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Review Article

Chemotherapy of filariasis – established strategies and new developments

Abstract

Lymphatic filariasis (lympoedema and hydrocoele) and onchocerciasis (dermatitis and ocular inflammation) caused by the parasitic filarial nematodes *Wuchereria bancrofti*, *Brugia* spp. and *Onchocerca volvulus* lead to severe morbidity in developing tropical countries. Mass drug administration (MDA) programmes use ivermectin or diethylcarbamazine, often combined with albendazole, with the aim to eliminate filarial diseases. However, these drugs primarily only kill the first stage larvae, the microfilariae. Removal of the parasites' mutualistic endosymbionts of the genus *Wolbachia* using anti-rickettsial drugs results in permanent worm sterility and death of the adult worms. Since it is currently not compatible with mass drug administration due to the comparatively long treatment time of 4–6 weeks, doxycycline has been recommended for physician-monitored treatment of individuals. For individuals suffering from filarial pathology, the use of doxycycline is the first drug to have the additional advantage of improving lymphoedema. However, new drugs and regimes need to be in the pipeline in order to tackle the upcoming or already existing problem areas, such as those with ivermectin resistance, areas coendemic for loiasis, or end-game scenarios. Here, we summarize current treatment options and review current research approaches for optimization of anti-helminthic therapy, including the exploration of optimized delivery strategies of ivermectin and albendazole, the discovery and development of new antibiotics for anti-wolbachial chemotherapy and macrofilaricidal antihelminthics.

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Introduction

Despite their high morbidity and negative impact on the local health services and economic development, infections by gastrointestinal or tissue-dwelling worms have only recently been recognized as neglected tropical diseases (NTDs) due to a lack of research and financial support compared to other diseases such as malaria, HIV and tuberculosis [1]. Currently more than one billion humans are parasitized by helminths worldwide, including more than 150 million cases of filarial nematode infections. The most important human-pathogenic filarial nematodes are *Wuchereria bancrofti, Brugia* spp. (lymphatic filariasis), *Loa loa* (loiasis) and *Onchocerca volvulus* (onchocerciasis). The resulting lymphatic, ocular and dermatological diseases have both economic and social consequences including poor school performance, low productivity, low income, high health related costs among infected adults, and a reduced life span, altogether adding up to an annual loss of 6.3 million DALY's (disability adjusted life years, disease burden metric combining mortality and morbidity accounting for years of life lost) [2].

All filarial nematodes have similar life cycles composed of the mammalian (human) definitive host and an obligate, blood-feeding insect vector (mosquitoes or flies of different genera) (http://www.cdc.gov/parasites/az/index.html). The adult worms are sexually dimorphic and mate within the definitive host. Female worms release larvae into the host tissue for most of their lifespan. The first stage larvae, called microfilaria (MF) migrate to their preferred tissue local (skin or blood) where they will be taken up by the insect vector. This intermediate host is required for development into the infectious third stage larval form (L3) which then migrates to the mouthparts of the vector. During the next blood meal, L3 are deposited on the skin of the bitten host, enter through the bite wound and migrate to their species-specific preferred tissue location to develop into adults and mate.

Onchocerciasis, caused by the filarial nematode *O. volvulus*, affects 37 million people worldwide and has constituted a major cause of infection-induced blindness in endemic regions, especially sub-Saharan countries in Central and West Africa [3] and formerly also in Central and South America [4]. Female worms, which reside in subcutaneous onchocercomata (or simply "nodules"), produce millions of MF in their lifetime. It is this parasitic stage that causes severe and debilitating skin disease (Figure 1B) and eye-related pathology, because MF migrate through the skin, many even passing through the anterior chamber of the eye. In a highly infected individual, over 50,000 MF can be produced on a daily basis. Since MF have a limited life span, antigen release by dying MF can induce an inflammatory reaction involving neutro-

