American Tegumentary Leishmaniasis (ATL) is a complex and heterogeneous disease caused by many *Leishmania* species. ATL is a neglected disease and treatment is still nowadays a great challenge. Despite American Tegumentary Leishmaniasis (ATL) is a complex and heterogeneous disease caused by several *Leishmania* species. ATL has a diverse clinical picture including cutaneous, mucosal, disseminated and diffuse leishmaniasis. ATL is a neglected disease and therefore, treatment is still nowadays a great challenge. Despite the high number of medications described in the literature, only a few drugs has proven different degrees of efficacy in the several manifestations of ATL. Unfortunately, most drugs are used by parenteral route, with important systemic toxicity. Additionally, ATL therapy relies still in monotherapy with increasing *Leishmania* resistance and therapeutic failure. This mini review aims to discuss the pros and cons of the main systemic drugs used in the control of ATL, in a scenario where the development of safer and more efficient drugs, along with the production of robust and well-designed trials with combined therapy is of utmost importance.

**Keywords:** American tegumentary leishmaniasis; Pentavalent antimony; Amphotericin B; Miltefosine; Pentamidine

**Introduction**

American Tegumentary Leishmaniasis (ATL) encompasses several diseases affecting skin and mucosae caused by different *Leishmania* species and transmitted by the bite of more than 54 species of the sandfly *Lutzomyia*. The main clinical forms are cutaneous leishmaniasis (CL), mucosal leishmaniasis (ML), disseminated leishmaniasis (DL) and diffuse cutaneous leishmaniasis (DCL). CL is the most common presentation of ATL accounting for at least 90% of cases in endemic regions and characterized by one or a few ulcers in exposed areas [1]. ML may occur concomitantly to CL but most cases manifests months or years after CL cure. ML affects nasal mucosa and can spread to larynx, pharynx and mouth mucosa, leading to destruction of the nasal septum, lips and palate with facial disfigurement and social stigmatization [2,3]. DL presents with more than ten lesions (papules, ulcers, nodules) in at least two non-contiguous regions of the body with mucosal nasal involvement in up to 53% of patients [4-6]. DCL or anergic diffuse leishmaniasis, which is the most uncommon ATL form, is characterized by multiple infiltrated nodular and non-ulcerated lesions, without mucosal involvement [7,8].

ATL is caused by 15 *Leishmania* species, grouped in the subgenera *Leishmania* and *Viannia*. In the subgenus *Leishmania*, *L. (L.) amazonensis*, *L. (L.) mexicana*, and *L. (L.) venezuelensis* are the main etiologic agents. The subgenus *Viannia* comprises a higher number of species, where the most common and important are *L. (V.) braziliensis*, *L. (V.) guyanensis*, *L. (V.) panamensis*, and *L. (V.) peruviana* [9,10]. In general, DCL cases in the New World are caused by *L. amazonensis*, and ML by *L. braziliensis* [2,3,8].

ATL is a complex disease, and successful therapy must consider at least clinical data, the species of *Leishmania* implicated and geographical location. However, treatment of ATL has been neglected over the years, and still relies in monotherapy with few toxic drugs presenting decreasing cure rates. Irrespective of
the clinical presentation of ATL, other common challenges are represented by long time to treat and to heal, important morbidity and absenteeism from work, contributing to the high socio-economic impact of ATL in a low income communities afflicted by the disease.

Despite the availability of various therapies for ACL, but there is no universal cure for all types of CL, the effectiveness also depends on the species in relation to the use of prevalent antimonials [11-13]. In addition, published literature reviews based on the species-specific efficacy of CL treatments are extremely scarce.

Thus, the objective of this mini-review is to summarize the therapeutic efficacy of the four systemic drugs most used in the management of ATL: pentavalent antimony, amphotericin B, pentamidine and miltefosine, highlighting the response to species-specific treatment. The authors only included trials carried out on the American continent in the three main clinical forms of the disease: cutaneous, mucosal and disseminated.

