International Journal of Antimicrobial Agents 54 (2019) 134–142

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Ivermectin: From theory to clinical application

Dalia S. Ashour

Medical Parasitology Department, Faculty of Medicine, Tanta University, Tanta, Egypt

ARTICLE INFO

Article history:
Received 14 January 2019
Accepted 1 May 2019

Editor: Paul Tulkins

Keywords:
Ivermectin
Mectizan
Filariasis
Onchocerciasis
Mass drug administration
Nanoformulation

ABSTRACT

Approximately 250 million people have been using ivermectin (IVM) annually to combat many parasitic diseases including filariasis, onchocerciasis, strongyloidiasis, scabies and pediculosis. Many clinical studies have proven its efficacy against these diseases and have reported the optimum dose and duration of treatment. Moreover, its antiparasitic range has increased to cover more parasitic infections, but it still requires further exploration, e.g. for trichinosis and myiasis. Furthermore, IVM showed high efficacy in killing vectors of disease-causing parasites such as mosquitoes, sandflies and tsetse flies. The World Health Organization (WHO) has managed many control programmes involving the use of IVM to achieve elimination of onchocerciasis and lymphatic filariasis and to reduce malaria transmission. However, IVM is not exempt from the possibility of resistance and, certainly, its intensive use has led to the emergence of resistance in some parasites. Recent research is investigating the possibility of novel drug delivery systems for IVM that increase its potential to treat a new range of diseases and to overcome the possibility of drug resistance. This review highlights the most common human uses of IVM, with special reference to the new and promising properties of IVM.

1. Introduction

Campbell and Omura were awarded the 2015 Nobel Prize in Physiology or Medicine for their discoveries regarding avermectin [1]. The avermectins were discovered in 1967 in fermentation broth of an actinomycete culture in Japan [2]. It was then found that avermectins are produced by *Streptomyces avermitilis* in the soil [3,4]. The avermectins are a class of macrocyclic lactones (MLs) with nematocidal, acaricidal and insecticidal activities [2]. MLs, including the avermectins, have gained a valuable therapeutic role since the 1980s as antiparasitic drugs for animals and humans [5].

The first avermectin drug was introduced as a veterinary drug by Merck & Co. in 1981 [6], and new formulations of ivermectin (IVM), a derivative of avermectin, were released almost every year. There was very little motivation to produce IVM for the human health market until its efficacy against filarial nematodes was shown. IVM was first registered as a human drug under the brand name Mectizan® in 1987 and was first used to treat onchocerciasis in humans in 1988 [7]. IVM was the only member of the MLs approved for human use until the recent approval of moxidectin by the US Food and Drug Administration (FDA) in June 2018 for the treatment of onchocerciasis in humans [8]. They have been labelled as 'wonder drugs' [9].

IVM is a derivative of naturally-produced avermectin B_1, comprised of approximately 80% 22,23-dihydro-avermectin B_{1a} (molecular weight, 875.10 g/mol) and approximately 20% 22,23-dihydro-avermectin B_{1b} (molecular weight, 861.07 g/mol) [10]. Oral IVM is the only licensed route of administration for human use, although it has been given successfully subcutaneously and topically [11,12].

IVM is incompletely absorbed following oral administration, with a peak plasma concentration achieved in approximately 4 h. Oral IVM is available in different forms, i.e. solution, tablets or capsules, however the solution has approximately twice the systemic availability compared with the solid forms (tablets and capsules). Owing to the high lipid solubility of IVM, its administration following a high-fat meal increases its bioavailability by approximately 2.5-folds [5]. IVM is metabolised in human liver microsomes by a cytochrome P450 (CYP) enzyme, converting the drug to at least 10 metabolites, mostly hydroxylated and demethylated derivatives [13]. IVM and its metabolites are excreted mainly in the faeces in about 12 days. Only small amounts (<1%) are excreted in urine. The plasma half-life of IVM ranges from 9.8–14.3 h and about 3 days for the metabolites [5].

IVM is an endectocide, i.e. active both against endoparasites and ectoparasites. Beside filarial nematodes, IVM is effective against a number of soil-transmitted helminths, myiasis and scabies. Since its discovery, the antiparasitic uses of IVM have increased and continue to accumulate [1].

This review highlights the most common clinical uses of IVM, with special reference to the promising impact of IVM against

E-mail addresses: daliaashour1@gmail.com, dalia.ashour@med.tanta.edu.eg

https://doi.org/10.1016/j.ijantimicag.2019.05.003
0924-8579/

other parasitic infections as well as the new formulations of IVM and their progress in the field.

2. Mechanism of action

MLs affect various life stages of many nematode and arthropod species, which can be attributed to modulation of the Cys-loop family of ligand-gated ion channels including glutamate-gated chloride channels (GluCls) [14]. IVM increases chloride conductance resulting in a long-lasting hyperpolarisation and less formation of action potentials and blocking of further functions [15]. It affects the motor neurons, interneurons and pharyngeal muscle cells leading to general locomotor paralysis, and also affects feeding *via* inhibition of pharyngeal pumping [16]. GluCls have recently been characterised in *Anopheles gambiae* mosquitoes, where they are predominantly expressed in the motor and sensory systems, which explains the reduced fertility and paralytic effects even at sublethal drug concentrations [14,17].

Many studies have shown that the activity of IVM may not be limited strictly to the neurophysiology of parasites but may also influence the host immune response [18], which may be an essential part of IVM's action. Moreno et al. identified ML receptor sites (a subunit of AVR-14 GluCls) in microfilariae of *Brugia malayi* [19]. These receptors are located exclusively close to the excretory–secretory (ES) apparatus. It was found that MLs induced a decrease in ES protein release from microfilariae and juvenile filariae as well as uterine fluid secretion from adult worms. ES proteins have immunomodulatory properties that allow the parasite to evade the host's innate immune system. Therefore, under the effect of MLs, the microfilariae and worms are recognised as foreign entities, followed by a systemic immune response capable of clearing the parasite with development of a memory response affecting new filarial infections [19–22]. Moreover, Sajid et al. demonstrated the immunostimulatory effect of IVM at therapeutic doses [23]. IVM treatment activates neutrophils and increases C-reactive protein and interleukin-6 (IL-6) levels in onchocerciasis patients [24,25]. Similarly, Vatta et al. showed that the *in vitro* serum-dependent adherence of peripheral blood mononuclear cells and neutrophils from dogs to *Dirofilaria immitis* microfilaria is increased by incubation with IVM [26].

Furthermore, the host immune response is required for full activity of MLs, as suggested from the higher efficacy observed in vivo as well as differences between the concentrations required *in vitro* and *in vivo*. It has been found that the efficacy of IVM is decreased in the treatment of patients co-infected with human T-cell lymphotropic virus type 1 (HTLV-1) and strongyloidiasis, mainly due to impairment of the Th2 immune response against *Strongyloides stercoralis* induced by the effect of HTLV-1, such as decreased IL-4 and IL-5 and lower levels of serum immunoglobulin E (IgE). Thus, it is likely that the efficacy of the drugs depends on an intact immune response [27].

3. Current clinical uses of ivermectin

IVM use has increased worldwide to overcome many parasitic diseases infecting millions of people, such as strongyloidiasis (infecting about 100 million people) and onchocerciasis (infecting about 18 million people) [28].

3.1. Lymphatic filariasis

Lymphatic filariasis is a mosquito-borne disease affecting approximately 120 million people worldwide, with approximately 36 million infected individuals seriously incapacitated or disfigured. Lymphatic filariasis is caused by either *Wuchereria bancrofti* in the tropics and subtropics or by *B. malayi* and *B. timori* in Southeast Asia [29,30]. These infections lead to lymphatic dysfunction resulting in progressive and irreversible swelling of the limbs, breasts and genitals [31].

