American cutaneous leishmaniasis in French Guiana: a retrospective comparison between liposomal amphotericin B and meglumine antimoniate

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American cutaneous leishmaniasis in French Guiana: a retrospective comparison between liposomal amphotericin B and meglumine antimoniate

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Dear Editor, New World cutaneous leishmaniasis (CL) is endemic in many countries of Latin America, including French Guiana.[1] While pentamidine is the first-line treatment against *Leishmania guyanensis* in this territory,[2] pentavalent antimonials such as meglumine antimoniate (MA) are recommended in case of *L. braziliensis* or pentamidine-resistant strains of other species.[2] Liposomal amphotericin B (L-AmB) (Ambisome®) is widely used against fungi and visceral leishmaniasis.[3] However, data concerning its efficacy in New World CL are scarce and contradictory.[4–7] Due to a shortage of MA, the Cayenne Hospital started using L-AmB as an alternative in 2015. We conducted a retrospective study to compare the efficacy and safety of L-AmB and MA in patients treated for CL.

We reviewed all cases treated from January 2015 to February 2019 with either L-AmB (4 mg kg^{-1} per day for 5 days; premedication with hydrocortisone 100 mg, dexchlorpheniramine and acetaminophen) or MA (75 mg kg^{-1} per day for 21 days). The dosage for L-AmB was based on our experience with American histoplasmosis and CL. The primary outcome was clinical cure, defined as complete re-epithelialization of all lesions. Failure was defined as absence of complete healing at 6 months or relapse during follow-up. Secondary outcomes were adverse events, defined as severe when leading to treatment interruption. We defined moderate adverse events as clinical symptoms without treatment interruption. Laboratory tests and electrocardiograms were performed two to three times per week.[8]

During the study period, 40 patients were included. Their characteristics and outcomes are shown in Table 1. Treatment with L-AmB or MA showed comparable efficacy, with cure rates of 72% [95% confidence interval (CI) 52–93] and 87% (95% CI 73–100), respectively. There was no significant difference in failure rates between L-AmB (17%, 95% CI 0–34) and MA (4%, 95% CI 0–13). In the L-AmB arm, out of 18 patients, failure was observed in two patients infected by *L. guyanensis* and in one case of *L. braziliensis*. We observed frequent asymptomatic hypokalaemia (40%), two cases of acute kidney failure and one anaphylactic reaction. In the MA arm, out of 23 patients, failure was observed in one case of *L. braziliensis*. The treatment was interrupted after 14 doses due to drug fever and hepatic cytolysis. The proportions of severe adverse events were

Table 1 Characteristics of 40 patients with cutaneous or mucocutaneous leishmaniasis treated with amphotericin B or meglumine antimoniate in French Guiana, 2015–2019

	Amphotericin B (n = 18)[a]	Meglumine antimoniate (n = 23)[a]
Demographic characteristics		
Age (years), median (range)	37·5 (17–63)	36 (18–64)
Male sex	13 (72)	21 (91)
Cardiovascular comorbidity	3 (17)	1 (4)
HIV positive	2 (11)	0
Clinical presentation		
Number of lesions, median	1	1
Largest lesion length (cm)	19	6
Mucosal involvement	0	3 (13)
Leishmania species[b]		
L. braziliensis	13 (72)	15 (65)
L. guyanensis	3 (17)	5 (22)
L. amazonensis	0	1 (4)
L. naiffi	0	1 (4)
Undetermined	2 (11)	1 (4)
Previous treatment with pentamidine	11 (61)	18 (78)
Days of treatment, median (range)	5 (1–9)	20·5 (14–28)
Outcome		
Complete clinical cure	13 (72)	20 (87)
Failure	3 (17)	1 (4)
Lost to follow-up	2 (11)	2 (9)
Months of follow-up, median (range)	17 (13–54)	24 (11–58)
Adverse events		
Severe	3 (17)	3 (13)
	Anaphylactic reaction,[a] acute kidney failure (2)	Chest pain (1), fever/chills (1), cytolysis five times above normal value (1)
Moderate	2 (11)	8 (35)
	Vasovagal syncope (1), headache with flush (1)	Arthralgia (6), myalgia (2), headaches (2)
Isolated biological abnormalities	11 (61)	11 (48)
	Hepatic cytolysis (3), renal failure (2), hypokalaemia (6)	Hyperlipasaemia (12), eosinophilia (8), cytolysis (5), neutropenia (1)

The data are presented as n (%) unless stated otherwise. [a]One patient was included in both groups as she was given meglumine antimoniate after an anaphylactic reaction to amphotericin B. [b]Species isolation was made with matrix-assisted laser desorption/ionization time-of-flight spectroscopy on positive cultures of skin biopsies or, in case of negative cultures, with polymerase chain reaction–restriction fragment length polymorphism on skin biopsies, or polymerase chain reaction and Hsp70 sequencing on cotton swabs.