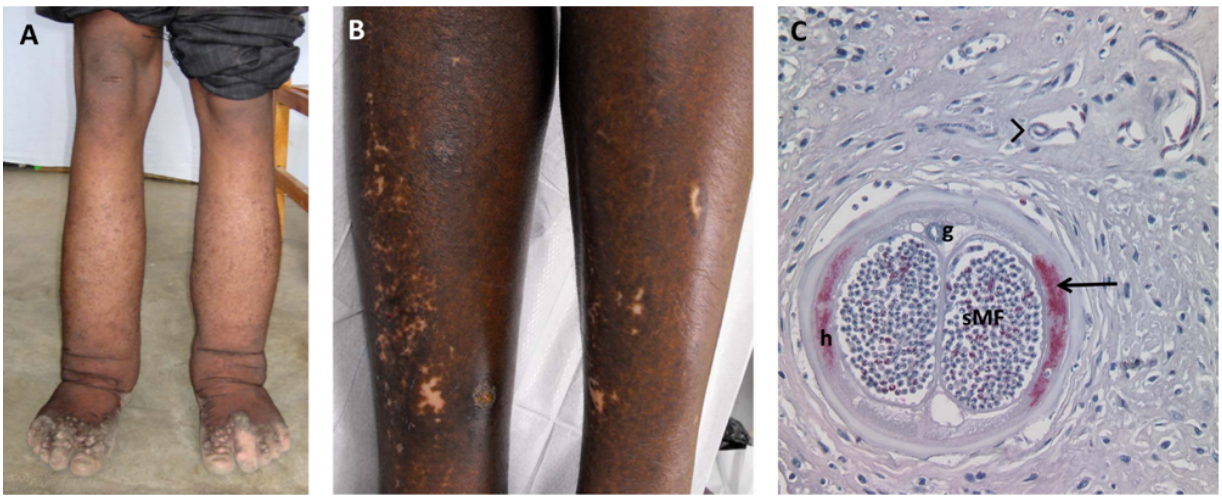

Figure 1: Filarial pathological outcomes

A) Lymphoedema and elephantiasis related to lymphatic filariasis. B) Depigmentation dermatitis (leopard skin) after chronic exposure to MF in onchocerciasis. C) Cross-section of an *Onchcerca volvulus* female, anti-WSP (*Wolbachia* surface protein) stain, h = hypodermis, g = gut, sMF = stretched MF within the uterus, arrow head = free MF within nodular tissue, arrow = *Wolbachia* in the hypodermis.

phils, eosinophils and macrophages. Cellular and humoral reactions to MF are usually strong in primarily infected individuals, killing the MF and often causing pathology with T helper type-2 immune responses being a major defence mechanism against the parasites. This immune reaction is even more apparent in a minority of infected individuals that develop a chronic hyperreactive form of the infection (known as sowda). Sowda is characterized by a sustained and strong immune response that is able to kill the MF at the expense of skin integrity and the individual's wellbeing. Control of the parasites is associated with high IgE and IL-4 responses as well as IL-5 and eosinophilia. In individuals infected with *O. volvulus* IL-5 is inversely correlated with the number of MF [5].

Infection with *L. loa* is confined to Africa. The adult worms also reside in the subcutaneous tissues but different to *O. volvulus* they migrate continuously and can cause a local immune reaction known as Calabar swelling. The worms also occasionally cross through subconjunctival tissues, where they can easily be observed. This manifestation resulted in the colloquial name "tropical eye worm", which should not be confused with ocular damage induced by *O. volvulus*, where the MF stage but not the adult invades deeper eye tissues. However, this parasite has gained attention in recent years due to the fact that increasing mass administration efforts to control onchocerciasis are associated with increased severe adverse events when the individuals were coinfected with *L. loa*. This is due the rapid killing of MF following drug intake [6]. Individuals with *L. loa* MF levels of >30,000 per ml blood are at higher risk of developing severe adverse events (SAE) [7]. Patients may experience symptoms of encephalopathy leading to a dysfunctional central nervous system that can manifest as coma and even death in rare cases. The mechanisms associated with the neurologic SAEs are poorly understood, but they have been associated with retinal haemorrhages and exudates evocative of an obstructive process and similar processes may occur in the brain [8].

