


Antileishmanial Activity of Tamoxifen by Targeting Sphingolipid Metabolism: A Review

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Abstract: Leishmaniasis is a widespread group of neglected parasitic diseases caused by protozoa of the genus *Leishmania*. Around 2 million new cases are reported each year and around 12 million people are at risk of being infected. Although various therapies have been used to treat leishmaniasis, they have been associated with increased cytotoxicity and drug resistance problems. Hence, the present review was intended to show the potential of tamoxifen as an alternative option for the treatment of leishmaniasis. Tamoxifen is a known selective estrogen receptor modulator and has been widely used for the treatment of early-stage breast cancer. Various experimental and clinical studies revealed that it has an antileishmanial effect by decreasing parasitic burden, with low cost and few side effects. The antileishmanial action of tamoxifen has been related to its potential effect on sphingolipid metabolism. Besides, it affects mitochondrial function by inducing alterations in the plasma membrane potential. However, further detailed studies are required to show the ultimate effects on health outcomes.

Keywords: tamoxifen, leishmaniasis, sphingolipid metabolism, estrogen receptor modulator

Introduction

Overview of Leishmaniasis

Leishmaniasis is a widespread vector-borne parasitic disease caused by protozoan flagellates (from the genus *Leishmania*). It is transmitted by the bite of infected female phlebotomine sandflies.^{1–3} Around 1.5–2 million new cases are reported each year and about 12 million people are at risk.⁴ Even though leishmaniasis has the ninth largest disease burden among infectious diseases, it is largely ignored by the global health community and is documented as a neglected tropical disease.^{5,6} Recent reports showed that 97 countries are considered endemic for leishmaniasis, and it continues to be a major health problem in four eco-epidemiological regions of the world.^{6,7}

Different species of *Leishmania* cause various clinical manifestations, ranging in severity from life-threatening visceral disease (visceral leishmaniasis) to self-curing cutaneous lesions (cutaneous leishmaniasis).⁸ Although treatments are available for curing leishmaniasis (including visceral leishmaniasis), most of the drugs are associated with increased cytotoxicity and augmented drug resistance.⁵ Therefore, drug repurposing is an attractive option for the discovery of new antileishmanial agents.⁹

The goal of repurposing is to expedite the drug development process by uncovering novel biological activity for existing pharmaceuticals and then employing them to treat new or existing ailments. Repurposing is a beneficial means of drug discovery since the medications have well-studied pharmacological and toxicological characteristics and are taken for an extended period.¹⁰ Hence, the goal of this study is to evaluate the potential of tamoxifen as an alternative medicine for the treatment of leishmaniasis using data from several experimental and clinical investigations.

Tamoxifen and Its Pharmacology

Tamoxifen is a selective estrogen receptor modulator (SERM) that is widely used for the treatment of early-stage breast cancer and the reduction of recurrences.^{11–13} It was discovered more than 40 years and remains one of the most effective therapies for the treatment of breast cancer.¹⁴ Tamoxifen belongs to the class of triphenylethylene molecules.^{15,16} It is a prodrug. After successive metabolic activation (mainly by CYP2D6), it is changed from pharmacologically inactive metabolites (tamoxifen and N-desmethyl) to active endoxifen, and finally results in the formation of 4-OH-tamoxifen,¹⁷ which has a high antiestrogenic potential.¹⁸ Genetic, environmental and/or drug-induced factors that change CYP2D6 enzyme activity affect the results of tamoxifen treatment. CYP2D6 comprises 2–3% of total liver CYPs and has several genetic polymorphisms.¹⁷ Based on an individual's metabolic activity, they can be a poor metabolizer (PM, two non-functional CYP2D6 alleles), an intermediate metabolizer (IM, one functional allele or two reduced function alleles), an extensive (normal) metabolizer (EM, two functional alleles) or an ultra-rapid metabolizer (UM, duplication of functional alleles).¹⁸ Therefore, patients with PM will possibly derive less benefit from tamoxifen treatment, so dose adjustment is required. Furthermore, no variations in the incidence of adverse drug reactions were detected when the tamoxifen dose was increased, and a 40–60 mg dose of tamoxifen was generally well tolerated.^{17,18}

SERMs have high bioavailability and are rapidly absorbed from the gastrointestinal tract. A high oral bioavailability reduces the risk of side effects and toxicity.^{11,12} Moreover, they are highly bound to plasma proteins (98–99%) and achieve equilibrium between the free drug and bound drug after reaching the systemic circulation. The free drug is then distributed throughout the body and reaches different parts of the body rapidly. Finally, SERMs are excreted through faeces, with small amounts in urine.¹⁹