Statement of Ethical Compliance
This article is based on previously published work and does not contain new data or information related to human or animal studies.

**Current chemotherapies for American Tegumentary Leishmaniasis**

ATL treatment depends predominantly on chemotherapy with parenteral and toxic drugs. Table 1 shows the characteristics, advantages and disadvantages of the main available and studied drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pentavalent antimony</th>
<th>Amphotericin B - deoxycholate and liposomal</th>
<th>Pentamidine</th>
<th>Miltefosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial name</td>
<td>Sodium stibogluconate (Pentostam™)</td>
<td>Deoxycholate (Fungizone™)</td>
<td>Pentacarinat, Pentam ®</td>
<td>Impavido ™</td>
</tr>
<tr>
<td></td>
<td>Meglumine antimoniate (Glucantime™)</td>
<td>Liposomal (AmBisome®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical formula</td>
<td>C₇H₁₈NO₈Sb</td>
<td>C₅₇H₇₃NO₁₇</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C₁₂H₃₈Na₃O₂₆Sb₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Decreases macromolecular synthesis; increases ROS production</td>
<td>Parasite membrane ergosterol complexes, pore formation and cell death</td>
<td>Binds to kinetoplast DNA; inhibits polyamine biosynthesis</td>
<td>Inhibits cytochrome C oxidase and phosphatidylethanolamine synthesis; apoptosis</td>
</tr>
<tr>
<td>Schedule</td>
<td>10 to 20 mg/kg/day for 20-30 days *</td>
<td>0.5 to 1.0 mg/kg every other day (total cumulative dosage ranges from 15-30 mg/kg or more)*</td>
<td>3-4mg/kg every other day (ranges from 3-10 doses with a maximum cumulative dosage of 2g)</td>
<td>2.5 mg/kg/day for 28 days</td>
</tr>
<tr>
<td>Administration</td>
<td>IV / IM</td>
<td>IV</td>
<td>IM</td>
<td>Oral</td>
</tr>
<tr>
<td>Main side effects</td>
<td>Cardiotoxicity, chemical pancreatitis, muscle and joint pain</td>
<td>Nephrotoxicity, hypokalemia, azotemia, anemia</td>
<td>Gastrointestinal effects and diabetes mellitus</td>
<td>Nausea, vomiting, diarrhea</td>
</tr>
</tbody>
</table>
Advantages | Short half-life; it can be used on an outpatient basis | Good efficacy and less drug toxicity (liposomal) | Easy to administer due to the short period of treatment, increasing adherence | Oral route; domiciliar use
---|---|---|---|---
Disadvantages | Toxic side effects and increasing resistance; painful injection if used by IM route | Toxic side effects; slow iv infusion; nephrotoxicity (mainly deoxycholate); hospital based care | Formation of abscess and pain at the application site | Gastrointestinal side effects may affect adherence

IM: intramuscular; IV: intravenous; ROS: Reactive oxygen species
* Different schedules are usual, depending on type of disease, geographic region and *Leishmania* species

Table 1: Summary of the most used anti-*leishmania* drugs available for systemic treatment of American Cutaneous Leishmaniasis and their characteristics.

### Pentavalent antimonials

Pentavalent antimonials (*Sb*<sup>v</sup>) are being used in the treatment of leishmaniasis since 1940s. The two presentations, sodium stibogluconate (*Pentostam®*) and meglumine antimoniate (*Glucantime®*), are used by parenteral route and share similar pharmacokinetics, toxicities and efficacies [10]. *Pentostam®* is available mainly in North America while *Glucantime®* is widely used in Central and South America. Systemic *Sb*<sup>v</sup> still nowadays represent the main systemic treatment for ATL in most American countries. The *Sb*<sup>v</sup> mechanism of action most known requires metabolic reduction to the trivalent form, with inhibition of glycolytic and oxidative pathways involved in the metabolism of fatty acids in amastigote forms; it is also possible that a adenosine triphosphate (ATP) and guanosine triphosphate (GTP) synthesis is impaired resulting in a decreasing of macromolecular synthesis [11].