An estimated 120 million people are infected with the filarial nematodes *Wuchereria bancrofti, Brugia malayi* and *B. timori*, the causative agents of lymphatic filariasis (LF). These parasites are evolutionary closely related and, whereas onchocerciasis is present only in Africa and the Americas, LF also occurs in India, Southeast Asia, the Caribbean and the South Pacific. Among adult residents of endemic areas, up to 12.5% have clinical manifestations [9] that develop progressively and may result in elephantiasis (Figure 1A) or hydrocoele. The adult worm resides in the lymphatic vessels and the MF released by the female worm migrate to the peripheral blood. Clinical symptoms include filarial fever, retrograde lymphangitis and lymphadenitis. During chronic infection these are followed by pathological changes including lymph fibrosis, subclinical lymph vessel dilation and extravasation of lymph fluid into the surrounding tissue. Two polar forms of the disease exist, one being presence of MF with high numbers of parasites and a down-regulated immune response, the other being absence of MF with few or no parasites but strong specific immune reactions, which eventually may cause lymphoedema or hydrocoele. Lymph vessel dilation is an early event following antigenic stimulation, which occurs while the adult worms are still alive, i.e. when offspring larvae are released. Many of these larvae are degenerated and will be taken up by phagocytic cells. It is known that exposure of phagocytes to filarial antigens is accompanied by triggering of the innate immune system with the release of proinflammatory cytokines, but also the release of molecules that promote lymphangiogenesis [10]. Further antigen release occurs when adult worms die naturally or are killed by chemotherapeutics. In addition to antigens derived from the worm itself, those from the obligate, intracellular *Wolbachia* bacteria that are present in many, i.e. *W. bancrofti, Brugia* spp., *O. volvulus*, but not all, i.e. *L. loa*, filarial

species appear to play a major role in pathogenesis, adding a type-1 response signature to the immunological profile of a filarial infection.
Reactivity however decreases with increasing worm burden in the majority of patients, leading to an adaptation in favour of both the parasite and the host. The immunological profile of these patients is hyporeactive and immunosuppressed, thus their immune system tolerates high MF loads (millions in the skin or blood) and reacts only against damaged and immobilized MF and adult worms rather than killing viable MF [11]. Proinflammatory responses are dampened by the induction of regulatory responses including antigen-specific regulatory T cells (Treg). Such Tregs have been localized within the subcutaneous nodules and constitute a portion of the peripheral blood lymphocytes. The presence of Tregs has been associated with high levels of IL-10, TGF-β and non-complement activating and therefore immunosuppressive immunoglobulin (Ig) G4 [12]. In fact, our recent data show that Tregs preferentially induce IgG4 secretion from B cells in a cell-contact, IL-10 and TGF-β dependent manner [13]. This is in contrast to other effector T cell populations that strongly induce IgE and other IgG subclasses. A complex response such as immunosuppression is usually based on several mechanisms, therefore it is not surprising that in patients tolerating high MF loads, adaptive immune responses were reduced [14], and that MF-positivity was associated with the presence of macrophages with an alternatively activated phenotype, another hallmark of immunosuppression [15]. Despite this immune regulation that is beneficial for the parasite and its host, many individuals suffer from disease-induced pathology and treatment is indispensable.

