchocerciasis (GEO), to severe pathology presenting as visual impairment and blindness and acute and chronic skin disease. A large body of evidence supports host immunity to the microfilarial stage as the cause of pathology, with a hyporesponsive immunological state present in the majority of asymptomatic infections. The type and magnitude of the immune response and consequent clinical manifestations may be influenced by host genetic factors.

Onchocerciasis is characterized by cutaneous and ocular pathology that occurs after the invasion and death of microfilariae in the skin and eye, while adult worms are enclosed in nodules (onchocercomas) in the subcutaneous and deeper tissues. Cutaneous pathology with troublesome itching is the most common manifestation in infected people, driving social stigma due to skin appearance and accounting for 60% of the 1 million disability-adjusted life
years (DALYs) for onchocerciasis. The spectrum of skin pathology manifestations is broad. The more common generalized form presents with subclinical or intermittent dermatitis (acute and chronic papular dermatitis) that may progress to skin hyperpigmentation or depigmentation (leopard skin) and atrophy with loss of elasticity (hanging groin). A less common but severe hyperreactive form (lichenified onchodermatitis or sowda), a feature of onchocerciasis common in certain geographical areas such as Yemen and Sudan, is characterized by pruritic hyperpigmented hyperkeratotic plaques, often asymmetrical and localized, associated with local lymphadenopathy.

Visual impairment and blindness represent the most severe pathological outcomes of onchocerciasis, with 500,000 and 270,000 cases estimated, respectively. Their incidence has been dramatically reduced in areas where control programs are implemented. The occurrence of ocular pathology varies between geographical locations, being more common in savannah areas of West Africa and Central Africa and in Latin America, and has been related to various factors, such as localization of nodules in the upper part of the body, vector species, microfilarial burdens, and parasite strain, and more recently to a higher Wolbachia load in the more virulent savannah strain. The most common ocular pathology involves the cornea, but other structures of the anterior segment and the posterior segment can also be affected. Corneal pathology begins with “fluffy” or “snow-flake” opacities (punctate keratitis), which later coalesce and may become hyperpigmented (sclerosing keratitis). In the anterior chamber dead microfilariae can cause uveitis with formation of sinechiae, cataract, and glaucoma. Posterior segment lesions include atrophy of the retinal-pigment epithelium, choroido-retinal scarring, subretinal fibrosis, and postneuritic optical atrophy.

ONCHOCHERCIASIS (RIVER BLINDNESS) CONTROL MEASURE
Until recently there has not been a satisfactory way of treating Onchocerciasis. For the last 60 years, two drugs have been in limited use for treating Onchocerciasis. The drugs are 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 them under close medical supervision.

Treatment with DEC (Banocid or Hetrazon) results in rapid destruction of the microfilaria in the tissue which is associated with significant allergic reaction: exacerbation of rashes, intense itching and scratching and must be administered under medical supervision. Some times in patients with eye involvement, mass destruction of microfilariae in the eye
associated with DEC administration worsens the existing eye lesions. Another major disadvantage of DEC is that treatment is for several weeks, which may be impractical in endemic communities where patient’s non-compliance may result from lack of understanding the severity of the side effects. As a result DEC has lost its therapeutic attractiveness.

Suramin (Anthropol) on the other hand kills adult parasites but has considerable intrinsic toxicity. It must in addition be given intravenously between 5 and 21 days under close medical supervision. Acute renal failure, shock, loss of consciousness exfoliative dermatitis, circulatory collapse, and even death are some of the adverse consequences of immediate hypersensitivity to suramin. Given these profiles, both DEC and surmain are indicated only when the need for treatment outweighs the clinical risks.

An ambitious, large, long-term control programme has operated in the worst affected areas of West Africa for the last decade. This programme, the Onchocerciasis control programmes (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. It has done that by spraying the breeding sites of the black fly with a selective larvicide (biodegradable insecticides). This method has been most successful in reducing the spread of the disease but its ultimate eradication seems difficult because of the following reasons:-

1. The almost inevitable invasion of the control areas by flies from neighboring, uncontrolled regions;
2. The development of vector resistance to insecticides;
3. A growing reluctance to the risk of hazards of long-term environmental pollution and
4. The cost of maintaining large control programmes.

The need therefore arose to find alternative chemotherapeutic agents against Onchocerciasis that can be used for mass treatment, without severe allergic reactions, tolerated under normal conditions, inexpensive, effective as a single dose for a long time. The search for an ideal drug began in the 1970s of all the drugs screened so far, ivermectin (MECTIZAN) has shown the greatest promise and has therefore revolutionized the treatment of one of the insidious and intractable of tropical diseases, Onchocerciasis.

