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Use of the intramuscular route to administer pentamidine isethionate in *Leishmania guyanensis* cutaneous leishmaniasis increases the risk of treatment failure

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ABSTRACT

Background: New world cutaneous leishmaniasis (NWCL) can be found in French Guiana as well as in several other parts of Central and South America. *Leishmania guyanensis* accounts for nearly 90% of cases in French Guiana and is treated with pentamidine isethionate, given by either intramuscular or intravenous injection. The military population is particularly exposed due to repeated missions in the rainforest. The purpose of the present study was to identify the factors associated with pentamidine isethionate treatment failure in a series of service members with *L. guyanensis* NWCL acquired in French Guiana.

Method: All the French service members reported as having acquired leishmaniasis in French Guiana from December 2013 to June 2016 were included.

Results: Seventy-three patients infected with *L. guyanensis* were included in the final analysis. Patients treated with IV pentamidine isethionate had better response rates than those treated with IM pentamidine isethionate ($p = 0.002$, adjusted odds ratio (AOR) = 0.15, 95% CI [0.04–0.50]). The rate of treatment success was 85.3% (95% CI [68.9–95.0]) for IV pentamidine isethionate and 51.3% (95% CI [34.8–67.6]) for IM pentamidine isethionate.

Conclusions: The use of intramuscular pentamidine isethionate in the treatment of *Leishmania guyanensis* cutaneous leishmaniasis is associated with more treatment failures than intravenous pentamidine isethionate.

1. Introduction

Cutaneous leishmaniasis seems to be a growing concern in endemic countries [1] and among travelers [2]. New world cutaneous leishmaniasis (NWCL), also called American tegumentary leishmaniasis, is endemic in several parts of Central and South America. In French Guiana, a French overseas entity in South America located between Suriname and Brazil, five species of parasite are known to infect humans: *Leishmania guyanensis, L. braziliensis, L. amazonensis, L. lainsoni*, and *L. naiffi* [3]. *L. guyanensis*, a species of the *Viannia* subgenus, is restricted to the rainforests of Brazil, Colombia, Guyana, Suriname, and French Guiana. It is the predominant species in French Guiana, accounting for nearly 90% of cases [3,4]. It is transmitted by a sand fly vector, *Lutzomyia umbratilis*. The main reservoir is the two-toed sloth (*Choleopus didactylus*) [5].

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In French Guiana, the military population is particularly exposed to the parasite's life cycle during repeated missions in the rainforest to control illegal gold mining [6], and even more during training periods at the Tropical Forest Training Center (Global Positioning System decimal degrees: 4.281285, −52.157639), a historical focus of NWCL [7–9]. Service members are trained there for several weeks and are exposed to the sand flies through various physical activities (including tree felling), occasionally at night.

Each year, fluctuations in incidence depend on the occurrence of military activities during seasonal peaks in the parasite's life cycle, which usually occur during the first semester, and on occasional outbreaks when preventive measures are misapplied [7–10]. Since each service member diagnosed with NWCL becomes unavailable until cured, the disease can strongly impact military operational capabilities. Therefore, the French Military Health Service is looking for the most effective and simple treatment to limit the period of unavailability.

Only a few studies have addressed improvement following treatment for NWCL in French Guiana [9–11]. The reported rates of treatment success vary widely. It was 89% in a study by Nacher et al., in 2001 [12] and 58% in a study by Neves et al., in 2011 after one round of treatment [13]. The current French treatment recommendations for *L. guyanensis* are to use intravenous (IV) or intramuscular (IM) pentamidine isethionate [5]. The choice of route of administration is left to the judgment of the physician. In fact, IM treatment is chosen in a large majority of cases [14]. In French Guiana, the habitual procedure is to use IM treatment because the most exposed populations in the forest are migrants, illegal gold miners who are usually poorly compliant and can be reluctant to be hospitalized. The IV route of administration for pentamidine isethionate is the preferred one in the United States and Canada according to the recent Infectious Diseases Society of America and American Society of Tropical Medicine and Hygiene guidelines, but without any study to support this choice [15]. Thus, evidence about the effect of the route of pentamidine isethionate administration on the treatment of NWCL due to *L. guyanensis* is needed.