Yates and Wolstenholme [32] and Ottesen et al. [33] demonstrated that IVM produced an initial considerable decrease in levels of circulating microfilariae, followed by long-term suppression of their production. The standard treatment is 150–200 μg/kg body weight. At these doses, the main actions are killing of microfilariae and long-term sterility of adult worms [22].

Interestingly, antibiotics such as doxycycline have been shown to increase the concentration of MLs in host cells [34]. A combination of doxycycline and IVM provides antifilarial effectiveness of approximately 80% compared with 9% for treatment with doxycycline alone [35,36]. Doxycycline, a macrofilaricidal drug, targets *Wolbachia* bacterial endosymbionts that are crucial for the survival of adult filarial worms [37].

The Global Programme to Eliminate Lymphatic Filariasis (GPELF) in endemic areas includes IVM in its mass drug administration (MDA) strategy to prevent the spread of infection. A combination of 150 μg/kg body weight IVM plus 400 mg albendazole is expected to reduce microfilariae, thus decreasing infection of the intermediate mosquito host [38] (Table 1). Recently, a single dose of triple therapy with IVM, diethylcarbamazine and albendazole was approved and was shown to be superior to other elimination programmes for lymphatic filariasis [40].

3.2. Onchocerciasis

Onchocerciasis is caused by the filarial worm *Onchocerca volvulus* through the bite of *Simulium* vector flies (so-called blackflies). This infection causes irreversible eye damage such as sclerosing keratitis and iridocyclitis and finally blindness, thus this disease is also known a 'river blindness'. It is one of the most important causes of infectious blindness worldwide, second to trachoma [41]. It has been estimated that approximately 18 million people are infected by *O. volvulus* and approximately 120 million people are at risk worldwide [42].

In cases of onchocerciasis, IVM rapidly decreases the number of microfilariae in the skin, thus reducing patient morbidity and preventing transmission to a subsequent vector [43]. Moreover, IVM causes long-term sterility of female worms, which eliminates the microfilariae population for several months. The highest microfilaricidal effect is at 30 days post-treatment. However, IVM does not kill the adult worms [22,44,45].

The recommended dose for treatment of onchocerciasis in endemic areas is a single oral dose of 150 μg/kg IVM every 6–12 months [44]. Since IVM has been used in the annual mass treatment of onchocerciasis in endemic areas, a reduction in the transmission and prevalence of infection was reported [46] (Table 1).

Similar to lymphatic filariasis, treatment with doxycycline and IVM is believed to cause microfilarial death by IVM and macrofilarial death by doxycycline. Thus, this combined approach allows the control of onchocerciasis whereby all stages of the worm's life cycle can be targeted [48,49].

3.3. Strongyloidiasis

Strongyloidiasis is caused by infection with *S. stercoralis*, which is acquired through direct contact with contaminated soil. Approximately 30–100 million people are infected worldwide. Strongyloidiasis usually presents with mild symptoms, however it may be severe and life-threatening in cases of immunodeficiency [50,51].

IVM is the drug of choice for treatment of strongyloidiasis. Satou et al. assessed the effect of IVM against *Strongyloides* larvae and found that IVM caused a satisfactory decrease in their viability [52]. The recommended dose is subcutaneous injection

Table 1
Mass drug administration (MDA) of ivermectin (IVM) in control programmes.

Programme	Organisation	Disease	Mode of IVM administration	Year	Area	Progress	Reference
Global Programme to Eliminate Lymphatic Filariasis (GPELF)	World Health Organization (WHO)	Lymphatic filariasis (LF)	Alb + IVM or Alb + DEC once/year for ≥5 years	2000	Americas	China and the Republic of Korea have eliminated LF in 2007 and 2008, respectively. Of 73 countries endemic for LF, 18 countries have completed interventions. Mass treatment is ongoing in 45 countries. An additional 22 countries had delivered MDA in all endemic areas and are also on track to achieve elimination. The remaining 33 countries have not been able to achieve 100% geographical coverage. Ten countries must initiate preventive chemotherapy or submit evidence that MDA is not required.	[39]
Onchocerciasis Elimination Program for the Americas (OEPA)	Pan American Health Organization (PAHO)	Onchocerciasis	Biannual IVM + vector control	1992	America (13 areas in 6 countries; Colombia, Guatemala, Mexico, Brazil, Ecuador and Venezuela)	All 13 foci in this region achieved coverage of >85% in 2006. Eliminate blindness caused by the disease in 13 areas. Successful interruption of transmission in 11 of 13 areas in 2017.	[47]
African Programme for Onchocerciasis Control (APOC)	Non-governmental development organisations	Onchocerciasis	Biannual IVM	1995–2010, then extended until 2015	Africa (19 countries; Angola, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Ethiopia, Equatorial Guinea, Gabon, Kenya, Liberia, Malawi, Mozambique, Nigeria, Rwanda, Sudan, Tanzania and Uganda)	More than 119 million people treated. Many countries greatly decreased the morbidity associated with onchocerciasis. More than 800 000 people in Uganda and 120 000 people in Sudan no longer required IVM.	[47]
Australian MDA for scabies	Australian New Zealand Clinical Trial Register (ANZCTR 12609000654257) approved by Northern Territory Department of Health and Menzies School of Health Research	Scabies	Two oral doses delivered 12 months apart	2010–2011	Australia	Scabies prevalence reduced in the 6 months after each MDA (overall prevalence 1–3%) with a low risk of acquisition (1–2%).	[83]

Alb, albendazole; DEC, diethylcarbamazine.

of 200 μg/kg/day for 2 days [53,54]. To confirm recovery from strongyloidiasis, at least three stool samples should be examined over the next 3 months after treatment. If any larvae are observed, re-treatment with IVM is indicated [55]. IVM treatment should be continued for 5–7 days in the case of hyperinfection and disseminated disease. For immunocompromised patients, treatment should be repeated monthly for ≥6 months [56]. In cases of refractory strongyloidiasis, longer-term IVM combined with albendazole has been effective [57].

3.4. Trichinellosis

Trichinellosis (also called trichinosis) is a zoonotic disease caused by ingestion of *Trichinella*-infected undercooked meat from pigs or horses [58]. Human trichinellosis has been documented in 55 countries and it recently became a re-emerging zoonotic disease with health and economic impacts in developing countries [59,60]. The clinical manifestations are variable and may be severe and even fatal. Trichinellosis usually presents as severe vomiting, epigastric pain, diarrhoea, generalised oedema and myalgia. Life-threatening myocarditis, encephalitis, hypokalaemia or adrenal gland insufficiency may develop [61].

Although not yet approved, experimental studies with IVM have shown promising effects. Soliman et al. reported that IVM was effective in reducing the adult worm burden of *Trichinella spiralis* and decreased the number of encysted larvae when given 10 days post-infection [62]. However, it failed to reduce the number of encysted larvae after they were well established in the diaphragm of infected rats. Moreover, Shoheib et al. showed that IVM was highly efficacious as a treatment for *T. spiralis* infection and as a control agent that might prevent further infection if the treated animal host meat is ingested since IVM affects the subsequent infectivity of *T. spiralis* larvae [63].

3.5. Ectoparasite infestation

IVM has been shown to be effective against ectoparasites in veterinary medicine. Clinicians have explored using IVM for human ectoparasites, specifically for head lice and scabies.

3.5.1. Pediculosis

Lice infesting humans include the head louse (*Pediculus humanus capitis*), the body louse (*Pediculus humanus humanus*) and the pubic louse (*Pthirus pubis*). Pediculosis is a major health problem in many countries, especially in children of primary school age and those of low socioeconomic status [64,65]. Approximately 6–12 million cases of infestation are reported annually in the USA among children aged 3–12 years [66].