Ivermectin (22- 23 dihydro-avermectin), a macrocyclic lactone, is a novel chemical entity, discovered and developed by Merck Sharpe and Dohme (MSD) research laboratories in New
Jersy USA. It is a chemical derivative of a naturally occurring fermentation product, abamectin (precursor), which is a substance in a series of compounds called the avermectins collected from culture of a soil sample on a golf course at Kawane, Ito city, Japan in 1975.

Ivermectin has an extremely low solubility in water, but is considerably more soluble in blood plasma. The apparent absence of peripheral receptor for ivermectin, its failure to cross the blood brain barrier, and its obvious high degree of susceptibility of a wide range of parasites at a very low dose are advantage. It is absorbed systemically after oral or subcutaneous administration and excreted almost exclusively in the faces, with less than 1% excreted in the urine. The largest amount of residue is found in the liver and body fat, and the major compound of the residue is unaltered drug.

Ivermectin possesses an unusually broad spectrum of potent activity. The efficacy of Ivermectin against nematode and arthropod parasites is unprecedented in potency and breadth of spectrum. It paralyses susceptible parasites by affecting gamma aminobutyric acid (GABA) mediated neurotransmission. By enhancing GABA release, and binding to its receptors, Ivermectin opens chloride channels and thereby reduces membrane resistance in motor neurons of the nematodes and muscle cells of arthropods. As a result, its use in veterinary proved exceptional and its efficacy in single-dose outstanding. Hence it was introduced to the market place as antiparasitic drug in veterinary in 1981 and was registered for animal health in up to 47 countries by 1986. It was based on these unprecedented advantages in animal health that led to the revealing, exploratory studies on its efficacy in the treatment of human onchocerciasis.

Like DEC, Ivermectin is microfilaricidal. The absence of servers side reactions in Ivermectin treatment, compared with DEC, may be explained by a different mechanism of microfilariae elimination. Dec achieves an enhancement of adherence of effectors cells to microfilariae resulting in microfilariae killing and consequent high level of antigenic materials. This therefore provokes the characteristic allergic severe reaction known as the mazzoti reaction observed in DEC treatment. On the other hand, Ivermectin paralyses microfilariae, which are then removed by the patient’s recticuloendothelial system; providing less antigenic materials and thus causing a less violent host response. Ivermectin eliminates microfilariae response. Ivermectin eliminates microfilariae from the anterior chamber of the eye slowly over several months. Thus, ocular inflammatory reaction is minimal, and functional deficit does not occur.
It is believed that slow action of Ivermectin on the eye may be partially attributed to its inability to cross the blood-aqueous humour barrier because of its molecular size.

Clinical trials of Ivermectin in more than 140,000 patients have shown that the optimal single dose of only 150-200 microgram ug/kg body weight per 12 months is effective against onchocerciasis, has an acceptable safety advantages and well tolerated superior to that of DEC.

Ivermectin can prevent River Blindness but it cannot cure people who are already blind. From our “Report Form For Reactions” the drug may not be safe for the following people:
(a) Children who are younger than five years old or who weighs less than 15 kilograms
(b) Pregnant Women
(c) Women who delivered a baby in the last week
(d) People who are too weak to walk or who are seriously sick

We must weigh a person to decide how many tablets of mectizan to give.

<table>
<thead>
<tr>
<th>Weight (Kilograms)</th>
<th>Dose (Number of tables) 6mg tab</th>
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<tbody>
<tr>
<td>Less than 15kg</td>
<td>None</td>
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<tr>
<td>15kg to 24kg</td>
<td>½ tablet</td>
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<tr>
<td>25kg to 44kg</td>
<td>1 tablet</td>
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<tr>
<td>45kg to 64kg</td>
<td>1½ tablets</td>
</tr>
<tr>
<td>More than 65kg</td>
<td>2 tablets</td>
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It may not be safe for a person to take too many tables or to take the drug more than once a year.

A further benefit of Ivermectin treatment is a reduction in the uptake of microfilariae by black flies. In another recently reported study it was showed that files 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. 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 Ivermectin possible just before the start of the transmission season. Such a programme could be based with the contest of a
country’s primary health care programme. It should not only offer optimal treatment to those already infected but also provide protection to others by reducing transmission.

With more than 1,000,000 people treated to date, Ivermectin shows great promise as a single dose oral treatment for the major scourge of onchocerciasis. It is both safe and effective in treating individuals and may also reduce transmission within a community.

REFERENCES