*Sb*<sup>v</sup> dosage and schedule may vary depending of the clinical presentation; CL may be treated with up to 20mg/kg/day for 20 days, whereas ML and DL will require the highest dosage for 28-30 days, with a maximum total daily dosage of 1,215 mg (15ml) for meglumine antimoniate [12,13]. *Sb*<sup>v</sup> should not be used by intramuscular route due to large volume employed (10–15ml) and daily applications during several consecutive days. Therefore, intravenous route should be preferred. Among the *Leishmania* species the cure rate (CR) in CL may vary widely, and even the same species present different responses to *Sb*<sup>v</sup> therapy according to geographical location (table 2).

<table>
<thead>
<tr>
<th>Study / Year/ Country</th>
<th><em>Leishmania</em> species</th>
<th><em>Sb</em>&lt;sup&gt;v&lt;/sup&gt; and CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navin 1992 / Guatemala</td>
<td><em>L. braziliensis</em></td>
<td>Sodium stibogluconate (96)</td>
</tr>
<tr>
<td>Arevalo 2007 / Peru</td>
<td><em>L. braziliensis</em></td>
<td>Sodium stibogluconate (70)</td>
</tr>
<tr>
<td></td>
<td><em>L. guyanensis</em></td>
<td>Sodium stibogluconate (92)</td>
</tr>
<tr>
<td>Llanos-Cuentas 2008 / Peru</td>
<td><em>L. braziliensis</em></td>
<td>Sodium stibogluconate (69)</td>
</tr>
<tr>
<td></td>
<td><em>L. guyanensis</em></td>
<td>Sodium stibogluconate (93)</td>
</tr>
<tr>
<td>Vélez 2010 / Colombia</td>
<td><em>L. braziliensis</em></td>
<td>Meglumine antimoniate (65)</td>
</tr>
<tr>
<td>Machado 2010 / Brazil</td>
<td><em>L. braziliensis</em></td>
<td>Meglumine antimoniate (53)</td>
</tr>
<tr>
<td>Talhari 2011 / Brazil</td>
<td><em>L. guyanensis</em></td>
<td>Meglumine antimoniate (54)</td>
</tr>
</tbody>
</table>
susceptibility to Sbv and primary resistance has been associated with Sbv has been described [11,14]. Decreasing in leishmanial species along with a higher failure rate of CL after monotherapy Leishmaniasis caused by adults over 50 to 60 years-old [11,12]. Therefore, Sbv use in ATL absenteeism form work; contra indication in pregnant woman and parenteral administration increasing patient difficulties, costs and consequently many side-effects that interfere with regular toxicity to several internal organs like heart, pancreas, liver chemotherapy are matter of concern and deserves attention: Resistance and risk factor has been described previously in Brazil and Peru [16,17]. More recently in an area of L. braziliensis in Brazil we documented that children with CL took a longer time to heal but presented similar CR when compared to adults in Peru and Colombia [16-17]. In Colombia, primary resistance against Sbv before treatment was described in 16% of strains of L. panamensis, L. braziliensis and L. guyanensis, increasing to 40% in cases with failure [14]. Main risk factors in Peru for Sbv failure were younger age, living less than 6 years in endemic region, and infection with L. braziliensis [16]. In Colombia, failure in CL caused by L. panamensis was associated with age lower than 8 years, lower adherence, and disease duration less than 1 month [17]. A short duration of disease as an important risk factor has been described previously in Brazil and Peru [16,18,19]. Other factors, including concomitant-distant lesions may also be important for predicting failure [20]. Resistance and failure to cure vary widely among species [11,14]. For instance, in Peru therapeutic failure for L. braziliensis was 30.4%, compared to 24.5% for L. peruviana and 8.3% for L. guyanensis [21]; in Brazil, CL therapeutic failure upon L. braziliensis infection may reach 46% in Northeast region [22].

