An Insight about Treatment Lines of *Trichinella. Spiralis* Infection

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Abstract
Trichinella. spiralis was first discovered in 1835 by an English first-year medical student called James Paget. However the parasite was named and published in a report by his professor, Richard Owen, who is now credited for the discovery of the T.spiralis larval form. The global burden of Trichinella infection is increasing due to difficulty of treatment. This difficulty depends on limited activity of the specific drugs against the migrating and encysted larvae. The early treatment of the infection may help prevent the establishment of the parasites in the skeletal muscles. The administration of efficacious anthelmintic drugs at the stage of intestinal invasion is remarkably important to obtain a better outcome. One of the first drugs used was mebendazole, and various antiparasitics such as albendazole, currently their use is little as none of these drugs are fully effective against the encysted or newborn larvae of *T.spiralis.* Also, they were poorly water soluble and highly lipophilic drugs and consequently, they can exhibit unfavorable bioavailability after oral administration, leading to variable degree of oral absorption. Nitazoxanide, ivermectin, quinfamide, have been evaluated in experimental models being effective.
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Introduction:
In Egypt, *T. spiralis* may be found in fresh and processed pork. In 1975 outbreak of human trichinosis was documented in French visitors with a prevalence rate of 4.5% in domestic pigs slaughtered at the Cairo Abattoir during this outbreak. After that the prevalence rate decreased to 1.7% in 1995–1999. However, risk of infection can still be considered. Trichinellosis has been detected in rats from Alexandria abattoirs, domestic pigs and in stray dogs with prevalence 13.3% (1).

T.spiralis is considered the smallest nematode parasite of humans . Both male and female are colorless. The cuticle is smooth but shows pseudo segmentation and is periodically interrupted by dorsal and ventral pairs of hypodermal gland cells. The somatic musculature formed of a single layer of muscle cells. They contain prominent contractile filaments, mitochondria and a large nucleus. The alimentary tract consists of an oral cavity, capillary oesophagus, midgut with brush border and hind gut. The oesophagus occupies about one-third of the body length and is surrounded by large cells. Its morphology is characteristic of the *Trichinellidae* family (2)

The administration of efficacious anthelmintic drugs at the stage of intestinal invasion is remarkably important to obtain a better outcome. One of the first drugs used was mebendazole, and various antiparasitics such as albendazole, currently their use is little as none of these drugs are fully effective against the encysted or newborn larvae of *T.spiralis*. Also, they were poorly water soluble and highly lipophilic drugs and consequently, they can exhibit unfavorable bioavailability after oral administration, leading to variable degree of oral absorption (3).

Nitazoxanide, ivermectin, quinfamide, have been evaluated in experimental models being effective. Likewise, there are alternative drugs such as resiniferatoxin which have an anti-inflammatory effect at the intestinal level and tamoxifen which decrease the parasitic load of *T.spiralis*. Rifampicin is effective against *T.spiralis* in the intestinal phase, since it had a direct action on the infectious larvae (4).

1. **Antihelmintic drugs**

a) Albendazole and mebendazole

Albendazole and mebendazole (benzimidazole derivatives) are considered the principal drugs for treatment of trichinellosis. They eliminate adult worms from the intestinal lumen, thus preventing the production of newborn larvae, muscle invasion and the development of trichinellosis. Antihelmintic drugs must be used during the period of intestinal invasion (i.e. less than 1 week after infection). However, this is rarely possible, and treatment is usually started at the beginning of larval development in muscle cells. Since it has not been clearly established how long the adult females survive and produce newborn larvae in the human intestine, it is recommended that antihelmintics should be administered to all persons with trichinellosis during the 4–6 weeks following infection (5).

Their mode of action is the inhibition of microtubule polymerization through selective binding to beta- tubulin monomer of the parasite, with little effect on binding of the host tubulin. Albendazole shows an effective action against both adult and larval stages of *T.spiralis* (6).

The effective dose of albendazole is 400mg twice daily for 8 to 14 days, while for mebendazole is 200-400mg 3 times per day for three days then followed by 400-500mg 3 times per day for ten days. Both drugs are recommended for adults and children above 2 years but contraindicated in pregnancy. Albendazole has an advantage over the mebendazole as its recommended plasma levels are achieved in most patients so do not need monitoring, while that of mebendazole vary among patients, so need monitoring and dosing (7).