17% (95% CI 0–34) for L-AmB and 13% (95% CI 0–27) for MA, with no significant difference.

Our results are close to previous findings in Israeli travellers infected with *L. braziliensis*, mostly returning from Bolivia.[5] The authors reported a cure rate of 100% with L-AmB, with no treatment interruption. Conversely, the cure rate with sodium stibogluconate (a pentavalent antimonial) was only 75%, with important side-effects in 65% of cases.[5] L-Amb was also associated with a 84% cure rate in 20 travellers returning from South America to the USA,[7] and a 100% cure rate in eight Brazilian patients with mucosal leishmaniasis.[6] The use of different dosages of L-AmB (3 mg kg^{-1} per day for 5 days, sixth dose after 10 days;[5] 3 mg kg^{-1} per day, up to 10 doses;[7] 3–5 mg kg^{-1} per day, mean total dose 35 mg kg^{-1})[6] did not seem to influence the outcome. Conversely, in a heterogeneous population of French travellers treated with L-AmB, this drug was associated with disappointing cure rates, as low as 27% in patients with New World CL.[4] However, data concerning the duration of treatment were missing for 44% of patients in this multicentric study. Discontinuation of L-AmB in these patients might be an explanation for this loss of efficacy.

In our setting, treatment with L-AmB costs 8300 USD (5 days), compared with 19 300 USD for MA (21 days), but it is more cost-effective given the high cost of hospitalization (910 USD per day). Indeed, clinicians working in European settings are usually required to use cardiac monitoring for patients treated with parenteral antimony compounds.[8] This cautious approach also applies to the setting of French Guiana, a high-income country with a low-income population.

Our study is limited by its retrospective nature. Several patients were lost to follow-up and the size of our sample was

relatively small. However, we present here the largest comparative study of L-AmB and a pentavalent antimonial in the referral centre of an endemic area. Most previous reports included only returning travellers.[4,5,7]

Although this small-size study does not formally establish the noninferiority of L-AmB, it supports the authorization of this drug on a regular basis against New World CL. Many patients would benefit from a shorter hospitalization but are denied this option because L-AmB is used off-label. Using this drug as a common alternative to MA would allow the constitution of larger cohorts or randomized trials comparing these two medications.

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Efficiency in patch testing: the number needed to test to get one relevant result as a new approach in the evaluation of baseline series

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Dear Editor, Patch testing is a common procedure, in which the baseline series is frequently used as a first screening. The number and the specific allergens of these series varies from country to country and keep changing over the years. Although the European Society of Contact Dermatitis (ESCD) made recommendations about patch testing,[1] the decisions about the European baseline series were traditionally delegated to the European Environmental and Contact Dermatitis Research Group (EECDRG).[2] A different, more reactive, approach has been proposed recently by the ESCD task force,[3] using data provided by the European Surveillance System on Contact Allergies (ESSCA) to generate an initial discussion. The main criteria for the addition of a new allergen is that the prevalence of allergy is 0·5–1% or higher,[4] and positive results should be relevant.

As a new indicator that considers both the frequency of positive tests and their relevance in a simple measure, we propose using the number of tests needed to get one relevant result to quantify efficiency (number of tests done/number of relevant results).

REVAC (Red Española de Vigilancia de Alergia de Contacto) is a surveillance system across Spain working with the ESSCA, with eight participants. It has been approved by the Hospital del Mar Ethics Committee (2008/3159/I). We reviewed all consecutive patch tests done between 2004 and 2014, including 9767 patients. The clinical relevance of the results was analysed in each case by the participating dermatologist and classified as present or past relevance by describing the association between exposure and contact dermatitis symptoms (e.g. allergic contact dermatitis).[4,5] The study includes the European baseline series, the Spanish baseline series, and some other allergens that participants test in all patients and which could become part of the baseline series.

A few allergens show high testing efficiency (between 16 and 52 tests needed to detect one positive currently relevant result). Many of the allergens are inefficient, with up to 2437 tests needed to detect one positive currently relevant result (Table 1). The results are slightly better for ever-relevant results.

The advantages of this study is that it is highly representative of patch testing in specialized care, and that all participants use the same method and are experts in the topic, decreasing measurement error. It is likely that results in less specialized settings could be less efficient, as the prevalence of contact allergy is lower. The main limitations to consider are the subjective definition of relevant results and the common difficulty to identify with certainty the source of exposure to the contact allergen. However, we have chosen positive and