Interventional drugs

Three drugs have been implemented within mass chemotherapy programmes to fight filariasis: ivermectin (IVM) and diethylcarbamazine (DEC) used singly or in combination with albendazole (ALB). IVM is a macrocyclic lactone that is exceptionally potent against nematodes and ectoparasites. In filarial infections IVM treatment causes prolonged disappearance of MF from the skin or blood, but without a pronounced killing of adult worms. It acts by opening glutamate-gated Cl^- channels (GluCls). Those molecules are encoded almost exclusively in the genome of the phyla Nematoda and Arthropoda, thereby limiting therapeutic action to these organisms [16]. Interestingly, IVM has limited or no evident effect on MF under *in vitro* culture conditions [17], yet it exerts a fast, profound and highly potent anti-microfilarial effect in the parasitized host, suggesting that the host immune system plays a role in the elimination of microfilariae. This is supported by the finding that the number of eosinophils surrounding MF within lymph nodes increased 100-fold in response to IVM and MF within the nodules were attacked by eosinophils, neutrophils and macrophages [18]. GluCls have recently been identified in the muscle surrounding the excretory vesicle rather than in the pharyngeal or somatic neuromuscular system in the filarial nematode *B. malayi* [19]. Ivermectin treatment was able to block the release of excretory/secretory (ES) products *in vitro*. Thus, the hypothesis has been made that when ES product release including those with immunosuppressive activity is blocked, it may inhibit parasite induced immune evasion and therefore worm survival. This in turn would allow the host's immune system to destroy MF. Whether the aforementioned potential mechanisms are the mode of action of IVM in the human host remains to be elucidated.
Diethylcarbamizine is a piperazine derivate that is active against all life cycle stages present in humans. Similar to IVM, it requires the presence of the host's immune system, as indicated by the species-dependent range of poor *in vitro* activity against MF. In contrast, when given to an infected mammalian host, DEC leads to a rapid decline in circulating MF and causes approximately 40% mortality of adult parasites, when used at clinical doses [20]. DEC treatment facilitates adherence of immune cells to MF followed by their destruction through antibodies, complement and toxic molecules derived from granulocytes and macrophages. It has been shown in mice to interfere with arachidonic acid metabolism in both the parasite [21] and the host [22], leading to vasoconstriction, amplified endothelial adhesion and immobilization of MF that enhances adherence and cytotoxic activity by host platelets and granulocytes. However, despite its introduction many years ago, no clear understanding of the mechanism of action exists. Adverse reactions that are associated with the rapid killing of the parasite can occur after DEC intake. Therefore, DEC is not used for MDA in Africa, where onchocerciasis is endemic in order to prevent local inflammation in patients with ocular MF [3].
Albendazole is a carbamate benzimidazole originally developed for veterinary use. It is a broad-spectrum antihelminthic whose effect was originally observed against intestinal helminths, but later discovered to also be effective against systemic helminth infections. Different to IVM, ALB interferes with a number of different sites that are involved in energy metabolism with the final common pathway leading to disruption of the nematode microtubule cytoskeleton by inhibition of tubulin polymerization [23]. ALB at a dose of 400 mg is routinely used in annual mass treatments together with DEC or IVM in lymphatic filariasis control programmes. Whether the addition of ALB enhances microfilaricidal or macrofiliaricidal activity is currently debated [20]. However, its activity against gastrointestinal nematodes may enhance compliance to control programmes due to the health benefits that are directly observable by the infected persons when they are often unable to see improvement in their filarial infections status, i.e. killing of MF.
To control filarial infections, communities participate in what is known as mass drug administration (MDA). Rather than identifying every individual that is infected, MDA relies on the treatment of every individual in meso- to hy-

perendemic communities. This is possible using IVM, DEC and ALB, which are safe for most members of a community to take without extensive medical supervision on an annual basis.