The effectiveness of both drugs depends on time of administration; their administration in early stage of the disease is effective, unfortunately, most patients are diagnosed so late when the larvae are already established themselves in the muscles. Side effects of albendazole are GIT upsets, dizziness, headache, urticarial, itching and leucopenia. Mebendazole side effects are allergic reaction, alopecia, bone marrow depression **(8).**

To date, the treatment of *T.spiralis* infection is far from ideal. Our arsenal of effective drugs against *Trichinella* is quite limited. The conventional treatment with benzimidazole derivatives, such as mebendazole (MBZ) and albendazole, is frequently used against trichinellosis. However, in addition to their imperfect action against the encapsulated larvae and the emerging resistance against them, both drugs have low water solubility that limits their absorption from the intestinal lumen resulting in reduced bioavailability. Therefore, high doses of the drugs are used with numerous adverse effects mainly gastrointestinal in nature. Furthermore, evidence of teratogenicity of MBZ in rats and mice has been shown experimentally **(9).**

b) **Pyrantel**

Pyrantel acts through inhibition of cholinesterase leading to parasite neuromuscular depolarization, spasm and paralysis, so the parasite loses its ability to adhere to the intestinal wall and expelled outside the body. The administrated dose is 10-20mg\kg in single dose and repeated for 2-3 days. It is active only against adult worms but don't has effect on neither newborn larvae nor muscle larvae. It used safely in children and pregnant women **(7).**

c) **Levamisole**

It shows anti parasitic effect against intestinal adults with no effect on NBL nor the muscle larvae, it is given in single dose 0.1mg\kg **(10).**

d) **Ivermectin**

Ivermectin (IVM) is one of the competitive treatments used for trichinellosis. However, several studies linked its efficacy with early diagnosis and administration to tackle the intestinal phase with limited activity being recorded against encysted larvae. IVM can bind selectively to glutamate and neurotransmitter gamma-aminobutyric acid (GABA)–gated chloride ion channels of the invertebrate nerve and muscle cells. Such binding results in chloride ions influx, hyperpolarization of nerve and/or muscle cells with subsequent paralysis, and death of the parasite **(11).**

However, the studies that reported its anti-*Trichinella* effect revealed a restricted effect on the encysted muscle larvae. This could be mainly attributed to the low oral bioavailability that results from its poor aqueous solubility, binding to organic materials and efflux transport by intestinal epithelial P-glycoprotein. Hence, researchers are motivated to find alternate solutions for these problems to increase the effectiveness of IVM mainly against migrating and encysted larvae. The early treatment with niosomal IVM during the migratory stage demonstrated improved efficacy against larval stages **(12).**

e) **Nitazoxanide**

Nitazoxanide (NTZ) is an anti-parasitic drug, used against intestinal cestodes, protozoa and nematodes. It has promising activity against enteral and more effect on the parenteral phases of

trichinellosis. It is also a safe drug because it is neither mutagenic nor teratogenic. The wide spectrum of NTZ against parasites suggests that its effect does not depend on a parasite specific mechanism but more likely it has an immunomodulatory action. Although oral administration of drugs has many advantages over the other routes, but the drug solubility and dissolution rate still have a vital role in its absorption (13)

Although NTZ was inferior to ivermectin in the treatment of trichinellosis during the intestinal phase, it was superior to it in the muscular phase. Loading NTZ on Solid lipid nanoparticles (SLNs) resulted in increasing its efficacy against both intestinal and muscular phases of *Trichinella spiralis* with better results than the crude NTZ. Using drug combinations like ivermectin with crude and loaded NTZ showed higher efficacies than using individual drugs (14).

f) **Thiabendazole**

Thiabendazole is an anti-parasitic drug. It was effective against muscle larvae however; it was poorly tolerated. In a blinded, placebo-controlled trial of antiparasitic drugs for the treatment of myositis during a trichinellosis outbreak (Thailand), mebendazole and thiabendazole were more efficient than placebo or fluconazole; however, 30% of volunteers did not tolerate the side effects of thiabendazole (15)

2. <u>Steroidal and anti-inflammatory drugs</u>

a) **Glucocorticosteroids**

Because of the worsening symptoms which occur commonly in patients treated with anti-helminthic therapy, prednisone is given in combination with anti-helminthic to prevent the worsen symptoms and shortening the symptomatic period. Glucocorticosteroids can also be used to treat acute vasculitis and myositis; in this case they can also help in prevention of complications by inhibiting eosinophil activation, degranulation and consequent cytotoxicity for endothelium (16). The most commonly used glucocorticosteroid is prednisolone, which is available in tablets of 1 mg or 5 mg and is administered at a dosage of 30 mg per day to 60 mg per day, in multiple doses, for 10–14 days (5).

b) **Resiniferatoxin**

It is a vanilloid derived from the cactus plant Euphoria resiniferous, an agonist of the transient receptor potential vanilloid (TRPV)-1 which activates and then desensitizes the TRPV1 receptor producing an analgesic effect. Studies in both models in vitro and in vivo have shown that resiniferatoxin has an important anti-inflammatory activity, inhibiting the expression of Nuclear factor kappa B (NF-κB), Inducible nitric oxide synthase (iNOS) and Cyclooxygenase-2 (COX-2) and the synthesis of Prostaglandin E2 (PGE2), NO and TNF-α (17).