Another important problems associated with Sbv chemotherapy are matter of concern and deserves attention: toxicity to several internal organs like heart, pancreas, liver and consequently many side-effects that interfere with regular treatment and adherence; long time to heal, from 2 to 3 months; parenteral administration increasing patient difficulties, costs and absenteeism form work; contra indication in pregnant woman and adults over 50 to 60 years-old [11,12]. Therefore, Sbv use in ATL should be an exceptional measure and not the rule.

Besides elderly and pregnant woman, children represent another special population afflicted by ATL. In 2016, 48,915 notified cases of CL were reported for the Americas, and 15.5% represented children aged ≤10 years [23]. Children are usually treated using tested and developed interventions for adults, and therefore, there is a lack of specific guidelines for the treatment of CL in the pediatric population. Some studies have shown higher rates of failure in children treated with Sbv when compared to adults in Peru and Colombia [16-17]. More recently in an area of L. braziliensis in Brazil we documented that children with CL took a longer time to heal but presented similar CR when compared to adults [24].

**Amphotericin B - deoxycholate and liposomal**

Amphotericin B deoxycholate (D-AmB) was first used in the treatment of systemic mycosis since the 1950s. The effectiveness of its use in ML was initially described by Furtado and Lacaz in 1959 in Brazil, and confirmed by Sampaio et al. [25,26]. The total dosage of D-AmB used in ATL varies from 15-30 mg/kg for CL and 20-45 mg/kg, with daily doses ranging from 0.5 to 1.0mg/kg according to tolerance and clinical response [13,26]. D-AmB may be a better choice in the management of refractory and hard to treat forms of ATL, immunosuppressed subjects and pregnant [13,27]. However, D-AmB intravenous administration and toxicity requires hospitalization or a hospital-day based strategy, limiting its use. Although nephrotoxicity is the main concern, many side effects are associated with D-AmB therapy, including fever, chills, headache, hypokalemia, hypomagnesemia, leukopenia, anemia, phlebitis and arrhythmias, requiring frequent laboratory and clinical evaluations. In clinical practice it is common alternating periods of use with pauses due to raised levels of creatinine and hypokalemia, and the achievement of total dosage may require several weeks and prolonged hospitalization. Therefore, D-AmB use implies higher costs, toxicity and morbidity [28,29], and although D-AmB may be considered as an effective drug against all *Leishmania* species that causes ATL, it is used only in selected cases where Sbv or other alternatives failed or cannot be used.

In this context, liposomal amphotericin B (L-AmB) represents a safer alternative, due to less toxicity, shorter time of administration and similar mechanism of action. The objectives of lipid formulations are to reduce side effects, especially nephrotoxicity. L-AmB (AmBisome®) is integrated with unilamellar liposomes added to cholesterol that provides greater stability in the formulation and keeps amphotericin (AmB) within the liposome layer [30]. When liposomes containing AmB get into contact with the cells of microorganisms, the lysosomal matrix
is degraded and AmB is released to bind to ergosterol in the cell membrane, causing its disintegration [28,30].

The reduced nephrotoxicity presented by L-AmB may be related to its higher affinity for high-density lipoproteins (HDL), which leads to preferential captation by the endothelial reticulum system and low concentrations in the kidneys [31]. Acute reactions related to infusion occur less frequently when compared to D-AmB as well as less leukopenia and thrombocytopenia, although significant frequencies of thrombocytopenia are described when high doses of L-AmB are used [31,32]. Normocytic and normochromic anemia with low reticulocytes and a decrease in erythropoietin production is not uncommon and seems not associated with renal failure [33,34].

