

## Evaluation of Different Concentrations of Imatinib on the Viability of *Leishmania major*: An *In Vitro* Study

### Abstract

**Background:** Leishmaniasis is an infectious disease caused by an intracellular parasite of *Leishmania* and is transmitted through the female sandflies bite and may lead to severe skin lesions. Although drugs such as antimony compounds are available, their side effects such as toxicity, low efficacy, and emergence of resistance have raised the importance of effective replacement. Imatinib, as an inhibitor of tyrosine kinase (TK) of *Leishmania*, stops abnormal function of TK such as Bcr-Abl through assembling into transmembrane pores in a sterol-dependent manner. Hence, the evaluation of killing effects of different concentrations of imatinib against *Leishmania major* amastigotes and promastigotes *in vitro* were the objectives of the present study. **Materials and Methods:** The killing effects of different concentrations of imatinib (25, 50, and 100 µg) and 25 µg amphotericin B (as positive control) were evaluated against RPMI 1640-cultured promastigotes and the amastigote/macrophage model by MTS cell proliferation assay kit (ab197010) and Giemsa staining method during 24, 48, and 72 h. **Results:** The results showed anti-*Leishmania* effect of imatinib in concentration and time-dependent manner. The lowest number of live promastigotes and amastigotes were obtained due to treat with 100 µg/ml imatinib at 72 h. Furthermore, 100 µg concentration of imatinib had the same effect as 25 µg amphotericin B on both *L. major* promastigotes and amastigotes ( $P < 0.001$ ). **Conclusion:** The anti-*Leishmania* effect of imatinib was confirmed by MTS and direct microscopy. Further study is recommended for evaluating possible therapeutic effects of imatinib on leishmaniasis *in vivo*.

**Keywords:** Amphotericin B, imatinib, *Leishmania major*, leishmaniasis

### Introduction

Leishmaniasis is the most complex disease which is manifested by 21 different species of *Leishmania* parasite in humans, carnivores, and rodents.<sup>[1]</sup> This parasite is transmitted by female sandfly bites of the *Phlebotomus* and *Lutzomyia* genera.<sup>[2]</sup> The disease is endemic in 98 countries of the world, 82% of them are considered as poor economic countries and is the most important disease in the tropical and subtropical areas, as the disease has affected more than 12 million people in the world annually.<sup>[3]</sup> Clinical manifestations of leishmaniasis are ranging from severity skin lesions (cutaneous leishmaniasis [CL]) to fatal systemic infection (visceral leishmaniasis or kala-azar).<sup>[4]</sup> Two distinct stages of *Leishmania* life cycle involve leptomonad promastigotes in the sand fly and *Leishmania* amastigotes in the mammalian host.<sup>[5]</sup>

Various pathogens have different signaling pathways along with various factors. Protein kinases (PK) are among the largest protein families coded in the genome of most organisms that mediates many regulatory, signal transduction, and cell development pathways.<sup>[6]</sup> PKs are classified according to the amino acid that they phosphorylate: serine/threonine PK or tyrosine protein kinases.<sup>[7]</sup> They are further classified into nine groups, based on their sequence similarity, according to the manning classification: (1) Protein kinase of A, G, and C; (the AGC group) (2)– Ca<sup>+</sup>/CAM-dependent kinases (CAMK group); (3)– cyclin-dependent kinases (CDK) (CMGC group), mitogen-activated protein kinases (MAPK), GSK3, and CLK; (4) CK1 – casein kinase 1 (CK) 1; (5)– homologs of yeast sterile 7, 11, and 20; (STE group) (6)– receptor guanylate cyclases (RGC group) (7) Tyrosine kinase (TK) (group – TK); (8) – TK-like (TKL group); and (9) “Other” group – several.<sup>[8]</sup>