The effectiveness of IVM has been compared with other products in many clinical trials and showed encouraging results for the treatment of head lice [67,68]. In a cohort of homeless subjects in Marseilles, France, an 85% prevalence of body lice was reduced to 19% with administration of three doses of 12 mg of oral IVM for each participant at 7-day intervals [69]. IVM does not have direct ovicidal activity but all of the hatched nymphs died when ova were exposed to topical 0.5% IVM lotion for 10 min [70]. However, its potential resistance was demonstrated in laboratory conditions [71]. The recommended dose differs according to the type of lice infestation; for *P.h. capitis*, oral IVM 400 μg/kg/dose every 7 days; for *P.h. corporis*, oral IVM 200 μg/kg/dose every 7 days; and for *P. pubis*, oral IVM 250 μg/kg/dose every 7 days or 250 μg/kg/dose every 14 days. A significant number of patients require a second dose to ensure complete eradication [11,72]. Oral IVM given twice at a 7-day interval in clinical trials showed that lice had been eliminated from 95.2% of subjects, which is more effective than topical 0.5% malathion lotion [73].

The FDA approved the use of 0.5% IVM lotion containing olive oil and Shea butter for the treatment of head lice infestations in patients aged ≥6 months. It has an emollient effect that is helpful in reducing pruritus [74].

3.5.2. Scabies

Scabies is infestation of the skin of the human host by the *Sarcoptes scabiei* mite through skin-to-skin contact. The worldwide prevalence is estimated to be 100 million people. The main manifestation is severe pruritis, especially at night [75,76].

Oral IVM is effective for treating people with classical or crusted scabies. In classical scabies, a single oral dose of 200 μg/kg IVM is used [77]. In crusted scabies it is recommended to use multiple doses of oral IVM and/or IVM in combination with topical therapy such as 5% permethrin [78] or 15% benzyl benzoate solution [79]. Nofal used three oral doses of 200 μg/kg IVM 2 weeks apart combined with topical therapy (5% permethrin and 5% salicylic acid) with no failure rate [80]. IVM is prescribed for two courses to kill mites that have hatched after the first treatment [81]. The 'whole-body bathing method' is a novel method that is expected to improve the safety of IVM. In a clinical trial, infected patients were bathed in a fluid containing IVM at a concentration of 150 ng/mL. IVM concentrations in the skin after bathing were >1000-fold higher than after oral IVM. No adverse events and no complaints about other cutaneous symptoms such as pruritus, redness, inflammation, tingling or dryness were reported. Thus, this method will be a preferable and safe drug delivery system for topical skin application of IVM compared with oral administration [82].

It is important to mention that MDA involving IVM for the control of scabies in Australia showed a significant reduction of its prevalence [83] (Table 1).

3.5.3. Myiasis

Myiasis is infestation of living tissue of human and other vertebrates by dipterous fly larvae [84]. There is a higher incidence of myiasis in rural zones and in elderly people who are ill or debilitated, especially in the tropics and third world countries [85].

Oral IVM 200 μg/kg has been used successfully to treat orbital myiasis prior to surgical debridement to prevent destructive surgery and to reduce the difficulty of mechanical removal of maggots [86,87]. In addition to oral IVM, Puthran et al. used 1% IVM drops instilled four times a day in the orbit for 1 week to ensure rapid wound healing [88]. IVM was used for the treatment of oral myiasis orally (150 μg/kg and repeated after 24 h) [85] and subcutaneously with phenol mixture as a local measure for the control of larvae [89].

3.5.4. Mosquitoes

Interestingly, IVM is capable of killing mosquitoes that feed on treated individuals. This property affects the malaria vector *Anopheles* mosquitoes and reduces malaria transmission [90]. IVM might inhibit *Plasmodium* sporogony in the mosquito and could influence liver schizonts as observed *in vitro* and in mouse models [91,92]. Moreover, sublethal concentrations of IVM in a blood meal of treated patients have been reported to decrease the fertility of *Anopheles* mosquitoes and to reduce the hatching of eggs [17,93]. In addition to other effects, lesser flight performance and reduced tendency to bite were observed [94,95]. Table 2 summarises the different clinical uses of IVM.

4. Safety and side effects

No serious adverse events were reported in patients treated with IVM [97]. However, headache, dizziness, muscle pain, nausea or diarrhoea may occur. Moreover, low IVM levels are detected in

Table 2
Clinical uses of ivermectin (IVM).

Clinical use	Dose	Route of administration	Reference(s)
Lymphatic filariasis	150–200 μg/kg body weight	Oral	[22]
Onchocerciasis	150 μg/kg single dose	Oral	[44]
Strongyloidiasis	200 μg/kg/day for 2 days	Oral or subcutaneous injection	[53,54]
Enterobiasis[a]	200 μg/kg single dose followed by a second dose 10 days later	Oral	[11]
Trichuriasis[a]	200 μg/kg daily for 3 days	Oral	[96]
Ascariasis[a]	150–200 μg/kg single dose	Oral	[96]
Cutaneous larva migrans[a]	200 μg/kg daily for 1–2 days	Oral	[11]
Gnathostomiasis[a]	200 μg/kg/day for 2 days	Oral	[96]
Lice infestation	For *Pediculus humanus capitis*, 400 μg/kg/dose every 7 days (2 doses)	Oral	[72]
	0.5% IVM lotion containing olive oil and Shea butter	Topical	[74]
	For *Pediculus humanus corporis*, 200 μg/kg/dose every 7 days (3 doses)	Oral	[72]
	For *Pthirus pubis*, 250 μg/kg/dose every 7 days (2 doses) or 250 μg/kg/dose every 14 days (2 doses)	Oral	[72]
Scabies	200 μg/kg single dose	Oral	[77]
	Three doses of 200 μg/kg 2 weeks apart + 5% permethrin and 5% salicylic acid	Oral Topical	[80]

[a] Uses are included in clinical guidelines but are not approved by the US Food and Drug Administration (FDA).

human breast milk after a single oral dose of 150–250 μg/kg for up to 14 days. Likewise, studies in experimental animals showed teratogenicity at 400 μg/kg given to the mother [90]. On the other hand, it was estimated that in *Onchocerca*-endemic areas, up to 50% of pregnant women in the first trimester are treated with IVM during MDA campaigns with no adverse effects in the pregnancy outcome [98]. However, data demonstrating the cytotoxicity, genotoxicity and reproductive toxicity are not conclusive and are based mainly on *in vitro* trials [99]. Therefore, some exclusion criteria for IVM use have been imposed to avoid adverse effects such as in children below 15 kg, pregnant women, lactating mothers in the first week postpartum, the severely ill and those with known hypersensitivity to the drug [100]. Moreover, little information is available about IVM treatment in patients aged >65 years and in cardiac, renal or hepatic patients regarding the safe dose [90].

Furthermore, in mammals IVM acts as an agonist of gamma-aminobutyric acid (GABA) receptors that are located on neurons in many central nervous system regions [15]. Therefore, the neurotoxic effects of IVM are well established in experimental and veterinary uses [101]. In humans, serious neurological events such as encephalopathy, confusion, stupor and coma were reported with IVM treatment for *O. volvulus* infection in African countries. Human clinical trials involving IVM reported some neurological events such as dizziness (2.8%), somnolence (0.9%), vertigo (0.9%) and tremor (0.9%) in the case of treatment of strongyloidiasis, and headache (0.2%) in trials for onchocerciasis treatment [102].