Although D-AmB and L-AmB may be indicated in the same ATL forms, the high cost of L-AmB limits its use. In specific situations like CL caused by L. braziliensis in subjects over 60 years old, or in severe forms like DL, atypical, refractory and in immunosuppressed hosts, L-AmB should be considered as the first choice, due to Sbv ineffectiveness or contraindication and D-AmB toxicity and longer time of use [35,36]. In Bolivia, 85% of CL patients treated with L-AmB were cured, compared with 70% of cure in those treated with Sbv. L-AmB was considered safer and less toxic than sodium stibogluconate [37].

L-AmB has been more employed in the management of ML. In Brazil, a retrospective study in 29 ML patients found a CR of 93%, but 17% of patients presented kidney failure [38]. Another retrospective study in 71 ML patients described a CR of 81% with L-AmB, that was considered more effective than amphotericin B lipid complex, D-AmB, Pentamidine, Itraconazole and amphotericin B lipid complex [39].

In 20 patients with DL, the use of L-AmB at a total dose ranging from 17-37 mg/kg in 7-14 days, cured 65% of cases, whereas historical use of Sbv for 30 days has a CR of 24%. Higher dosage of more than 30mg/kg increased the CR to 75% [36].

In conclusion, L-AmB should be more studied and employed in ATL, especially in ML, DL and severe or refractory cases. Although there is a lack of randomized and controlled trials, L-AmB may also be considered as a first choice therapy in CL caused by L. braziliensis in the elderly as well as in immunosuppressed patients. Although recommended, the use of L-AmB in the treatment of ATL in the elderly requires trials regarding efficacy, dosage and safety.

Pentamidine

Pentamidine is a diamidine synthesized in the 1940’s initially used in the treatment of Pneumocystis jirovecii pneumonia, with activity also against protozoa like Leishmania and Trypanosoma. Pentamidine isothionate (Pentacarinat®, Pentam®) is used at several different schedules, according to geographical location and Leishmania species; in general 3-4mg/kg by parenteral route (in general intramuscular) every other day, and depending upon the schedule, for 3-10 doses with a maximum dosage of 2g. Pentamidine therapy may have an advantage related to the low number of applications and short time of use [12,40]. The mechanism of action of pentamidine, not fully defined, includes binding to kinetoplastid DNA, inhibition of polyamine biosynthesis, and interference on mitochondrial membrane [41]. Leishmania resistance has been described [42], as well as decreasing CR that may be explained by the use of low doses and co-infection with the Leishmania RNA virus 1 among other factors [43,44].

Pentamidine should be applied by deep intramuscular route to avoid sterile abscesses and ulceration at the site of injection. Diabetes may develop mainly when total doses are higher than 3g and with pentamidine mesylate (Lomide®) injections, which was withdrawn from the market in the 1980s [45]. Side effects reported include nausea, asthenia, fever, dizziness, myalgia, headache, taste change, hypotension, syncope, and transient hyperglycemia and hypoglycemia. To avoid hypoglycemia, patients should be fed before administration and rest for approximately 15 minutes after the injections.

Pentamidine therapy in ATL is associated with higher efficacy in CL caused by L. guyanensis, with high CRs in Suriname and French Guiana [46,47]. In the Amazon region in Brazil, pentamidine and Sbv had a similar CR of 58% and 55% respectively, in a trial that included CL caused by L. guyanensis [48]. CL caused by L. panamensis in Colombia is another indication for the use of pentamidine, achieving 96% of cure [49]. The use of pentamidine in the treatment of CL by L. braziliensis is not yet established due to few data with different CR according to country and schedule [50,51]. More recently, three pentamidine schedules (1, 2 and 3 doses of 7 mg/kg within an interval of 7 days) were compared in CL caused by L. guyanensis, showing a similar efficacy when used in 2 or 3 doses (81% CR and 96% CR respectively), suggesting that in Brazilian amazon region it should be the first choice for CL cases [52].

Pentamidine has also been used to treat ML, with few reports in a low number of patients showing 90-94% CR with a total dosage between 2-4g, which limit its use due to toxicity [53,54]. In DCL, pentamidine is used in high dosage and associated to other anti Leishmania drugs, with variable results; however a higher toxicity is almost inevitable due to the dosage and schedule required [55,56].