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There are a large number of protein TK (PTK) enzymes in the body, including the insulin receptor.<sup>[9]</sup> TKs attach phosphate groups to other amino acids (serine and threonine). Phosphorylation at tyrosine residues controls a wide range of properties in proteins such as enzyme activity, subcellular localization, and interaction between molecules. Furthermore, TKs function in many signal transduction cascades where in extracellular signals are transmitted through the cell membrane to the cytoplasm and often to the nucleus, where gene expression may be modified.<sup>[10]</sup> Dysregulation of PTK activity by overactivity of PTK receptors as an important class of transmembrane receptors causes a variety of diseases such as atherosclerosis, psoriasis, and particularly cancer.<sup>[11]</sup>

*Leishmania* also utilizes PTKs to facilitate intracellular survival, intracellular trafficking, and spread from cell to cell.<sup>[12]</sup> CK1 and CK2 are PTKs that are released by promastigotes of several *Leishmania* species. Constitutive or induced release of CK1 and CK2 from promastigotes could be modulated by temperature and pH, two important environmental cues for *Leishmania* differentiation from promastigotes to amastigotes and vice versa.<sup>[13]</sup> Furthermore, *Leishmania* impairs protein kinase C-dependent signaling in infected macrophages. As in *Leishmania*-infected cells, expression and activation of PK such as the mitogen-activated PK, kinases in the PI3-kinase signaling pathway, and kinases in the nuclear factor- $\kappa$ B-signaling pathway, are modulated in some manner.<sup>[14]</sup> During the last decades, several chemical drugs have been developed to control and treatment of leishmaniasis. For example, amphotericin B as an antifungal, and anti-*Leishmania* agent has been used for mucosal leishmaniasis and CL treatment.<sup>[15]</sup> This drug increases the permeability of the cell membrane and decreases intracellular Na, K, and nutrients.<sup>[16]</sup> Since the serious limitations such as toxicity to other cells and lack of efficacy in endemic areas show the need for new antileishmanial compounds, and thus the development of safe, potent, and cost-effective antileishmanial agents are a critical public health priority.<sup>[8]</sup>

Over the past decade, development of small molecule inhibitors of Abl1 (the Abelson proto-oncogene) and BCR-ABL, such as imatinib mesylate (imatinib, Gleevec) have dramatically reduced mortality rates in patients with chronic myeloid leukemia (CML), acute lymphocytic leukemia, and some types of gastrointestinal stromal tumors.<sup>[17]</sup>

Imatinib is a 2-phenylaminopyrimidine derivative that was discovered in 1992, and as a specific inhibitor (in a dose-dependent manner) which is able to occupy the active site of TKs such as Abl, C-kit, and platelet-derived growth factor receptor (PDGF-R), leading to a decrease their activity.<sup>[18]</sup> As each PTK has a binding site for ATP (Adenosine Tri Phosphate) and transfers the terminal

phosphate from ATP to tyrosine residues on its substrates, a process known as protein tyrosine phosphorylation.<sup>[19]</sup>

Imatinib locks PTKs in a self-inhibited conformation by binding to the ATP binding site and therefore inhibits the enzyme activity.<sup>[20]</sup> Imatinib also (at low doses) enhances host anti-microbial immunity and has efficacy against various pathogens such as mycobacteria.<sup>[21]</sup> For example, it decreases the pH of intracellular compartments which, in turn, reduces *Mycobacterium tuberculosis* intracellular growth *in vitro* and *in vivo*.<sup>[21]</sup> Recently, imatinib as an anti-parasitic drug has been shown to be effective in controlling metazoan parasites. For the first time, O'Connell *et al.* found that imatinib and its two analogs with the same doses of cancer patients had antifilarial effects in the culture medium, as adult parasites eliminated by high dose of drugs used to treat cancers.<sup>[22]</sup> In other studies, the mature worms of *Brugia malayi* and *Schistosoma mansoni* inactivated due to treating with imatinib after a 24-h period.<sup>[23]</sup> Moreover, early studies on *Leishmania* PK has suggested that chemical inhibition by various inhibitors or genetic knockdown of *Leishmania* CDK and MAPK could reduce viability and inhibit the proliferation of amastigotes within infected macrophages.<sup>[24]</sup> Imatinib had been shown not to have a direct effect on parasite viability and primary targets parasite receptor TKs.<sup>[25]</sup> It has been shown that imatinib is able to decrease opsonized polystyrene bead phagocytosis and *Leishmania* uptake, indicating that Abl and Arg are involved in phagocytosis and thus in *Leishmania* infection.<sup>[26]</sup>