However, according to Gardon et al. [103] and Boussinesq et al. [104], adverse effects of IVM treatment in *Loa loa* patients are probably not due to the direct toxic effect of the drug. The main factor is probably the dying of *L. loa* microfilariae, especially if the parasite burden is high (>30 000 parasites/mL). Central and peripheral nervous disorders such as encephalopathy, headache, abnormal gait and coma have been reported. Some other adverse events have been reported in other systems, including asthenia, conjunctival haemorrhage, fever, back pain, urinary incontinence and psychiatric disorders such as agitation, abnormal behaviour and personality disorders. However, outside *L. loa*-endemic areas the drug is remarkably safe [105].

Similarly, other adverse events caused by IVM treatment in onchocerciasis are induced by the immune response to dead microfilariae in the body (Mazzotti reaction). The reaction is characterised by fever, skin rash, tachycardia, lymph node swelling and inflammation of the eye. It is usually mild and transient according to the intensity of microfilarial infection [106,107].

Hypersensitivity reactions caused by oral IVM for scabies treatment were reported due to mass destruction of mites and release of their antigens [108].

Of similar importance is to consider IVM residue in animal products such as meat and milk. Avermectins are used in veterinary medicine to control parasites and they are excreted in the milk of cattle with a half-life of IVM in milk varying between 2–4 days up to 23 days following treatment [109,110]. In 2009, the European Union determined the withdrawal periods of the drug from meat and other edible tissues by 49 days [111]. Therefore, for human safety it has been suggested to avoid using meat, milk and their products within the abovementioned durations following treatment of cattle [112].

5. Potential drug resistance

Many studies have reported that intensive use of MLs creates a drug pressure on parasite populations and leads to the emergence of drug resistance in small ruminants, cattle and some humans. However, exploring the mechanisms responsible for this resistance remains an important challenge today [112,113].

Resistance to IVM had been previously found in nematodes infecting animals. Human resistance of *O. volvulus* to IVM was reported as a suboptimal response to IVM treatment in Sudan [114], Cameroon [115] and northern Ghana [116]. However, until now no confirmed resistance to IVM in lymphatic filariasis has been reported. Resistance to IVM could be manifested as reduced microfilaricidal or antifecundity effects. It has been observed that microfilariae remain viable in the uteri of adult worms for 90 days after IVM treatment and can repopulate the skin more rapidly than had been previously detected. These observations could be indicative of developing resistance caused by suboptimal IVM doses [117,118]. Despite the common ML structure and similar modes of action on GluCls, resistance to IVM is much more widespread than resistance to moxidectin in animals [119,120].

However, the mechanism of resistance that allow some parasites to survive under the effect of IVM treatment is still unclear and remains an essential challenge today. The mechanism of resistance is suggested to be due to changes in some proteins such as β-tubulin, protein 60, P-glycoprotein and ATP-binding-cassette (ABC) transporters or to genetic polymorphisms of multidrug resistance gene 1 (MDR1) and CYP3A genes with suboptimal response to the drug [112,121,122]. In *Caenorhabditis elegans*, IVM resistance involves simultaneous mutation of three GluCl genes (*glc-1, avr-14* and *avr-15*) [123]. In addition, mutation of the *dyf-7* gene was

Table 3
Nano-enabled approaches for enhanced therapeutic efficacy of ivermectin (IVM).

Nanocarrier system	Characteristics	Parasite	Response	Reference
Lipid nanoparticle	High encapsulation capacity of 99% and the nanoparticles were stable over 120 days	*Pediculus humanus capitis*	Significantly faster mortality response due to increased penetration of IVM into the cuticle of lice	[139,140]
Poly(lactic-co-glycolic acid)	High encapsulation capacity of 74.12%, stable and long-circulating	*Brugia malayi*	Significantly improved the adulticidal efficacy of IVM; 36.67% worm mortality and 98.97% sterilisation	[129]
Amphiphilic polyanhydride nanoparticles	High encapsulation capacity of 100%, confers sustained, constant and predictable release of IVM	*B. malayi*	Effectively kills adult *B. malayi* filarial worms 8-fold faster with up to a 4000-fold reduction in the amount of drug used	[136]
Chitosan–alginate nanoparticles	Entrapment efficiency of IVM 75.67% with maintained sustained release	*B. malayi*	Significantly improved microfilaricidal and macrofilaricidal action	[138]

linked to IVM resistance in *C. elegans* and *Haemonchus contortus* [124].

Doyle et al. provided an insight into the genomics of IVM response, showing that there are population genetic changes associated with drug selection pressure [125]. Thus, they concluded that *O. volvulus* populations can be structured due to allele frequency change, i.e. because of genetic drift rather than genetic selection of suboptimal-responder parasites. Several genome-wide sequencing and genetic crossing approaches are now being applied to define the major mechanism of resistance [126].

6. Future perspectives and concluding remarks

Drug delivery systems can affect drug pharmacokinetics, the duration of its therapeutic effect and toxicity. Innovative drug delivery approaches and formulations such as slow-release formulations, IVM skin patches and IVM-impregnated clothing are being developed [11].

IVM nanoformulations can prolong the microfilaricidal action, which has a great potential in endemic areas compared with conventional treatments mostly due to improvement of poor pharmacokinetics or bioavailability of the drug [127] or possibly due to sustained release kinetics or because these systems can overcome systemic barriers [128]. In addition, there are many other advantages including fewer side effects, reduced doses and increased patient compliance [129]. Many experimental studies have been conducted to test the efficacy of different nanocarrier systems. For example, improvement in therapeutic efficacy of antifilarial drugs using liposomal-based drug delivery systems has been reported [127,130,131]. Liposomal antifilarial drugs improved the macrofilaricidal and microfilaricidal activities at lower doses of subcutaneous IVM owing to safe delivery and sustained release of the drug in the lymphatic system [132,133]. Moreover, IVM delivery through liposomes showed up to five times reduced cytotoxicity [134].

Camargo et al. showed that microparticle permeability can be improved by the addition of hydrophilic polyvinylpyrrolidone polymer, thus increasing IVM release from poly(lactide-co-glycolide) (PLGA) and poly(DL-lactide) IVM-loaded microparticles [135]. IVM-loaded PLGA or polyanhydride nanoparticles eliminated filarial parasites from the circulation with several thousand-fold dose-sparing effects because these nanoparticles penetrate and persist in the worm cuticle and provide sustained release of IVM, in contrast to soluble drugs alone [129,136]. Thus, nanoparticle formulations result in enhanced and rapid killing of filarial worms with a significantly reduced dose [136].

Recently, IVM in chitosan–alginate nanoparticles given subcutaneously at a suboptimal dose of 100 μg/kg body weight completely eliminated filarial worms at 60 days post-infection in *B. malayi*-infected animals [137]. Table 3 shows different carrier systems for IVM that require further research for safety, biocompatibility, cost effectiveness and feasibility for clinical trials.

In conclusion, IVM is a broad-spectrum antiparasitic agent primarily developed to treat veterinary and human parasites [11]. Since its discovery, the benefits of IVM in terms of global public health and socioeconomic welfare are endless and continue to accumulate [140].

Funding

None.

Competing interests

None declared.

Ethical approval

Not required.