Several factors are associated with treatment failure: geographic distribution [15], *Leishmania* species [15,16], meteorological parameters [17], dissemination [12], higher number of lesions [14,18], younger age [18], early or delayed treatment [18,19], shorter duration of exposure in an endemic region [18], intralesional interleukin-10 and Foxp3 mRNA expression [20], and HIV co-infection [21]. Some of these factors may appear paradoxical and could account for a poor immune response [22].

In addition, *Leishmania guyanensis, L. braziliensis, L. amazonensis,* and *L. lainsoni* can be infected by a virus belonging to the *Totiviridae* family: *Leishmania* RNA virus type 1 (LRV). It was discovered in 1988 in a sample originally isolated from a visitor to Suriname [23]. The presence of this virus in the parasites seems to influence the cure rate [14,18,24,25]. The infected parasites tend to spread, and Bourreau et al. have shown that the presence of the virus increases the risk of treatment failure and relapse [14].

The purpose of the present study was to identify the factors associated with pentamidine isethionate treatment failure in a series of service members with *L. guyanensis* NWCL acquired in French Guiana.

2. Methods

2.1. Study design

This study is a case series. Diagnostic samples and treatment were performed in the context of routine care. Data were then collected with patient consent. The end-point was defined as patient recovery, confirmed by the epithelialization of the lesion, measured six weeks after the beginning of treatment.

2.2. Diagnosis and case definition

A complete diagnostic strategy was used for all patients in French Guiana: direct smear examination and two intra-lesional punch biopsies for species diagnosis (culture, PCR) and LRV diagnosis by quantitative reverse transcription-PCR [14]. A restriction fragment length polymorphism-PCR analysis was performed on parasite cultures for the patients treated in French Guiana [4,11]. For the patients diagnosed in continental France after returning from French Guiana, various methods were used [26].

A leishmaniasis case was defined as any cutaneous lesion associated with confirmed parasitological evidence (*Leishmania* spp. in direct smear examination, culture, or polymerase chain reaction (PCR)) contracted in French Guiana.

2.3. Treatment strategy

The treatment was left to the appreciation of the physician taking care of the patient, either a general practitioner or a hospital specialist. The L. *guyanensis*-infected patients were included in the final analysis; they were treated by pentamidine isethionate (Pentacarinat, Sanofi-Aventis), either IV or IM. A bottle of Pentacarinat contains 300 mg of pentamidine diisethionate (171 mg of pentamidine). Treatment with intravenous pentamidine isethionate consisted of one injection of 4 mg/kg repeated every 48 h for a total of three times. The IM pentamidine isethionate was administered in two injections given on a single day in two different sites at the same time for a total of 7 mg/kg.

All patients attended a follow-up visit six weeks after the onset of the treatment.

Treatment failure was defined as the persistence of the lesion without improvement six weeks after treatment, which led to a second treatment.

2.4. Data collection

Cases were reported to the French armed forces epidemiological surveillance system in French Guiana (autochthonous cases) and in continental France (imported cases).

All the French service members reported to have had leishmaniasis in French Guiana or on returning from French Guiana from December 2013 to June 2016 were included.

Physicians were called to collect data about species, presence of LRV, treatment strategy, and follow-up. Suspected area of contamination, number of lesions, dissemination—defined as secondary lesions surrounding the initial lesion or a certain distance from it—, diameter, time between diagnosis and treatment, and side effects were recorded.

Only L. *guyanensis*-infected patients with a complete follow-up were included in the final analysis. Those infected with another species were included for epidemiological purposes.

2.5. Statistical analysis

Statistical analyses were done using SAS University® software (SAS Institute Inc., NC, USA). Given the small sample sizes, the Fisher exact test was used for univariate analysis. Logistic regression was used for multivariate analysis. All statistical analyses used a 5% significance level. The following variables were included in the analyses: age, number of lesions, diameter of lesions, dissemination, stays at gold-mining site, presence of LRV, time between diagnosis and treatment and route of administration of treatment.

3. Results

Ninety-seven patients were included (Fig. 1), 50 in French Guiana and 47 in continental France. Five were included in 2013, 53 in 2014, 22 in 2015, and 17 in 2016.