Tamoxifen is a SERM, which binds and acts as an agonist and an antagonist with estrogen receptors (ER α or ER β) depending on the tissue in which it acts.^{11,12} Normally, estrogen binds to the ER (nuclear receptor) and induces DNA synthesis and cell replication, which may lead to breast cancer.¹⁷ However, tamoxifen can treat breast cancer by competing with estrogen and preventing its binding to ERs, thereby inhibiting the growth-stimulating effect of estrogen in the breast. It can also inhibit tumour growth through other mechanisms, by regulating oncogene expression and growth factors, and inducing apoptosis.¹⁹ Besides, in recent years experimental and clinical studies have shown that tamoxifen is also active against several species of *Leishmania* (Trinconi et al, 2018).⁹

Tamoxifen and Leishmaniasis

Leishmaniasis can be treated with pentavalent antimonial meglumine antimonite, sodium stibogluconate and liposomal amphotericin B. However, the treatment is relatively expensive and usually requires additional medical supervision, such as ECG and liver function tests, owing to the side effects of the medication, such as vomiting, cardiotoxicity and hepatotoxicity.^{20,21} Because of differences in the effectiveness of antimonial agents against the various *Leishmania* species and emerging drug resistance, amphotericin B is currently recommended as first-line treatment.^{22,23} However, it has also side effects, including infusion reactions such as chills and fever, and serious toxicity has been reported in some patients.²⁴ Therefore, drug repurposing is an attractive option for the discovery of newer antileishmanial drugs. Various in vivo and in vitro studies have revealed that tamoxifen is active against several species of *Leishmania*, with low cost and relatively few side effects.^{25–30}

Tamoxifen is a multi-target drug interfering in sphingolipid (SL) metabolism.³¹ SLs are an essential component of the cell membrane of *Leishmania* and are important mediators of cell signalling and control several cell biological processes, such as endocytosis, cell growth, differentiation, apoptosis and oncogenesis.^{31–33} Inositol phosphorylceramide (IPC) is the most abundant SL in *Leishmania*, but is not present in mammalian cells, which is of help for selective toxicity.^{9,28,29} It also interacts with the parasites' mitochondria, which results in mitochondrial dysfunction by inducing alterations in the plasma membrane potential, leading to depolarization of the membrane, with no disruption of the integrity,³⁴ and inducing apoptosis.^{30,33} Reimão and Uliana (2018) showed that tamoxifen caused mitochondrial damage, with loss of membrane potential, and also led to plasma membrane depolarization without general membrane disruption or permeabilization. Therefore, the effect of tamoxifen on *Leishmania* is mediated, in part, by disorder in the parasite's membranes, which triggers a series of lethal events.³⁴

Preclinical and Clinical Studies on the Effect of Tamoxifen on Leishmaniasis

As shown in Table 1, several experimental studies have demonstrated the activity of tamoxifen against different species of *Leishmania* (Table 1). An in vitro study by Miguel et al (2007) showed the effectiveness of tamoxifen against several species of *Leishmania*: *L. braziliensis*, *L. major*, *L. chagasi*, *L. amazonensis* and *L. donovani*.³⁵ In 2008, an in vivo study was conducted on *L. amazonensis*-infected BALB/c mice to assess the potential effect of tamoxifen in cutaneous leishmaniasis. In this study, a significant decrease in the total parasite number per lesion was observed in tamoxifen-treated groups when evaluated immediately after the interruption of treatment (7 weeks after infection) and 6 weeks later (13 weeks after infection). At the end of the experiment, the average number of parasites was reduced by at least 99.7% in treated groups, in comparison to untreated animals.²⁶

Another study, by Trinconi et al (2018), revealed that *L. amazonensis* promastigotes treated with tamoxifen showed a meaningful perturbation of SL metabolism, leading to the reduction of IPCs and phosphatidylinositols (PIs), and accumulation of acyl ceramide. Two hypotheses were formulated to explain the reduction of PIs and IPC levels in tamoxifen-treated parasites: 1) tamoxifen interferes with inositol and/or ceramide availability, both of which are critical elements for IPC synthesis; or 2) tamoxifen inhibits IPC and/or PI synthesis.⁹

An in vivo study by Coelho et al (2015) showed that *Leishmania* is not likely to develop tamoxifen resistance. In this study, treatment with tamoxifen was initiated after 5 weeks of infection. Intraperitoneal injections of 30.4 mg tamoxifen citrate/kg/day (equivalent to 20 mg/kg/day tamoxifen) were administered to the infected mice for 15 days. Sixty days after the end of treatment, mice were euthanized and amastigotes were purified from lesions. In this study, the resistance pattern of tamoxifen in leishmaniasis was also investigated by comparing it with miltefosine. These findings are consistent with a multi-target mode of action to explain the leishmanicidal properties of tamoxifen, and support the proposition of using tamoxifen as a partner in drug combination schemes for the treatment of leishmaniasis.³⁷