References

[1] Chen WJ. Honoring antiparasitics: the 2015 Nobel Prize in Physiology or Medicine. Biomed J 2016;39:93–7.
[2] Lasota JA, Dybas RA. Avermectins, a novel class of compounds: implications for use in arthropod pest control. Annu Rev Entomol 1991;36:91–117.
[3] Kwon DH, Yoon KS, Clark JM, Lee SH. A point mutation in a glutamate-gated chloride channel confers abamectin resistance in the two-spotted spider mite, *Tetranychus urticae* Koch. Insect Molec Biol 2010;19:583–91.
[4] Hüter OF. Use of natural products in the crop protection industry. Phytochem Rev 2011;10:185–94 Erratum in: Phytochem Rev 2011;10:195.
[5] González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans—a mini-review. AAPS J 2008;10:42–6.
[6] Omura S, Crump A. Ivermectin: panacea for resource-poor communities? Trends Parasitol 2014;30:445–55.
[7] Laing R, Gillan V, Devaney E. Ivermectin—old drug, new tricks? Trends Parasitol 2017;33:463–72.
[8] MOXIDECTIN tablets, for oral use Melbourne. Victoria, Australia: Medicines Development for Global Health; 2018 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210867lbl.pdf. [Accessed 10 January 2018].
[9] Omura S. Ivermectin: 25 years and still going strong. Int J Antimicrob Agents 2008;31:91–8.
[10] Campbell WC, Fisher MH, Stapley EO, Albers-Schönberg G, Jacob TA. Ivermectin: a potent new antiparasitic agent. Science 1983;221:823–8.
[11] Crump A. Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. J Antibiot (Tokyo) 2017;70:495–505.
[12] Marty FM, Lowry CM, Rodriguez M, Milner DA, Pieciak WS, Sinha A, et al. Treatment of human disseminated strongyloidiasis with a parenteral veterinary formulation of ivermectin. Clin Infect Dis 2005;41:e5–8.
[13] Zeng Z, Andrew NW, Arison BH, Luffer-Atlas D, Wang RW. Identification of cytochrome P4503A4 as the major enzyme responsible for the metabolism of ivermectin by human liver microsomes. Xenobiotica 1998;28:313–21.
[14] Meyers JI, Gray M, Kuklinski W, Johnson LB, Snow CD, Black WC, et al. Characterization of the target of ivermectin, the glutamate-gated chloride channel, from *Anopheles gambiae*. J Exp Biol 2015;218:1478–86.
[15] Menez C, Sutra JF, Prichard R, Lespine A. Relative neurotoxicity of ivermectin and moxidectin in Mdr1ab (−/−) mice and effects on mammalian GABA(A) channel activity. PLoS Negl Trop Dis 2012;6:e1883.

