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REVIEW

Lipsosomal amphotericin B: a review of its properties, function, and use for treatment of cutaneous leishmaniasis

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Abstract: The genus *Leishmania* includes a number of protozoan parasites that cause a wide range of infections named leishmaniasis. Leishmaniasis may be appear in three clinical forms — cutaneous (CL), visceral, and mucocutaneous (MCL) — with variation in their presentation and severity: diffuse CL and post–kala-azar dermal leishmaniasis). The prevalent signs of CL are nonhealing ulcers on exposed skin, but infected patients may have other dermatologic symptoms. In the 1960s, amphotericin B deoxycholate was introduced as a second-line therapy for CL and MCL. However, widespread administration of the agent was prevented, due to its renal and systemic toxicity, high price, and obstacles to intravenous use in leishmaniasis-endemic regions. Amphotericin B binds to ergosterol in the photogenic cell membranes and causes changes in membrane permeability, leakage of ions, and finally cell death. Compared to amphotericin B deoxycholate, a higher dose of liposomal amphotericin B should be administered to show the treatment effect. A high percentage of liposomal amphotericin B is "fastened" in the liposome and not biologically effective. Amphotericin B deoxycholate has some toxic effects, and liposomal amphotericin B is meaningfully less toxic compared to it. Treatment options for CL are limited, due to variation in species causing CL and pharmacokinetic issues. Amphotericin B is effective against some particular forms of CL.

Keywords: liposomal amphotericin B, cutaneous leishmaniasis, *Leishmania*

Introduction

The genus *Leishmania* includes a number of protozoan parasites that cause a wide range of infections named leishmaniasis. Three clinical forms of leishmaniasis are cutaneous (CL), visceral (VL), and mucocutaneous, with variation in their presentation and severity: diffuse CL and post–kala-azar dermal leishmaniasis. In the Old World, majority of CL cases were caused by *L. major* or *L. tropica* but these are not the only *Leishmania*spp. that cause these diseases. *L. donovani* (post–kala-azar dermal leishmaniasis), *L. aethiopica* (diffuse CL), and other *Leishmania* spp. are also responsible for CL. In the New World, CL is caused by a large variety of species (at least eleven) with some (three) causing mucocutaneous infections.[1,2]

There are a number of available chemotherapeutic protocols to treat leishmaniasis, including pentavalent antimonials, paromomycin, pentamidine, miltefosine, amphotericin B deoxycholate, and liposomal amphotericin B.[3] Increasing levels of resistance against antimonials and potentially miltefosine is an important drawback in the treatment of leishmaniasis. Existing treatment alternatives are restricted in

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some patients, such as children with leishmaniasis and HIV patients coinfected with leishmaniasis. Liposomal amphotericin B has been shown to be useful in the treatment of leishmaniasis.[3]

Amphotericin B deoxycholate has been administered as a second-line therapy for the treatment of CL and mucosal leishmaniasis since the 1960s. Amphotericin B is a polyene macrocyclic antifungal molecule generated by *Streptomyces nodosus*.[4,5] Widespread administration of the agent has been prevented, due to its renal and systemic toxicity, price, and obstacles to intravenous use in leishmaniasis-endemic regions.[1]

Lipid-supplemented derivatives of amphotericin B have been introduced to reduce renal toxicity of the drug and enable more extensive administration. Liposomal amphotericin B, amphotericin B incorporated into a bilayer liposome, is an approved lipid formulation of amphotericin B to treat a wide spectrum of infections (eg, leishmaniasis).[6] In 1997, liposomal amphotericin B was introduced to maintain the antifungal action and reduce the toxicity of amphotericin B .[6,7]

Amphotericin B, initially described as an alternative to stibnite for the treatment of mucocutaneous CL, has also been successfully used to treat severe VL and HIV–*Leishmania* coinfection.[8] Therapeutic failure or relapse after treatment has been reported, but is currently rare.[9,10] Currently, amphotericin (especially in its liposomal form) is recommended by the World Health Organization and the main scientific societies as the first-line drug to treat any form of VL worldwide, not only severe or HIV-associated conditions but also in children and immunocompetent adults.