Miltefosine

Miltefosine (hexadecylphosphocholine) is an alkylphosphocholine analogue that inhibits phospholipid and sterol biosynthesis interfering with cell signal-transduction pathways. In vitro and in vivo studies have shown that miltefosine activity
against several *Leishmania* species [57,58]. Miltefosine may be considered as the first effective oral drug for the treatment of CL, offering accessibility and practical use in the endemic regions. Miltefosine was initially used for topical treatment of cutaneous lymphoma in the 1990s; the initial successful data on the oral treatment of visceral leishmaniasis in India, with up to 94% cure rate was the basis for its use in CL [59]. Soto et al. published the first pilot dose-ranging study of miltefosine for treatment of CL using from 50 mg/day for 20 days up to 150 mg/day for 28 days, in a total of 72 patients divided in 4 groups. A CR of 81% with the highest dosage was described [60].

Miltefosine (Impavido®) is presented in capsules containing 50mg of the drug; the daily dose is 2.5 mg/kg up to the maximum dose of 150 mg/day, for 28 days, preferably after meals. Miltefosine cannot be used during pregnancy due to teratogenicity, and women in childbearing age must use contraception during and up to 5 months after use. Gastro-intestinal toxicity is common in up to 60% of patients, and the most reported symptoms are nausea and vomiting. Diarrhea and abdominal pain are not uncommon, but in the majority of the cases these side effects are considered mild and decrease over time. Other less frequent adverse events are dizziness, headache, drowsiness, lack of appetite, and rarely described: testicular pain, urticaria and Steven-Johnson syndrome. Mild and transient increases in blood urea nitrogen, creatinine and liver enzymes are reported in a minority of cases, ranging from 5 to 32% [61-64].

Miltefosine CR varies according to *Leishmania* species and geographic localization, like other anti-*Leishmania* drugs. In a placebo-controlled trial conducted in CL subjects in Colombia and Guatemala, the highest CR found was 91% in patients infected with *L. panamensis* compared to 64% of CL caused by *L. mexicana* and only 33% in *L. braziliensis* CL [61]. In Bolivia, a CR of 88% in *L. braziliensis* CL was documented [65], compared with only 49% in cases from the same species in Colombia with the same schedule in another randomized and controlled trial (RCT) [62]. In Brazil, another RCT described 75% of cure in CL caused by *L. braziliensis* compared with 53% of CR in the group treated with Sb [63]. Miltefosine was also superior when compared to Sb in a RCT conducted in Amazon region, in CL caused by *L. guyanensis*, with 71.4% and 53.6% CR respectively [64]. All these studies used the same miltefosine dosage and schedule (2.5 mg/kg/day, administered 2-3 times a day, for 28 days). In children, miltefosine was considered non-inferior to Sb when tested in 116 children aged 2-12 years, with 82.8% of CR versus 69% in the Sb group [66].

There are few trials regarding the use of miltefosine in the management of ML. Table 3 shows efficacy data with miltefosine use in ML in different American countries. The miltefosine CR in these studies varies from 58% to 91.6%, with different schedules and criteria for cure.