[16] Kotze AC, Hines BM, Ruffell AP. A reappraisal of the relative sensitivity of nematode pharyngeal and somatic musculature to macrocyclic lactone drugs. Int J Parasitol Drugs Drug Resist 2012;2:29–35.
[17] Fritz ML, Siegert PY, Walker ED, Bayoh MN, Vulule JR, Miller JR. Toxicity of blood meals from ivermectin-treated cattle to *Anopheles gambiae* s.l. Ann Trop Med Parasitol 2009;103:539–47.
[18] Lopez-Olvera JR, Hofle U, Vicente J, Fernandez-De-Mera IG, Gortazar C. Effects of parasitic helminths and ivermectin treatment on clinical parameters in the European wild boar (*Sus scrofa*). Parasitol Res 2006;98:582–7.
[19] Moreno Y, Nabhan JF, Solomon J, Mackenzie CD, Geary TG. Ivermectin disrupts the function of the excretory–secretory apparatus in microfilariae of *Brugia malayi*. Proc Natl Acad Sci USA 2010;107:20120–5.
[20] Carithers DS. Examining the role of macrolides and host immunity in combatting filarial parasites. Parasit Vectors 2017;10:182.
[21] Chehayeb JF, Robertson AP, Martin RJ, Geary TG. Proteomic analysis of adult *Ascaris suum* fluid compartments and secretory products. PLoS Negl Trop Dis 2014;8:e2939.
[22] Wolstenholme AJ, Maclean MJ, Coates R, McCoy CJ, Reaves BJ. How do the macrocyclic lactones kill filarial nematode larvae? Invert Neurosci 2016;16:7.
[23] Sajid MS, Iqbal Z, Muhammad G, Sandhu MA, Khan MN, Saqib M, et al. Effect of ivermectin on the cellular and humoral immune responses of rabbits. Life Sci 2007;80:1966–70.
[24] Njoo FL, Hack CE, Oosting J, Stilma JS, Kijlstra A. Neutrophil activation in ivermectin-treated onchocerciasis patients. Clin Exp Immunol 1993;94:330–3.
[25] Njoo FL, Hack CE, Oosting J, Luyendijk L, Stilma JS, Kijlstra A. C-reactive protein and interleukin-6 are elevated in onchocerciasis patients after ivermectin treatment. J Infect Dis 1994;170:663–8.
[26] Vatta AF, Dzimianski M, Storey BE, Camus MS, Moorhead AR, Kaplan RM, et al. Ivermectin-dependent attachment of neutrophils and peripheral blood mononuclear cells to *Dirofilaria immitis* microfilariae in vitro. Vet Parasitol 2014;206:38–42.
[27] Hirata T, Uchima N, Kishimoto K, Zaha O, Kinjo N, Hokama A, et al. Impairment of host immune response against *Strongyloides stercoralis* by human T cell lymphotropic virus type 1 infection. Am J Trop Med Hyg 2006;74:246–9.
[28] dos Santos AR, Falcão CA, Muzitano MF, Kaiser CR, Rossi-Bergmann B, Férézou J. Ivermectin-derived leishmanicidal compounds. Bioorg Med Chem 2009;17:496–502.
[29] Hotez PJ, Kamath A. Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. PLoS Negl Trop Dis 2009;3:e412.
[30] Global Programme to Eliminate Lymphatic Filariasis: progress report, 2016. Wkly Epidemiol Rec 2017;92:594–607.
[31] Dickson BFR, Graves PM, Aye NN, Nwe TW, Wai T, Win SS, et al. The prevalence of lymphatic filariasis infection and disease following six rounds of mass drug administration in Mandalay Region, Myanmar. PLoS Negl Trop Dis 2018;12:e0006944.
[32] Yates DM, Wolstenholme AJ. An ivermectin-sensitive glutamate-gated chloride channel subunit from *Dirofilaria immitis*. Int J Parasitol 2004;34:1075–81.
[33] Ottesen EA, Hooper PJ, Bradley M, Biswas G. The Global Program To Eliminate Lymphatic Filariasis: health impact after 8 years. PLoS Negl Trop Dis 2008;2:e317.
[34] Dupuy J, Lespine A, Sutra JF, Alvinerie M. Fumagillin, a new P-glycoprotein-interfering agent able to modulate moxidectin efflux in rat hepatocytes. J Vet Pharmacol Ther 2006;29:489–94.
[35] Bazzocchi C, Mortarino M, Grandi G, Kramer LH, Genchi C, Bandi C, et al. Combined ivermectin and doxycycline treatment has microfilaricidal and adulticidal activity against *Dirofilaria immitis* in experimentally infected dogs. Int J Parasitol 2008;38:1401–10.
[36] Menozzi A, Bertini S, Turin L, Serventi P, Kramer L, Bazzocchi C. Doxycycline levels and anti-*Wolbachia* antibodies in sera from dogs experimentally infected with *Dirofilaria immitis* and treated with a combination of ivermectin/doxycycline. Vet Parasitol 2015;209:281–4.
[37] Sharma R, Al Jayoussi G, Tyrer HE, Gamble J, Hayward L, Guimaraes AF, et al. Minocycline as a re-purposed anti-*Wolbachia* macrofilaricide: superiority compared with doxycycline regimens in a murine infection model of human lymphatic filariasis. Sci Rep 2016;6:23458.
[38] Molyneux DH, Zagaria N. Lymphatic filariasis elimination: progress in global programme development. Ann Trop Med Parasitol 2002;96(Suppl 2):S15–40.
[39] World Health Organization (WHO). *Global Programme to Eliminate Lymphatic Filariasis*. Geneva, Switzerland: WHO. http://www.who.int/lymphatic_filariasis/elimination-programme/en/ [Accessed 25 May 2018].
[40] Fischer PU, King CL, Jacobson JA, Weil GJ. Potential value of triple drug therapy with ivermectin, diethylcarbamazine, and albendazole (IDA) to accelerate elimination of lymphatic filariasis and onchocerciasis in Africa. PLoS Negl Trop Dis 2017;11:e0005163.
[41] Little MP, Basanez MG, Breitling LP, Boatin BA, Alley ES. Incidence of blindness during the Onchocerciasis Control Programme in western Africa, 1971–2002. J Infect Dis 2004;189:1932–41.
[42] World Health Organization (WHO). *Onchocerciasis*. Geneva, Switzerland: WHO. https://www.who.int/news-room/fact-sheets/detail/onchocerciasis [Accessed 30 May 2019].
[43] Ottesen EA. Lymphatic filariasis: treatment, control and elimination. Adv Parasitol 2006;61:395–441.
[44] Nana-Djeunga HC, Bourguinat C, Pion SD, Bopda J, Kengne-Ouafo JA, Njiokou F, et al. Reproductive status of *Onchocerca volvulus* after ivermectin treatment in an ivermectin-naïve and a frequently treated population from Cameroon. PLoS Negl Trop Dis 2014;8:e2824.
[45] Lloyd MM, Gilbert R, Taha NT, Weil GJ, Meite A, Kouakou IM, et al. Conventional parasitology and DNA-based diagnostic methods for onchocerciasis elimination programmes. Acta Trop 2015;146:114–18.
[46] Traore MO, Sarr MD, Badji A, Bissan Y, Diawara L, Doumbia K, et al. Proof-of-principle of onchocerciasis elimination with ivermectin treatment in endemic foci in Africa: final results of a study in Mali and Senegal. PLoS Negl Trop Dis 2012;6:e1825.
[47] World Health Organization (WHO). *Onchocerciasis*. Geneva, Switzerland; WHO. http://www.who.int/en/news-room/fact-sheets/detail/onchocerciasis [Accessed 25 May 2018].
[48] Tamarozzi F, Halliday A, Gentil K, Hoerauf A, Pearlman E, Taylor MJ. Onchocerciasis: the role of *Wolbachia* bacterial endosymbionts in parasite biology, disease pathogenesis, and treatment. Clin Microbiol Rev 2011;24:459–68.
[49] Abegunde AT, Ahuja RM, Okafor NJ. Doxycycline plus ivermectin versus ivermectin alone for treatment of patients with onchocerciasis. Cochrane Database Syst Rev 2016(1):CD011146.
[50] Puthiyakunnon S, Boddu S, Li Y, Zhou X, Wang C, Li J, et al. Strongyloidiasis—an insight into its global prevalence and management. PLoS Negl Trop Dis 2014;8:e3018.
[51] World Health Organization (WHO). *Strongyloidiasis*. Geneva, Switzerland; WHO. https://www.who.int/intestinal_worms/epidemiology/strongyloidiasis/en/ [Accessed 16 February 2019].
[52] Satou T, Koga M, Koike K, Tada I, Nikaido T. Nematocidal activities of thiabendazole and ivermectin against the larvae of *Strongyloides ratti* and *S. venezuelensis*. Vet Parasitol 2001;99:311–22.
[53] Tarr PE, Miele PS, Peregoy KS, Smith MA, Neva FA, Lucey DR. Case report: Rectal administration of ivermectin to a patient with *Strongyloides* hyperinfection syndrome. Am J Trop Med Hyg 2003;68:453–5.
[54] Salluh JI, Feres GA, Velasco E, Holanda GS, Toscano L, Soares M. Successful use of parenteral ivermectin in an immunosuppressed patient with disseminated strongyloidiasis and septic shock. Intensive Care Med 2005;31:1292.
[55] Merck & Co. *Stromectol®*. https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/50-742s001_Stromectol_PrntLbl.pdf [Accessed 17 April 2018].
[56] Segarra-Newnham M. Manifestations, diagnosis, and treatment of *Strongyloides stercoralis* infection. Ann Pharmacother 2007;41:1992–2001.
[57] Pornsuriyasak P, Nitiharoenpong K, Sakapibunnan A. Disseminated strongyloidiasis successfully treated with extended duration ivermectin combined with albendazole: a case report of intractable strongyloidiasis. Southeast Asian J Trop Med Public Health 2004;35:531–4.
[58] Dimzas D, Diakou A, Koutras C, Gómez Morales MA, Psalla D, Keryttopoulos P, et al. Human trichinellosis caused by *Trichinella britovi* in Greece, and literature review. J Helminthol 2019;13:1–4.
[59] Pozio E. World distribution of *Trichinella* spp. infections in animals and humans. Vet Parasitol 2007;149:3–21.
[60] Onkoba NW, Chimbari MJ, Mukaratirwa S. Malaria endemicity and co-infection with tissue-dwelling parasites in sub-Saharan Africa: a review. Infect Dis Poverty 2015;4:35.
[61] Bruschi F, Murrell KD. New aspects of human trichinellosis: the impact of new *Trichinella* species. Postgrad Med J 2002;78:15–22.
[62] Soliman GA, Taher ES, Mahmoud MA. Therapeutic efficacy of dormectin, ivermectin and levamisole against different stages of *Trichinella spiralis* in rats. Turkiye Parazitol Derg 2011;35:86–91.
[63] Shoheib ZS, Ashour DS, Soliman NA, Shafik NM. Infectivity of ivermectin-treated *Trichinella spiralis* larvae: a new challenge for control. PUJ 2013;6:193–204.
[64] Burgess IF. Head lice. BMJ Clin Evid 2009:2009 pii: 1703.
[65] Lopatina YV. Pediculosis: current aspects of the old problem [in Russian]. Med Parazitol (Mosk) 2015(2):44–51.
[66] Frankowski BL, Weiner LBCommittee on Infectious Diseases. Head lice. Pediatrics 2002;110:638–43.
[67] Nofal A. Oral ivermectin for head lice: a comparison with 0.5% topical malathion lotion. J Dtsch Dermatol Ges 2010;8:985–9.
[68] Pariser DM, Meinking TL, Ryan WG. Topical ivermectin lotion for head lice. N Engl J Med 2013;368:967.
[69] Foucaulf C, Ranque S, Badiaga S, Rovery C, Raoult D, Brouqui P. Oral ivermectin in the treatment of body lice. J Infect Dis 2006;193:474–6.
[70] Strycharz JP, Berge NM, Alves A, Clark JM. Ivermectin acts as a posteclosion nymphicide by reducing blood feeding of human head lice (Anoplura: Pediculidae) that hatched from treated eggs. J Med Entomol 2011;48:1174–82.
[71] Yoon KS, Strycharz JP, Baek JH, Sun W, Kim JH, Kang JS, et al. Brief exposures of human body lice to sublethal amounts of ivermectin over-transcribes detoxification genes involved in tolerance. Insect Mol Biol 2011;20:687–99.
[72] Ameen M, Arenas R, Villanueva-Reyes J, Ruiz-Esmenjaud J, Millar D, Domínguez-Dueñas F, et al. Oral ivermectin for treatment of pediculosis capitis. Pediatr Infect Dis J 2010;29:991–3.
[73] Chosidow O, Giraudeau B, Cottrell J, Izri A, Hofmann R, Mann SG, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. N Engl J Med 2010;362:896–905.
[74] Koch E, Clark JM, Cohen B, Meinking TL, Ryan WG, Stevenson A, et al. Management of head louse infestations in the United States—a literature review. Pediatr Dermatol 2016;33:466–72.
[75] Currier RW, Walton SF, Currie BJ. Scabies in animals and humans: history, evolutionary perspectives, and modern clinical management. Ann N Y Acad Sci 2011;1230:E50–60.

[76] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2163–96.