Liposomal amphotericin B (AmBisome; Astellus Pharma, Deerfield, IL, USA) was approved by the US Food and Drug Administration for treatment of VL at a dose of 3 mg/kg/day for seven doses (given on days 1–5, 14, and 21; total dose 21 mg/kg).[11] A number of physicians have reported success with administration of AmBisome as a highly tolerable drug for CL.[12–15]

Mechanism of action

The efficacy of AmBisomeis related to its ability to reach the site of infection. In in vivo preclinical model systems, the drug accumulates at sites or near fungal infections. Mechanistic studies disclosed that AmBisome binds to the fungal cell wall where amphotericin B is released from the liposome, traverses through the cell wall, and binds to ergosterol in the fungal cell membrane.[16–18]

As mentioned, amphotericin B acts through binding to ergosterol in the cell membranes.[4,5] The binding may lead to changes in cell-membrane permeability, formation of pores, leakage of ions, induction of metabolic shock, and promoting cell death.[4–6,19]

Fluorescently labeled and gold-labeled liposomes (loaded with amphotericin B or blank liposomes) have been used in vitro and in vivo to illustrate the binding of liposomes to cell walls of the pathogens responsible for infection.[20,21] Empty liposomes (without amphotericin) remained intact and did not cause disruption in cells. However, the binding of liposomes loaded with amphotericin B led to cell death.[20] This may have been due to disruption of liposomes and discharge of amphotericin B to bind to the ergosterol of the cell membrane and show antiparasitic activity.[6]

Amphotericin B can transfer from the liposome to the fungal or parasitic cell membranes, since its binding affinity to fungal or parasitic ergosterol is higher than cholesterol (main lipid part of the liposome).[22]

Transfer of amphotericin B from the liposome to the cell membrane happens most efficiently at body temperature. As such, temperature may be a significant factor that assists the transferal process.[23]

Pharmacodynamics

Compared to amphotericin B deoxycholate, a higher dose of liposomal amphotericin B should be administered to show a treatment effect. In vitro studies have shown that potent doses of liposomal amphotericin B and amphotericin B deoxycholate were 1.03 and 0.12 mg/L, respectively, for 50% antipathogenic effect. These results indicate the differences of the two drugs in the term of the exposure–response relationship.[6,21] Studies in animal models suggest that a high percentage of liposomal amphotericin B is "fastened" in the liposome and not biologically effective.[24,25]

Pharmacokinetics of liposomal amphotericin B in humans

Pharmacokinetic parameters of intravenous liposomal amphotericin B have been comprehensively described elsewhere,[3,5,6,19,26,27] and are briefly reviewed here.

Pharmacokinetic characteristics of the medicine were first assessed based on its plasma concentrations in patients with febrile neutropenia.[28] Over a dosage range of 1–7.5 mg/kg/day, the pharmacokinetics of the medicine

were nonlinear.[28] Compared to amphotericin B in the deoxycholate form, liposomal amphotericin B has a considerably dissimilar pharmacokinetic profile, and after single and multiple intravenous doses, the drug is distributed broadly and quickly.[4,5] Within 4 days (after multiple doses of 1–7.5 mg/kg/day), amphotericin B reaches a steady-state plasma concentration more quickly than the deoxycholate formulation.[4]

Amphotericin B deoxycholate is highly bound to some plasma proteins, such as human serum albumin and α_1-acid glycoprotein.[29] In patient biopsies, the highest concentration of the drug is found in the liver and spleen, with moderate concentrations in the kidneys, lungs, myocardium and brain.[30]

The terminal half-life of liposomal amphotericin B in plasma is longer than other formulations (about 152 hours).[27]

Compared to amphotericin B deoxycholate, liposomal amphotericin B has a higher total plasma concentration. As mentioned earlier, a high percentage of circulating liposomal amphotericin B is probably inactive, since a high percentage of the drug is fastened in the liposome and not biologically effective. By direct contact with protozoan or fungal cell walls, the biologically active drug is released.[27] The mechanism of amphotericin B metabolism is unknown.[4]

In the kidney, the largeness of the liposomes prevents glomerular filtration of the drug and drug interaction with distal tubuli cells. This results in reduced drug nephrotoxicity.[4]

At the end of the first week of administration, urinary clearance of liposomal amphotericin B is near 4.5% of the dose, which is meaningfully lower than for amphotericin B deoxycholate. Compared to amphotericin B deoxycholate, active excretion of liposomal amphotericin B into bile and clearance by feces occur to a minor extent. These findings suggest that liposomes around amphotericin B may prevent these clearance mechanisms from accessing the liposomally enclosed drug.[27] Both amphotericin B deoxycholate and liposomal amphotericin B are excreted mainly as unaltered drugs through urinary and biliary excretion.[31] Hepatic excretion of amphotericin B is moderate and not influenced by alterations in hepatic blood flow. Intact liposomes are not excreted into the urine and bile.[27]

Toxicity

Some toxic adverse effects are attributed to amphotericin B deoxycholate. However, liposomal amphotericin B has been showedn to be meaningfully less toxic compared to amphotericin B deoxycholate.[32,33] Toxic effects of amphotericin B include nephrotoxicity and infusion-related toxicity.