Considering that imatinib primary targets are parasite receptor TKs, which do not express in the human, this compound can be used to inactive *Leishmania* TKs and treat leishmaniasis. Hence, in this study, the anti-leishmanial activity of the imatinib in various concentrations evaluated *in vitro*.

## Materials and Methods

Experimental protocols of this study as PhD thesis (No. 396465) were approved by the Institutional Research and Ethics Committee from Isfahan University of Medical Science.

This experimental study was composed of two steps. In the first step, the killing effect of different doses of imatinib was evaluated against promastigotes in the RPMI 1640 culture medium, and in the second step, the killing effect of imatinib was evaluated in the amastigote/macrophage infection model. The reference strain of *Leishmania major* (MRHO/IR/75/ER) was used in the current study.

### Parasite culture

*L. major* promastigotes (MRHO/IR/75/ER) were obtained from the Department of Parasitology and Mycology, Isfahan University of Medical Sciences, Iran, and cultured in complete RPMI 1640 (Gibco, USA) supplemented with

10% fetal bovine serum (FBS), 100 U/ml penicillin, and 100 µg/ml streptomycin (Gibco, Pen-Strep15140) at 25°C, and subcultured by subtilizing suspension 2–3 fold in fresh media every 2 days.

### **In vitro assessment by using different promastigotes morphology**

The parasites were harvested from the final stage of culture, were diluted with RPMI 1640 medium until the parasite density of 1 million/ml was achieved. The dilution was distributed in the wells of the culture plate, 200 µl each. Triplicate wells were considered for each concentration of 25, 50, and 100 µg of imatinib (LC Laboratories, Woburn, MA, USA), positive control of amphotericin B 25 µg (DB00681 [APRD00797]), three negative controls (drug solvent), and three exposure times of 24, 48, and 72 h. After these exposure times and preparation processes, the viability of parasites in each well was assessed through MTS assay.<sup>[27]</sup>

### **MTS assay**

The MTS assay was used for the viability assessment of *Leishmania*. The supernatant was discarded from the wells, and the MTS solution was added to each well. Parasites were incubated with the MTS solution for 4 h, and then absorbance was read by an ELISA reader at 490 nm, and the viability of cells was calculated.<sup>[27]</sup>

### **In vitro assay using amastigote/macrophage model**

J774 Murine macrophage cell line was purchased from the Pasteur Institute, Tehran, Iran, and subcultured using 25 ml culture flasks and after well propagation in 250 ml of culture flasks were harvested, washed and distributed in 6-well plates which the bottom of the wells was covered with 24 × 24 coverslips. All wells were then infected with *Leishmania* parasite promastigotes in stationary phase using 10 parasites/cell and incubated at 37°C and 5% CO<sub>2</sub> and optimum humidity for 24 h. Afterward, the wells were substituted with fresh completed medium and treated triplicate with three concentrations of 25, 50, and 100 µg at intervals of 24, 48, and 72 h and the positive control of amphotericin B 25 µg/ml. All of the coverslips were removed from the plates and stained with Giemsa and examined under a light microscope at ×100 magnification. Then, parasites were counted in 100 macrophages and the mean of intact parasites calculated in each group.<sup>[28]</sup>

### **Statistical methods**

Results were expressed as means ± standard error of mean in the sample characterization for continuous variables as well as the proportion for the categorical variables. The data were analyzed by the repeated-measure ANOVA and qualitative data analysis. All statistical analyses were done using SPSS software, version 20 (International Business Machines Corporation (IBM) technology company, New York).

Differences were considered significant when  $P < 0.05$ .