Programmes to control filarial infections

The first programme to be initiated was the Onchocerciasis Control Programme (OCP) in the 1970's aiming at the elimination of onchocerciasis as a public health problem. OCP greatly improved the situation in Africa through control of the *Simulium* vector by insecticide spraying to prevent transmission of the disease in 11 West African countries. Some regions have since become free of onchocerciasis for 20 years [24], [25]. However, vector control, whilst dramatically successful when implemented, is unsustainable, and as soon as it ceases, vector flies may repopulate the endemic areas and are capable of re-establishing disease transmission. Subsequently, IVM was introduced as treatment for onchocerciasis in the 80's. The success of IVM led its manufacturer, Merck & Co, to establish the Mectizan Donation Programme in 1988 to provide medical, technical and administrative support for the free distribution of IVM for treatment of onchocerciasis. The standard regimen of IVM in onchocerciasis is 150 µg/kg, since higher concentrations have not been shown to enhance activity [26], [27]. With high efficacy against MF, it leads to a marked and prolonged reduction of MF in tissues as well as the reproductive capacity of adult female worms. This regime is therefore very effective at reducing morbidity and is a substantial benefit to the individual as well as the community and has been calculated to have averted 8.2 million DALYs between 1995–2010 [28] within the African Programme for Onchocerciasis Control (APOC, http://www.who.int/apoc/en/). This programme was initiated in 1995, with the purpose of providing systems for distributing IVM by local communities across Africa. Critically, IVM is microfilaricidal, i.e. lethal to the pathogenic microfilariae, but has only limited effects on adult worms [29]. Therefore, a few months after IVM administration, female worms resume MF production to levels high enough to continue transmission to uninfected people. Thus, many repetitive cycles of IVM treatment are required for the life span of the adult worms that can live an average of 15 years. In the Americas, the introduction of the Onchocerciasis Elimination Program of the Americas (OEPA, http://www.cartercenter.org/health/river_blindness/oepa.html) has significantly reduced the community microfilarial load [4]. OEPA has provided encouraging evidence that elimination (interruption of transmission in a limited geographical area) and possibly also eradication (worldwide interruption of transmission) may be achieved [30] when high coverage including several rounds of drug application per year is maintained. However, different obstacles have to be faced in Africa such as the presence of more efficient vectors, increased genetic diversity and larger foci to be treated [31].

In 2000 the Global Programme to Eliminate Lymphatic Filariasis was launched (GPELF, http://www.filariasis.org/) to eliminate LF by 2020. With a combination of IVM/ALB or DEC/ALB the aim is to interrupt transmission of blood-circulating MF to mosquito vectors [3]. Examples for the success of GPELF in which transmission has been interrupted are reported from some parts of Nigeria, in Egypt and in Togo with microfilaredemia levels below 1% [30]. In 2010, South Korea was the second country after China to announce the elimination of the disease [32], [33]. China achieved this goal by making DEC fortified cooking salt available to its population. This approach is also under discussion for other areas, in particular those with high transmission and limited success with other approaches so far. There is evidence that in LF the addition of ALB prolongs the time span for which the individual remains amicrofilaremic. Currently, in an attempt to develop joint programmes for neglected tropical diseases, several African countries are developing national regimes, where in areas coendemic for LF and onchocerciasis, IVM and ALB are used. Controlled studies are currently investigating whether individuals benefit from the addition of ALB (e.g. DOLF, http://www.dolf.wustl.edu/).

Anti-wolbachial therapy

The discovery of the essential role of *Wolbachia* in worm fertility and survival has resulted in the development of an alternative anti-filarial chemotherapy using doxycycline (Figure 1C), which depletes the *Wolbachia* endosymbionts from the worm [34]. In lymphatic filariasis, this treatment resulted in a high macrofilaricidal (adult worm killing) effect with a much better efficacy than the MDA combination used in Africa, i.e. IVM plus ALB [35]. Similar results were obtained in onchocerciasis [36] and mansonellosis [37], another human filarial disease that has generally few disease symptoms. Studies for the evaluation of treatment regimens have shown that duration of doxycycline therapy could be reduced from the initial 6 weeks to 3 and 5 weeks for LF and onchocerciasis, respectively, to achieve permanent worm sterility [3].