<table>
<thead>
<tr>
<th>Study / Year / Country / Number of patients</th>
<th>Leishmania species</th>
<th>Design</th>
<th>Miltefosine schedule and CR (%)</th>
<th>Control and CR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soto / 2007 / Bolivia 72 (MF) 14 (D-AmB)</td>
<td><em>L. braziliensis</em></td>
<td>Nonrandomized controlled open trial</td>
<td>2.5 mg/kg/day for 28 days (83) mild disease; (58) extensive disease</td>
<td>D-AmB total dose of 45mg/kg (50)</td>
</tr>
<tr>
<td>Soto / 2009 / Bolivia 20 (MF)</td>
<td><em>L. braziliensis</em></td>
<td>Nonrandomized non controlled open trial</td>
<td>2.5 mg/kg/day for 42 days (75)</td>
<td>ND</td>
</tr>
<tr>
<td>Garcia Bustos / 2014 / Argentina 9 (MF) 10 (Sb)</td>
<td><em>L. braziliensis</em> <em>L. amazonensis</em></td>
<td>Randomized controlled open trial</td>
<td>MF 2.5–3.3 mg/kg/day for 28–35 days (87.5)</td>
<td>Sb 10–20 mg/kg/day for 28–35 days (80)</td>
</tr>
<tr>
<td>Sampaio / 2019 / Brazil 20 (MF) 20 (Sb)</td>
<td><em>L. braziliensis</em></td>
<td>Randomized controlled open trial</td>
<td>MF 1.3–2.0 mg/kg/day for 28 days (91.6)</td>
<td>Sb 10–20 mg/kg/day for 30 days (70)</td>
</tr>
</tbody>
</table>

Taken into account these data, miltefosine use in ATL represents obvious advantages due to oral route and less toxicity than parenteral drugs. However, there is a clear need for more clinical trials to confirm its usefulness not only in ML but also in difficult to treat forms, like DL, DCL and atypical or refractory cases, where longer time of use as well as local or systemic associations must
be explored. Furthermore, miltefosine may be a useful therapeutic approach in the elderly, in order to avoid parenteral toxic drugs and hospitalization.

**Pentoxifylline**

CL and ML pathogenesis are associated with a specific immune inflammatory host response that amplifies tissue damage, like increased levels of TNF in peripheral blood mononuclear cells and tissue [66], rich inflammatory infiltrate with few parasites [67] and CD8+ cytotoxicity [68], giving rationale to the use of immunotherapeutic approaches associated with anti-Leishmania drugs, in order to decrease inflammation, increase CR, and accelerate the time to cure.

Pentoxifylline (PTX) is a methylxanthine that inhibits phosphodiesterase IV and the degradation of the cAMP and of prostanooids, raising the intracellular concentration of the cAMP in pro-inflammatory and immune cells. The increase of cAMP down regulates the expression of transcription factor NF-xB and NF-AT transcription factors, leading to inhibition of TNF-α synthesis and to anti-inflammatory effects [69]. PTX (400mg three times a day for 30 days) associated with Sbv was first used in 10 refractory cases of ML, providing clinical cure for 9 of 10 patients. The complete reepithelization of mucosal lesions was observed 60 days after start of therapy in 8 patients, in parallel with a decrease in the TNF-α levels [70]. A randomized, double-blind, placebo-controlled clinical trial demonstrated that PTX combined with Sbv significantly accelerates the healing time of newly diagnosed ML patients, along with a 100% CR with one course of treatment compared with 58% CR in the control group [71]. In CL, a report described two refractory CL patients successfully treated with PTX and Sbv [72]. However, a randomized and placebo controlled trial in 164 patients with CL caused by *L. braziliensis* showed no benefit for the association [73].

Therefore, the association of PTX and Sbv is useful in ML but not in CL reflecting a more important role for TNF and other inflammatory cytokines in mucosal disease than CL.

**Future directions and conclusion**

The complex interaction between the host, *Leishmania* species, environment and many other factors in ATL, results in a complex, heterogeneous and challenging disease. Nowadays, the choice of the best therapeutic approach has to consider the causative species, endemic region location, and the clinical characteristics of ATL. Therefore the proposal of a standard and uniform treatment is not possible. Furthermore, leishmaniasis is a neglected disease with low resources to support robust clinical trials with less toxic and more effective medications. There is an urgent need to develop better drugs and different strategies, where combined therapies may be important to avoid parasite resistance, decrease toxicity and morbidity, offering higher cure rates and shorter disease activity. Future directions should consider all these requirements but unfortunately this achievement seems distant, due to the lack of resources and investment in the countries where leishmaniasis is a burden. The real solution represented by an effective vaccine also seems far away, despite the effort of several groups of researchers.

**References**