Another study, by Abbasi et al (2015), demonstrated the in vitro antileishmanial effect of tamoxifen. Promastigotes and amastigotes were cultured and treated with various concentrations of tamoxifen after 24, 48 and 72 hours of culture. The number of parasites was 1.07×10^6 per mL in the control group, and the parasite numbers in the concentrations of 1 and 50 $\mu\text{g/mL}$ tamoxifen were 0.95×10^6 and 0.06×10^6 , respectively. The IC_{50} value of tamoxifen was 2.64 $\mu\text{g/mL}$.³⁹

A study conducted by Eissa et al (2011) investigated groups of infected mice that were given tamoxifen, orally, at a dose of 20 mg/kg/day for 15 days. The results showed that tamoxifen caused a marked improvement in the cutaneous lesions and reduction of the parasitic burden. However, the untreated infected mice suffered from autoamputation of the inoculated foot pad.²⁷ Similarly, Trinconi et al (2014) showed that the lesion size was reduced by 55% in the group assigned to low-dose combined therapy, by 25% in the 6.5 mg/kg/day tamoxifen group and by 0% in the 1.2 mg/kg/day amphotericin B group. When parasitic burdens were considered, a 75% reduction was noted in the group treated with the low-dose combined therapy and a 36% reduction in the 6.5 mg/kg/day tamoxifen group, but an increase in the 1.2 mg/kg/day amphotericin B group. So, in both cases, the effect of combined therapy was superior to the sum of effects of the individual drugs, and therefore tamoxifen and amphotericin B have additive and possibly synergistic behaviour in vivo.³⁶

Doroodgar et al (2016) showed 2% apoptosis in the control group after 48 hours, and 59.7% apoptosis with a 50 $\mu\text{g/L}$ concentration of tamoxifen. Therefore, the parasite's growth rate was decreased by increasing the dose and duration of the drug; by increasing the concentration and duration of the drug, the viability of the promastigotes and intracellular amastigotes decreased.³⁰

A clinical study by Machado et al (2018) involved a total of 38 subjects, of whom 23 were treated with the combination of tamoxifen and meglumine antimoniate and 15 with standard meglumine antimoniate. Of those treated with combined therapy, 12 received tamoxifen orally and 11 were treated with topical tamoxifen. Tamoxifen administered by the oral or topical route was well tolerated. After 6 months of treatment, a 40% cure rate was reported in the group treated with standard meglumine antimoniate, compared with 36.4% in the group treated with meglumine antimoniate plus topical tamoxifen and 58% in the group treated with meglumine antimoniate plus oral tamoxifen.⁴⁰

Table 1 Experimental Studies Revealing the Activity of Tamoxifen Against Different Species of *Leishmania*

Study Design	Methods and Animals Used	Type of Leishmaniasis	Intervention	Major Findings	Reference
Experimental study	In vitro activity against axenically grown promastigotes and amastigotes	–	Cell counting of amastigotes, infected macrophage cultures, and the number of intracellular parasites was evaluated	Tamoxifen killed <i>L. amazonensis</i> promastigotes and amastigotes with IC ₅₀ of 16.4±0.2 and 11.1±0.2 μM, respectively. It was also effective against <i>L. (Viannia) braziliensis</i> , <i>L. major</i> , <i>L. chagasi</i> and <i>L. donovani</i> . Conclusion: tamoxifen effectively kills several <i>Leishmania</i> species	[35]
Experimental study	<i>L. amazonensis</i> -infected BALB/c mice	Cutaneous	Five weeks post-infection, treatment with 15 daily intraperitoneal injections of 20 mg/kg tamoxifen	A significant decrease in lesion size and ulcer development was noted in mice treated with tamoxifen compared to untreated control animals. Parasite load was also reduced in the draining lymph nodes	[26]
Experimental study	In vivo study on <i>L. braziliensis</i> -infected BALB/c mice and <i>L. chagasi</i> -infected hamsters	Cutaneous and visceral	Tamoxifen was administered for 15 days by the intraperitoneal route. Efficacy was evaluated through measurements of lesion size, parasitic burden at the lesion site or liver and spleen, and survival rate	Tamoxifen killed <i>L. braziliensis</i> and <i>L. chagasi</i> intracellular amastigotes with IC ₅₀ of 1.9±0.2 and 2.4±0.3 μM, respectively. Tamoxifen produced a 99% decrease in parasitic burden and lesion size in <i>L. braziliensis</i> -infected mice. <i>L. chagasi</i> and <i>L. donovan</i> -infected hamsters treated with tamoxifen showed significant reductions in liver parasite load	[25]
Experimental study	In vivo activity of tamoxifen against <i>L. major</i> in an experimental model	Cutaneous	Efficacy was assessed clinically, parasitologically and histopathologically by light and transmission electron microscopy	Tamoxifen showed marked improvement of the cutaneous lesions and reduction of parasitic burden; however, scrotal swelling was seen in male mice	[27]
Experimental study	In vivo study in <i>L. amazonensis</i> -infected BALB/c mice	Cutaneous	A combination of tamoxifen with amphotericin B was administered	Tamoxifen does not hinder amphotericin B activity. Lower doses of the two drugs combined result in good clinical and parasitological responses	[36]
Experimental study	<i>L. amazonensis</i> -infected female BALB/c mice	Cutaneous	Five weeks post-infection, treatment with 15 daily intraperitoneal injections of 20 mg/kg tamoxifen	A dose-dependent effect was seen. Tamoxifen-treated groups showed decreased lesion size and parasite number. Drug resistance rate was decreased upon increasing drug dose	[37]