In addition to the importance for worm survival, *Wolbachia* are also activators of innate immunity. This has been shown in different model systems, ranging from *in vitro* cell culture assays to animal models [5]. Removal of the bacteria not only reduces eye pathology in a murine model of onchocercal antigen induced ocular disease [38], but also in the release of lymphangiogenic factors in humans, which precedes lymphatic vessel dilation in humans [39]. The cascade begins with the activation of the innate immune system that can result in the induction of members of the VEGF-family. We have observed that VEGF-A/C/R3 levels are increased in patients with lymphatic filariasis and even more so in those with lymphoedema. Other parameters may also be correlated with chronic manifestations [40]. Following *Wolbachia*

depletion by doxycycline there is a reduction in VEGF-C/R3 levels that leads to a reduction in lymph dilation and improvement of early stage lymphoedema symptoms [39] and hydrocoele [41]. This is a major advantage of doxycycline over other drugs, as no other treatment besides hygiene and costly surgical procedures are available to improve filarial disease symptoms. The benefits of hygiene are limited and quickly lost when not maintained.
It is important to note that when lymphoedema or hydrocoele has progressed, in many cases adult worms are no longer detectable. A recent placebo-controlled, double-blind study compared doxycycline treatment in pathology patients with and without active worm infection, which can be differentiated by measurement of circulating filarial antigen (CFA) [42]. This study showed an improvement of lymphoedema in both patients with ongoing infection (CFA positive), thus harbouring *Wolbachia* as targets for doxycycline, and also in patients without ongoing infection. This has been explained by off-target drug effects of doxycycline, i.e. direct antiproliferative effects on mammalian cells. This finding offers, for the first time, a medical treatment and prevention for all people suffering from filarial lymphoedema.
Despite the many positive effects of doxycycline therapy, it is of limited suitability for MDA due to a longer treatment time, the contra-indications for children under 9 years of age and pregnant or breast-feeding women, two groups that cannot be ignored if the necessary coverage needed to eliminate onchocerciasis and LF is to be achieved. With these considerations in mind, anti-wolbachial therapy has been approved and is recommended for individual drug administration (IDA) [43].

The need for new drugs

A major problem with the current control MDA is that while IVM and DEC efficiently kill MF, they have limited efficacy against adult worms and do not permanently stop MF production. Simulation studies have suggested that giving IVM at 6 or 12 month intervals has a high likelihood of eliminating the infection [44], [45], but incurring large logistical costs on the health infrastructures of the endemic countries. Given the longevity of adult worms (>10 years), a high-coverage (>80%) and many rounds of treatment required, the set goal of elimination in a majority of endemic countries may extend given time lines. In many mainly African countries MDA has not even begun or is behind schedule. An assessment of the impact of IVM on transmission showed that, while community microfilarial loads can be reduced to near zero and prevalence can be low, well documented situations exist where transmission is continuing even after 10–17 years of IVM treatment [46], [47]. Immigration of infected persons from such foci into areas where filariasis is considered eliminated and IVM treatment has ceased may occur. Not only may this lead to rapid re-emergence of the infection but, because these populations may not have been exposed to challenge, or even if they were whilst receiving IVM, they may be fully susceptible to the parasites [48]. Consequently, new infections may present higher worm burdens and microfilarial loads. For the individual this can result in more severe disease, while at the community level transmission potential is increased.
Another challenge for stakeholders and researchers are areas where *L. loa* is coendemic. In these communities MDA programmes have not been implemented due to the risk of severe adverse events in coinfected patients due to rapid killing of MF [6]. Also, difficult financial and logistical situations remain in unstable regions of Africa, e.g. Democratic Republic of Congo, Congo, Central African Republic, Angola and Liberia.
Equally important is the fact that indication of IVM resistance is emerging [49], [50], which have alerted experts in the filariasis community since there is currently no alternative treatment suitable for mass administration. The poor responsiveness may be due to genetic selection of adult parasites that are simply less susceptible to the drug. For example, genomic analysis of several strains of *O. volvulus* has revealed a significant loss of diversity in the P-glycoprotein gene after repeated rounds of IVM. The same group has also found a significant selection pressure on the β-tubulin I gene after IVM treatment. IVM selected for one allele that was extremely rare in *O. volvulus* populations that had not been under IVM pressure [51], [52]. Interestingly, homo- or heterozygosity of the respective allele could be associated with female worm fertility [53].
The observation of a quick repopulation of MF after IVM can be infrequently observed also in an IVM-naïve individual revealing another important potential cause for suboptimal performance of IVM, i.e. the genetic background of the host. A recent study has indicated the presence of single nucleotide polymorphisms (SNPs) within the MDR1, CYP3A4, and CYP3A5 genes, encoding proteins known to be involved in drug excretion/inactivation, to be more frequent in individuals responding poorly to IVM, suggesting that host genetics may contribute to a reduced efficacy of IVM [54].
However, in individuals lacking the ability to kill MF, one could easily overlook immunological adaptation as a possible explanation, as suggested in a study in which MF repopulated more rapidly after initial MF disappearance in patients after several rounds of IVM [55]. Recently, we have observed in a small number of nodules that the expression of the immunosuppressive cytokine TGF-β as well as IgG4 is elevated following repeated IVM applications but not after doxycycline [56]. Furthermore, epidemiological data suggest the presence of a sustained immunoregulatory environment after 16 years of MDA rather than a reestablishment of Th1 or Th2 responses [57]. If this applies, suboptimal responses will be observed in the future in many areas where onchocerciasis is to be controlled by long-term mass administration of IVM and thus will have tremendous practical implications for public health, such as the necessity for prolonged or more frequent IVM application with less time intervals between the applications.