[77] National Institute for Health and Care Excellence (NICE). Difficult-to-treat scabies: oral ivermectin. Evidence summary [ESUOM29]. London, UK: NICE; 2014 https://www.nice.org.uk/advice/esuom29/chapter/Key-points-from-the-evidence [Accessed 29 May 2019].

[78] Huffam SE, Currie BJ. Ivermectin for *Sarcoptes scabiei* hyperinfestation. Int J Infect Dis 1998;2:152–4.

[79] Alberici F, Pagani L, Ratti G, Viale P. Ivermectin alone or in combination with benzyl benzoate in the treatment of human immunodeficiency virus-associated scabies. Br J Dermatol 2000;142:969–72.

[80] Nofal A. Variable response of crusted scabies to oral ivermectin: report on eight Egyptian patients. J Eur Acad Dermatol Venereol 2009;23:793–7.

[81] Anderson KL, Strowd LC. Epidemiology, diagnosis, and treatment of scabies in a dermatology office. J Am Board Fam Med 2017;30:78–84.

[82] Miyajima A, Komoda M, Akagi K, Yuzawa K, Yoshimasu T, Yamamoto Y, et al. Experimental study of pharmacokinetics of external, whole-body bathing application of ivermectin. J Dermatol 2015;42:87–9.

[83] Kearns TM, Speare R, Cheng AC, McCarthy J, Carapetis JR, Holt DC, et al. Impact of an ivermectin mass drug administration on scabies prevalence in a remote Australian aboriginal community. PLoS Negl Trop Dis 2015;9:e0004151.

[84] Maurya RP, Mishra D, Bhushan P, Singh VP, Singh MK. Orbital myiasis: due to invasion of larvae of flesh fly (*Wohlfahrtia magnifica*) in a child; rare presentation. Case Rep Ophthalmol Med 2012;2012:371498.

[85] Shinohara EH, Martini MZ, de Oliveira Neto HG, Takahashi A. Oral myiasis treated with ivermectin: case report. Braz Dent J 2004;15:79–81.

[86] Osorio J, Moncada L, Molano A, Valderrama S, Gualtero S, Franco-Paredes C. Role of ivermectin in the treatment of severe orbital myiasis due to *Cochliomyia hominivorax*. Clin Infect Dis 2006;43:e57–9.

[87] Pandey TR, Shrestha GB, Sitaula RK, Shah DN. A case of orbital myiasis in recurrent eyelid basal cell carcinoma invasive into the orbit. Case Rep Ophthalmol Med 2016;2016:2904346.

[88] Puthran N, Hegde V, Anupama B, Andrew S. Ivermectin treatment for massive orbital myiasis in an empty socket with concomitant scalp pediculosis. Indian J Ophthalmol 2012;60:225–7.

[89] Duque SFL, Valderrama HR, Gonzalez RJ. Tratamiento de miasis oral con ivermectina. Notificación de tres casos causados por *Cochliomyia hominivorax* (Coquerel) [Treatment of oral myiasis with ivermectin. Notification of three cases caused by *Cochliomyia hominivorax* (Coquerel)]. Rev Fac Odontol Univ Ant 1998;10:41–7.

[90] Chaccour C, Hammann F, Rabinovich NR. Ivermectin to reduce malaria transmission I. Pharmacokinetic and pharmacodynamic considerations regarding efficacy and safety. Malar J 2017;16:161.

[91] da Cruz FP, Martin C, Buchholz K, Lafuente-Monasterio MJ, Rodrigues T, Sonnichsen B, et al. Drug screen targeted at *Plasmodium* liver stages identifies a potent multistage antimalarial drug. J Infect Dis 2012;205:1278–86.

[92] Kobylinski K, Ubalee R, Ponlawat A, McCardle W, Foy B, Szumlas D, et al. Ivermectin inhibits the development of *Plasmodium vivax* in *Anopheles dirus*. In: 64th Annual Meeting of the American Society of Tropical Medicine and Hygiene; 25–29 October 2015, Philadelphia, PA. Arlington, VA. ASTMH; 2015.

[93] Seaman JA, Alout H, Meyers JI, Stenglein MD, Dabiré RK, Lozano-Fuentes S, et al. Age and prior blood feeding of *Anopheles gambiae* influences their susceptibility and gene expression patterns to ivermectin-containing blood meals. BMC Genomics 2015;16:797.

[94] Kobylinski KC, Deus KM, Butters MP, Hongyu T, Gray M, da Silva IM, et al. The effect of oral anthelmintics on the survivorship and re-feeding frequency of anthropophilic mosquito disease vectors. Acta Trop 2010;116:119–26.

[95] Butters MP, Kobylinski KC, Deus KM, da Silva IM, Gray M, Sylla M, et al. Comparative evaluation of systemic drugs for their effects against *Anopheles gambiae*. Acta Trop 2012;121:34–43.

[96] González P, González FA, Ueno K. Ivermectin in human medicine, an overview of the current status of its clinical applications. Curr Pharm Biotechnol 2012;13:1103–9.

[97] Crump A, Ōmura S. Ivermectin, 'wonder drug' from Japan: the human use perspective. Proc Jpn Acad Ser B Phys Biol Sci 2011;87:13–28.

[98] Pacque M, Munoz B, Poetschke G, Foose J, Greene BM, Taylor HR. Pregnancy outcome after inadvertent ivermectin treatment during community-based distribution. Lancet 1990;336:1486–9.

[99] Molinari G, Soloneski S, Larramendy M. New ventures in the genotoxic and cytotoxic effects of macrocyclic lactones, abamectin and ivermectin. Cytogenet Genome Res 2010;128:37–45.

[100] World Health Organization (WHO). Preventive chemotherapy in human helminthiasis. Coordinated use of anthelminthic drugs in control interventions. A manual for health professionals and programme managers. Geneva, Switzerland: WHO; 2016 http://apps.who.int/iris/bitstream/10665/43545/1/9241547103_eng.pdf [Accessed August 2016].

[101] Trailovic SM, Nedeljkovic JT. Central and peripheral neurotoxic effects of ivermectin in rats. J Vet Med Sci 2011;73:591–9.

[102] Chandler RE. Serious neurological adverse events after ivermectin—do they occur beyond the indication of onchocerciasis? Am J Trop Med Hyg 2017;98:382–8.

[103] Gardon J, Gardon-Wendel N, Demanga N, Kamgno J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for *Loa loa* infection. Lancet 1997;350:18–22.

[104] Boussinesq M, Gardon J, Gardon-Wendel N, Chippaux JP. Clinical picture, epidemiology and outcome of *Loa*-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. Filaria J 2003;2(Suppl 1):S4.

[105] Nzolo D, Anto F, Hailemariam S, Bakajika D, Muteba D, Makenga JC, et al. Central and peripheral nervous system disorders following ivermectin mass administration: a descriptive study based on the Democratic Republic of Congo pharmacovigilance system. Drugs Real World Outcomes 2017;4:151–8.

[106] Mackenzie CD, Geary TG, Gerlach JA. Possible pathogenic pathways in the adverse clinical events seen following ivermectin administration to onchocerciasis patients. Filaria J 2003;2(Suppl 1):S5.

[107] Kamgno J, Gardon J, Gardon-Wendel N, Demanga N, Duke BO, Boussinesq M. Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. Trans R Soc Trop Med Hyg 2004;98:496–504.

[108] Usha V, Gopalakrishnan Nair TV. A comparative study of oral ivermectin and topical permethrin cream in the treatment of scabies. J Am Acad Dermatol 2000;42:236–40.

[109] Imperiale F, Lifschitz A, Sallovitz J, Virkel G, Lanusse C. Comparative depletion of ivermectin and moxidectin milk residues in dairy sheep after oral and subcutaneous administration. J Dairy Res 2004;71:427–33.