Among commercially introduced lipid formulations of amphotericin B, liposomal amphotericin B has reliably the least nephrotoxicity.[32,33] Low toxicity of liposomal amphotericin B may be due to the small number of preferential HDL receptors responsible for binding to the drug in the kidney.[34,35] Renal toxicity is probably due to interaction of subcompartments of the kidney with free (diffusible) amphotericin B. The drug component of liposomal amphotericin B is enclosed in the liposome and not accessible for interaction with renal distal tubules. Large size of the liposomes prevents glomerulofiltration of the drug, and may explain the reduced renal toxicity of liposomal amphotericin B.[36]

The infusion of amphotericin B deoxycholate may result in the infusion-related toxicity that causes the acute fever and chills, likely because of proinflammatory cytokine reactions.[37]

The infusion-related-toxicity of liposomal amphotericin B is reliably lower than amphotericin B deoxycholate and other amphotericin B–lipid complexes.[38]

Known adverse effects of liposomal amphotericin B areidiosyncratic, including flank/abdominal pain, chest pain/discomfort, and dyspnea that initiate in the first few minutes after infusion. With termination of the infusion and an antihistamine drug, these can be resolved.[39] The clinical pattern of the infusion reaction is similar to liposome-linked drugs, and may be caused by liposomes, rather than the potent drug. The mechanism of such reaction is unknown, but assumed to be mediated by the complement system.[40]

In a study on the hepatotoxicity of liposomal amphotericin B, pediatric patients who received injectable liposomal amphotericin B were examined.[41] During injection of the drug, mild–moderate increase in hepatic transaminases was observed in 59% of patients. After cessation of the treatment course, such increase was observed in one patient.[41] Coadministration of liposomal amphotericin B with other hepatotoxic drugs may lead to abnormal liver function–test results in a dose-independent manner.[42,43] The mechanism of liposomal amphotericin B hepatotoxicity remains unclear, and hepatic cells do not reveal any direct histopathological symptoms of toxicity.[44]

Cutaneous leishmaniasis

Phlebotomine sand flies are the vectors that transmit protozoan parasites to humans at the site of the bite. In the

Table 1 Summary of published studies and clinical trials on liposomal amphotericin B use for CL (since 2011)

Study	Type	Treatment regimen	Clinical manifestation	Immunosuppression	Patients, n	Species	Outcome	Median follow-up
Guery et al[62]	Retrospective analysis	20 mg/kg (total dose)	Nodular lesion(s)	12% of patients had HIV infection or received prolonged corticosteroid therapy and/or immunosuppressive treatment for autoimmune diseases.	43	Leishmania *infantum*	Cure rate 58%	79 days
Layegh et al[63]	Randomized clinical trial	Topical liposomal formulation: 3–7 drops into each lesion twice daily	Papuloplaque, nodule or ulcer	—	50	-	Cure rate 90%	6 months
Motta et al[64]	Controlled open-label trial	1.5 mg/kg/day	Presenting up to six lesions (ulcers or plaques)	—	16	*L.* (Viannia) *braziliensis L.amazonensis L (V) shawi*	Cure rate 50%	12 months
Hamzavi[65]	Case report	1 mg/kg for 1 month; retreated with 3 mg/kg for 2 weeks	Multiple nodular, ulcerative. and crusted lesions	No	1	*L. major*	Cure	3 months
Islam[66]		3, 4, 4, 5, and 5 mg/kg/day over 5 days	Rapidly progressing crusting and ulcerative facial rash	—	1	*L. tropica*	Cure	5 months
Cunha et al[67]	Retrospective study	Mean total dose 32.5 mg/kg	Lesion(s) in the nasal or oral mucosa	No	29	*L. (V) braziliensis*	Cure rate 93.1%.	—
Butsch et al [68]	Case report (two cases)	3 mg/kg/day for 10 days	Nodules on the face, trunk, arm, and foot	Case 1: no Case 2: diabetic	2	*L. major*	Cure	24 months
Zanger et al [69]	Case report	3 mg/kg/day for 22 days	Lesions on the face	Treated rheumatoid arthritis	1	*L. aethiopica*	Cure	12 months
Ono et al[70]	Case report	3 mg/kg/day for 5 consecutive days with additional dose on the 10th day for a total of 6 days of treatment	A tender erythematous nodule on the right elbow	—	1	*L. major*	Cure	—
Solomon et al[71]	Nonrandomized study with a small number of patients	Five days of 3 mg/kg, followed by a sixth dose on day 10	Lesions on the face and/or body	—	13	*L. tropica*	Cure	11 months

(*Continued*)

Table 1 (Continued).