Although anti-wolbachial therapy with doxycycline does achieve permanent sterilization and killing of adult worms, it is less suitable for MDA due to the reasons outlined above. On the other hand, the macrofilaricidal effect of anti-wolbachial therapy results in the slow death of the adult worms [3]. This "soft kill" is a desired outcome in order to reduce the rapid release of antigens that can induce a strong pro-inflammatory response and thereby adverse side effects. However, the shortest regime that achieves the desired positive effects is three weeks of daily doxycycline treatment. This approach however can be used for problem areas, such as those with IVM resistance or in areas where *L. loa* coinfections occur. It may also be used for other special intervention zones, such as "end-game" scenarios, when smaller areas are reaching possible elimination. At this time point, treatment will be shifted from MDA to the finding of index cases and followed by test & treat strategies, the application of doxycycline will be a cost effective option.

Investigational drugs and treatments

Since the benefits of anti-wolbachial therapy are great, research has been focused on discovering new or repurposing current antibiotics without the caveats of doxycycline. Within the Anti-Wolbachial Consortium (A-WOL, http://www.a-wol.net/), scientists screened existing drug libraries for such compounds. In addition, the target based search for new anti-wolbachial drugs was aided by identification of the essential gene set of *Wolbachia* bacteria based on comparison of the *Wolbachia* spp. genomes with the prokaryotic Database of Essential Genes (DEG) and subtracting out those with orthologues in eurkaryotes [58]. By mining the *Wolbachia* DEG one can find gene products or pathways that have been validated in several other prokaryotic systems and therefore should represent the best candidates for a target based discovery model.

One such essential target identified in the *Wolbachia* DEG was the bacterial DNA dependent RNA polymerase (RNAP). The RNAP is a well-studied target of antibiotics, e.g. the rifamycins [59]. For this reason, rifampicin has also been tested against filarial worms and has proven to effectively deplete *Wolbachia* and result in the expected positive phenotypes seen with doxycycline treatment [60], [61], [62]. RNAP is also inhibited by the natural compound corallopyronin A [63]. It has a binding site and mode of action different from the rifamycins and is therefore effective against rifampicin-resistant *Staphylococcus aureus* [63], [64]. The efficacy of corallopyronin A against *Wolbachia* RNAP was examined in insect cells infected with *Wolbachia* and *in vivo* in *L. sigmodontis* worms. Corallopyronin A proved highly effective against *Wolbachia* in the cell line and was equivalent to doxycycline or rifampicin [65]. More importantly, corallopyronin A was effective at depleting the endobacteria from filarial worms in the *L. sigmodontis* rodent infection, demonstrating that it is bioavailable, and depletion resulted in a block in larval development seen with all previous anti-wolbachial antibiotics.