(Continued)

Table 1 (Continued).

Study Design	Methods and Animals Used	Type of Leishmaniasis	Intervention	Major Findings	Reference
Experimental study	In vitro and in vivo study on <i>L. amazonensis</i> -infected BALB/c mice	Cutaneous	Four weeks post-infection, mice were treated with the half-maximal effective dose (ED ₅₀) or half the ED ₅₀ of tamoxifen and miltefosine orally for 15 days	No in vitro interactions between tamoxifen and miltefosine were found. The combination of tamoxifen and miltefosine was more effective than monotherapy with either tamoxifen or miltefosine. In vitro, tamoxifen was able to retard or suppress the growth of parasites treated with miltefosine	[29]
Experimental study	In vitro study against <i>L. major</i> promastigotes	–	Promastigotes and amastigotes were treated with different concentrations and periods of tamoxifen	IC ₅₀ of tamoxifen on promastigotes was 2.6 µg/mL after 24-hour treatment. Tamoxifen induced early and late apoptosis in <i>Leishmania</i> promastigotes. Conclusion: based on the in vitro antileishmanial effect, tamoxifen might be used for leishmaniasis treatment	[30]
Experimental study	In vitro study against <i>L. amazonensis</i> promastigotes with tamoxifen	–	A combination of metabolic labelling with [³ H]sphingosine and myo-[³ H]inositol, alkaline hydrolysis, HPTLC fractionations and mass spectrometry analyses was employed	Perturbation in the metabolism of inositol phosphoryl ceramides and phosphatidylinositols was observed	[9]
Clinical study	Randomized controlled pilot clinical trial in 38 subjects	Cutaneous	Oral/topical tamoxifen was administered by combining with meglumine antimoniate for 20 days	Tamoxifen administered by the oral or topical route was well tolerated. Cure rates 6 months after the end of treatment per intention to treat were 40% in the group treated with the standard Sb ^V scheme, and 36.4% and 58%, respectively, for groups treated with Sb ^V plus topical or oral tamoxifen. Conclusion: co-administration of oral tamoxifen and Sb ^V resulted in higher cure rates	[38]

Abbreviations: IC₅₀, half-maximal inhibitory concentration; ED₅₀, effective dose for 50% of the population; HPTLC, high-performance thin-layer chromatography.

In a study by Trinconi et al (2018), infected BALB/c mice were treated with tamoxifen cream as monotherapy or in combination with pentavalent antimonial. At the end of treatment, the combined scheme containing tamoxifen and pentavalent antimonial was found to be more effective in reducing lesion size and parasitic burden than monotherapy.⁴¹

Conclusion and Future Perspectives

Overall, this article provides a review of the use of tamoxifen as an alternative agent for the management of leishmaniasis. Tamoxifen has been used for the treatment of breast cancer in clinical practice. Although several agents have been used for the management of leishmaniasis, they have been associated with various detrimental effects. More recently, various clinical and animal studies have revealed that tamoxifen has antileishmanial activity. It is a selective estrogen receptor modulator with high bioavailability, low cost, high safety and a low resistance profile. Its main mechanism of action is through interfering with distinct cell pathways (sphingolipid metabolism). In addition, it causes mitochondrial dysfunction by interfering with the parasites' mitochondria. However, more information and further detailed understanding are needed to show the ultimate effects on health outcomes.

Disclosure

The authors report no conflicts of interest for this work.

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