Finally, recent studies showed that treatment with resiniferatoxin during the intestinal phase of infection by *T.spiralis* decreased the levels of PGE2, NO, TNF-α, IL-1β, IL-12 and INF-γ, as well as the number of eosinophils in blood. While in the muscular phase of *T.spiralis* infection, treatment with resiniferatoxin significantly decreased implantation and parasite burden of L1-*T.spiralis*. These findings suggest that resiniferatoxin may be a potential drug in the treatment of inflammatory diseases (18).

3. **Immunomodulating drugs**

They involve Thymus factor-X which extracted from calf thymuses, levamisole and L-tetramisole HCL; these drugs potentiate the therapy of trichinellosis in patients with severe disease showing immunosuppression signs **(19).**

Some chlorine and bromine derivatives of 8-quinolyloxsalicylanlidis were synthesized and their anti-*Trichinella* effect was tested. These **(20).**

4. **Probiotics**

Probiotics are living microorganisms which when administrated in adequate amount confer a health benefit on the host. The potential use of probiotics to control enteric infections has great interest in the last decade. Probiotics can prevent enteric infections by three major strain-specific mechanisms depending on modulation of the intestinal environment, immune modulation and secretion of active molecules **(21).**

Lactobacilli are the most commonly used probiotics. The inherent biological features permit them to predominate and overcome the potential pathogens infecting the human digestive tract. *Lactobacillus casei (L. casei*) is the most popularly used probiotic for protection against *T. spiralis* infection. Several strains of *L. casei* that have proven efficacy against trichinellosis include *L. casei* ATCC 7469, *L. casei* ATCC469 and *L. casei* Shirota strains **(21).**

L. casei applied to mice before *T. spiralis* infection protected against *T. spiralis* infection, both in adult worms in the intestine and muscular larvae, ranging from 78.6% to 100%, depending on the challenging dose. In addition, (IgG) and IgA antibody levels and interleukin 4 levels increased significantly in *L. casei* -treated mice as compared with controls **(21).**

It has been reported that the protective efficacy of new safe probiotic strains, *L.plantarum* P164 and *L. acidophilus* P110, isolated from faeces of breastfed infants, against experimental trichinellosis. *L. plantarum* P164 was superior in parasitological and histopathological improvement against *T.spiralis* infection **(22).** This promising probiotic strain may be a safe natural protective agent against *T. spiralis* infection.

Prevention

According to **Gottstein *et al.* (7)** the main strategies of prevention of *Trichinella* infection are:

- Education of the consumers about the risk of raw or inadequately cooked meat of both domestic (e.g, pigs, horses and dogs) and sylvatic (e.g, bear, wild boars, foxes and walruses) animals that are regarded nowadays, the main hosts of *Trichinella.*
- Farming of the pig which is considered the principal host of *T.spiralis* infection to human in modern, industrialized, indoor pig sites under strict veterinary control **(23).**
- Control of both susceptible animals (both domestic and sylvatic), by a standardized artificial digestion method at slaughtering or after hunting.

- The main effective method to control the infection by *Trichinella* is inactivation of the larvae in the meat products of the animal hosts that may be done through many ways:
  Cooking to reach a core temperature that not less than 71C° for at least 1 minute i.e., the meat must change the color from pink to gray, and muscle fibers are easily separated from each other.Freezing to inactivate *Trichinella larvae* in meat, freeze pork less than 6 inches thick for 20 days at -15C° **(23).**

Vaccination against trichinellosis

Aim of vaccine is induction of therapeutic and protective responses against *T.spiralis* infection through activation of both innate and acquired immunological mechanisms that block the establishment of parasite in the host. Unfortunately, in trichinellosis, host-parasite interaction is complicated by *T.spiralis* life cycle that includes a diversity of stage-specific antigens, immune evasion mechanisms and modulatory effects on the host responses so, achieving effective protective responses is challenging. Therefore, vaccination approaches against *T.spiralis* in murine experimental models have involved a wide range of strategies that include whole extract and excretory-secretory products, recombinant proteins, epitope- peptides and DNA vaccines along with various adjuvants and different routes of antigen administration **(24).**

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