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Invited review

Research for new drugs for elimination of onchocerciasis in Africa

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ABSTRACT

Onchocerciasis is a parasitic, vector borne disease caused by the filarial nematode *Onchocerca volvulus*. More than 99% of the population at risk of infection live in Africa. Onchocerciasis control was initiated in West Africa in 1974 with vector control, later complemented by ivermectin mass drug administration and in the other African endemic countries in 1995 with annual community directed treatment with ivermectin (CDTI.) This has significantly reduced infection prevalence. Together with proof-of-concept for onchocerciasis elimination with annual CDTI from foci in Senegal and Mali, this has resulted in targeting onchocerciasis elimination in selected African countries by 2020 and in 80% of African countries by 2025. The challenges for meeting these targets include the number of endemic countries where conflict has delayed or interrupted control programmes, cross-border foci, potential emergence of parasite strains with low susceptibility to ivermectin and co-endemicity of loiasis, another parasitic vector borne disease, which slows down or prohibits CDTI implementation. Some of these challenges could be addressed with new drugs or drug combinations with a higher effect on *Onchocerca volvulus* than ivermectin. This paper reviews the path from discovery of new compounds to their qualification for large scale use and the support regulatory authorities provide for development of drugs for neglected tropical diseases. The status of research for new drugs or treatment regimens for onchocerciasis along the path to regulatory approval and qualification for large scale use is reviewed. This research includes new regimens and combinations of ivermectin and albendazole, antibiotics targeting the *O. volvulus* endosymbiont *Wolbachia*, flubendazole, moxidectin and emodepside and discovery of new compounds.

Contents

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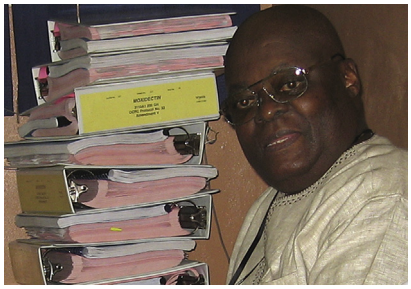
1. Introduction

1.1. Onchocerciasis



Dr. Awadzi (13.06.1939-16.03.2011)

Father of ethical, systematic and evidence based clinical research in onchocerciasis Dr. Awadzi was instrumental in development of the methods for assessing the efficacy and safety of anti-onchocercal drugs, providing training and collaboration for many young scientists and physicians. He evaluated nearly all drug candidates for onchocerciasis proposed before and after the development of ivermectin. This picture shows him with the case report forms of the last clinical trial he lead as principal investigator, the Phase 2 study of moxidectin. He then 'retired' and was the scientific advisor on the Phase 3 study and trained, together with his collaborators at the Onchocerciasis Chemotherapy Research Center, Hohoe, Ghana (now University of Health and Allied Sciences Research Centre (UHASRC), School of Public Health, Ghana) the principal investigators of that study in Liberia and the Democratic Republic of the Congo.

Onchocerciasis (river blindness) is a parasitic, vector borne disease caused by the filarial nematode *Onchocerca volvulus*. Four life stages of *Onchocerca volvulus* live in humans: the infective (L3) larvae injected by the vector undergo two moultings to develop via L4 larvae into juvenile adults (L5) and mature to reproductively competent adults (macrofilariae) within around 1 year (Duke, 1991; Basanez and Ricardez-Esquinca, 2001). The macrofilariae (adult worms) have an estimated mean reproductive life span of 9–11 years (Plaisier et al., 1991), reside primarily in subcutaneous and deep tissue nodules and produce embryos (microfilariae). The microfilariae live for around 1 year, reside primarily in the subepidermal layer of the dermis and can invade the eyes. The immunological response to the death of the microfilariae, which includes inflammatory components, is responsible for the symptoms of the disease which range from itching to blindness. The vectors are species of the genus *Simulium* (black flies), in Africa primarily *Simulium damnosum* s.l.. During a blood meal, the blackflies ingest microfilariae present in the skin which develop into infective (L3) larvae. Transmission of the infective larvae to humans upon another blood meal closes the transmission cycle (World Health Organization, 1995).

1.2. Onchocerciasis control programmes

The significant public health and resulting socio-economic burden of onchocerciasis have motivated large scale disease control and elimination programmes in all endemic countries. The vast majority of these countries are in Africa, where more than 100 Million people live in onchocerciasis endemic areas (Noma et al., 2014; Zoure et al., 2014; O'Hanlon et al., 2016). Around 0.56 Million people were estimated to live in the 13 small endemic foci in 6 countries in Central and South America (Center for Disease Control (CDC), 2013) and around 0.3 Million in Yemen (Mackenzie et al., 2012) Onchocerciasis control started in 1974 with the Onchocerciasis Control Programme in West Africa (OCP) which conducted large scale larviciding of vector breeding sites in the West African Savannah. The vector-control based strategy was complemented with mass drug administration (MDA) (Boatin and Richards, Jr. 2006) after ivermectin (Mectizan®) had been registered and Merck decided to donate ivermectin for onchocerciasis control for as long and in the amounts needed (Campbell, 2012). At the closure of OCP in 2002, onchocerciasis had been eliminated as a public health problem in the programme area (Benton et al., 1998; Boatin, 2008; Campbell, 2012).

Mass ivermectin administration was the sole strategy in the countries of the Onchocerciasis Elimination Program for the Americas (OEPA). The public health system distributed ivermectin initially annually, then twice yearly in all villages in which onchocerciasis was endemic. This was complemented for several years by two additional distributions in the majority of hyper-endemic communities (≥60% prevalence before the start of interventions) and a few meso-endemic communities (≥20% to <60% prevalence before start of interventions). In all but the large focus spanning areas of Venezuela and Brazil, this strategy has or is likely to have permanently interrupted transmission of the parasite (Convit et al., 2013; Anonymous 2013; West et al., 2013; Center for Disease Control (CDC), 2013; Lovato et al., 2014; Rodriguez-Perez et al., 2015; Anonymous 2015).

In Yemen, ivermectin has been offered since 1992 at least biannually to those with symptoms (Al-Qubati, 1994; Al-Qubati et al., 1997). Yemen is targeting onchocerciasis elimination