[110] Cerkvenik-Flajs V, Grabnar I, Kozuh Erzen N, Marc I, Antonic J, Vergles-Rataj A, et al. Kinetics of abamectin disposition in blood plasma and milk of lactating dairy sheep and suckling lambs. J Agric Food Chem 2007;55:9733–8.

[111] Escribano M, San Andrés MI, de Lucas JJ, González-Canga A. Ivermectin residue depletion in food producing species and its presence in animal foodstuffs with a view to human safety. Curr Pharm Biotechnol 2012;13:987–98.

[112] Cobo F. Determinants of parasite drug resistance in human lymphatic filariasis. Rev Esp Quimioter 2016;29:288–95.

[113] Ménez C, Alberich M, Kansoh D, Blanchard A, Lespine A. Acquired tolerance to ivermectin and moxidectin after drug selection pressure in the nematode *Caenorhabditis elegans*. Antimicrob Agents Chemother 2016;60:4809–19.

[114] Ali MM, Mukhtar MM, Baraka OZ, Homeida MM, Kheir MM, Mackenzie CD. Immunocompetence may be important in the effectiveness of Mectizan (ivermectin) in the treatment of human onchocerciasis. Acta Trop 2002;84:49–53.

[115] Pion SDS, Nana-Djeunga HC, Kamgno J, Tendongfor N, Wanji S, Njiokou F, et al. Dynamics of *Onchocerca volvulus* microfilarial densities after ivermectin treatment in an ivermectin-naive and a multiply treated population from Cameroon. PLoS Negl Trop Dis 2013;7:e2084.

[116] Awadzi K, Boakye DA, Edwards G, Opoku NO, Attah SK, Osei-Atweneboana MY, et al. An investigation of persistent microfilaridermias despite multiple treatments with ivermectin, in two onchocerciasis-endemic foci in Ghana. Ann Trop Med Parasitol 2004;98:231–49.

[117] Albonico M, Levecke B, LoVerde PT, Montresord A, Pricharde R, Vercruysseb J, et al. Monitoring the efficacy of drugs for neglected tropical diseases controlled by preventive chemotherapy. J Glob Antimicrob Resist 2015;3:229–36.

[118] Osei-Atweneboana MY, Eng JK, Boakye DA, Gyapong JO, Prichard RK. Prevalence and intensity of *Onchocerca volvulus* infection and efficacy of ivermectin in endemic communities in Ghana: a two-phase epidemiological study. Lancet 2007;369:2021–9.

[119] Ranjan S, Wang GT, Hirschlein C, Simkins KL. Selection for resistance to macrocyclic lactones by *Haemonchus contortus* in sheep. Vet Parasitol 2002;103:109–17.

[120] Milillo P, Boeckh A, Cobb R, Otranto D, Lia RP, Perrucci S, et al. Faecal cyathostomin egg count distribution and efficacy of anthelmintics against cyathostomins in Italy: a matter of geography? Parasit Vectors 2009;2(Suppl 2):S4.

[121] Sakaeda T, Nakamura T, Okumura K. Pharmacogenetics of MDR1 and its impact on the pharmacokinetics and pharmacodynamics of drugs. Pharmacogenomics 2003;4:397–410.

[122] Bourguinat C, Ardelli BF, Pion SD, Kamgno J, Gardon J, Duke BO, et al. P-glycoprotein-like protein, as possible genetic marker for ivermectin resistance selection in *Onchocerca volvulus*. Mol Biochem Parasitol 2008;158:101–11.

[123] Dent JA. The genetics of ivermectin resistance in *Caenorhabditis elegans*. Proc Natl Acad Sci U S A 2000;97:2674–9.

[124] Urdaneta-Marquez L, Bae SH, Janukavicius P, Beech R, Dent J, Prichard R. A *dyf-7* haplotype causes sensory neuron defects and is associated with macrocyclic lactone resistance worldwide in the nematode parasite *Haemonchus contortus*. Int J Parasitol 2014;44:1063–71.

[125] Doyle SR, Bourguinat C, Nana-Djeunga HC, Kengne-Ouafo JA, Pion SDS, Bopda J, et al. Genome-wide analysis of ivermectin response by *Onchocerca volvulus* reveals that genetic drift and soft selective sweeps contribute to loss of drug sensitivity. PLoS Negl Trop Dis 2017;11:e0005816.

[126] Howe KL. WormBase 2016: expanding to enable helminth genomic research. Nucleic Acids Res 2016;44:D774–80.

[127] Dangi A, Dwivedi V, Vedi S, Owais M, Misra-Bhattacharya S. Improvement in the antifilarial efficacy of doxycycline and rifampicin by combination therapy and drug delivery approach. J Drug Target 2010;18:343–50.

[128] Chrastina A, Massey KA, Schnitzer JE. Overcoming in vivo barriers to targeted nanodelivery. Wiley Interdiscip Rev Nanomed Nanobiotechnol 2011;3:421–37.

[129] Ali M, Afzal M, Verma M, Bhattacharya SM, Ahmad FJ, Samim M, et al. Therapeutic efficacy of poly (lactic-co-glycolic acid) nanoparticles encapsulated ivermectin (nano-ivermectin) against brugian filariasis in experimental rodent model. Parasitol Res 2014;113:681–91.

[130] Bajpai P, Vedi S, Owais M, Sharma SK, Saxena PN, Misra-Bhattacharya S. Use of liposomized tetracycline in elimination of *Wolbachia* endobacterium

of human lymphatic filariid *Brugia malayi* in a rodent model. J Drug Target 2005;13:375–81.
[131] Owais M, Misra-Bhattacharya S, Haq W, Gupta CM. Immunomodulator tuftsin augments antifilarial activity of diethylcarbamazine against experimental brugian filariasis. J Drug Target 2003;11:247–51.
[132] Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. Int J Nanomedicine 2006;1:297–315.
[133] Ali M, Afzal M, Bhattacharya SM, Ahmad FJ, Dinda AK. Nanopharmaceuticals to target antifilarials: a comprehensive review. Expert Opin Drug Deliv 2013;10:665–78.
[134] Croci R, Bottaro E, Chan KW, Watanabe S, Pezzullo M, Mastrangelo E, et al. Liposomal systems as nanocarriers for the antiviral agent ivermectin. Int J Biomater 2016;2016:8043983.
[135] Camargo JA, Sapin A, Daloz D, Maincent P. Ivermectin-loaded microparticles for parenteral sustained release: in vitro characterization and effect of some formulation variables. J Microencapsul 2010;27:609–17.
[136] Binnebose AM, Haughney SL, Martin R, Imerman PM, Narasimhan B, Bellaire BH. Polyanhydride nanoparticle delivery platform dramatically enhances killing of filarial worms. PLoS Negl Trop Dis 2015;9:e0004173.
[137] Ali M, Afzal M, Verma M, Misra-Bhattacharya S, Ahmad FJ, Dinda AK. Improved antifilarial activity of ivermectin in chitosan–alginate nanoparticles against human lymphatic filarial parasite, *Brugia malayi*. Parasitol Res 2013;112:2933–43.
[138] Faria Cola D, Morais Gonçalves da Silva C, Fernandes Fraceto L. Lipid nanoparticles as carrier systems for ivermectin and methoprene aiming veterinary applications. Toxicol Lett 2015;238:S201.
[139] Ullio-Gamboa G, Palma S, Benoit JP, Allemandi D, Picollo MI, Toloza AC. Ivermectin lipid-based nanocarriers as novel formulations against head lice. Parasitol Res 2017;116:2111–17.
[140] Omura S. A splendid gift from the earth: the origins and impact of the avermectins (Nobel Lecture). Angew Chem Int Ed Engl 2016;55:10190–209.