## **Results**

Furthermore, results showed that imatinib with the dose of 100 µg had the same effect as 25 µg amphotericin B on the viability of *L. major* promastigotes. In addition, imatinib with the dose of 100 µg had almost the same effect as 25 µg amphotericin B on the viability of *L. major* amastigotes [Table 1].

Three-way repeated ANOVA measurements showed that both two cyclic forms of parasites ( $P < 0.001$ ), both different doses of imatinib ( $P < 0.001$ ), and duration of exposure to imatinib ( $P < 0.001$ ) were effective on survival percentage of parasite stages. As seen in Table 1, the average survival of amastigotes is significantly higher than promastigotes. Increasing the concentration of imatinib, the percentage of survival has declined, as well as with increasing exposure time, the parasite survival rate has decreased. As a result, it can be stated that the percentage of viability of promastigotes and amastigotes produced reverse ratio with the exposure time and drug dosage. For more investigation, the estimated marginal means for different groups and treatment type were presented in Table 2.

## **Discussion**

Imatinib, as a multitarget inhibitor of C-kit, PDGF-R, and Abl/Arg kinases, is an oral anticancer drug approved for the treatment of CML and related cancers.<sup>[29]</sup> The therapeutic effects of imatinib have been attributed to its cell-autonomous effects on tumor cells expressing oncogenic kinases or to its inhibition of cellular kinases and pathogenesis in infected cells.<sup>[11]</sup>

TKs are proteins that cells use to transfer signals to each other to grow, and TK inhibitors such as imatinib are able to suppress the BCR-ABL and induce molecular remission.<sup>[30]</sup>

**Table 1: Average survival of two cyclic stages of *Leishmania* parasites treated with different doses of imatinib and different periods of time presented as number and mean±standard deviation**

Group (µg/ml)	Time (h)	Promastigotes	Amastigotes	P
Imatinib 25	24	20.7±0.8	67±3.3	<0.001
	48	16±0.35	53.5±9.5	
	72	9.3±0.52	35.6±6.2	
Imatinib 50	24	13.8±0.83	53.3±8.8	<0.001
	48	10.7±0.7	43±12.9	
	72	6.5±0.5	28.5±3.5	
Imatinib 100	24	6.9±0.76	47±10	<0.001
	48	4.6±0.62	35.7±6.2	
	72	2.33±0.7	21.4±3.6	
Amphotericin B 25	24	1.13±0.11	50±8.8	<0.001
	48	0.8±0.6	28.5±3.5	
	72	0.6±0.1	15.4±2.1	

**Table 2: Estimated marginal means for different groups and treatment type**

Type × time	Mean difference (T24–T48) <sup>a</sup>	P	Mean difference (T48–T72) <sup>a</sup>	P
Promastigote	2.09 (28.50–26.41)	0.012	2.65 (26.41–23.67)	0.001
Amastigote	11.19 (63.30–52.11)		11.92 (52.11–40.19)	
Group × time	Mean difference (T24–T48)	P	Mean difference (T48–T72) <sup>a</sup>	P
NC (Negative Control)	0 (100.00–100.00)	<b>0.031</b>	0 (100.00–100.00)	<b>0.047</b>
Amphotericin B	10.88 (25.55–14.67)		6.65 (14.67–8.02)	
Imatinib 25	8.9 (43.65–34.75)		12.28 (34.75–22.47)	
Imatinib 50	6.84 (33.57–26.73)		9.2 (26.73–22.47)	
Imatinib 100	6.6 (26.73–20.13)		8.26 (20.13–11.87)	
Group × type × time	Mean difference (T24–T48)	P	Mean difference (T48–T72) <sup>a</sup>	P
Promastigote and NC	0 (100.00–100.00)	0.112	0 (100.00–100.00)	0.011
Amastigote and NC	0 (100.00–100.00)		0 (100.00–100.00)	
Promastigote and amphotericin B	0.33 (1.13–0.80)		0.17 (0.80–0.63)	
Amastigote and amphotericin B	21.44 (49.97–28.53)		13.13 (28.63–15.40)	
Promastigote and imatinib 25	4.7 (20.67–15.97)		6.67 (15.97–9.30)	
Amastigote and imatinib 25	13.1 (66.63–53.53)		17.9 (53.53–35.63)	
Promastigote and imatinib 50	3.16 (13.83–10.67)		4.14 (10.67–10.53)	
Amastigote and imatinib 50	10.5 (53.30–42.80)		14.27 (42.80–28.53)	
Promastigote and imatinib 100	2.27 (6.87–44.60)		2.27 (4.60–2.33)	
Amastigote and imatinib 100	10.93 (46.60–35.67)		14.27 (35.67–21.40)	