Study	Type	Treatment regimen	Clinical manifestation	Immunosuppression	Patients, n	Species	Outcome	Median follow-up
Solomon et al[72]	Prospective observational study	Five days of 3 mg/kg and a sixth dose on day 10	Cutaneous lesions	No	34	*L. (V) braziliensis*	Cure	29 months
Hervas et al[46]	Case report	3 mg/kg/day for 13 days	Lesion on cheek	—		*L. infantum*	Poor response	—

Old World, *Leishmania major* and *L. tropica* mainly cause CL and *L. infantum* and *L. donovani* cause the infection at lower frequences. In the New World, *L. peruviana, L. guyanensis, L. braziliensis*, or *L. mexicana* spp. mainly cause CL.[45,46]

Treatment options for CL are limited, due to the variation of species that cause it, as well as pharmacokinetic issues.[47,48] The efficiency of pentavalent antimonials against the various species of *Leishmania* is unknown.[49] Amphotericin B and pentamidine are restricted to particular forms of CL.[49] Different topical formulations of paromomycin have shown different clinical outcomes.[50–53] The efficiency of oral miltefosine against CL is variable and species-dependent .[54,55] Liposomal amphotericin B has been shown to be useful in the treatment of CL.[56]

Some Old World trials showed that fluconazole and itraconazole (antifungal azoles) can be effective against *L. major* and *L. tropica*, respectively.[57,58] A limited number of New World trials have shown that miltefosine, ketoconazole, and oral allopurinol may be effective for treatment of CL.[59]

Pentoxyphylline is an anti-inflammatory medicine that may be useful as adjunct therapy for CL.[48] Imiquimod (an antiviral TLR7 agonist) and immunomodulators (bacillus Calmette–Guérin and trehalose dimycolate) have been reported to act as other adjunct therapies.[48,50,60,61]

Leishmaniasis coinfections

Co-infections of *Leishmania*and HIV have been reported for CL and VL. Since the first illustrated case of HIV–VL coinfection in 1985, 35 countries have described such coinfections, with a growing number of cases in East Africa. In northeast Ethiopia, new cases are 23% of all VL patients.[48]

Liposomal amphotericin B for treatment of CL

In recent years, successes with the usage of liposomal amphotericin B to treat CL have been described. Here, the literature describing the outcome of CL patients managed with liposomal amphotericin since 2011 was reviewed. Studies and clinical trials that reported the usage of liposomal amphotericin B for CL treatment before 2011 have been reviewed elsewhere.[1]

A summary of published studies and clinical trials (since 2011) on the use of liposomal amphotericin B to treat CL[46,62–72] are shown in Table 1. Epidemiological and

clinical data of *Leishmania* spp. and treatment results are included in Table1.

Most of the reports mentioned include a limited number of adults and children, individuals with immunosuppressive conditions, or people who had shown failure with early treatment by pentavalent antimony. The trials report drug effectiveness from just one geographic area or against just one species of *Leishmania*.

Considering Table 1, studies that involved patients infected with *L. tropica* showed positive outcomes. In the case of *L. infantum*,[46,62] the infecting species may affect the effectiveness of liposomal amphotericin B, although age and existence of immunosuppressive conditions or comorbidities may also influence outcomes.[46,62] Guery et al[62] showed a low cure rate for liposomal amphotericin B against *L. infantum* (Table 1). This may have been because the different populations investigatied included people visiting relatives and friends, emigrants, military individuals, and travelers. However, part of the low cure rate in that study may have arisen from repeated termination or alteration of the liposomal amphotericin B regimen.[62]

Motta et al tested a low-dosage amphotericin B regimen (1.5 mg/kg/day) against *L*. (*Viannia) braziliensis, L. amazonensis*,*and L*. (*V*) *shawi*.[64] The cure rate of liposomal amphotericin B was low (50%; Table 1). The authors suggested that a higher dose (>1.5 mg/kg/day) of the medicine is required to obtain better outcomes.[64]

Disclosure

The author reports no conflicts of interest in this work.

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