Another validated target from the *Wolbachia* DEG is the second protein in the heme biosynthesis pathway ALAD (δ-aminolevulinic acid dehydratase). Heme is important for energy metabolism, molting, detoxification, and other metabolic processes in the worm, yet the filarial genome does not encode all of the proteins necessary for the *de novo* synthesis of heme and are therefore dependent upon their endosymbionts or parasitized host for this necessary co-factor [66]. Using a high-throughput, simplified enzymatic assay screen, a species-specific inhibitor of ALAD from *Wolbachia* (wALADin1) has been identified. It is effective in the low micromolar range, has a novel mode of action, and kills *L. sigmodontis* worms in culture, making wALADin1 an exciting scaffold molecule for further medicinal chemistry to develop a new anti-wolbachial drug [67].

Other targets of interest include components of the cell wall and outer membrane, other co-factor synthesis pathways, and proteins that can be dysregulated so that they are overactivated. It has been shown *in vitro* that the *Wolbachia* cell biosynthesis, as in most bacteria, is an ideal target for antibiotics that is being taken advantage of by several groups [68], [69], [70]. The riboflavin pathway is also a validated target for drug discovery due to the fact that the *Wolbachia* genome encodes the necessary proteins, but the nematodes do not [71], [72]. Finally, new drugs need not only be inhibitory, they can also be effective if they dysregulate enzyme activity. This has been shown for the ClpP protease that is involved in degrading misfolded or damaged proteins [73]. Recently it has been shown that acyldepsipeptides, which alter ClpP activity such that it indiscriminately digests flexible proteins, deplete *Wolbachia in vitro*, opening up a new avenue of drug development [74].

The development of antihelmintic reagents that safely kill the adult worm remains a major goal of research activities. Developed in the 1970's, flubendazole is another benzimidalzole currently registered for use against intestinal helminths. In a number of experimental filarial models, flubendazole has shown 100% efficacy against adult worms. Interestingly, it does not target the microfilarial stage, giving an additional advantage in areas where *L. loa* infection coincides. However, the formulation of this drug has low oral bioavailability accompanied by side effects. Current approaches to apply new oral formulation techniques may enhance the potential to develop flubendazole as a macrofilaricide [75]. Moxidectin is another anti-filarial drug currently in a Phase III trial (unpublished). Being a macrocyclic lactone, it is closely related to IVM, but has a longer half-life. Therefore moxidectin might be more efficacious than IVM when given on an annual basis [76].

Conclusion

Research in the field of neglected tropical diseases, in particular filariasis, has led to a broad understanding of the interaction between the parasite and the host. In the light of global efforts to eliminate filarial infections, this research will help to understand mechanisms of re-emergence of the disease, drug resistance or to identify new drug targets. The development and implementation of new drugs or improvement of existing regimens are needed to fill present or emerging gaps to achieve filariasis elimination in a reasonable time frame in the future.

Glossary

APOC – African Programme for Onchocerciasis Control
CFA – Circulating Filarial Antigen
DALY – Disability Adjusted Life Years
DEC – Diethylcarbamazine
DEG – Database of Essential Genes
ES – Excretory/Secretory products from filarial worms
GPELF – Global Programme to Eliminate Filariasis
IDA – Individual Drug Administration
IVM – Ivermectin
L3 – Third stage larvae
LF – Lymphatic filariasis
MDA – Mass Drug Administration
MF – Microfilariae, first stage larvae
NTD – Neglected Tropical Diseases
OCP – Onchocerciasis Control Programme
OEPA – Onchocerciasis Elimination Program of the Americas

Notes

Competing interests

The authors declare that they have no competing interests.

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