<sup>a</sup>The mean difference is significant at the 0.05 level

Although the research on the treatment of CL has significantly progressed during the past two decades, the identification of suitable drug targets or development of effective drugs to combat leishmaniasis is far from satisfactory.<sup>[31]</sup> *Leishmania* protein kinase is the most important virulence factors and has vital role in metabolic or biochemical pathways of parasite that have been identified as suitable drug targets. Imatinib reduces C3bi-opsonized promastigotes uptake down to comparable levels as the Abl<sup>-/-</sup>. Imatinib also results in significantly reduced uptake of opsonized amastigotes.<sup>[32]</sup>

The presented work is the first report of the imatinib inhibitory effect on *Leishmania* PK compared to amphotericin B *in vitro*. As the inhibitory potential of imatinib on *L. major* promastigotes and amastigote viability was evaluated using MTS assay and under a light microscope, respectively, after parasite exposure by various concentrations of drug at different times.

The results showed that *L. major* promastigotes and amastigotes have high sensitivity to imatinib, in a concentration and time-dependent manner *in vitro*. As the inhibitory effect of imatinib at 100 µg/ml and at 72 h was significantly higher than other concentrations and times. Furthermore, Sanderson *et al.* surveyed the antileishmanial effect of imatinib at the same time with 9 protein kinase inhibitors against both *Leishmania donovani* and *Leishmania amazonensis* strains cultured in mouse peritoneal macrophages *in vivo* and orally in *L. donovani*-infected mice. In contrast to our results, they identified that only three inhibitors, namely sunitinib, lapatinib, and sorafenib showed significant activity against the visceral disease-inducing strain *L. donovani*, with IC<sub>50</sub> values of 1, 2–3, and 3–4 µM, respectively, compared

to miltefosine, which had an IC<sub>50</sub> value of 1.0 µM.<sup>[25]</sup> Furthermore, in another study, imatinib exhibited EC<sub>50</sub> of 9 µM against *Trypanosoma cruzi* in comparison with the control.<sup>[33]</sup> The activity of imatinib against *L. major* in the mice model following this study is planned further. Wetzel *et al.* showed that because of imatinib inhibited kinase-related signaling pathways, so orally imatinib-treated mice caused smaller lesions with few parasites of *T. cruzi* in comparison with control group.<sup>[26]</sup> According to the reference literature on the antiparasitic properties of imatinib *in vitro* and *in vivo*, it can be used clinically and there is a need for further evidence of potential drug prescription.

## Conclusion

Despite the importance and wide application of drugs in the treatment of leishmaniasis, the problem of leishmanial resistance is also increasing. Therefore, the need for new therapeutic goals and better understanding of host and parasite interactions are necessary. With regard to inhibitory effect of imatinib on *L. major* growth and division, this study suggests the possibility of repurposing the anticancer drugs as antileishmanial and consequently reducing the cost of developing new drugs. Hence, to achieve a good therapeutic option for treatment of leishmaniasis, it is recommended to identify more protein kinase enzymes as putative targets for antileishmanial chemotherapy and survey the effect of other inhibitors of *Leishmania* PK and design clinical trials with optimized dose of imatinib or other inhibitors.

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### Conflicts of interest

There are no conflicts of interest.

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